THE BEHAVIOURAL PHENOTYPE OF CHILDREN WITH CHARGE SYNDROME

By

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College of Life and Environmental Sciences

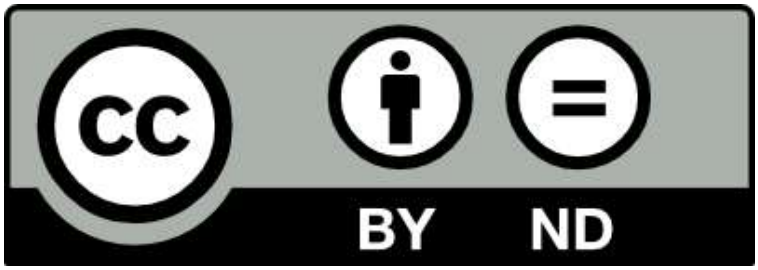
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ABSTRACT

Background: CHARGE syndrome is a highly variable, rare multisystemic condition, with an estimated prevalence of 1 in 8500 live births. Given the multitude of medical difficulties experienced by children with CHARGE syndrome, research to date has focused on understanding the physical phenotype. However, while there is limited research available, the studies that have been undertaken suggest that there may also be a behavioural phenotype associated with the syndrome, and that delineation of this phenotype could help to improve the availability and specificity of clinical support provided to people with CHARGE syndrome.

Methods: A large-scale systematic review and meta-analysis yielding 42 articles including 1556 participants was employed to elucidate the prevalence of phenotypic characteristics and variability in CHARGE syndrome. A syndrome profile comparison survey was conducted to compare sleep and behaviour characteristics between CHARGE syndrome and five clinical neurodevelopmental groups matched on age and ability level. The sample included 26 participants (13 female) with CHARGE syndrome (Mage = 8.12 years; SD 3.47). A multi method sleep study (N=7, Mage=8.14; SD = 3.39) using actigraphy and standardised questionaries was conducted to identify the sleep profile of children with CHARGE syndrome and to examine how this compared to an age-matched typically developing group. Finally, an interview study was conducted to assess the severity and function of behaviours that challenge in children with CHARGE syndrome with a particular focus on aggressive behaviour (N=14; Mage = 9.91; SD = 3.46).

Results: The meta-analysis revealed a high prevalence of aggressive (48%) and self-injurious behaviours (44%) and a high prevalence of sleep problems in CHARGE syndrome (45%).

However, syndrome profile comparisons revealed no significant difference between CHARGE syndrome and the five age and ability matched clinical groups on behaviours that challenge. The thesis found weak evidence for the null and alternative hypotheses in the Bayesian t-tests comparing children with CHARGE syndrome to typically developing children on sleep and behaviours that challenge. The interview study revealed that aggression commonly required immediate intervention, and that reinstatement of routine / repetitive behaviour was a common function for behaviours that challenge.

Conclusion: This thesis has provided a robust delineation of several, clinically relevant aspects of the behavioural phenotype of children with CHARGE syndrome. The behavioural phenotype of CHARGE syndrome includes behaviours that challenge and sleep difficulties. Specifically, it includes aggressive behaviour. Regular assessment is important to ascertain when behavioural intervention is required, and functional assessment can be used as part of this assessment to help tailor interventions.

DEDICATION

"Half working, half dancing - that is the right mixture. I myself have danced and played too little."

Elizabeth Küber-Ross

To my children Tanya, Taylor and Harrison, and my Husband Chris for reminding me to dance.

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PUBLICATIONS AND CONFERENCE PRESENTATIONS

The following preregistrations, publications, and presentations are directly relevant to the work presented in this thesis. This thesis includes one of these papers, which corresponds to an empirical chapter. For those listed, secondary researchers provided guidance on data analysis, project design, presentation content, or manuscript editing.

Preregistrations:

Thomas, A., Waite, J., Oliver, C. & Richards C. (2021, June 8). Sleep Pain and Behaviour in CHARGE Syndrome. Retrieved from https://osf.io/xzmr4/

Thomas, A., Waite, J., Oliver, C. & Richards C. (2021, June 7). CHARGE Syndrome: Insight from an Investigation of Behavioural and Adaptive Functioning. Retrieved from https://osf.io/qbkps/

Publications:

Thomas, A. T., Waite, J., Williams, C. A., Kirk, J., Oliver, C., & Richards, C. (2022). Phenotypic characteristics and variability in CHARGE syndrome: a PRISMA compliant systematic review and meta-analysis. Journal of neurodevelopmental disorders, 14(1), 49.

Conference presentations:

Thomas, A., Williams, C., Kirk, J., Oliver, C., & Richards, C. (2023). Identifying barriers to quality of life in charge syndrome: A systematic review and meta-analysis. *Presented at the 55th Annual Gatlinburg Conference, Kansas City, Missouri, US*

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Invited Presentations

Thomas, A. Waite, J., Kirk, J., Oliver, C., & Richards, C. (2023) Towards a behavioural phenotype of CHARGE syndrome. *Presented at the Endocrine Research Group, Birmingham Woman's and Children's Hospital*

·**Thomas, A**. Synthesising Behaviour: A Systematic Review and Meta-Analysis Approach (2021) *Presented at The Richards Lab, University of Birmingham*

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CHAPTER ONE

THE BEHAVIOURAL PHENOTYPE OF CHILDREN WITH CHARGE SYNDROME: AN INTRODUCTION

1.1 Introduction

This chapter provides an overview of the challenges experienced by people with intellectual disability, including physical health, pain, sleep, sensory differences, psychopathology, and neurodevelopmental conditions. A final focus is on behaviours that challenge, risk markers and risk factors for these behaviours and consequences for the wellbeing of the person with intellectual disability and their family. Subsequent sections of the chapter discuss these characteristics and concerns in relation to genetic syndromes associated with intellectual disability, with a specific focus on CHARGE syndrome.

1.1.1 Intellectual Disability

The American Psychiatric Association (2013) defines intellectual disability as intellectual and adaptive functioning limitations that originate during the developmental period. Intellectual functioning includes learning, problem solving and judgement. Adaptive functioning refers to daily activities, including conceptual, social and practical skills. Confirmation of intellectual disability and subclassification of mild, moderate, severe or profound intellectual disability is ascertained based on clinical assessment and standardised testing where possible (American Psychiatric Association, 2013). In individuals with severe or profound intellectual disability, it may be more challenging to assess intellectual functioning using traditional testing methods accurately. Challenges arise because these individuals may need more communication skills and help understanding or completing tests

as they are typically administered (Carnaby, 2007). In such cases, adaptive behaviour can be a more reliable measure of intellectual functioning because it assesses an individual's real-life skills and abilities. Furthermore, persons with intellectual disability may need life-long support to achieve equity, equality and inclusion. A better understanding of the support needs of persons with intellectual disability can help to ensure that they receive the appropriate care and services to meet their unique needs.

1.1.2 Intellectual Disability and Physical Health

The physical health needs of individuals with intellectual disability are higher than for those of the general population (Liaoi et al., 2021). The most prevalent health conditions include epilepsy, ear and eye disorders, congenital heart defects, and thyroid disorders (Liaoi et al., 2021). Risk factors for health difficulties include medication and lifestyle. For instance, McMahon et al. (2020) highlight polypharmacy associated with the high prevalence of epilepsy, psychiatric disorders and other severe health conditions. The use of multiple medications increases the risk of side effects to drugs, including akinesia, dystonia or neuroleptic malignant syndrome (McMahon et al., 2020). Lifestyle factors, such as limited physical activity due to physical impairments and constraints on staffing, funding, or transport, and inadequate nutrition associated with dysphagia, hyperphagia, or pica contribute to the risk of people with intellectual disability developing type 2 diabetes, cardiovascular disease, and hypertension (Hsieh et al., 2014). Communication challenges and the severity of intellectual disability can be a barrier to proactive help-seeking behaviours. Inadequate inclusion of individuals with intellectual disability in screening programs impedes early detection and optimal management of physical conditions, leading to underdiagnosis and premature mortality (O'Leary et al., 2018). Therefore, healthcare providers must be aware of

the burden of physical health needs of individuals with intellectual disability and address them proactively.

1.1.3 Intellectual Disability and Pain Experiences

Individuals with intellectual disability are at greater risk of experiencing pain and discomfort due to their increased physical health burden. Physical pain can affect daily life and emotional well-being, sleep patterns, appetite and social motivation (Doody & Bailey, 2019; McGuire et al., 2010). Because pain is a subjective experience, clinicians and researchers primarily rely on self-report to assess its presence, severity, and impact. Consequently, pain and discomfort may not be identified and thus can remain untreated in individuals with impaired communication capacity (McGuire et al., 2010). Alternative methods for pain assessment may be necessary. Alternative methods may include observation, assessment of physical symptoms and asking caregivers and other support staff to provide information (Cascella et al., 2019; Symons et al., 2008). By taking a comprehensive approach to pain assessment, individuals with intellectual disability can receive the treatment they need to manage pain and improve their overall quality of life.

1.1.4 Intellectual Disability and Sleep

People with intellectual disability experience more severe and persistent sleep disturbances than those without intellectual disability (Browne et al. 2023 Surtees et al., 2018). The prevalence of sleep difficulties in intellectual disability varies between 13% and 86%, depending on the participant's age and the methods and definitions of sleep problems used in the study (Didden & Sigafoos, 2001). Sleep disturbances in intellectual disability correlate positively with cognitive difficulties, behaviours that challenge, medication use, physical

health problems and undiagnosed pain, and comorbid sensory, psychiatric and neurodevelopmental conditions (Belli et al., 2022; Didden & Sigafoos, 2001; Van de Wouw et al., 2012). These correlations are likely multifactorial and bidirectional (Belli et al., 2022), and researchers must consider these factors when assessing sleep in individuals with intellectual disability.

1.1.5 Intellectual Disability and Sensory Differences

Sensory differences are common in persons with an intellectual disability. For example, the prevalence of hearing impairment in persons with intellectual disability is forty times higher than in the general population (Warburg, 2001). In addition, hearing impairment compromises learning, decreasing the ability to process auditory information cognitively and exacerbating the effects of intellectual disability (Carvill, 2001). The prevalence of intellectual disability and combined hearing and vision loss is 21.4% (Hoevenaars-van den Boom et al., 2009). Combined hearing and vision loss impedes incidental learning with cascading effects on cognitive, psychosocial and language development (Dammeyer, 2011). Therefore, it is crucial for professionals working with individuals with intellectual disability to be aware of the prevalence and impact of sensory differences to facilitate effective support and accommodations.

1.1.6 Psychopathology, Neurodevelopmental Conditions, and Intellectual disability

People with intellectual disability are more likely to have a co-occurring neurodevelopmental condition or mental health condition than people without intellectual disability (Dykens, 2000). People with intellectual disability can experience a range of challenges, including mood and psychotic disorders, anxiety and impulsivity, as well as

specific behaviours such as stereotypies and self-injury (Dykens, 2000). The prevalence of these challenges is highest for individuals with mild intellectual disability (Dykens, 2000), likely reflecting the challenge of accurate identification and diagnosis in individuals with severe or profound intellectual disability who may have limited ability to self-report (Szymanski et al., 1999). Further, the appropriateness of applying diagnostic criteria and thresholds developed for people without intellectual disability to persons with intellectual disability who may experience symptoms of the same conditions in qualitatively different ways remains a debate (Dykens, 2000).

1.1.7 Intellectual Disability and Behaviours that Challenge

1.1.7.1 Defining Behaviours that Challenge

Emerson and Bromley (1995) define behaviour as 'challenging' if it is culturally abnormal and so intense, frequent, or long-lasting that it is likely to severely compromise the safety of the individual or others. Examples of challenging behaviour include self-injury, aggression, destruction of property, eating inedible objects (pica), non-compliance, overactivity, and regurgitation of food (Emerson & Bromley, 1995). This thesis will use the term behaviours that challenge when referring to challenging behaviour. Emerson and Einfeld (2011) coined the term behaviours that challenge to emphasise that the challenging aspect of behaviour is socially constructed, and that behaviour can be challenging to others while simultaneously being functional for the person with intellectual disability. Kiernan and Moss (1990) and Poppes et al. (2010) have reported prevalence rates as high as 50-80%, and Laverty et al. (2020) note that once behaviours that challenge are established, they are highly persistent. Identification of risk markers can inform pre-emptive support strategies, and risk factors can serve as points of entry for effective intervention.

1.1.7.2 Risk Markers and Factors for Behaviours That Challenge

People with intellectual disability are at increased risk for engaging in behaviours that challenge, and specific risk markers and factors may predict or exacerbate this risk. Risk markers include a genetic aetiology of intellectual disability, increasing intellectual disability levels, autism or behaviour indicative of an autism diagnosis and communication difficulties (Hill & Furniss, 2006; McClintock et al., 2003). Risk factors associated with the precipitation and prediction of behaviours that challenge in intellectual disability include poor sleep, auditory impairments, and pain and discomfort (Kennedy, 2021; Poppes et al., 2016).

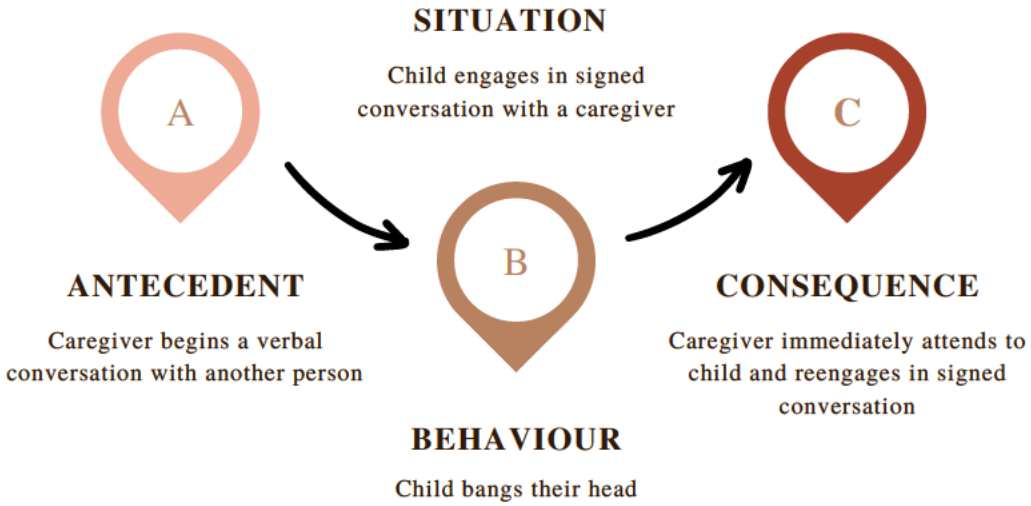
1.1.7.3 Psychological Models of Behaviours that Challenge

Psychological models help identify factors associated with behaviour, understand the factors that reinforce or modify these behaviours and determine targets for intervention. Operant learning theory suggests that behaviours are influenced by their consequences (Blackman, 2017). These consequences can increase the likelihood of a behaviour happening again though positive reinforcement (adding a positive stimulus) or negative reinforcement (removing an aversive stimulus), (Blackman, 2017). This cycle of operant learning can be described clinically using the ABC (Antecedent, Behaviour, Consequence) behaviour model (Blackman, 2017). For example, a child with intellectual and hearing impairments engages in a signed conversation with a caregiver. The caregiver begins conversing verbally with another person, excluding the child (the antecedent). The child feels frustration and starts crying loudly (the behaviour). The caregiver responds be redirecting their attention to the child (the consequence). In this situation, the child may learn an association between loud crying and the reinstatement of the reinforcer (attention). It is the connections that make it more likely

that the child will repeat the behaviour the next time lowered attention occurs. Here the function of behaviour is to reinstate attention.

Figure 1. 1

The Antecedent, Behaviour, Consequence model of behaviour (Blackman, 2017)



1.1.7.4 The Broader Implications of Behaviours that Challenge

The effects of behaviours that challenge on individuals with intellectual disability and their families can be devastating. When individuals with intellectual disability engage in behaviours that challenge, this can lead to increasing infringements on quality of life, including restrictive practices, exclusion from services and costly out-of-area placements (Cooper et al., 2009; Holden & Gitlesen, 2006). In addition, parents of the individual with intellectual disability may be challenged by physical behaviour and may experience sleep deprivation, high levels of stress, depression and social isolation (Biswas et al., 2015; Griffith & Hastings, 2014; Hubert, 2011).

1.1.8 The Aetiology of Intellectual Disability

Individuals with intellectual disability form an aetiologically heterogeneous group. For example, mild intellectual disability is more likely to be caused by environmental factors (Patel & Brown, 2017). Whereas, biological and neurological factors are more common in the aetiology of severe and profound intellectual disability (Patel & Brown, 2017). The most prevalent causes of intellectual disability include chromosomal and genetic disorders such as Down syndrome and Fragile X syndrome (Coughlin, 2007; Curry et al., 1997). With the delineation of over 1,000 genetic conditions, a genetic cause of intellectual disability can be established in approximately 50% of individuals (Shashi et al., 2014). Differentiating individuals with intellectual disability into aetiological groups helps to explain person variability and group similarities (Oliver et al., 2010). Therefore, aetiology-based research has greater power to predict phenotypic outcomes and develop care provision frameworks.

1.1.9 The Behavioural Phenotype

Behavioural phenotype research promotes rigorous enquiry of pathways from genetic origins to behavioural outcomes. What constitutes a behavioural phenotype has been debated. The total specificity model of the behavioural phenotype argues that differences at the molecular level will have unique effects on neurological functioning and, thus, cognition and behaviour (Flint & Yule, 1994). In this model, a behavioural phenotype is always only seen in one genetic or chromosomal disorder (Flint & Yule, 1994). However, few gene-cognition-behaviour associations adhere to the total specificity model (Hodapp & Dykens, 2001). Even in Lesch–Nyhan syndrome in which self-injury is particularly prevalent, it is not ubiquitous (Oliver et al., 2013). Furthermore, genetic conditions do not affect cognition and behaviour

uniformly (Hodapp & Dykens, 2001) and the resultant phenotype is influenced by multiple factors including the pathogenic gene variant, the individual's many thousands of other genes, and the dynamic and ongoing interactions between the environment and the individual, exemplified by the ABC model outlined in section 1.1.7.3. In this vein, Dykens (1995) defined a partial specificity model, where the behavioural phenotype is described as the increased probability that one syndrome group will exhibit particular behavioural, emotional, cognitive or developmental sequelae compared to individuals without that syndrome. Notably, the partial specificity model incorporates within and between-syndrome variability, thus facilitating the enquiry of pathways to cognitive and behavioural characteristics.

1.1.10 Examples of Behavioural Phenotypes

Examples of well-delineated behavioural phenotypes that have recently been reviewed include Williams syndrome (Kozel et al., 2021), fragile X syndrome (Crawford et al., 2020), and Prader-Willi syndrome (Szabadi et al., 2022).

1.1.10.1 Williams Syndrome

Williams syndrome is a rare genetic syndrome caused by the deletion of genetic material on chromosome 7q11.23 (McKusick, 2020). Williams syndrome is characterised by distinctive facial features, cardiac, endocrine and renal anomalies, mild to moderate intellectual disability and developmental delay (Morris et al., 2020; Pober, 2010). Individuals show relative strengths in music, language and nonverbal reasoning (Lenhoff et al., 1997). The behavioural phenotype of Williams syndrome includes hypersociability, anxiety, emotional overactivity, and attentional difficulties (Kozel et al., 2021). Behaviour in Williams

syndrome frequently satisfies diagnostic criteria for anxiety disorder, attention deficit hyperactivity disorder and autism (Kozel et al., 2021).

1.1.10.2 Fragile X Syndrome

The full mutation of the FMR1 gene causes fragile X syndrome. Males with fragile X syndrome commonly have lower FMRP levels than females (Protic et al., 2022). Males with fragile X syndrome typically present with characteristic faces, joint hypermobility, and macroorchidism at puberty (Protic et al., 2022). Cognitive, behavioural and psychological manifestations include intellectual disability, speech and language delay, autism, social anxiety, sensory hyperarousal, attention deficit hyperactivity disorder, aggressive behaviour, sleep problems and obsessive-compulsive disorder (Protic et al., 2022).

1.1.10.3 Prader-Willi Syndrome

Prader-Willi syndrome is a rare neuroendocrine disorder arising from the loss of expression of paternal chromosome 15q11.2-q13 (Whittington & Holland, 2022). Developmental delay, intellectual disability, short stature, impaired sexual development and an obsessive desire for food (hyperphagia) characterise the Prader-Willi syndrome phenotype (Whittington & Holland, 2022). The behavioural phenotype of Prader-Willi syndrome includes temper outbursts, ritualistic behaviours, skin picking, sleep problems and an increased probability of developing a psychotic illness or being diagnosed with autism (Whittington & Holland, 2022).

1.1.11 Methods for Behavioural Phenotype Studies

1.1.11.1 Research Design

Several methods have been used to advance behavioural phenotype research, including case and cohort studies, case-control studies, syndrome profile comparison studies and systematic literature reviews. For example, diagnostic criteria development relies on case studies that provide rich qualitative information when a genetic syndrome is first identified. As more individuals are diagnosed, cohort studies help describe the prevalence, intra-group variability and genotype-phenotype correlations. Systematic reviews and meta-analyses are essential in synthesising the best available evidence for quantifying and exploring data quality. Subsequently, more refined and systematic methodologies are required to move beyond description to elucidate whether the prospect of the identified characteristics are shown at increased rates compared to individuals from other groups (Dykens, 1995).

1.1.11.2 Case-Control and Comparison Groups

Behavioural phenotype research offers methodological challenges. For example, when selecting groups for case-control studies, certain theorists argue for comparison with typically developing individuals matched on chronological age (Burack, 1995). In contrast, developmental theorists argue for a control group with intellectual disability of heterogeneous aetiology matched on intellectual or adaptive functioning (Burack, 1995). Chronological age matched control groups are necessary to highlight areas of difficulty in pursuing equity. However, chronological age matched control groups cannot estimate the extent to which a particular aetiological group's behavioural, emotional or cognitive ability is a relative strength, relative difficulty or common characteristic compared to other groups of similar ability levels. Using a control group matched on intellectual or adaptive functioning enables

inferences about phenotypic characteristics to be made while controlling for behaviours associated with intellectual disability levels (Hodapp & Dykens, 2001). However, considerable variability remains between individuals matched on intellectual disability regarding behavioural, cognitive, psychological, and physiological characteristics (section 1.3-1.8).

1.1.11.3 Syndrome Profile Comparisons

Hodapp and Dykens (2001) developed the 'same-but-different' approach to behavioural phenotype research. This research strategy involves comparing similar characteristics or behaviours in groups with different underlying aetiologies (Hodapp & Dykens, 2001). For example, Abbeduto and Murphy (2004) used the same-but-different approach to compare cognition and behaviour in Down syndrome and fragile X syndrome. This research highlighted relative strengths and limitations in both groups, informing syndrome-specific assessment and support strategies (Abbeduto & Murphy, 2004). The same-but-different approach has been widely adopted in behavioural phenotype research as it allows researchers to disentangle how genetic differences mediate specific behavioural and cognitive characteristics.

1.1.12 Benefits to the Broader Intellectual Disability Population

Behavioural phenotype research has been instrumental in informing anticipatory and preventive support for individuals within the broader intellectual disability population. Examples include research into self-injury, self-restraint and hyperactivity in Cornelia de Lange syndrome, which identified a potentially common association with behaviour regulation (Hyman et al., 2002a; Petty & Oliver, 2005). In addition, in males with fragile X

syndrome, evidence of executive deficit has been suggested to be an influential factor in the variability and severity of repetitive behaviour across fragile X syndrome (Wilding et al., 2002) and autism (Turner, 1997). Therefore, exploring within and between group variation, identified through rigorous behavioural phenotype research, has considerable implications for the broader intellectual disability population.

1.1.13 The Distribution of Research Efforts and Methodological Quality in the Field of Behavioural Phenotype Research

Many factors influence the quantity and quality of research across genetic syndromes; however, this is rarely made explicit. These factors may include prevalence of the syndrome, ethical issues around acquiring consent and practical challenges associated with assessing syndrome groups that experience multiple or profound disabilities. For example, the unequal distribution of research efforts is evident in the study of anxiety in 7q11.23 duplication syndrome (Dup7). Despite the 70% prevalence of anxiety disorders in Dup7 (Mervis et al., 2015), a recent review by Edwards et al. (2022) reported only three low-quality studies reporting anxiety in Dup7. Similarly, while the prevalence of autism characteristics in Rett syndrome is high (61%), Richards et al. (2015) reported only five cohort studies in their review of autism phenomenology across genetic syndromes. The extent of research interest in emotional and behavioural challenges in Rett syndrome and Dub7 can be contrasted with increased research interest (two and five times greater) in the comparatively lower rates of anxiety (9%) and autism characteristics (16%) in Downs syndrome (Edwards et al., 2022; Richards et al., 2015). Further, when reviewing sleep disorders in genetic syndromes, Agar et al. (2021) reported seven higher-quality research studies investigating sleep in WS but only

two lower-quality studies reporting sleep in Mucopolysaccharidosis Type II despite sleep difficulties being more than twice as prevalent in Mucopolysaccharidosis Type II than WS.

1.1.14 CHARGE Syndrome

One syndrome group in which the behavioural phenotype needs to be better delineated is CHARGE syndrome. CHARGE syndrome is a rare genetic syndrome associated with intellectual disability. Estimates suggest a 70% prevalence of intellectual disability and 100% prevalence of developmental delay in CHARGE syndrome (Hale et al., 2016; Sanlaville & Verloes, 2007), and the phenotype of CHARGE syndrome bears similarity to that of individuals with intellectual disability of heterogeneous aetiology. There are several reasons for studying the CHARGE syndrome phenotype in detail. While CHARGE syndrome is often grouped under the broader category of intellectual disability, this category includes a wide range of neurodevelopmental and other conditions, making it very heterogeneous. Therefore, it is crucial to recognise CHARGE syndrome as a distinct condition and to research it independently to more precisely understand the unique characteristics and needs of the people who live with this rare syndrome. CHARGE syndrome is a complex condition affecting multiple organ systems (Blake et al.,1998). Studying the phenotype of CHARGE syndrome can begin to develop preliminary insights into this rare condition, which will form the basis of personalised medicine. Furthermore, CHARGE Syndrome is associated with disparate physical characteristics (Trider et al., 2017), poor sleep quality (Hartshorne et al., 2009) and multisensory impairments that will likely influence the behavioural repertoire, all of which increase the likelihood of behaviours that challenge (Brown, 2005). As such, research into the behavioural phenotype is essential. While behaviours that challenge are common in intellectual disability, research has shown that individuals with specific syndromes present, or

do not present, with qualitatively different behaviours despite the presence of intellectual disability (Oliver, 2017). For example, skin picking in Prada Willi syndrome but not in Fragile X syndrome, and hand biting in Fragile X syndrome that is absent in Prada Willi syndrome (Oliver, 2017). Understanding these specific challenges provides the foundations for understanding causal mechanisms that can lead to genetic counselling and pre-emptive interventions. Considering the heterogeneity in CHARGE syndrome, such research is fundamental to start recognising clusters of behaviours and physical characteristics that may reduce this heterogeneity and lead to a more precise understanding of this syndrome.

1.1.14.1 Delineation and Aetiological Basis

CHARGE syndrome is a rare multi-system neurogenetic condition affecting ~1/8500 newborns (Issekutz et al., 2005). CHARGE is an acronym based on anomalies commonly associated with the syndrome: Coloboma, Heart defects, Atresia choanae, Retardation of growth or development, Genital anomalies and Ear anomalies (Pagon et al., 1981). In addition, diagnostic criteria have been revised to accommodate new insights, including orofacial cleft, tracheoesophageal fistula and cranial nerve anomalies (Blake et al., 1998), hypoplasia of the semicircular canals (Verloes, 2005) and most recently, identification of a pathogenic CHD7 variant (Hale et al., 2016; Vissers et al., 2004).

As CHD7 preferentially regulates genes associated with the formation and guidance of neural crest cells, CHARGE Syndrome belongs to a class of rare conditions called neurocristopathies (Schulz et al., 2014). Neurocristopathies are characteristically heterogeneous and phenotypically complex conditions that affect cardiac, vagal, trunk and sacral development (Bérubé-Simard & Pilon, 2019). As such, all associated characteristics

vary from severe to absent in CHARGE syndrome, manifesting in different combinations across individuals.

1.1.14.2 Physical Characteristics and Conditions

CHARGE syndrome is associated with many physical conditions requiring health monitoring throughout life (Trider et al., 2017). CHARGE syndrome affects the eyes, ears, nose and throat, the neurological, cardiovascular, respiratory, endocrinological, muscular-skeletal and immune systems, and physical development (Trider et al., 2017). Trider et al. (2017) have developed a checklist to guide health supervision across the lifespan, ensuring that individuals with CHARGE syndrome receive appropriate and timely health care.

1.1.14.3 Pain Experiences

Individuals with CHARGE syndrome commonly experience migraines, constipation, otitis media and gastroesophageal reflux, which is challenging to predict (Stratton & Hartshorne, 2019). As noted in section 1.3, pain and discomfort can go undetected or poorly managed in individuals with intellectual disability who cannot effectively self-report. Given the combined impact of cognitive and hearing impairments in CHARGE syndrome, language is particularly delayed, and the risk of poor pain management is likely increased (Vesseur et al., 2016). Developing proactive pain assessment strategies is a research priority for individuals with CHARGE syndrome (Stratton & Hartshorne, 2019).

1.1.14.4 Sleep

As outlined in section 1.5, persons with intellectual disability experience more severe and persistent sleep disturbances than those without intellectual disability (Surtees et al., 2018).

Almost 60% of children with CHARGE syndrome experience sleep difficulties, which positively correlate with behaviours that challenge and negatively correlate with parental well-being (Hartshorne et al., 2009). Sleep problems can emerge from circadian rhythm dysfunction due to visual impairment (Lockley et al., 1997). In addition, they may be exacerbated by the high prevalence of breathing difficulties, visual impairments, pain and discomfort (Hartshorne et al., 2009). However, findings are based on a few studies using questionnaire surveys or direct observation (Hartshorne et al., 2009; Kennert et al., 2020; Trider et al., 2012; Trider & Blake, 2012). Given the recall bias associated with questionnaire surveys and the possibility that direct observation can disturb sleep, further research using objective measures of sleep, such as polysomnography or actigraphy, may provide more accurate and detailed insights into sleep disturbances in CHARGE syndrome.

1.1.14.5 Sensory Differences

People with CHARGE syndrome commonly experience multisensory impairment, involving disturbances in hearing, vision, combined hearing and vision, smell, taste, touch, proprioception, and balance (Hefner & Davenport, 2021). Multisensory impairments contribute to communication and access to information challenges, which can limit social interaction (Hefner & Davenport, 2021). Individuals may use alternative methods of communication and access, including braille, tactile graphics and specialist deafblind assistance (Hefner & Davenport, 2021). However, few adaptations will be suitable for all persons, and individuals will commonly develop adaptive or maladaptive accommodations to help compensate for their sensory differences (Brown, 2005).

1.1.14.6 Co-Occurring Neurodevelopmental and Mental Health Diagnosis

Evidence for co-occurring neurodevelopmental and mental health diagnoses in CHARGE syndrome is limited. However, combined visual and hearing impairment and intellectual disability, common in CHARGE syndrome, increase the risk of developing these conditions (Blake et al., 1998; Dammeyer, 2011). Studies have reported behaviours indicative of obsessive-compulsive disorder, autism, anxiety and depression in CHARGE syndrome (Bernstein & Denno, 2005; Hartshorne, Grialou, et al., 2005; Hartshorne & Cypher, 2004; Smith et al., 2005; Souriau et al., 2005). However, combined visual and hearing impairment independent of CHARGE syndrome is associated with psychosis, mood disorders, obsessive-compulsive disorder, conduct disorder, anxiety, autism and intellectual disability (Dammeyer, 2011) and intellectual disability is associated with mood and psychotic disorders, attention deficit hyperactivity disorder, autism and anxiety (Dykens, 2000).

The challenges associated with diagnosing neurodevelopmental and mental health conditions in persons with combined visual and hearing impairment are similar to those outlined in section 1.7 for persons with intellectual disability. An intact sensory system is a prerequisite for most diagnostic tools. Triangulation of standardised and non-standardised assessments is required to disentangle the aetiology of behaviour in persons with combined visual and hearing impairment (Hoevenaars-van den Boom et al., 2009; Rönnberg & Borg, 2001). For example, as noted in section 1.6, combined visual and hearing impairment impedes incidental learning with cascading effects on cognitive, psychosocial and language development (Dammeyer, 2011). Subsequent topographical similarities, including sensory sensitivity, differences in social interaction, communication, and restricted patterns of behaviour, interests and activities, can be seen in individuals with combined visual and hearing impairment and their autistic peers (Hoevenaars-van den Boom et al., 2009). As such,

differentiating psychiatric and neurodevelopmental conditions in persons with CHARGE syndrome is extremely difficult.

Hartshorne and Cypher (2004) investigated 71 behaviours typical of individuals with combined visual and hearing impairment, autism, attention deficit hyperactivity disorder and obsessive-compulsive behaviour. The study highlighted a distinct pattern of behaviours best explained at the item level. Indeed, this is the case in other genetic syndromes associated with intellectual disability. For example, approximately 60% of individuals with fragile X syndrome meet diagnostic criteria on standardised tests of autism due to their profile of gaze avoidance, stereotyped behaviours, and repetitive vocalisation (Moss & Howlin, 2009). However, individuals with fragile X syndrome exhibit more social anxiety, extreme shyness, and fewer difficulties with emotional sensitivity and social motivation than their autistic peers (Moss & Howlin, 2009). Such research indicates that psychiatric labels may not adequately capture the unique behaviours affecting individuals with genetic syndromes (Jenner et al., 2023).

1.1.14.7 Behaviours That Challenge

There has been limited research on behaviours that challenge in CHARGE syndrome. However, available evidence indicates that behaviours that challenge in CHARGE syndrome may enter the behavioural repertoire as adaptions to a combination of impaired vision and hearing, proprioception, touch, temperature and olfaction (Brown, 2005). Moreover, as undiagnosed pain is a common cause of behaviours that challenge for individuals with genetic syndromes (Waite et al., 2014) and given the increased health burden for individuals with CHARGE syndrome, unresolved pain is likely to be a contributing factor when behaviours

that challenge are present. These behaviours are then likely to be subject to operant reinforcement contingencies. Given the paucity of research and the implications of behaviours that challenge in section 1.8.4, delineating the behavioural phenotype of CHARGE syndrome is a research priority.

There are conflicting reports of behaviours that challenge in the literature on CHARGE syndrome. For example, cohort studies including Johansson et al. (2006), Blake et al. (2005) and Hartshorne et al. (2016) have reported aggression, self-injury and adherence to rituals and routines in around half of individuals with CHARGE syndrome. Whereas Graham et al. (2005) reported a low risk for maladaptive behaviours in their cohort, and Smith et al. (2005) found no evidence for internalising or externalising behaviour difficulties. Given the disparity between findings, there is limited understanding of which behaviours are typical of CHARGE syndrome or how these behaviours might develop in association with individual characteristics. However, it is generally agreed that there is something unique about the pattern of behaviour and cognition in CHARGE syndrome that is not seen in other clinical groups of a similar age, functional ability, or level of sensory disability (Denno & Bernstein, 1997).

1.1.14.8 Lifespan Changes in CHARGE Syndrome: Advantages of Prioritising Research with Children

Research in age-related change in CHARGE syndrome is limited, primarily for two reasons. CHARGE syndrome is a relatively new diagnosis that was only recognised as a condition in 1979; as such, many adults with CHARGE syndrome were not diagnosed as children and may have remained undiagnosed (Blake et al., 2005). The diagnostic criteria has also been changed several times, making diagnosis more complex. The second reason is that

until relatively recently, children with CHARGE syndrome did not survive into adulthood. Two studies have reported CHARGE syndrome in adult cohorts: Blake et al. (2005) and Hartshorne et al. (2016). Blake et al. (2005) report several new issues reported for adults with CHARGE syndrome. These included scoliosis, sleep aphonia, abdominal cholic, and retinal detachment (Blake et al., 2005). Hartshorne et al. (2016) reported new issues in adulthood, such as bone health, sleep apnea, retinal detachment, seizures, and urinary tract infections. Regarding other issues, almost half of the adults experienced obsessive-compulsive behaviour, and one-third reported anxiety disorders and autism (Blake et al., 2005; Hartshorne et al., 2016). More information must be provided regarding which diagnostic algorithm was used in these studies. As such, it is still being determined how homogenous the samples were. However, when the prevalence of diagnostic characteristics was compared to previous data, they were representative.

1.1.14.9 Methods Used to Understand Behaviour in CHARGE Syndrome

As with other syndrome groups, different methods have been used to build an understanding of the behavioural phenotype of CHARGE syndrome. The study design has predominantly consisted of in-depth case studies, small cohort studies with high-quality, standardised assessments, or larger studies using lower-quality questionnaire measures. As is common in rare syndrome research, the literature is predominated by convenience sampling, and details of diagnostic status either need to be ascertained or published (Richards et al., 2015). The methodological quality of CHARGE syndrome case studies is typically high, with detailed behavioural analysis, objective behavioural assessments and intervention strategies (Bernstein & Denno, 2005; Nannemann et al., 2017). These studies highlight environmental influences on specific behaviours that challenge for specific individuals and are therefore not

generalisable to all people with CHARGE syndrome. Larger scale studies, for example Deuce et al. (2012), and Hartshorne and Cypher (2004), have used non-standardised questionnaires to assess more nuanced aspects of the behavioural phenotype of CHARGE syndrome. While non-standardised assessments may help identify strengths and limitations based on the syndrome group's behavioural nuances, the absence of a common taxonomy across research and clinical practice impedes essential communication and syndrome profile comparison.

1.2 Summary

Individuals with intellectual disability form a heterogeneous group with different aetiologies and differing cognitive, social and adaptive functioning levels. When compared to individuals without intellectual disability, individuals with intellectual disability are at heightened risk of experiencing physical conditions, pain, sleep issues, sensory differences, psychopathology and neurodevelopmental conditions. These characteristics increase the likelihood of behaviours that challenge. The functions of behaviours that challenge can be assessed using psychological models drawing on operant learning paradigms. These models provide a dynamic way to understand ongoing associations between the individual, their environment, and the potential functions of their behaviour.

Aetiology-based research can be used to understand the heterogeneity within the intellectual disability population and improve the precision of research findings. Behavioural phenotype research provides a way to investigate the probability that individuals with a particular syndrome will exhibit specific behavioural, emotional, cognitive, or developmental characteristics compared to individuals without the syndrome. This type of research helps

understand the variability within and between different syndromes and can provide insights into the pathways that lead to cognitive and behavioural characteristics.

Several methods have been used for behavioural phenotype research. The field has primarily used small-N studies of varying methodological quality. As such, systematic reviews and meta-analysis provide a valuable tool to synthesise and quantify the data while considering variations in methodological quality. Intellectual and chronological age matched, and syndrome profile "same-but-different" comparisons facilitate investigation of aetiology-informed profiles of behaviour and cognition. Finally, fine-grained research can provide a more detailed understanding of the unique strengths, challenges, and treatment targets for individuals with intellectual disability, helping families access evidence-based interventions.

Despite many risk factors for behaviours that challenge and reports of cognitive, behavioural and emotional challenges associated with CHARGE syndrome, there remains limited information about the profile of this group.

1.3 Special Considerations

Data collection for the thesis, involving Chapters 3, 4 and 5, was conducted between December 2020 and December 2022. This corresponds with the COVID pandemic of 2019 – 2023 (a timeline for the COVID pandemic is available in Appendix 1A). The pandemic caused considerable anxiety for families who were faced with the threat of contracting a potentially life-threatening disease for a child with an already compromised immune system (Sanders, 2020; Theodoropoulos, 2003). There were several periods of "lockdown", and the restrictions imposed varied by region and medical status, with individuals considered

medically vulnerable facing the most stringent conditions (Sanders, 2020). Restrictions meant that parents were home-schooling their children; they had restricted access to services and were often isolated from close and extended family, leading to increased stress, anxiety and low mood (Sanders, 2020). As is typical for children with neurodevelopmental conditions, coping with such change can be particularly challenging (Masi et al., 2019). Children may experience low mood, anxiety, behaviours that challenge and challenges with executive functioning and sleep as a result (Haig & Woodcock, 2017).

Furthermore, families who have a child with a disability are at increased risk of poverty due to the financial and social impact of caring (Emerson, 2007). However, parents of children with disabilities who belong to parent support groups tend to be more affluent (Zeutenhorst, 2017). This is typically because more affluent parents have greater access to resources, including time and money, which enables them to seek out and participate in such groups (Zeutenhorst, 2017). Participants for the studies in this thesis were primarily recruited from parent support groups.

Recruitment for all studies in this thesis was fully transparent. Parents who participated in the syndrome comparison research were informed that the study focused on behaviour and well-being in CHARGE syndrome. Similarly, parents involved in the sleep study were recruited by being told that it was explicitly a study about sleep. The same transparent approach was applied to parents participating in the study on behaviours that challenge. Parents of children already facing these challenges were likely more motivated to participate in this research, potentially introducing bias into the sample.

1.4 Thesis Aims

The thesis has five aims.

1.4.1 Aim 1

Given the potentially devastating effects of behaviours that challenge for persons with CHARGE syndrome and their families (section 1.8.4) and evidence for the prevalence and persistence of these behaviours in persons with intellectual disability (section 1.8.2), it is a research priority to elucidate the phenotypic profile of behaviours in CHARGE syndrome. As outlined in section 1.16, the CHARGE syndrome literature primarily consists of higher-quality small-N or lower-quality larger cohort studies. Only some assessments are appropriate for individuals with multisensory impairments. Reporting of CHARGE syndrome's cognitive, behavioural, and emotional characteristics is typically drawn from studies using triangulation of standardised and non-standardised assessments or idiosyncratic descriptions (section 1.17). Such methodological challenges have likely contributed to the contradictory reports of the prevalence of behaviours that challenge in CHARGE syndrome discussed in section 1.15.7. However, there is considerable intragroup variability in CHARGE syndrome concerning risk markers and risk factors associated with behaviours that challenge (outlined in section 1.8.2), raising the possibility of associations between behavioural, cognitive, and physical characteristics. As outlined in section 1.8.2, elucidating such associations can help identify opportunities for effective intervention. As such, the first aim of the thesis is to use systematic review and meta-analysis methods to identify and estimate the prevalence of behavioural, cognitive and physical characteristics and conditions among persons with CHARGE syndrome and to explore putative associations between these characteristics.

1.4.2 Aim 2

As discussed in section 1.10, behavioural phenotype research uses systematic and rigorous methods to investigate pathways from genetic origins to behavioural outcomes. The partial specificity model (section 1.10) proposed by Dykens (1995) posits that individuals with a specific syndrome are more likely to show behavioural, emotional, cognitive, or developmental characteristics when compared to those without the syndrome. This model can be explored through cross-syndrome comparison methods, as described in section 1.12.3. Cross-syndrome comparison research, as mentioned in section 1.10, investigates within and between syndrome variability. This type of research is a crucial step in understanding the behaviours outlined in section 1.8.3. This research informs syndrome-based intervention and support strategies for individuals experiencing challenging behaviours or at risk of developing them. As such, the second aim of this thesis is to explore the profile of behaviours, skills and challenges in a new cohort of children with CHARGE syndrome and how this profile compares to children without CHARGE syndrome.

1.4.3 Aim 3

Sleep problems are common in several genetic syndromes associated with intellectual disability, including fragile X syndrome (section 1.11.2), Prader-Willi syndrome (section 1.11.3) and Mucopolysaccharidosis Type II (section 1.14). Sleep problems are also likely to be common in CHARGE syndrome. As discussed in section 1.15.4, breathing difficulties, sensory impairments, pain and discomfort can exacerbate sleep disturbances. As argued in sections 1.5 and 1.15.1, there are positive correlations between level of intellectual disability, behaviours that challenge, undiagnosed pain, and sleep issues. These correlations could be

multifactorial and bidirectional. Researchers need to consider these factors when studying sleep problems, especially in syndrome groups where these factors are known to be present. Therefore, the third aim of this thesis is to describe the profile of sleep in CHARGE syndrome and investigate possible associations between sleep quality, behaviour, and behavioural indicators of pain. Furthermore, this thesis compares sleep quality between children with CHARGE syndrome and typically developing children. As outlined in section 1.12.2, typically developing control groups matched on chronological age are necessary to highlight areas of difficulty in pursuing equity.

1.4.5 Aim 4

As discussed in section 1.8.3, psychological models can be used to identify the factors that influence behaviour, understand what reinforces or shapes these behaviours, and identify appropriate targets for intervention. The potential persistence of behaviours that challenge (section 1.8.2) and its devastating impact on the individual and their family (section 1.8.4), as well as the association between increasing levels of intellectual disability and behaviours that challenge (section 1.8.2), make it essential to investigate the common functions of behaviours that challenge in CHARGE syndrome. Therefore, the final aim of this thesis is to explore common functions of behaviours that challenge in CHARGE syndrome.

1.5 Thesis Objectives

The objective of this thesis is to elucidate the putative behavioural phenotype of CHARGE syndrome. The thesis is organised into four empirical chapters. Chapter 2 focuses on aim 1, Chapter 3 addresses aim 2, Chapter 4 focuses on aim 3. Chapter 5 addresses aim 4.

Chapter 2: Systematic review and meta-analysis focused on aim 1. This chapter will collate and evaluate empirical evidence for behavioural, cognitive and physical characteristics associated with a clinical diagnosis of CHARGE syndrome. Statistical associations between characteristics will be explored to identify prospective intervention targets. The prevalence index will be calculated for each characteristic. Behavioural characteristics with the highest prevalence rates will inform the focus of the following chapters.

Chapter 3: Online survey study addressing aim 2 will explore behaviours, skills and challenges in individuals with CHARGE syndrome, including repetitive behaviour, hyperactivity, and behaviours that challenge social functioning, sleep quality and health. These behaviours, abilities and challenges will be compared with matched comparison groups that do not have CHARGE syndrome. Similarities and differences between individuals with and without CHARGE syndrome will be compared on the behaviours, skills and challenges measured.

Chapter 4: A direct sleep assessment study addressing aim 3. This chapter will investigate sleep quality in CHARGE syndrome and interactions between sleep quality, pain and behaviour using objective (actigraphy) and subjective (standardised questionnaire) methods. The sleep parameters of children with CHARGE syndrome will also be compared to a group of typically developing children.

Chapter 5: Interview study that focuses on aim 4. Selecting children with CHARGE syndrome that engage in behaviours that challenge, Chapter 5 will use standardised

interviews to investigate potential functions of behaviour and associations with adaptive behaviour skills.

1.6 Empirical Papers

Chapter 2 is presented as an individual empirical paper within the thesis. Notably, this paper aligns with the overarching themes of the thesis outlined in Chapter 1. The authors of the paper are Andrea Thomas (AT), Jane Waite (JW), Caitlin Williams (CW), Jeremy Kirk (JK), Chris Oliver (CO), and Caroline Richards (CR). Their contributions are as follows: CR, CO and AT conceptualised and AT designed the study. AT conducted literature searches, data extraction and write-up (including initial analysis of results and interpretation of findings. CW took the role of second reviewer to ascertain inter-rater reliability for quality criteria. CR, JW and CO held supervisory roles. CO, JW, JK and CR reviewed and revised the manuscript. All authors approved the final manuscript.

CHAPTER TWO

Phenotypic characteristics and variability in CHARGE syndrome: a PRISMA compliant systematic review and meta-analysis

Thomas, A. T., Waite, J., Williams, C. A., Kirk, J., Oliver, C., & Richards, C. (2022)

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CHAPTER TWO

PHENOTYPIC CHARACTERISTICS AND VARIABILITY IN CHARGE SYNDROME: A META-ANALYSIS

2.1 Preface

Chapter 1 highlighted the importance of research into behaviours that challenge due to their negative consequences. It also outlined the limitations of current research in CHARGE syndrome, including small-scale studies or lower-quality larger cohort studies. Additionally, Chapter 1 highlights the importance of identifying prevalence rates for characteristics and for investigating associations between these characteristics. In this chapter, to fulfil the first aim of the thesis, a systematic review and meta-analysis will be conducted to investigate the prevalence of clinical features, physical characteristics and conditions, cognitive, psychological and behavioural characteristics, and their associations in CHARGE syndrome. The literature search for Chapter 2 was conducted in May 2019, and the results were published in December 2022. Due to the publication date, the literature search was not updated for the thesis.

2.2 Introduction

2.2.1 CHARGE Syndrome Overview and Prevalence

CHARGE syndrome is a highly variable multisystemic condition, with an estimated prevalence of 1 in 8500 live births (Issekutz et al., 2005). The acronym refers to the prominent congenital malformations first used to delineate the syndrome: Coloboma, Heart defects, Atresia choanae, Retardation of growth or development, Genital abnormalities, and Ear anomalies (Pagon et al., 1981). Clinical characteristics are categorised into major and

minor diagnostic criteria. Major criteria are characteristics that are common to CHARGE syndrome but rare in other clinical groups. Minor criteria are characteristics that are common to CHARGE syndrome and to other clinical groups (Table 2.1).

Table 2. 1

Diagnostic criteria for CHARGE syndrome based on the four major revisions of the criteria since CHARGE was identified in 1979

	Pagon et al. (1981)	Blake et al. (1998)	Verloes (2005)	Hale et al. (2016)
Major Criteria	Choanal atresia Ocular coloboma	Ocular coloboma Choanal atresia or stenosis Cranial nerve anomalies Characteristic ears anomalies	Ocular Coloboma Choanal atresia Hypoplasia of the semicircular canals	Coloboma Choanal atresia or cleft pallet Abnormal external, middle, or inner ears Pathogenic CHD7 variant
Minor Criteria	Heart defect Retardation[a] (of growth or development) Genital anomalies Ear anomalies	Characteristic CHARGE facies Cardiovascular malformations Tracheoesophageal fistula Growth deficiency Genital hypoplasia Cleft lip or palate Developmental delay	Rhombencephalic dysfunction Hypothalamo-hypophyseal dysfunction Abnormal external or internal ear Malformation of mediastinal organs Mental retardation[a]	Cranial nerve dysfunction (including hearing loss) Dysphagia or feeding difficulties Structural brain anomalies Developmental delay, intellectual disability, or autism Hypothalamo-hypophyseal dysfunction, genital anomalies Heart or oesophageal malformation Renal anomalies skeletal or limb anomalies

	Pagon et al. (1981)	Blake et al. (1998)	Verloes (2005)	Hale et al. (2016)
Occasional Findings		Renal anomalies Spinal anomalies Hand anomalies Neck/shoulder anomalies		
Inclusion Rule	Four criteria, including one major criteria	Four major criteria or three major and three minor criteria	Typical CHARGE: Three major or two major and two minor criteria Partial CHARGE: Two major and one minor criteria Atypical CHARGE: Two major but no minor or one major and two minor criteria	Two major and any minor criteria

[a] "Mental retardation" is an archaism superseded by DSM-5 intellectual disability/intellectual developmental disorder or ICD-11 disorders of intellectual development.

2.2.2 Role of CHD7 in CHARGE Syndrome

Heterozygous variants in the chromodomain helicase DNA binding protein 7 (CHD7) cause CHARGE syndrome (Vissers et al., 2004). Mechanistically, CHD7 is essential for the differentiation of gene expression at thousands of sites in the human genome (Basson & van Ravenswaaij-Arts, 2015). The prevailing hypothesis is that the dynamic role of CHD7 during gene expression and neural crest development may account for the pleiotropic signs and symptoms of CHARGE syndrome (Basson & van Ravenswaaij-Arts, 2015). Prospective investigation of genotype-phenotype correlations has been performed (Bergman et al., 2011; Jongmans et al., 2006; Legendre et al., 2017) with an association between truncating CHD7

variants and more severe heart defects being identified (Legendre et al., 2017). However, given the rarity of CHARGE syndrome and the spectrum of clinical findings, better delineation of genotype-phenotype associations requires pooling of data across data sets (Meisner & Martin, 2020).

2.2.3 Physical Characteristics and Conditions in CHARGE Syndrome

CHARGE syndrome is associated with many disparate physical conditions requiring health monitoring throughout life (Trider et al., 2017). Trider et al. (2017) developed a comprehensive checklist for proactive monitoring of common or critical physical conditions and characteristics. These conditions will likely have a deleterious impact on emotional and psychological wellbeing. Identifying and understanding these impacts can help build resilience and early support strategies utilising multidisciplinary practices.

2.2.4 Challenges in Assessing Development and Behaviour

While physical health in CHARGE syndrome has been extensively documented (Trider et al., 2017) research on development and behaviour is sparce. Developmental delay and intellectual disability have received the most attention and feature in all diagnostic algorithms (Table 1). Direct cognitive assessments are rarely appropriate as performance requires adequate communication and minimal sensory impairment (La Spata, 2019). Consequently, intellectual disability is often based on informant measures of adaptive behaviour that might not correlate well with cognitive performance (Abadie et al., 2020; Johansson et al., 2010; Wulffaert et al., 2009).

2.2.5 Behavioural and Psychiatric Features

Moreover, sleep problems, anxiety, emotional dysregulation, aggression, self-injurious behaviour, and tactile defensiveness are reported in adolescents and adults with CHARGE syndrome (Hartshorne et al., 2016). Psychiatric diagnoses in children and adults include anxiety, obsessive-compulsive disorder, attention deficit hyperactivity disorder, and autism (Blake et al., 2005; Hartshorne et al., 2016; Wachtel et al., 2007). Data reporting cognitive, behavioural, and psychiatric features in CHARGE syndrome warrant synthesis to definitively describe the behavioural phenotype in the condition.

2.2.6 Evolution of Diagnostic Criteria

Diagnostic criteria have been revised several times to accommodate new insights (e.g. Blake et al. (1998); Hale et al. (2016); Verloes, (2005) see Table 1). Before the identification of the molecular etiology of CHARGE syndrome in 2004, individuals were diagnosed based on clinical characteristics. Around 90% of individuals that meet clinical criteria for CHARGE syndrome have an identifiable CHD7 variant (Basson & van Ravenswaaij-Arts, 2015). However, there remains substantial heterogeneity in phenotypic presentation and CHD7 variants. A meta-analytic strategy would be informative to generate pooled prevalence estimates for clinical features based on a diagnosis of CHARGE syndrome (see Table 1). This would enable quantification of phenotypic characteristics and variability between individuals and further evaluation of moderating and co-occurring characteristics to assist in the exploration of potential subgroups within the clinically diagnosed CHARGE syndrome phenotype.

2.2.7 Objectives and Aims of the Study

This chapter applies meta-analytic techniques to synthesise prevalence estimates across published studies. Given the challenges of assessing behavioural, cognitive and sleep characteristics in CHARGE syndrome and potential for varying methodological quality, studies are quality weighted prior to meta-analysis. Pooled prevalence estimates facilitate subgroup meta-regression analyses to elucidate and quantify interrelated characteristics. The aims of this study are the following:

1. To provide pooled prevalence estimates for clinical features for CHARGE syndrome.

2. To calculate pooled prevalence data for any physical characteristics and conditions frequently reported in the literature as associated with a diagnosis of CHARGE syndrome.

3. To provide quality adjusted prevalence estimates for behavioural, psychological, cognitive and sleep characteristics in CHARGE syndrome.

4. To conduct an exploratory meta-regression to systematically evaluate:

    a. The extent to which clinical features and physical characteristics and conditions can explain variability between cohort studies reporting on developmental delay, behavioural, psychological, cognitive and sleep characteristics in CHARGE syndrome.

b. The extent to which developmental delay, behavioural, psychological, cognitive and sleep characteristics co-occur in CHARGE syndrome.

5. To systematically quantify and explore genotype-phenotype associations for evidence of potential subgroups within the clinically diagnosed CHARGE syndrome phenotype as follows:

a. To calculate the pooled prevalence of a CHD7 positive status in CHARGE syndrome

b. To calculate pooled prevalence estimates for truncating and non-truncating mutations within individuals with CHARGE syndrome that have a CHD7 positive status.

c. To explore the extent to which developmental, psychological, cognitive and sleep characteristics can explain the variability between individuals with or without an identified CHD7 variant, or between truncating and non-truncating CHD7 mutations.

2.3 Methods

2.3.1 Search Strategy

The databases Ovid MEDLINE, Ovid PsycINFO, Ovid Embase, Ovid Embase Classic and PubMed, were searched from database creation to May 16, 2019. Search terms for CHARGE syndrome were generated from OMIM and are outlined in Table 2.2. Due to the heterogeneity

of the CHARGE population, and the research base being in its infancy, a broad strategy was employed to avoid loss of data.

Table 2. 2

Search Terms Used to Conduct the Literature Review

Free text search terms	Method of search	Limiters
"CHARGE syndrome*" "CHARGE association*" "Coloboma Heart anomaly Choanal atresia Retardation Genital Ear Anomalies" "Hall-Hittner syndrome" "CHD7" "SEMA3A"	All free search terms were combined with *OR*	No limiters

Note. Some search terms were followed by the suffix (*) to allow for variations in terminology.

Hand searches of recent review articles (Hartshorne et al., 2017; Hsu et al., 2014; Trider et al., 2017), key journals (American Journal of Medical Genetics Part A (1979-2019), B (2003-2019) and C (2003-2019) and using the term "CHARGE syndrome" additional searches were conducted for gene review databases: Gene Reviews "CHARGE Syndrome" and UniProtKB. Search strategy is detailed in Appendix 2A.

2.3.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are set out in Table 2.3 Inclusion criteria permit any peer-reviewed article reporting original data on developmental delay, behavioural, psychological, cognitive and sleep characteristics in CHARGE syndrome. This broad strategy was employed to ensure the maximum breadth of literature to facilitate a comprehensive investigation. The

only restriction on study sample specified a minimum diagnosis of atypical CHARGE syndrome (at least two major and no minor signs, or one major and two minor signs; Verloes, 2005). This restriction was applied in molecularly and clinically confirmed cases to control for unconfirmed or ambiguous diagnosis. Where clinical diagnosis was reported but not adequately detailed (e.g., no information on which diagnostic criteria were fulfilled), the study was included to avoid loss of data. No restrictions were placed on sample size or participant age.

Table 2. 3

Description of inclusion and exclusion criteria used for study selection.

Inclusion criteria	Exclusion criteria
Title and abstract screening	
Published or available in English.	Published or only available in a non-English language. English abstract where full text is not available in English.
An original empirical study using human participants.	Review articles, review chapters and published conference abstracts, animal studies, genetic studies without person details.
Includes at least one of the search terms in the title, abstract or key words, or include individuals with a sensory or neurodevelopmental disability.	Not relevant to CHARGE syndrome (e.g., without any of the OMIM terms for CHARGE syndrome in the title abstract or key words) and does not include data on individuals with sensory or neurodevelopmental disabilities. (e.g., impairment of one or more of the five senses, or a neurodevelopmental condition as specified in the DSM-5 (American Psychiatric Association, 2013).
Full text screening	
Reports data that can be extrapolated to CHARGE syndrome.	Article reports data that are not directly relevant and cannot be extrapolated to CHARGE syndrome (e.g., studies reporting on Kallmann syndrome).
Reports on an unbiased participant population.	Reported sample was not biased (e.g., by recruiting participants based on a given medical condition).

Inclusion criteria	Exclusion criteria
Participants have a clinical diagnosis of CHARGE syndrome or atypical CHARGE syndrome.	Article includes participants that have a genetic (*CHD7*) mutation but do not reach clinical criteria for CHARGE syndrome or atypical CHARGE syndrome.

2.3.3 Data Extraction

Data were extracted for: (1) study characteristics (including year of publication, recruitment of sample and sample size); (2) participant characteristics (including age and gender); (3) diagnostic details (including major and minor clinical signs and *CHD7* status); (4) physical characteristics associated with a diagnosis of CHARGE syndrome (i.e. gross motor difficulties, vision and hearing loss and any potentially painful conditions) and (5) developmental delay, behavioural, psychological, cognitive and sleep characteristics. Information that was unavailable or ambiguous was not included.

2.3.4 Quality Assessment

2.3.4.1 Development and Adaptation of a Quality Framework for Meta-analysis

Following data extraction, an appropriate quality framework was developed to control for the risk of methodological bias between the individual studies included in the meta-analysis. The framework used was adapted from those previously used by Richards et al., (2015) and Surtees et al. (2018). Inter-rater reliability was good to excellent for the original versions ($r(52) = 0.78$, $p < 0.001$; Richards et al., 2015: $\alpha = .94$; Surtees et al., 2018). For sample identification, confirmation of syndrome and quality of autism assessment, the framework provided independent quality scores (from poor, weighted 0, to excellent, weighted 3). However, the original criteria were developed for studies reporting on the prevalence of

autism in genetic syndromes, and therefore required adaptation for the present study. Confirmation of syndrome was adapted to reflect the ambiguity of *CHD7* positive diagnosis in the absence of clinical CHARGE characteristics. The original quality weighting framework for the assessment of autism (Richards et al., 2015) was generalised to include assessment of other behavioural and psychological characteristics. A new quality weighting framework was developed for the assessment of cognitive characteristics. A quality weighting for sleep assessment was also included based on (Surtees et al., 2018).

2.3.4.2 Adapted Quality Criteria for Evaluating Research Studies

The adapted quality criteria are presented in Table 2.4. In summary, papers including participants whose clinical and genetic status were confirmed and reported in detail at the time of the study were weighted higher than those using clinical or unspecified clinical criteria alone. Sampling method was rated highest for random or total population studies with lower scores awarded to single or multiple restricted or non-random samples. Given the questionable validity of many standardised instruments for individuals with sensory impairments (Rowland & Fried-Oken, 2010), assessment of behaviour, psychological and cognition using standardised tools, supported by additional assessment were given the highest scores. Standardised and non-standardised informant reports were awarded scores of two and one respectively. Studies reporting incomplete measurement of sleep, for example a single question, were weighted lower than papers using standardised questionnaires. Studies using direct sleep assessments received a score of three for observation or four for objective measurement. Good inter-rater reliability was ascertained by a second researcher (weighted Kappa 85%; Cohen, 1960) using a 25% random sample of cohort studies.

Table 2. 4

Quality Framework to Control for Methodological Variation Between Individual Cohort Studies Reporting on Developmental Delay, Behavioural, Psychological, Cognitive and Sleep Characteristics. Red Shading for Poor Quality Data, Orange for Adequate, Yellow for Good and Green for Excellent

	1 - Poor	2 - Adequate	3 - Good	4 – Excellent
Sample identification	Not specified / reported	Single restricted or non-random sample (e.g., a specialist clinic or a previous research study)	Multiple restricted or non-random samples (e.g., multiregional specialist clinics)	Random or total population sample
Confirmation of syndrome	Not reported or diagnosis using unstated criteria	Specified clinical diagnosis reported (e.g., Pagon *et al.* 1981; Blake *et al.* 1998; Verloes, 2005).	Specified clinical diagnosis reported and genetic testing undertaken, but not confirmed at the time of the study [a]	Specified clinical diagnosis and genetic testing undertaken at the time of the study [a]
Assessment of behavioural and psychological characteristics [b]	Description of behaviours based on non-standardised informant report or review of clinical information	Standardised informant report measure (e.g., Repetitive behaviour questionnaire, autism diagnostic interview), or clinical judgment against specified diagnostic criteria (e.g., DSM-IV or ICD10) [a]	Standardised behavioural or observational assessment (e.g., neuropsychiatric evaluation, autism Diagnostic Observation Schedule). [a]	Consensus from multiple assessments, including at least one standardised behavioural or observational assessment [a]
Assessment of cognition [c]	Description or estimation of cognitive capacity based on non-standardised informant report or review of	Standardised informant report measure (e.g., Vineland adaptive behaviour scales; BRIEF / BRIEF-P) [a]	Standardised behavioural or observational assessment (e.g., neuropsychiatric evaluation; Bayley Scales of Infant Development) [a]	Consensus from multiple assessments, including at least one standardised assessment [a]

	1 - Poor	2 - Adequate	3 - Good	4 – Excellent
	clinical information.			
Assessment of sleep	Response to a single question or use of an unvalidated questionnaire	Validated sleep questionnaire (e.g., The Sleep Disturbance Scale for Children (SDSC))[a]	Informant report diary or direct clinical observation (e.g. video footage or observation made within a hospital or clinical setting – not polysomnography or actigraphy) [a]	Use of polysomnography or actigraphy [a]

Note. a = quality weighting applicable to at least 90% of the study sample – when applied to less that 90% subtract one quality point. b = behaviour includes psychiatric diagnosis and unique behavioural symptoms. c = cognition includes intellectual disability, developmental delay, adaptive and executive functioning.

2.3.5 Data Analysis

All analyses were conducted in R version 3.62. A p -value of <0.05 was used for all analysis and adjusted for multiple comparisons where stated. Prevalence estimates from studies included in the meta-analysis and meta-regression were log transformed prior to numerical synthesis. Values presented in tables and figures have been transformed back for clarity of presentation.

2.3.5.1 Summary Measures

Crude prevalence data from cohort studies were calculated based on the number of participants reported to present or not to present with the characteristic of interest. Where multiple measures of the same construct were reported across multiple subgroups, data were

combined into one quantitative outcome. Where this was not possible, subgroups were reported separately.

2.3.5.1.1 Random Effects Models

A random-effects model (REM) was used to provide a mean of the distribution where five or more study effects could be synthesised. Where a study estimate was based on data from less than five participants these data were not included in the REM. Visualisation of Quantile Quantile (QQ) plots was used to estimate the distribution of study effect for each REM. Where the study effect sizes followed an approximate normal distribution, the DerSimonian-Laird estimate (DL; Dersimonian & Laird, 1986) was used to calculate between studies variance (tau). Where QQ plots suggested a non-Gaussian distribution, the restricted maximum-likelihood (ReML) estimator was used. ReML avoids over-fitting, providing an efficient estimator of tau when effects are not normally distributed (Cheung, 2013).

2.3.5.1.2 Quality Effects Models

Estimates from REMs assume that studies are selected at random. Where studies of developmental delay, behavioural, psychological, cognitive and sleep characteristics were assigned different quality ratings (Table 2.3), and five or more effect estimates could be synthesised, a quality weighted random-effects model (QEM) was conducted. Where a study estimate was based on data from less than five participants these data were not included in the QEM. QEM is a special case of REM in which pooled prevalence estimates additionally incorporate the quality weightings, described above in Table 2.3, that are assigned to each study. Given that this is the first meta-analysis of developmental delay, behavioural, psychological, cognitive and sleep characteristics in CHARGE syndrome, the lower threshold

of five or more effect estimates for QEM models was chosen to limit loss of potentially important data.

2.3.5.2 Synthesis of Results

Pooled prevalence estimates, 95% confidence intervals (CIs) and associated *z* and *p* values were reported for each meta-analysis. Chi squared (*Q*; Higgins et al., 2003) and I squared (I^2; Higgins et al., 2003) statistics were reported as a measure of between study heterogeneity. Between study effects are heterogeneous if they present with variation from the meta-analysis that cannot be attributed to sampling error. As considerable variation within samples and methods were anticipated, problematic heterogeneity was set at a Higgins I^2 value of 75% or greater.

2.3.5.2.1 Sensitivity analysis

Potential sources of heterogeneity were investigated. For outcomes with *k* study estimates ≥10, small study effects were evaluated visually with a funnel plot and statistically with Egger's regression test (Egger et al., 1997). Small study effect refers to the bias for publishing significant over non-significant findings. For a small study to show significant results the effect size would need to be large, this can lead to a bias of small studies showing large effect sizes. Inclusion of such studies in the meta-analysis would likely inflate the pooled effect size. Where small study bias was identified, the 'trim and fill' method was used (Duval & Tweedie, 2000). The fail-safe *N* was calculated for each meta-analysis to evaluate publication bias (Rosenthal, 1979) and a 'leave-one-out' procedure was conducted to evaluate whether the pooled prevalence estimate was driven by the inclusion of any single study. Details of the

funnel plot, trim and fill, fail-safe *N* and 'leave-one-out' procedure are included in Appendix 2B.

2.3.5.3 Subgroup Analysis

To assess the impact of potentially moderating factors on the heterogeneity of each meta-analysis, a series of sub-group analysis were conducted. Where ≥ 2 studies could be included in each group, studies were stratified by year of publication (published before 01/01/2006 or published after 01/01/2006[1]), confirmation of syndrome (rated as 'poor' or 'adequate' quality, or of 'good' or 'excellent' quality as set out in Table 2.3), mean age (mean age <10 years or >10 years), mean age at walking (mean age <3 years or >3 years) and use of standardised or non-standardised assessment. Sub-group analysis was evaluated by comparison of 95% confidence intervals. Findings were initially reported using the *Q* and *p*-value and then significance was adjusted using the Hochberg method. The Hochberg adjustment for multiple comparisons computes significance in a stepwise procedure based on the rank value given to each of the original p-values. Step 1: p-values are ordered from highest to lowest and ranked from 1 to n. Step 2: the adjusted p-value for each of the ranks is computed based on the number of ranks and the original significance level. Step 3: Starting from the highest-ranked p-value, once the first significant p-value is identified, all subsequent p-values are deemed significant.

[1] 2006 is the median data of the 42 studies eligible for meta-analysis

2.3.5.4 Meta-Regression

Exploratory random-effects meta-regressions were also conducted. Associations were appraised systematically within and between developmental delay, behavioural, psychological, cognitive and sleep difficulties, and between these features and each of the diagnostic and physical characteristics included in the meta-analysis. Meta-regressions were limited to opportunities where five or more study effects could be regressed. Due to the high number of regressions, the Hochberg adjustment method for multiple comparisons was applied (Hochberg, 1988).

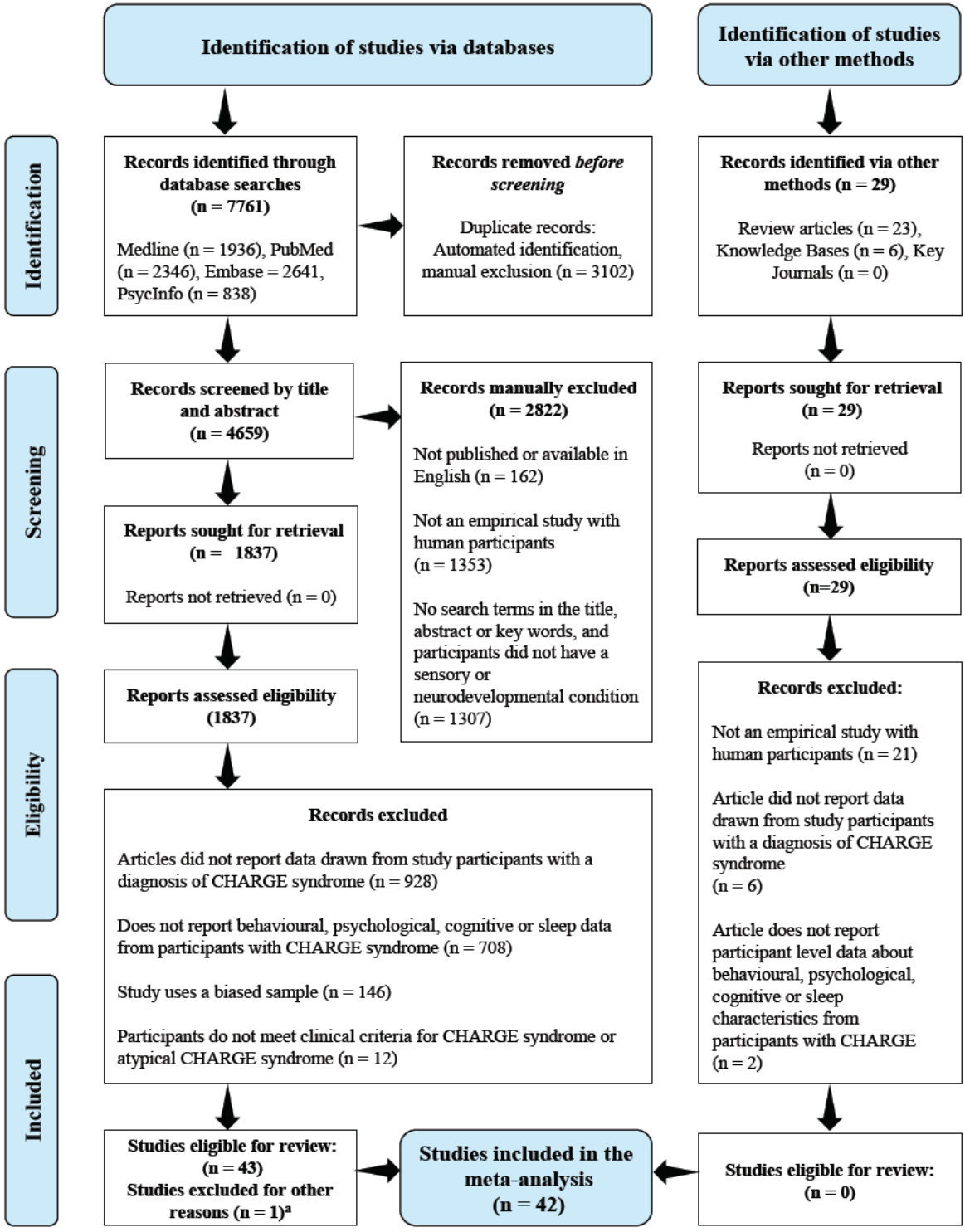
2.4 Results

2.4.1 Study Selection

This study adheres to the PRISMA guidelines for reporting systematic reviews and meta-analyses (Page et al., 2021). The process used for study selection is described in Figure 2.1. In total, 7761 citations were retrieved through the search, and an additional 29 studies were identified through manual searches. After removing duplicates, 4659 unique articles remained. These articles underwent screening based on the inclusion and exclusion criteria outlined in Table 2.2. Title and abstract screening led to the exclusion of 2822 articles, resulting in 1837 articles that underwent full-text screening. One article was excluded as its data could not be combined with the data from any other papers. Finally, 42 studies met the eligibility criteria and were included in the meta-analysis.

Figure 2. 1

PRISMA diagram of papers included and excluded at each stage of the review process



a: Hartshorne, T.S., Nicholas, J., Grialou, T.L. and Russ, J.M., 2007. Executive function in CHARGE syndrome. Child Neuropsyc. 13, 333-344. Novel (executive functioning) data could not be pooled with findings from any of the 47 other eligible studies.

2.4.2 Descriptive data

Table 2.5 presents the descriptive data and clinical features for CHARGE syndrome extracted from eligible studies. In the total sample, 1556 participants were reported to have typical or atypical CHARGE syndrome, and 362 diagnoses were confirmed genetically. Studies were published between 1979 and 2020. The mean age of participants was 9.5 years (range < 1 to 53 years) and 51% of participants were male.

Table 2. 5

Descriptive Data and Clinical Features of CHARGE Syndrome

	Sample Size (Male)	Mean Age (range)	CHD7 positive	Coloboma	Choanal Atresia	Anosmia	Facial Palsy	Feeding and swallowing difficulties	External Ear anomaly	Middle Ear anomaly
Abadie et al. (2020)	64 (29)	10.7 (.75-30)	80% (51/64)	75% (46/61)	37% (22/59)	-	46% (22/48)	-	-	-
Asher et al. (1990)	16 (-)	-	-	-	100% (16/16)	-	-	-	-	-
Bernstein and Denno (2005)	29 (-)	- (3-21)	-	-	-	-	-	-	-	-
Blake and Brown (1993)	39 (22)	6 (1.5-20)	-	85% (33/39)	64% (25/39)	-	56% (22/39)	85% (33/39)	87% (34/39)	62% (23/37)
Blake et al. (2005)	50 (29)	-	-	91% (43/47)	60% (28/47)	-	45% (21/47)	88% (44/50)	100% (50/50)	66% (33/50)
Blake et al. (1990)	30 (14)	17.6 (13-30)	-	90% (27/30)	63% (19/30)	-	-	-	-	-
Cheng et al. (2020)	12 (10)	11.9 (.25-21)	100% (12/12)	67% (6/9)	0% (0/10)	-	30% (3/10)	70% (7/10)	83% (10/12)	0% (0/4)
Dammeyer, (2012)	17 (6)	9 (3-15)	-	-	-	-	-	-	-	-
Davenport et al. (1986)	9 (6)	12.2 (1.5-27)	-	89% (8/9)	29% (2/7)	33% (1/3)	29% (2/7)	60% (3/5)	78% (7/9)	50% (1/2)
Deuce et al., (2012)	44 (-)	7.9 (1-15)	64% (18/28)	95% (40/42)	55% (23/42)	100% (20/20)	52% (22/42)	84% (37/44)	25% (11/44)	-
Deuce (2017)	52 (-)	-	-	-	-	-	-	-	-	-

	Sample Size (Male)	Mean Age (range)	CHD7 positive	Coloboma	Choanal Atresia	Anosmia	Facial Palsy	Feeding and swallowing difficulties	External Ear anomaly	Middle Ear anomaly
Dobbelsteyn et al. (2008)	39 (24)	6.8 (0.5-17)	-	86% (32/37)	41% (16/39)	-	59% (23/39)	90% (35/39)	-	-
Hale et al., (2016)	24 (15)	-	67% (16/24)	78% (18/23)	42% (10/24)	-	-	83% (19/23)	96% (23/24)	-
Hartshorne et al. (2009)	87 (52)	11.1 (6-18)	50% (16/32)	84% (73/87)	60% (52/87)	40% (35/87)	48% (42/87)	70% (61/87)	-	-
Hartshorne et al., 2016)	53 (33)	- (13-39)	-	77% (41/53)	64% (34/53)	-	-	-	-	-
Hartshorne and Cypher, (2004)	100 (43)	7* (1-30)	-	86% (86/100)	54% (54/100)	-	48% (48/100)	74% (74/100)	-	-
Hartshorne et al. (2005)	160 (85)	10.9 (3-33)	-	85% (136/160)	64% (102/160)	-	48% (77/160)	79% (126/160)	-	-
Harvey et al. (1991)	17 (8)	- (0.5-15)	-	88% (15/17)	82% (14/17)	41% (7/17)	100% (9/9)	94% (16/17)	-	100% (9/9)
Hittner et al. (1979)	10 (5)	-	-	100% (10/10)	-	-	60% (6/10)	-	100% (10/10)	-
Hsu et al. (2016)	20 (6)	9 (0.6-18)	95% (19/20)	95% (19/20)	60% (12/20)	-	-	-	-	-
Husu et al., (2013)	18 (6)	8.3 (1-15)	100% (18/18)	94% (16/17)	41% (7/17)	29% (2/7)	40% (6/15)	67% (12/15)	88% (15/17)	-
Issekutz et al. (2005)	77 (40)	-	-	77% (59/77)	64% (49/77)	-	49% (38/77)	70% (54/77)	75% (12/16)	81% (13/16)
Johansson et al. (2006)	31 (15)	8.9 (0.1-31)	-	-	-	-	39% (12/31)	-	-	23% (7/31)
Jongmans et al., (2006)	46 (22)	11.2 (0–40)	100% (46/46)	72% (33/46)	37% (17/46)	-	22% (10/46)	-	-	-

	Sample Size (Male)	Mean Age (range)	CHD7 positive	Coloboma	Choanal Atresia	Anosmia	Facial Palsy	Feeding and swallowing difficulties	External Ear anomaly	Middle Ear anomaly
Lasserre et al. (2013)	8 (7)	9.8 (7-13)	-	63% (5/8)	-	-	-	-	-	-
Legendre et al. (2017)	119 (57)	11 (<1-53)	79% (93/118)	72% (82/117)	43% (49/114)	82% (23/28)	70% (54/77)	84% (65/77)	87% (100/115)	39% (45/115)
Oley et al. (1988)	20 (14)	- (0-14)	-	85% (17/20)	65% (13/20)	-	60% (12/20)	25% (5/20)	80% (16/20)	-
Raqbi et al. (2003)	21 (11)	8.6 (5-12)	-	90% (19/21)	33% (7/21)	22% (2/9)	76% (16/21)	81% (17/21)	-	-
Reda and Hartshorne (2008)	25 (11)	- (1-4.5)	-	88% (22/25)	60% (15/25)	20% (5/25)	36% (9/25)	88% (22/25)	84% (21/25)	-
Roger et al. 1999)	45 (23)	-	-	69% (31/45)	60% (27/45)	-	27% (12/45)	70% (31/44)	84% (36/43)	-
Salem-Hartshorne and Jacob (2004)	100 (50)	-	-	83% (83/100)	65% (65/100)	-	-	-	-	-
Shiohama et al. (2019)	10 (7)	14.7 (-)	-	70% (7/10)	60% (6/10)	60% (6/10)	-	-	-	-
Shoji et al. (2014)	25 (13)	9.7 (1-25)	81% (17/21)	56% (14/25)	12 (3/25)	24% (6/25)	24% (6/25)	-	52% (13/25)	-
Smith et al. (2005)	13 (8)	9 (3-24)	-	85% (11/13)	62% (8/13)	-	55% (6/11)	83% (10/12)	100% (12/12)	92% (12/13)
Sohn et al. (2016)	18 (8)	4.7 (0-20)	100% (18/18)	72% (13/18)	22% (4/18)	50% (2/4)	78% (14/18)	72% (13/18)	100% (18/18)	54% (7/13)
Souriau et al. (2005)	71 (-)	8 (<1-30)	-	-	-	55% (17/31)	-	-	-	-

	Sample Size (Male)	Mean Age (range)	CHD7 positive	Coloboma	Choanal Atresia	Anosmia	Facial Palsy	Feeding and swallowing difficulties	External Ear anomaly	Middle Ear anomaly
Strömland et al. (2005)	31 (15)	8.1 (0.1-31)	-	90% (28/31)	35% (11/31)	-	32% (10/31)	81% (25/31)	90% (28/31)	23% (7/31)
Tellier et al. (1998)	47 (17)	-	-	79% (37/47)	57% (27/47)	-	36% (17/47)	96% (45/47)	100% (47/47)	27% (3/11)
Thelin & Fussner, (2005)	28 (11)	7* (3-27)	-	-	75% (21/28)	11% (3/28)	-	86% (24/28)	-	-
Wessels et al. (2010)	13 (7)	5.5 (<1-19)	62% (8/13)	62% (8/13)	54% (7/13)	-	-	-	-	-
Wincent et al. (2008)	15 (8)	-	60% (9/15)	80% (12/15)	27% (4/15)	-	21% (3/14)	-	87% (13/15)	-
Wulffaert et al. (2009)	22 (16)	11 (2-22)	95% (21/22)	-	-	-	-	-	-	-

	Inner Ear Anomaly	Heart Defect	Growth Deficiency	Genital Hypoplasia	Cleft Lip or Palate	Tracheo-esophageal Fistula	Brain Anomaly	Characteristic Face	Hearing Impairment
Abadie et al. (2020)	95% (61/64)	62% (38/61)	46% (25/55)	51% (24/47)	17% (10/58)	29% (14/48)	50% (26/52)	-	81% (46/57)
Asher et al. (1990)	-	-	-	-	-	-	25% (3/12)	-	-
Bernstein and Denno (2005)	-	-	-	-	-	-	-	-	100% (29/29)
Blake and Brown, (1993)	70% (26/37)	79% (31/39)	64% (25/39)	51% (20/39)	18% (7/39)	-	-	-	92% (34/37)
Blake et al. (2005)	38% (19/50)	84% (42/50)	91% (39/43)	93% (25/27)	16% (8/50)	11% (5/44)	38% (18/47)	-	74% (37/50)

	Inner Ear Anomaly	Heart Defect	Growth Deficiency	Genital Hypoplasia	Cleft Lip or Palate	Tracheo-esophageal Fistula	Brain Anomaly	Characteristic Face	Hearing Impairment
Blake et al. (1990)	-	77% (23/30)	70% (21/30)	73% (22/30)	57% (17/30)	27% (8/30)	-	-	-
Cheng et al. (2020)	100% (5/5)	83% (10/12)	63% (5/8)	67% (8/12)	10% (1/10)	-	71% (5/7)	-	100% (12/12)
Dammeyer, (2012)	-	-	-	-	-	-	-	-	89% (17/19)
Davenport et al. (1986)	-	56% (5/9)	67% (6/9)	100% (9/9)	25% (2/8)	33% (1/3)	40% (2/5)	-	100% (8/8)
Deuce et al. (2012)	82% (27/33)	30% (13/44)	18% (8/44)	9% (6/44)	7% (3/44)	-	-	5% (2/44)	93% (41/44)
Deuce, (2017)	-	-	-	-	-	-	-	-	94% (49/52)
Dobbelsteyn et al. (2008)	-	79% (31/39)	69% (25/36)	70% (21/30)	26% (10/39)	8% (3/39)	-	59% (17/29)	-
Hale et al. (2016)	100% (17/17)	83% (20/24)	70% (16/23)	64% (14/22)	29% (7/24)	17% (4/24)	47 (9/19)	-	96% (23/24)
Hartshorne et al. (2009)	-	78% (68/87)	82% (71/87)	62% (54/87)	29% (25/87)	22% (19/87)	-	-	85% (74/87)
Hartshorne et al. (2016)	-	74% (39/53)	85% (45/53)	-	42% (22/53)	9% (5/53)	-	75% (40/53)	95% (50.5/53)
Hartshorne and Cypher (2004)	-	75% (75/100)	62% (62/100)	39% (39/100)	27% (27/100)	14% (14/100)	-	-	91% (86/94)
Hartshorne et al. (2005)	-	80% (128/160)	74% (118/160)	56% (90/160)	29% (46/160)	22% (35/160)	-	-	-
Harvey et al. (1991)	-	82% (14/17)	100% (10/10)	56% (5/9)	35% (6/17)	29% (5/17)	24 (4/17)	71% (12/17)	47% (8/17)
Hittner et al. (1979)	-	100% (10/10)	-	-	-	-	100% (3/3)	-	100% (10/10)

	Inner Ear Anomaly	Heart Defect	Growth Deficiency	Genital Hypoplasia	Cleft Lip or Palate	Tracheo-esophageal Fistula	Brain Anomaly	Characteristic Face	Hearing Impairment
Hsu et al., (2016)	95% (19/20)	-	-	-	-	-	60% (12/20)	-	-
Husu et al. (2013)	90% (9/10)	78% (14/18)	60% (9/15)	28% (5/18)	50% (6/18)	19% (3/16)	-	94% (17/18)	93% (14/15)
Issekutz et al. (2005)	90% (9/10)	84% (65/77)	58% (45/77)	38% (29/77)	18% (14/77)	19% (15/77)	54% (36/67)	55% (42/77)	58% (15/26)
Johansson et al. (2006)	68% (21/31)	-	-	-	-	-	-	-	-
Jongmans et al. (2006)	77% (20/26)	65% (30/46)	68% (21/31)	39% (18/46)	37% (17/46)	17% (8/46)	9% (4/46)	-	90% (36/40)
Lasserre et al. (2013)	100% (8/8)	-	-	-	-	-	-	-	100% (8/8)
Legendre et al. (2017)	95% (107/113)	65% (76/117)	34% (23/67)	53% (54/101)	18% (21/117)	20% (21/107)	49% (50/102)	81% (92/113)	93% (105/113)
Oley et al. (1988)	-	80% (16/20)	85% (17/20)	70% (14/20)	-	-	-	-	95% (19/20)
Raqbi et al. (2003)	-	76% (16/21)	67% (14/21)	48% (10/21)	14% (3/21)	-	-	-	100% (21/21)
Reda and Hartshorne (2008)	-	88% (22/25)	60% (15/25)	48% (12/25)	12% (3/25)	28% (7/25)	-	-	84% (21/25)
Roger et al. (1999)	-	78% (35/45)	78% (31/40)	-	13% (6/45)	11% (4/45)	18% (5/28)	-	86% (37/43)
Salem-Hartshorne and Jacob (2004)	-	81% (81/100)	80% (80/100)	61% (61/100)	32% (32/100)	25% (25/100)	-	-	82% (82/100)
Shiohama et al. (2019)	50% (5/10)	80% (8/10)	90% (9/10)	60% (6/10)	40% (4/10)	20% (2/10)	30% (3/10)	100% (10/10)	-

	Inner Ear Anomaly	Heart Defect	Growth Deficiency	Genital Hypoplasia	Cleft Lip or Palate	Tracheo-esophageal Fistula	Brain Anomaly	Characteristic Face	Hearing Impairment
Shoji et al. (2014)	48% (12/25)	76% (19/25)	72% (18/25)	40% (10/25)	44% (11/25)	24 (6/25)	8% (2/25)	-	96% (24/25)
Smith et al. (2005)	92% (12/13)	69% (9/13)	62% (8/13)	67% (8/12)	23% (3/13)	17 (2/12)	-	-	-
Sohn et al. (2016)	72% (13/18)	72% (13/18)	56% (10/18)	83% (15/18)	-	0% (0/18)	28% (5/18)	-	100% (18/18)
Souriau et al. (2005)	-	-	-	-	-	-	-	-	100% (71/71)
Strömland et al. (2005)	~ 63% (29/46)	52% (16/31)	48% (15/31)	39% (12/31)	19% (6/31)	16% (5/31)	87% (27/31)	-	74% (23/31)
Tellier et al. (1998)	100% (12/12)	85% (40/47)	71% (5/7)	34% (16/47)	36% (17/47)	15% (7/47)	83% (39/47)	81% (38/47)	62% (23/37)
Thelin and Fussner (2005)	-	75% (21/28)	57% (16/28)	-	32% (9/28)	-	-	-	96% (27/28)
Wessels et al. (2010)	100% (1/1)	69% (9/13)	57% (4/7)	73% (8/11)	25% (3/12)	25% (3/12)	67% (6/9)	43% (3/7)	-
Wincent et al. (2008)	83% (5/6)	80% (12/15)	79% (11/14)	57% (8/14)	27% (4/15)	-	-	-	64% (7/11)
Wulffaert et al., (2009)	-	-	-	-	-	-	-	-	77% (17/22)

2.4.3 Overlapping Datasets and Precedence for Meta-Synthesis

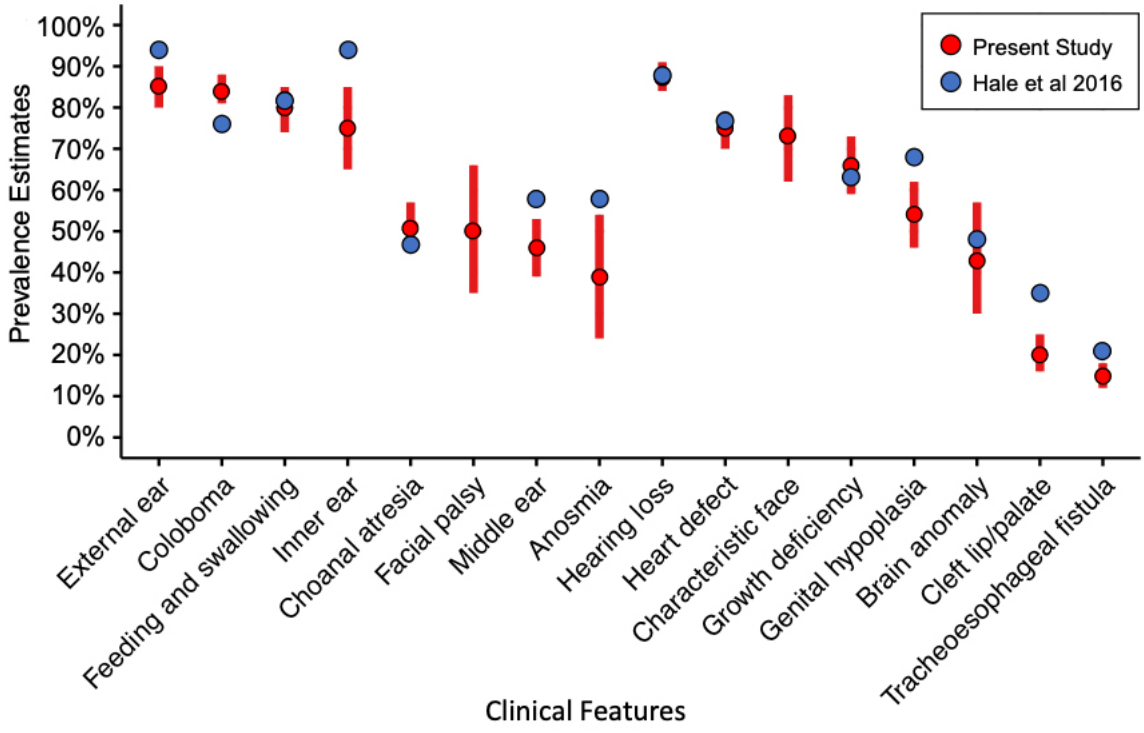
The following studies had overlapping datasets: Smith et al. (2005) and Issekutz et al. (2005), Johansson et al. (2006) and Strömland et al. (2005), Hartshorne et al. (2016) and Salem-Hartshorne and Jacob (2004), and Wincent et al. (2008) and Strömland et al. (2005). In this scenario, earlier data sets were given precedence for meta-synthesis, with later studies contributing only original previously unpublished data. Six participants were omitted from Davenport et al. (1986) that were previously reported as a familial case series. Four participants from Hale et al. (2016), one participant from Jongmans et al. (2006) and five participants from Wessels et al. (2010) were excluded because they did not meet clinical criteria for CHARGE Syndrome.

2.4.4 Comparative Prevalence Analysis of Clinical Features in CHARGE Syndrome Studies

Figure 2.2 presents the pooled prevalence estimates and 95% CIs for clinical features of CHARGE Syndrome drawn from eligible studies. Sufficient data were also available to calculate subcategories of coloboma, choanal atresia, heart defects and structural brain anomalies (for forest plots and sensitivity analyses see Appendix 2C). For comparison, estimates from the present study are presented alongside the largest and most recent review of clinical characteristics in CHARGE syndrome by Hale et al. (2016). The prevalence of coloboma were higher and the prevalence of ear anomalies, anosmia, genital hypoplasia, facial clefts, and tracheoesophageal fistula were lower in the present study than in Hale et al., (2016).

Figure 2. 2

Pooled Prevalence Estimates and 95% CIs of Clinical Features in CHARGE Syndrome: Comparison with Hale et al. 2016 Study

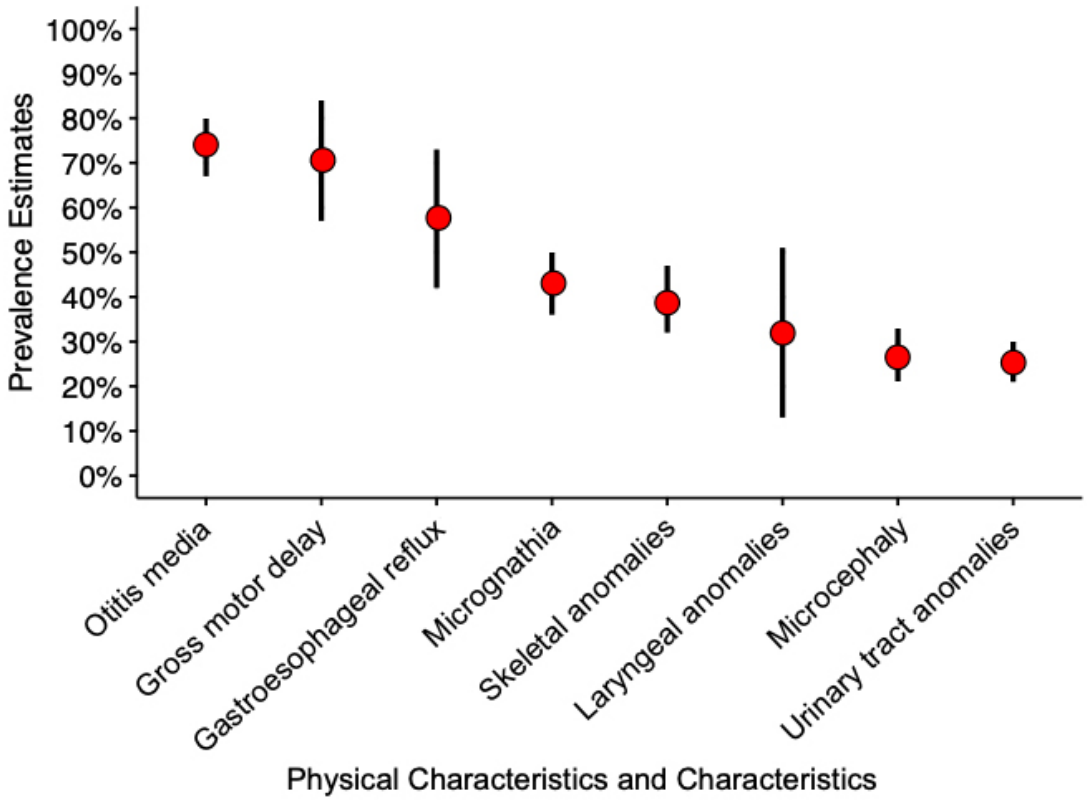


2.4.5 Prevalence Estimates and Confidence Intervals for Physical Characteristics and Conditions

Figure 2.3 presents pooled prevalence estimates and 95% CIs for physical characteristics and conditions associated with CHARGE syndrome. Estimates included otitis media (74%, 95% CI = 67–80), gross motor difficulties (71%, 95% CI = 13–51%), gastrointestinal reflux (58%, 95% CI = 42–73%), micrognathia (43%, 95% CI = 57–84%), microcephaly (43%, 95% CI = 21–33%) and a 32% (95% CI = 13–51%) prevalence of laryngeal anomalies. Sufficient data were available to explore types of skeletal anomalies: spinal anomalies (including scoliosis, 28%, 95% CI = 19–36%) and hand anomalies (15%, 95% CI = 11–20%).

Figure 2. 3

Pooled Prevalence Estimates and 95% CIs of Physical Characteristics and Conditions associated with CHARGE Syndrome



2.4.6 Behavioural, Psychological, Cognitive and Sleep Characteristics

Table 2.6 presents data on the study-level prevalence of behavioural, psychological, cognitive and sleep characteristics including: developmental delay, intellectual disability, autism, aggression, self-injurious behaviour, obsessive or compulsive behaviour, tactile defensiveness and sleep problems. Two studies used a whole population sample (Abadie et al., 2020; Issekutz et al., 2005), with 25 studies (60%) using single restricted or non-random samples, and 15 studies (36%) using multiple restricted or non-random samples. Seven studies (17%) reported details of clinical diagnosis and genetic testing, with 3 studies (7%)

confirming these findings at the time of data collection. Of the remaining 32 articles, 16 (38%) reported which clinical diagnosis participants were assessed against, and 16 (38%) did not. Assessment methods were typically ‘poor’ (64%) with 22% rated as ‘adequate’, 11% as ‘good’ and 4% were rated ‘excellent’.

Table 2. 6

Quality Rating and Study-Level Prevalence of Behavioural, Psychological, Cognitive, and Sleep Characteristics in CHARGE Syndrome

	Sample Identification	Confirmation of Syndrome	Assessment of Cognition	Assessment of Behaviour	Assessment of Sleep	Quality Weighting: Cognition	Quality Weighting: Behaviour	Quality Weighting: Sleep
Abadie et al. (2020)	4	2	2	*NA*	*NA*	67%	67%	*NA*
Asher et al. (1990)	2	1	1	*NA*	*NA*	33%	*NA*	*NA*
Bernstein and Denno, (2005)	2	1	1	2	*NA*	33%	42%	*NA*
Blake and Brown, (1993)	2	2	1	*NA*	*NA*	42%	*NA*	*NA*
Blake et al. (1990)	3	2	1	*NA*	*NA*	50%,	*NA*	*NA*
Blake et al. (2005)	3	1	1	1	1	42%	42%	42%
Cheng et al. (2020)	2	3	1	1	1	50%	50%	50%
Dammeyer (2012)	2	1	3	*NA*	1	50%	*NA*	33%
Davenport et al. (1986)	3	2	2	*NA*	*NA*	58%	*NA*	*NA*
Deuce et al. (2012)	3	1	1	1	1	*NA*	42%	42%
Deuce (2017)	2	1	1	*NA*	1	33%	*NA*	33%

	Sample Identification	Confirmation of Syndrome	Assessment of Cognition	Assessment of Behaviour	Assessment of Sleep	Quality Weighting: Cognition	Quality Weighting: Behaviour	Quality Weighting: Sleep
Dobbelsteyn et al. (2008)	3	1	1	*NA*	*NA*	42%	*NA*	*NA*
Hale et al. (2016)	2	4	1	*NA*	*NA*	58%	*NA*	*NA*
Hartshorne et al. (2009)	2	1	*NA*	*NA*	2	*NA*	*NA*	42%
Hartshorne et al. (2016)	3	1	1	1	1	42%	42%	42%
Hartshorne and Cypher (2004)	2	1	*NA*	1	*NA*	*NA*	33%	*NA*
Hartshorne, Grialou, et al. (2005)	2	1	*NA*	2	*NA*	*NA*	42%	*NA*
Harvey et al. (1991)	2	2	2	*NA*	*NA*	50%	42%	*NA*
Hittner et al. (1979)	2	1	2	*NA*	*NA*	42%	*NA*	*NA*
Hsu et al. (2016)	2	4	1	*NA*	*NA*	58%	*NA*	*NA*
Husu et al. (2013)	3	3	1	*NA*	*NA*	58%	*NA*	*NA*
Issekutz et al. (2005)	4	2	*NA*	1	1	*NA*	58%	58%
Johansson et al. (2006)	2	2	2	3	1	50%	58%	42%
Jongmans et al. (2006)	2	3	1	*NA*	*NA*	50%	*NA*	*NA*
Lasserre et al. (2013)	2	2	3	*NA*	*NA*	58%	*NA*	*NA*
Legendre et al. (2017)	3	3	1	*NA*	*NA*	58%	*NA*	*NA*

	Sample Identification	Confirmation of Syndrome	Assessment of Cognition	Assessment of Behaviour	Assessment of Sleep	Quality Weighting: Cognition	Quality Weighting: Behaviour	Quality Weighting: Sleep
Oley et al. (1988)	3	2	3	*NA*	*NA*	50%	*NA*	*NA*
Raqbi et al. (2003)	2	2	1	*NA*	*NA*	42%	*NA*	*NA*
Reda and Hartshorne (2008)	2	1	*NA*	2	*NA*	*NA*	42%	*NA*
Roger et al. (1999)	3	2	1	*NA*	4	50%	*NA*	75%
Salem-Hartshorne and Jacob (2004)	2	1	2	*NA*	*NA*	42%	*NA*	*NA*
Shiohama et al. (2019)	2	2	1	*NA*	*NA*	42%	*NA*	*NA*
Shoji et al. (2014)	2	2	1	*NA*	*NA*	42%	*NA*	*NA*
Smith et al. (2005)	3	2	1	1	*NA*	50%	50%	*NA*
Sohn et al. (2016)	3	4	3	*NA*	*NA*	83%	*NA*	*NA*
Souriau et al. (2005)	3	1	*NA*	1	*NA*	*NA*	42%	*NA*
Strömland et al. (2005)	2	2	2	3	*NA*	50%	58%	*NA*
Tellier et al. (1998)	3	2	1	*NA*	4	50%	*NA*	75%
Thelin and Fussner (2005)	2	1	*NA*	1	*NA*	*NA*	33%	*NA*
Wessels et al. (2010)	2	3	1	*NA*	*NA*	50%	*NA*	*NA*
Wincent et al. (2008)	2	3	1	*NA*	*NA*	50%	*NA*	*NA*

	Sample Identification	Confirmation of Syndrome	Assessment of Cognition	Assessment of Behaviour	Assessment of Sleep	Quality Weighting: Cognition	Quality Weighting: Behaviour	Quality Weighting: Sleep
Wulffaert et al. (2009)	3	3	2	*NA*	*NA*	67%	*NA*	*NA*

	Developmental delay	Intellectual Disability (ID)	Mild or Moderate ID	Severe or Profound ID	Autism Diagnosis
Abadie et al. (2020)	-	70% (45/64)	55% (35/64)	16% (10/64)	54% (25/46)
Asher et al. (1990)	-	100% (14/14)	50% (7/14)	50% (7/14)	-
Bernstein and Denno (2005)	-	90% (26/29)	66% (19/29)	24% (7/29)	-
Blake and Brown, (1993)	-	63% (19/30)	-	33% (10/30)	-
Blake et al. (1990)	76% (26/34)	-	-	-	-
Blake et al. (2005)	100% (30/30)	-	-	-	23% (7/30)
Cheng et al. (2020)	-	90% (9/10)	78% (7/9)	11% (1/9)	22% (2/9)
(Dammeyer, 2012)	-	18% (3/17)	18% (3/17)	-	-
Davenport et al. (1986)	-	100% (7/7)	-	-	-
Deuce et al. (2012)	-	-	-	-	-
Deuce (2017)	-	40% (21/52)	-	-	-

	Developmental delay	Intellectual Disability (ID)	Mild or Moderate ID	Severe or Profound ID	Autism Diagnosis
Dobbelsteyn et al. (2008)	95% (35/37)	-	-	-	-
Hale et al. (2016)	100% (23/23)	-	-	-	-
Hartshorne et al. (2009)	-	-	-	-	-
Hartshorne et al. (2016)	85% (45/53)	-	-	-	26% (14/53)
Hartshorne and Cypher (2004)	-	-	-	-	6% (6/100)
Hartshorne, Grialou, et al. (2005)	-	-	-	-	28% (44/160)
Harvey et al. (1991)	-	29% (2/7)	14% (1/7)	14% (1/7)	-
Hittner et al. (1979)	-	100% (7/7)	-	71% (5/7)	-
Hsu et al. (2016)	100% (20/20)	-	-	-	-
Husu et al. (2013)	85% (11/13)	-	-	-	-
Issekutz et al. (2005)	-	-	-	-	-
Johansson et al. (2006)	-	79% (22/28)	36% (10/28)	43% (12/28)	-
Jongmans et al. (2006)	-	74% (23/31)	-	-	37% (17/46)
Lasserre et al. (2013)	-	63% (5/8)	63% (5/8)	-	-

	Developmental delay	Intellectual Disability (ID)	Mild or Moderate ID	Severe or Profound ID	Autism Diagnosis
Legendre et al. (2017)	-	66% (63/96)	-	-	18% (21/117)
Oley et al. (1988)	-	60% (12/20)	-	15% (3/20)	-
Raqbi et al. (2003)	-	53% (11/21)	29% (6/21)	24% (5/21)	14% (3/21)
Reda and Hartshorne, (2008)	-	-	-	-	12% (3/25)
Roger et al. (1999)	74% (28/38)	-	-	-	13% (6/45)
Salem-Hartshorne and Jacob (2004)	-	46% (46/100)	-	-	32% (32/100)
Shiohama et al. (2019)	100% (10/10)	-	-	-	-
Shoji et al. (2014)	-	100% (25/25)	-	-	-
Smith et al. (2005)	100% (8/8)	100% (11/11)	-	-	60% (6/10)
Sohn et al. (2016)	-	94% (17/18)	-	-	-
Souriau et al. (2005)	-	-	-	-	-
Strömland et al. (2005)	82% (23/28)	-	-	-	20% (5/25)
Tellier et al. (1998)	100% (47/47)	-	-	-	-
Thelin and Fussner (2005)	-	-	-	-	-

	Developmental delay	Intellectual Disability (ID)	Mild or Moderate ID	Severe or Profound ID	Autism Diagnosis
Wessels et al. (2010)	100% (9/9)	-	-	-	-
Wincent et al. (2008)	-	-	-	-	-
Wulffaert et al. (2009)	78% (7/9)	75% (15/20)	35% (7/20)	40% (8/20)	-

	Aggression	Self-Injurious Behaviour	Obsessive Compulsive Behaviour	Tactile Defensiveness	Sleep Issues
Abadie et al. (2020)	-	-	-	-	-
Asher et al. (1990)	-	-	-	-	-
Bernstein and Denno (2005)	-	-	72% (21/29)	-	-
Blake and Brown, (1993)	-	-	-	-	-
Blake et al. (1990)	-	-	-	-	-
Blake et al. (2005)	53% (16/30)	50% (15/30)	43% (13/30)	40% (12/31)	50% (15/30)
Cheng et al. (2020)	-	-	-	-	17% (2/12)
(Dammeyer, 2012)	-	-	-	-	88% (15/17)
Davenport et al. (1986)	-	-	-	-	-

	Aggression	Self-Injurious Behaviour	Obsessive Compulsive Behaviour	Tactile Defensiveness	Sleep Issues
Deuce et al. (2012)	-	-	9% (4/44)	-	14% (6/44)
Deuce (2017)	-	-	-	-	52% (27/52)
Dobbelsteyn et al. (2008)	-	-	-	-	-
Hale et al. (2016)	-	-	-	-	-
Hartshorne et al. (2009)	-	-	-	-	57% (50/87)
Hartshorne et al. (2016)	51% (27/53)	47% (25/53)	49% (26/53)	51% (27/53)	58% (31/53)
Hartshorne and Cypher (2004)	38% (38/100)	34% (34/100)	3% (3/100)	53% (53/100)	-
Hartshorne, Grialou, et al. (2005)	-	-	-	-	-
Harvey et al. (1991)	-	-	-	29% (2/7)	-
Hittner et al. (1979)	-	-	-	-	-
Hsu et al. (2016)	-	-	-	-	-
Husu et al. (2013)	-	-	-	-	-
Issekutz et al. (2005)	-	-	44% (7/16)	-	31% (5/16)
Johansson et al. (2006)	68% (19/28)	54% (15/28)	-	-	29% (8/28)
Jongmans et al. (2006)	-	-	-	-	-

	Aggression	Self-Injurious Behaviour	Obsessive Compulsive Behaviour	Tactile Defensiveness	Sleep Issues
Lasserre et al. (2013)	-	-	-	-	-
Legendre et al. (2017)	-	-	-	-	-
Oley et al. (1988)	-	-	-	-	-
Raqbi et al. (2003)	-	-	-	-	-
Reda and Hartshorne, (2008)	-	-	-	40% (10/25)	-
Roger et al. (1999)	-	-	-	-	55% (24/44)
Salem-Hartshorne and Jacob (2004)	-	-	-	-	-
Shiohama et al. (2019)	-	-	-	-	-
Shoji et al. (2014)	-	-	-	-	-
Smith et al. (2005)	-	-	-	-	-
Sohn et al. (2016)	-	-	-	-	-
Souriau et al. (2005)	42% (27/67)	44% (28/63)	-	-	-
Strömland et al. (2005)	-	-	-	-	-
Tellier et al. (1998)	-	-	-	-	43% (3/7)

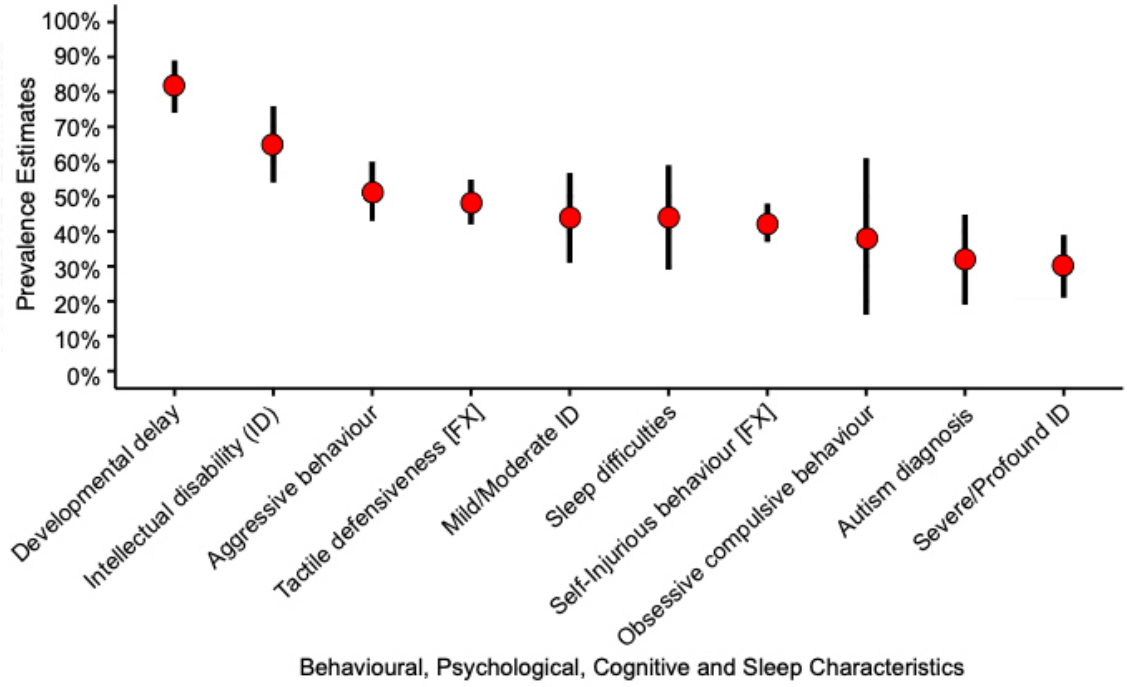
	Aggression	Self-Injurious Behaviour	Obsessive Compulsive Behaviour	Tactile Defensiveness	Sleep Issues
Thelin and Fussner (2005)	46% (13/28)	-	-	-	-
Wessels et al. (2010)	-	-	-	-	-
Wincent et al. (2008)	-	-	-	-	-
Wulffaert et al. (2009)	-	-	-	-	-

2.4.7 Prevalence Estimates and Subgroup Differences in Cognitive, Behavioural, Psychological, and Sleep Characteristics

Quality weighted random effects meta-analyses were conducted for cognitive, behavioural, psychological and sleep characteristics. Pooled prevalence estimates included aggression (48%, 95% CI = 40–57%), tactile defensiveness (48%, 95% CI = 42–55%), sleep problems (45%, 95% CI = 31–59%), self-injurious behaviour (44%, 95% CI = 36–51%), obsessive or compulsive behaviours (36%, 95% CI = 14–57%) and autism (28%, 95% CI = 16–41%), developmental delay (84%, 95% CI = 77–91%), intellectual disability (64%, 95% CI = 54–75%), mild to moderate intellectual disability (43%, 95% CI = 31–56%) and severe or profound intellectual disability (28%, 95% CI = 19–37%). A subgroup difference was identified for studies rated ‘good’ or ‘excellent’ and studies rated ‘poor’ or ‘adequate’ for confirmation of syndrome in the meta-analysis of intellectual disability. Specifically, the studies categorised as 'good' or 'excellent' provided a significantly higher level of confirmation for the syndrome compared to the studies classified as 'poor' or 'adequate.' Results are summarised in Figure 2.4 and detailed in Appendix 2D and 2E.

Figure 2. 4

Pooled Prevalence Estimates and 95% Confidence Intervals of Cognitive, Behavioural, Psychological, and Sleep Characteristics in CHARGE Syndrome

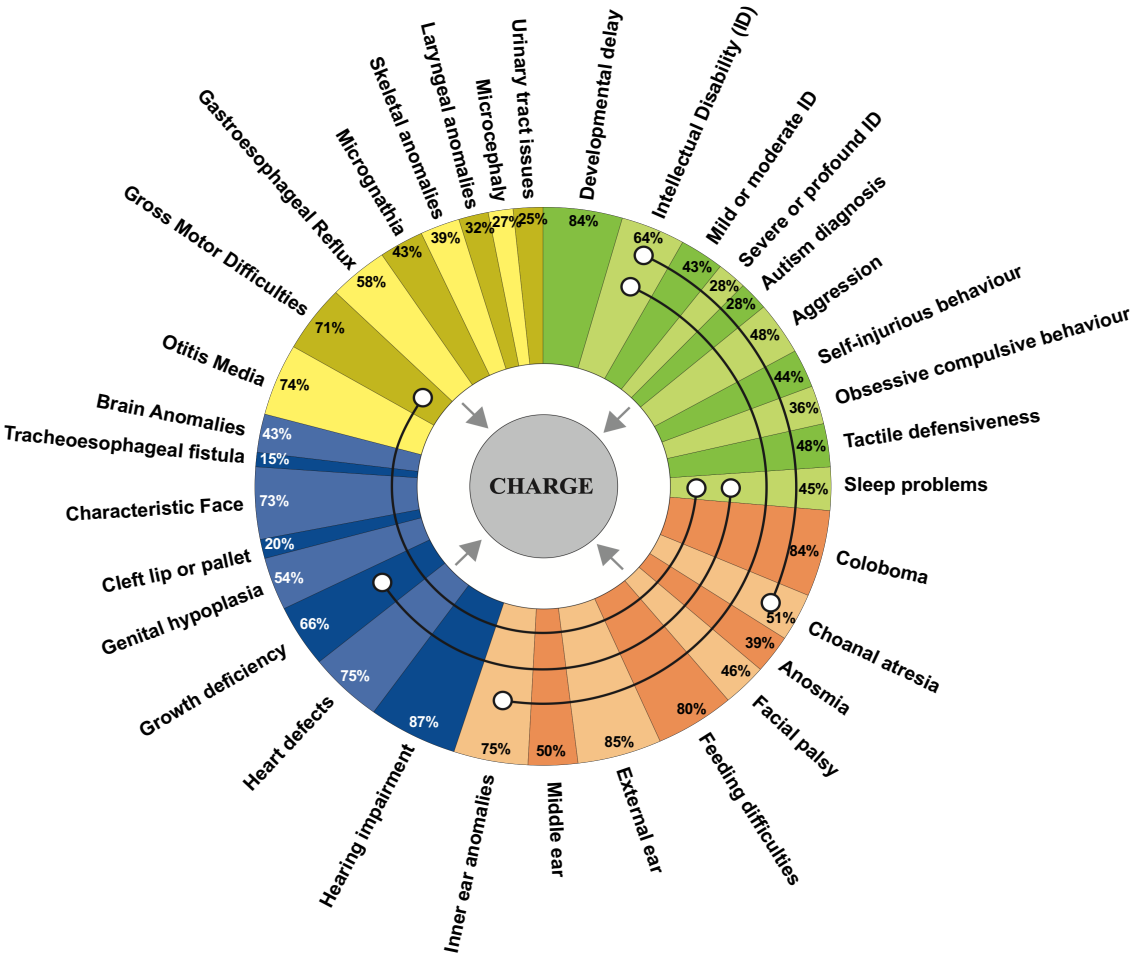


2.4.8 Meta-Regression

Statistically significant associations between features of the physical and behavioural phenotype included more intellectual disability and less choanal atresia (p = 0.01), more intellectual disability and less inner ear anomalies (p = 0.01), more sleep problems and more growth deficiency (p = 0.01) and more sleep difficulties and more gross motor difficulties (p = 0.03). Details are provided in Appendix 2F. A summary of results is presented in Figure 2.5.

Figure 2. 5

Prevalence estimates and co-occurrence of characteristics in CHARGE syndrome. Legend: pooled prevalence estimates (represented as section size), major clinical features (orange), minor clinical features (blue), physical characteristics and conditions associated with a diagnosis of CHARGE syndrome (yellow), and behavioural, psychological, cognitive and sleep characteristics (green), with nodes connected by black lines depicting associations between characteristics, for example the association between sleep problems and growth deficiency.



2.4.9 Genotype-Phenotype Associations

An estimated 84% (k = 10; 95% CI = 75–93%) of individuals with CHARGE Syndrome that had received genetic testing had an identifiable CHD7 mutation. Eleven studies reported prevalence rates for truncating (deletions, frameshift, nonsense and splice site) CHD7 mutations. These studies were amalgamated in a REM, resulting in a pooled prevalence estimate of 80% (95% CI = 71–89%). Prevalence estimates for deletions, frameshift, nonsense and splice site CHD7 mutations were 8%, 24%, 32% and 15% respectively.

A series of meta-regressions were calculated to evaluate evidence for genotype-phenotype associations. There were no statistically significant associations in this series of meta-regressions between genotype and any aspect of the physical or behavioural phenotype (details provided in Appendix 2D).

2.5 Discussion

In this comprehensive systematic review and meta-analysis, results indicate that cognitive, behavioural, psychological and sleep difficulties are prevalent in CHARGE syndrome. There is substantial variability in the quality of studies and significant differences between study estimates. These prevalence estimates have enabled investigation of relationships between characteristics, facilitating a comprehensive method for describing CHARGE syndrome.

2.5.1 Clinical Features

Pooled prevalence estimates of clinical features were largely consistent with previous reports by Hale et al. (2016), with the greatest discrepancy being lower estimates for inner ear

anomalies. Hale et al. (2016) estimates were drawn from studies published between 2005 and 2016, whereas the present meta-analysis incorporated research from 1979 to 2020. As inner ear anomalies were not recognised as a clinical feature of CHARGE syndrome until 2001 (Amiel et al., 2001), it is possible that the prevalence estimate is conservative. However, there was no significant difference between prevalence rates reported before or after 2001 in the analysis ($p = 0.11$). Therefore, in line with the first aim of the study, the results present an up-to-date prevalence estimate of characteristic features for future clinical and research practice.

2.5.2 Physical Characteristics and Conditions

Of the physical conditions identified in accordance with the second aim of the study, the highest prevalence estimates were for otitis media (74%) and gastroesophageal reflux (58%). There is an established causal link between otitis media and gastroesophageal reflux in typical development (Wu et al., 2021), but there were too few reports in the current review to assess this association. Gastroesophageal reflux is associated with failure to thrive and with significant mortality in young children with CHARGE syndrome (Bergman et al., 2010; Blake et al., 1990; Issekutz et al., 2005). In Cornelia de Lange Syndrome, behavioural indicators of gastroesophageal reflux include night-time agitation, hyperactivity, and self-injurious behaviour (Luzzani et al., 2003). Research is required to prospectively identify specific behavioural markers of reflux in CHARGE syndrome.

Additional physical characteristics reported by five or more eligible studies included: gross motor difficulties (71%), micrognathia (43%), skeletal anomalies (39%), laryngeal anomalies (32%) and microcephaly (27%). Micrognathia was the only feature of the characteristic

CHARGE face described by Blake et al., (1998) that was frequently reported as an independent observation. Similarly, almost one third of individuals with CHARGE syndrome were estimated to have laryngeal anomalies. These presentations are worthy of consideration in clinical contexts as laryngeal anomalies and micrognathia are known to increase the burden of respiratory and therefore sleep disordered breathing for example in 22q11.2 deletion (Imran et al., 2021), Treacher Collins and Nager syndromes (Hong et al., 2012).

2.5.3 Behavioural, Psychological, Cognitive and Sleep Characteristics

In addressing the third aim of the study, quality adjusted prevalence estimates for behavioural, psychological, cognitive and sleep characteristics were calculated. The estimated prevalence rates for aggression (48%) and self-injurious behaviour (44%) are concerning, given the likely impact on parenting stress (Wulffaert et al., 2009) and quality of life (Hartshorne et al., 2016). Once present, self-injury and aggression often persist (Laverty et al., 2020; Totsika et al., 2008). Comparable incidence rates of self-injury and aggression have been reported in fragile X (51% and 52%) and Prader-Willi (52% and 43%) (Arron et al., 2011), and gaps between service need and service provision are reported, despite the availability of evidence-based treatment (Awan et al., 2018). This is an area that requires careful monitoring in the CHARGE syndrome community. Future research should aim to determine the intensity, frequency and duration of aggression and self-injurious behaviour, through comparison with different genetic syndromes that have shared characteristics. Such research provides the groundwork for tailored interventions based on the specific strengths and difficulties of the individual with CHARGE syndrome.

Obsessive-compulsive behaviour was detailed in one of eight studies in which it was reported, despite these behaviours being described as a pervasive manifestation in CHARGE syndrome (Hartshorne et al., 2005). Given the salience of obsessive-compulsive behaviour, a pragmatic decision was made to include both a clinical diagnosis of obsessive-compulsive disorder (Blake et al., 2005; Hartshorne & Cypher, 2004) and observations reported as obsessive-compulsive behaviour (Bernstein & Denno, 2005; Deuce et al., 2012; Hartshorne et al., 2016; Issekutz et al., 2005). While estimates did not significantly differ between obsessive-compulsive behaviour and obsessive-compulsive disorder ($p = 0.41$), the quality of assessments was poor for all but one study and estimates ranged from 3% to 72%.

Study estimates for a clinical diagnosis of autism were variable, ranging from 6% to 50%, and this may reflect the range of assessment strategies. Four studies included in the meta-analysis assessed autism, each with a different measure or combination of measures. autism could not be reliably assessed in 8–12% of participants in two of these studies due to severe sensory impairment and intellectual disability (Smith et al., 2005; Strömland et al., 2005). This is concerning, given the increased likelihood of autistic behaviour in this sub-group (Johansson et al., 2006). The evidence indicates a need for the development of assessments and interventions for autism in CHARGE syndrome that are sensitive to the spectrum of reported autistic behaviours.

Given the detrimental effect of poor sleep on learning, behaviour regulation, physical, psychological, and social wellbeing (Friman & Schnoes, 2020), the estimated 45% prevalence

of sleep difficulties in CHARGE syndrome should not be overlooked. A more nuanced understanding of the characteristics and aetiology of sleep difficulties is required to develop proactive assessment and timely interventions.

The quality weighted pooled prevalence estimate for developmental delay was 84%, with a 64% pooled estimate for intellectual disability, and an estimated 28% of people with CHARGE syndrome experiencing severe or profound intellectual disability. While prevalence estimates were characterised by wide CIs, they do suggest greater potential for cognitive development than has been described in previous reviews (Bergman et al., 2011; Hsu et al., 2014).

2.5.4 Exploration of Co-Occurring Characteristics

A series of exploratory meta-regression analysis were conducted to explore co-occurring characteristics in accordance with the fourth aim of the study. Meta-regression analysis revealed associations between sleep problems and gross motor difficulties, and sleep problems and growth deficiency. The association between sleep problems and growth deficiency in CHARGE syndrome is likely to be multifaceted. For example, growth can be limited by feeding difficulties and chronic illness that may cause pain or necessitate overnight monitoring, compromising sleep (Trider et al., 2017). There is also an association between obstructive sleep apnoea and growth failure (Esteller et al., 2018). Where this condition is due to enlarged tonsils and adenoids, improvement in growth has been reported following adenotonsillectomy (Esteller et al., 2018). Growth hormone deficiency is also associated with CHARGE syndrome (Dijk et al., 2019) and monitoring is recommended as part of

multidisciplinary care (Trider et al., 2017). Disordered growth hormone secretion can be a consequence of disordered sleep because most growth hormone secretion is triggered by the onset of slow-wave sleep (Lieb et al., 2000; Steiger, 2003). As such, pain and discomfort, obstructive sleep apnoea and a sleep disorder related growth hormone deficit are worthy of consideration in the workup and management of growth deficiency in CHARGE syndrome.

With reference to the associations between sleep problems and gross motor difficulties, it is notable that sleep disordered breathing has been shown to have a negative impact on motor development in Down syndrome (Weber et al., 2020). Furthermore, children with more gross motor difficulties are likely to walk at a later age. A later age of walking in CHARGE syndrome is associated with more 'challenging behaviour' (Hartshorne & Cypher, 2004), 'autistic behaviour' (Hartshorne et al., 2005) and adaptive functioning limitations (Salem-Hartshorne & Jacob, 2004). This evidence suggests that gross motor development could be a key intervention target for multidisciplinary assessment, including otolaryngology, occupational therapy and developmental paediatrics. In summary, the bidirectional association between sleep and gross motor difficulties, potentially predicted by a later age of walking, warrants further investigation.

The relationship between intellectual disability and less choanal atresia seemed unlikely given links between early psychomotor delay and severe respiratory distress (Raqbi et al., 2003). However, as reported in Tellier et al. (1998), 48% of infants with bilateral choanal atresia died in the first year of life, before intellectual disability could be assessed. Therefore,

the association between intellectual disability and choanal atresia may simply be an artefact of the data.

2.5.5 Exploration of Genotype-Phenotype Associations

Consistent with previous reports (Basson & van Ravenswaaij-Arts, 2015), an estimated 84% of study participants that received genetic testing had an identifiable CHD7 variant. To address aim five, a series of meta-analysis and meta-regression were run with these CHD7-positive participants to evaluate evidence for genotype-phenotype associations.

There is some evidence to suggest that truncating mutations are associated with a more severe CHARGE syndrome phenotype (Bergman et al., 2011; Legendre et al., 2017). No such association was identified in the current meta-analysis. Based on these findings, and the available literature, no inference can be made to genetically mediated sub-groups within the clinically diagnosed CHARGE syndrome population. However, given the pleotropic nature of CHD7, it is conceivable that the available data was not detailed enough to capture genotype phenotype interactions. Further exploration of CHD7 function through gene expression studies may advance understanding of Genotype-Phenotype Associations and the pathogenesis of CHARGE syndrome.

2.5.6 Limitations

This study has some limitations. First, the methodology excluded participants with CHD7 disorder that did not fulfil the clinical criteria for CHARGE syndrome. Therefore, participants

with milder CHARGE syndrome phenotypes may have been excluded. Conversely, including CHARGE syndrome participants for whom clinical features were not reported may have led to the inclusion of non-CHARGE syndrome participants. As such, the findings should be treated as preliminary. However, there was no statistical difference between studies that did or did not detail the CHARGE syndrome diagnosis. Second, synthesis of the CHARGE syndrome literature was hampered by the large number of idiosyncratic descriptions used. For example, the 60% prevalence of 'increased levels of stress and anxiety' (Deuce, 2017) and 35% incidence of 'often seemed anxious' (Souriau et al., 2005) could not be reliably pooled with the 37% and 45% prevalence of anxiety diagnosis reported by Blake et al. (2005) and Hartshorne et al. (2016) respectively. Anxiety is a multifaceted construct that requires a fine-grained appraisal to facilitate meta-synthesis. Edwards et al. (2022) have used such an approach and report a 37% (95% CI 10–64%; k = 2) quality weighted pooled prevalence estimates for anxiety in CHARGE syndrome. A statement on the use of specific, explicit, and appropriate definitions for behaviour in CHARGE syndrome should be developed through multidisciplinary collaboration to enable data sharing and pooling. Availability of such data, particularly longitudinal data, would allow researchers to go beyond co-occurring characteristics to understand varying developmental trajectories. Lastly, meta-analytic estimates were limited by the paucity of available data and the wide CIs for the pooled prevalence estimates were not fully explained by meta-regression or subgroup analysis. As such these findings and recommendations should be considered as preliminary. Similarly, the use of univariate analysis to understand causal pathways in a heterogeneous syndrome such as CHARGE is less than adequate. However, multivariate analysis was precluded by the paucity of data. It is possible for co-occurring characteristics to arise independently, so it is important

to note that the findings and recommendations from this systematic review and meta-analysis should be interpreted with caution.

2.5.7 Conclusion

Cognitive, behavioural, psychological and sleep difficulties are highly prevalent in CHARGE syndrome. Future research should address the conceptualisation and description of behaviour in CHARGE syndrome, the development of valid and reliable instruments for psychological diagnosis, and an observational checklist for behavioural signs of gastrointestinal reflux. Future research should use syndrome profile comparison to understand the clinical presentation of CHARGE syndrome. The data from this systematic review and meta-analysis support the ongoing efforts of family support groups, researchers, and practitioners to strengthen understanding and develop appropriate interventions and supports for individuals with CHARGE syndrome, their families and professionals involved in their care.

CHAPTER THREE

SYNDROME PROFILE COMPARISON

3.1 Preface

A high prevalence of sleep disturbance in CHARGE syndrome was highlighted in the meta-analytic data reported in Chapter 2. However, most studies assessed sleep disturbance using a single question or an unvalidated questionnaire. Chapter 3 addresses this limitation by using validated measures suitable for persons with an intellectual disability. Additionally, Chapter 2 highlighted the high prevalence of behaviours that challenge in CHARGE syndrome, particularly self-injurious behaviour and aggression. Chapter 3 extends this research by describing the prevalence and profile of behaviours that challenge in CHARGE syndrome, undertaking cross-syndrome comparisons to refine the behavioural phenotype of CHARGE syndrome. Using the same-but-different approach (see section 1.12.3), Chapter 3 compares the prevalence and severity of behaviours that challenge in individuals with CHARGE syndrome and those with intellectual disability of heterogeneous aetiology, Cornelia de Lange syndrome, Lowe syndrome, Down syndrome, and autistic people.

3.2 Introduction

3.2.1 Sleep and Behaviour in Children with CHARGE Syndrome

CHARGE syndrome is a multisystem congenital disorder with an estimated prevalence of 1 in 8,500 births. CHARGE syndrome is caused by the haploinsufficiency of the CHD7 gene, which plays a critical role in neural crest development (Hsu et al., 2014). Disruption of neural

crest development likely leads to the phenotypic heterogeneity seen in CHARGE syndrome (Hsu et al., 2014) (see section 2.2.2).

Chapter 2 described the considerable heterogeneity in CHARGE syndrome, identifying 24 common physical characteristics and conditions. These characteristics vary from severe to absent, and many, such as gastrointestinal reflux and otitis media, are associated with pain. In addition to painful health conditions, individuals with CHARGE syndrome typically have multiple sensory impairments, including challenges with vision, hearing, and mobility (see section 2.4.4 to 2.4.5). The combination of visual and auditory difficulties can significantly impact communication, mobility, sensory sensitivity, and sleep patterns (Hartshorne et al., 2009; Hersh, 2013). Furthermore, motor impairments, such as those present in children with CHARGE syndrome, are associated with more profound intellectual disability and a higher frequency of health and behavioural issues (Patel et al., 2020). In the context of multi-sensory impairment, behaviours that challenge can be seen as adaptive responses for children with CHARGE syndrome (Brown, 2005). This conceptualisation of behaviour underscores the critical need for a research approach that acknowledges the diverse medical, physical, and behavioural characteristics intertwined with multi-sensory impairment. Recognising and addressing these interrelated challenges is imperative in providing comprehensive support and care for children with CHARGE syndrome.

3.2.1.1 Sleep in Children with CHARGE Syndrome

Pain and sensory impairments often lead to a decline in the overall quality of one's sleep (Mazurek & Petroski, 2015). The prevalence of sleep disturbances for children with

CHARGE syndrome varies significantly, ranging from 58% to 93% (Hartshorne et al., 2009; Kennert et al., 2020). Hartshorne et al. (2009) and Kennert et al. (2020) reported that the most prevalent sleep disturbances in children with CHARGE syndrome when assessed with the Sleep Disturbance Scale for Children (Bruni et al., 1996) were difficulties in initiating and maintaining sleep, sleep breathing and sleep-wake transition. Similarly, the meta-analytic results in this thesis demonstrated that poor sleep occurs in 45% of people with CHARGE syndrome (see section 2.4.7). This estimate is lower than for children with multiple disabilities (80%; Jan & Freeman, 2004) but higher than for typically developing children (30% to 40%; Fricke-Oerkermann et al., 2007).

When delineating sleep and sleep disturbances in children with CHARGE syndrome, it is important to use measures that are suitable and sensitive for use with children with intellectual disability. The suitability of a sleep assessment tool hinges on several critical factors, including the individual's level of cognitive functioning, communication abilities, and the nature of their sleep-related challenges (Belli et al., 2022). To improve the quality of evidence, researchers should evaluate sleep patterns and disturbances using standardised questionnaires which have been validated for people with intellectual disabilities. Two studies have examined sleep patterns in children with CHARGE syndrome using standardised sleep questionnaires (Hartshorne et al., 2009; Kennert et al., 2020). Hartshorne et al. (2009) and Kennert et al. (2020) used the short, 25 item Sleep Disturbances Scale for Children (Bruni et al., 1996) to measure sleep in children with CHARGE syndrome. Findings from both studies indicated that the most commonly reported sleep problems were sleep initiation and maintenance. However, this limited body of research does not fully describe the population's complex interplay between sleep difficulties and other associated challenges. Further studies

are needed to replicate these findings using more comprehensive standardised measures and including objective measures alongside subjective tools.

3.2.1.2 Behavioural Aspects of CHARGE Syndrome

Compared to aspects of the physical phenotype such as health and sensory profiles, cognition, emotion, and behaviour are under-researched in CHARGE syndrome. The meta-analysis in Chapter 2 described three diagnoses (intellectual disability, developmental delay, autism) and five behaviours (aggression, self-injury, obsessive-compulsive behaviour, and tactile defensiveness) that were common in CHARGE. However, these behaviours received 2.5 times less research attention than the physical diagnostic features, with the greatest research interest in intellectual disability (21 studies) and the least interest in tactile defensiveness (5 studies) and self-injurious behaviour (5 studies). This relative scarcity of behavioural research is partly attributable to a prevailing emphasis on medical interventions for CHARGE syndrome, particularly in early childhood (Hartshorne et al., 2005). However, the link between health conditions and behaviours that challenge is gaining research and clinical interest (Kennedy, 2021). Furthermore, 65% of the data describing cognitive, emotional, and behavioural characteristics were derived from non-standardised informant reports or reviews of clinical information. It is problematic when reporting is not standardised because internal validity becomes a problem and it can also lead to inconsistencies across studies, impacting the validity and reliability of findings. Therefore, to improve the utility and consistency of research findings, more robust and standardised measures must be used for assessing cognitive, emotional and behavioural aspects of the phenotype of CHARGE syndrome. Chapter 2 also highlighted a 48% prevalence of aggression and a 44% prevalence

of self-injurious behaviour. As such, more research is required to replicate the available findings, to use standardised measures and where possible to compare results with individuals with 'same but different' characteristics to help elucidate the behavioural phenotype of CHARGE syndrome.

In summary, children with CHARGE syndrome present many physical and behavioural characteristics and conditions, some of which can cause pain. Sensory impairments (vision, hearing, mobility) are also common. Behavioural factors have received less attention but are vital, as behaviours like aggression and self-injury may result from sensory impairments and pain. Sleep problems are common in children with CHARGE syndrome and affect daytime behaviour. Addressing sleep issues and behaviours that challenge is essential for overall well-being, and further research should explore these characteristics using measures that have been validated for children with an intellectual disability.

3.2.2 Syndrome Profile Comparisons

In section 1.8.3, operant learning theory is described as the predominant clinical model for understanding behaviours that challenge. However, this model primarily focuses on the influence of environmental and sensory contingencies and may overlook individual differences. Consequently, despite intellectual disability being a risk marker for challenging behaviours (as detailed in section 1.8.2), application of operant theory in isolation can fall short in explaining why certain syndromes linked to intellectual disability exhibit elevated instances of specific behaviours compared to others (the behavioural phenotype). For example, self-injurious behaviour is more prevalent in conditions like Lesch–Nyhan, Smith–

Magenis, and Prader–Willi syndromes but not in Angelman Syndrome (Oliver et al., 2013). Additionally, the model fails to elucidate the observed behavioural patterns, such as hand biting in Fragile X syndrome or skin picking in Prader–Willi syndrome (Oliver et al., 2013). It is imperative to investigate the prevalence and varied typologies of challenging behaviours to construct comprehensive causal models. This exploration can provide valuable insights for identifying areas that require additional support and intervention, yielding rich data on underlying mechanisms and explaining why certain behaviours or typographies of behaviour emerge and are maintained.

As outlined in section 1.12.3, the "same but different" approach provides a powerful method for identifying behavioural phenotypes by comparing groups of individuals who share certain similarities but also have distinct differences (Dykens, 1995). Comparing a less well-documented syndrome with a well-documented one can uncover new insights and hypotheses regarding shared behavioural mechanisms. For instance, both Prader-Willi syndrome and Fragile X syndrome exhibit repetitive behaviours. However, cross-syndrome analysis reveals that individuals with Prader-Willi syndrome tend to display a higher frequency of temper outbursts when experiencing change in comparison to those with Fragile X syndrome (Woodcock et al., 2009). This observation suggests that distinct underlying factors may contribute to these behavioural manifestations in each syndrome.

3.2.2.1 Clinical Groups

Examples of well-delineated clinical groups that are similar but also different to CHARGE syndrome include autism, Cornelia de Lange Syndrome (CdLS), Down Syndrome (DS) and Lowe syndrome (LS).

3.2.2.1.1 Autism

Autism is a neurodevelopmental condition characterised by distinctive social communication differences and repetitive interests or activities. Diagnosing autism relies on observing these specific traits since there are no reliable biomarkers available (American Psychiatric Association, 2013). Autism manifests across a spectrum and can vary in prevalence in rare genetic syndromes (Richards et al., 2015). However, meeting the threshold for an autism diagnosis does not mean that the person with a genetic syndrome will show the same strengths and differences as an autistic person without that genetic syndrome (Jenner et al., 2023; Moss & Howlin, 2009) Similarly, children who have intellectual disabilities and combined vision and hearing impairments associated with conditions like CHARGE syndrome may display behaviours that can superficially resemble autism (Hoevenaars-van den Boom et al., 2009). These behaviours, including delays in social affective development and repetitive behaviours, likely contribute to the reported autism prevalence, estimated at 28% in section 2.4.7 (Johansson et al., 2010).

3.2.2.1.2 Cornelia de Lange Syndrome (CdLS)

CdLS is a rare neurogenetic syndrome, affecting approximately 1 in every 10,000 to 30,000 live births (Mannini et al., 2013). This syndrome is linked to variants in five cohesin-

related genes: NIPBL, SMC1A, SMC3, RAD21, and HDAC8. Notably, NIPBL mutations are the most common, accounting for roughly 60% of cases (Mannini et al., 2013). Like CHARGE syndrome, CdLS is associated with intellectual disability (Kline et al., 2018). The behavioural phenotype of CdLS shares characteristics with CHARGE syndrome (see Chapter 2), including self-injury and aggression, social difficulties and repetitive behaviours that may reach the threshold for an autism diagnosis (Kline et al., 2018). Like the profile of physical characteristics of CHARGE syndrome reported in section 2.4.5, CdLS is associated with a high incidence of gastroesophageal reflux and otitis media. These painful conditions can lead to behaviours like aggression and hyperactivity in individuals with CdLS who have a limited ability to report their discomfort (Kline et al., 2018).

3.2.2.1.3 Down Syndrome (DS)

DS is usually caused by an extra copy of chromosome 21 (Chapman & Hesketh, 2000). There are approximately 8.27 people with DS per 10,000 population (Presson et al., 2013). The behavioural phenotype of DS includes heightened social motivation alongside delays in nonverbal cognitive development, speech and language production, auditory short-term memory deficits and intellectual disability (Chapman & Hesketh, 2000). DS has been extensively studied, and a substantial body of research on this condition's cognitive and behavioural aspects makes it a valuable and accessible comparison group.

3.2.2.1.4 Lowe Syndrome (LS)

LS is a rare X-linked neurogenetic condition associated with congenital cataracts, intellectual disability, and proximal renal tubular dysfunction (Bökenkamp & Ludwig, 2016).

The behavioural phenotype of LS includes aggression, temper tantrums, stubbornness, and repetitive behaviour (Bökenkamp & Ludwig, 2016). The shared features of aggression, visual impairment and intellectual disability, as outlined in sections 2.4.5 to 2.4.7, make LS an appropriate comparison group for CHARGE syndrome.

3.2.2.1.5 Intellectual Disability of Heterogeneous Aetiology

A final comparison group that is commonly used when investigating behaviour in rare genetic syndromes is Intellectual disability of heterogeneous aetiology (ID) (Moss et al., 2009; Oliver et al., 2011; Royston et al., 2017). As outlined in section 1.8, individuals with intellectual disability form an aetiologically heterogeneous group, with mild intellectual disability typically caused by environmental factors. In contrast, biological and neurological factors are more common in the aetiology of severe and profound intellectual disability (Patel & Brown, 2017). The benefit of using an ID comparison group is that it can be used to differentiate between characteristics associated with intellectual disability and those associated with CHARGE syndrome specifically.

In summary, the behavioural characteristics of CHARGE syndrome can be understood through comparison to groups like autism, CdLS, DS, LS and ID. While each group is distinct, they also show overlapping characteristics. These overlapping characteristics allow for meaningful comparisons that offer insight into the distinctive challenges of persons with CHARGE syndrome. Furthermore, including a comparison group with intellectual disability allows the differentiation between characteristics associated with intellectual disability and

those associated with CHARGE syndrome. In conclusion, the same but different methodology contributes to a deeper understanding of the behavioural phenotype of CHARGE syndrome.

3.2.3 Summary

CHARGE Syndrome is a rare and heterogeneous neurogenetic syndrome that affects multiple body systems. Children with CHARGE Syndrome often experience various painful health conditions, including gastroesophageal reflux and otitis media. There is a risk that such pain remains unnoticed and consequently untreated in children with limited expressive communication, and this could lead to behaviours that challenge. Furthermore, CHARGE syndrome presents various sensory and interconnected challenges, necessitating a research approach that acknowledges the diverse medical, physical, and behavioural characteristics intertwined with multi-sensory impairment. Given the negative impact of poor sleep on learning, behavioural regulation, physical and mental health and social well-being, it is important not to overlook sleep issues in children with CHARGE syndrome. Cognition, emotion and behaviour have been under-researched compared to the physical phenotype in CHARGE syndrome. Future research should employ more comprehensive methods to better understand CHARGE syndrome's behavioural dimensions. It remains uncertain whether the prevalence of behaviours that challenge is higher in children with CHARGE syndrome compared to those without the syndrome or those with autism or ID. The "same but different" approach identifies patterns in how individuals from different clinical groups behave. Furthermore, research can be improved by using robust and standardised measurements appropriate for children with intellectual disabilities.

3.2.4 Research Objectives

1. To compare the prevalence and severity of behaviours that challenge between children with CHARGE syndrome, autism, CdLS, DS and LS and ID matched on age and ability.

2. To elucidate the experience of children with CHARGE syndrome in relation to sleep.

3. To evaluate the potential influence of ability level, sensory and mobility factors on sleep and behaviours that challenge in children with CHARGE syndrome.

4. To explore how behaviours that challenge and sleep issues might be associated with adaptive behaviour, executive functioning, social communication, mood, hyperactivity and repetitive behaviour as well as dimensions of physical health.

To meet these objectives, this chapter will present a cross-sectional study of individuals with CHARGE Syndrome and comparison groups of Autistic individuals and individuals with CdLS, DS, LS and ID taken from historical datasets. Participants will be matched on age and adaptive functioning (used as a proxy for intellectual disability). Data will be collected using robust measures appropriate for individuals with intellectual disabilities. They will include assessments of ability, executive function, social communication, hyperactivity and overactivity, repetitive behaviour, mood, and health, in addition to behaviours that challenge and sleep. Autism, ID, CdLS, DS, and LS datasets include fewer variables, but all include data for behaviours that challenge. Data will be analysed using descriptive and inferential

statistics to explore factors that may influence or co-occur with behaviours that challenge and sleep differences in individuals with CHARGE Syndrome and, where possible, compared to autism, CdLS, DS, LS, and ID.

3.3 Methods

The study was conducted as part of a wider research project at the Cerebra Network for Neurodevelopmental Disorders.

NHS ethics were granted by Coventry and Warwick NHS Research and Development (IRAS Project ID: 20638; Sponsor amendment reference: RG_09-081 NSA_02) see Appendix 3A.

3.3.1 Recruitment

3.3.1.1 CHARGE Syndrome

Families with a child with CHARGE syndrome were recruited from December 2020 to December 2021 specifically for the present study. Perspective participants were recruited through social media groups affiliated with the USA and UK CHARGE family support groups, through the specialist multidisciplinary NHS CHARGE Syndrome clinic, and the charity Sense. Families were included if they were the parent/caregiver of an individual with CHARGE syndrome aged 4 to 15 years, diagnosed by a medical professional.

3.3.1.2 Autism, ID, CdLS, DS and LS

Individuals diagnosed with autism, ID, CdLS, DS and LS were selected from a pre-existing dataset of participants held by the Cerebra Centre for Neurodevelopmental Disorders, University of Birmingham. Participants were included if they were ages 4 to 15 and were diagnosed by a medical professional. Participants with autism or ID were excluded if they had an additional genetic syndrome, and participants with autism were excluded if they had a total score below the autism cut-off score of 15 on a validated autism screening tool, the Social Communication Questionnaire (Berument et al., 1999), see Table 3.1.

Table 3. 1

Inclusion and exclusion criteria for each of the clinical groups and the matching criteria for each of the comparison groups

Clinical Group	CS	Autism	ID	CdLS	DS	|LS
Age 4 to15 years (± 3 years)[a]	**l**	**l**	**l**	**l**	**l**	**l**
Have a clinical diagnosis from a medical professional e.g., clinical geneticist, GP, Paediatrician	**l**	**l**	**l**	**l**	**l**	**l**
Wessex Self-Help score available	**l**	**l**	**l**	**l**	**l**	**l**
Total score of 15 or above on the SCQ		**l**				
No secondary syndrome diagnosis		**l**	**l**	**l**	**l**	**l**

Note. l = True. Two participants with CHARGE syndrome had secondary syndrome diagnosis.

[a] Comparison groups may include individuals three years younger or older than the CHARGE syndrome group.

3.3.1.3 Matching Procedure

The matching process within each comparison group (autism, ID, CdLS, DS and LS) was a crucial step in this study. Individuals were arranged by age and self-help score in ascending order, using the Wessex (Kushlick et al., 1973) self-help score as a proxy for ability level. Each participant with CHARGE syndrome was sequentially matched to one participant with autism, ID, CdLS, DS and LS, first according to self-help score (± 2 points) and then chronological age (± 3 years). The goal was to ensure an equal number of participants in each group, which meant that a participant was excluded if a suitable match could not be found. Priority was given to finding an exact match for self-help skills, with a three-year age range allowed. If an exact match was not possible, the next criteria considered were self-help skills within a one-point range, followed by a two-point range.

The original samples used for matching included children and adults. Table 3.2 details the children from the ID, CdLS, DS, and LS datasets before and after matching. This table presents the sample sizes, means, and standard deviations for each group before and after matching concerning age and self-help skills. It also includes proportion values for the presence of self-injury, aggression, and property destruction from the CBQ. Notably, the CHARGE syndrome group exhibited the highest Wessex self-help score. Table 3.2 provides data that show whether there are any statistical differences in the autism, intellectual disability, Cornelia de Lang syndrome, Down syndrome and Lowe syndrome groups before and after matching. A significantly higher proportion of individuals with autism displayed property destruction behaviours after matching compared to before. Furthermore, the mean

self-help score for individuals with Cornelia de Lange Syndrome was significantly higher after matching than before. These findings have significant implications for understanding the characteristics of these groups and the matching process.

Considering how representative the comparison groups are compared to the broader literature, the autism group is approximately representative (48%-64%), as reports suggest a 56% to 94% prevalence of behaviours that challenge autism (Rattaz et al., 2018). The intellectual disability sample presented with proportionally fewer behaviours that challenge (20%-53%) compared to the 50% to 80% reported in the literature (Kiernan & Moss, 1990; Poppers et al., 2010). Behaviours that challenge are reported to occur in around 56% of individuals with CdLS (Kline et al., 2018), which suggests that the sample used for this study was approximately representative (42%-58%). Tassé et al. (2016) report a 7% prevalence of behaviours that challenge in Down Syndrome, suggesting that the sample used for matching in the present study presented a higher than previously reported prevalence of challenging behaviour (5%-46%). Arron et al. (2011) reported a 64% prevalence of challenging behaviour in Lowe syndrome, suggesting that the sample used for matching in the present study (55%-64%) is approximately representative.

Considering the participants with CHARGE syndrome who could not be matched within each comparison group is crucial. While all participants in the autism group were successfully matched, 10 participants in the intellectual disability group could not be matched. In this group, there was no statistical association between the matched and the unmatched children on mean age ($t = 2.09$, $p= 0.05$, adj $p = 0.12$), mean Wessex self-help score ($t = -1.29$, $p =$

0.21, adj p = 0.37) or the proportion of children exhibiting self-injury (χ^2 = 0.36, p = 0.55, adj p =0.78), aggression (χ^2 = 0.63, p = 0.43, adj p = 0.73), or destruction of property (χ^2 = <0.01,p = 1.00, adj p = 1.00). Twenty-three children with CHARGE syndrome were matched with children with Down syndrome, and two children could not be matched. Comparing the matched and unmatched children, the unmatched sample was younger than the matched sample (mean = 6(SD = 2)) compared to mean 8.41(SD = 3.63)), they also had a lower self-help score (mean = 3(SD = 0) compared to mean 7.59 (SD = 2.26). Furthermore, it is notable that none of the unmatched samples presented with self-injury, aggression or destruction of property. Similarly, 24 children could be matched with the Cornelia de Lang syndrome group, and one child was unmatched. The unmatched child was younger than the mean group age (5 compared to 8.25(SD = 3.55)) and had a higher self-help score (10 compared to 7.75(SD = 2.25)). The unmatched child in the Cornelia de Lange syndrome group exhibited no self-injury but did present with aggression and destruction of property. Finally, 22 children with CHARGE syndrome could be matched with the Lowe syndrome participants. However, three children could not. The mean age of the group that was not matched was 6.33(SD = 1.53) compared to that of the matched children with CHARGE syndrome (8.36(SD = 3.68)). The three unmatched children had a higher mean self-help score (10.33(SD = 0.58)) than the matched children (7.50(SD = 2.18)). None of the unmatched children presented with self-injury or destruction of property and one of the three children exhibited aggression

Table 3.2:

Overview of original and matched sample sizes, means, and standard deviations for CHARGE Syndrome, Intellectual Disability, Cornelia de Lange Syndrome, Down Syndrome, and Lowe Syndrome children

		Sample size	Mean age (SD)	Mean self-help score (SD)	Proportion of children with self-injury	Proportion of children with aggression	Proportion of children with destruction of property
CHARGE syndrome		25	8.12 (3.54)	7.84 (2.25)	38.4%	42.3%	50.0%
Autism	Before matching	223	9.14 (3.18)	7.31 (1.53)	40.1%	65.0%	55.2%
	After matching	25	8.20 (3.54)	7.40 (1.87)	48.0%	64.0%	64.0%
			t = 1.37	t = -0.23	χ^2 = 0.33	χ^2 = 0.03	χ^2 = 10.50
			p = 0.18	p = 0.82	p = 0.57	p = 0.85	p = <0.01
			Adj: 0.35	Adj: 1.00	Adj 0.78	Adj: 1.00	Adj: 0.03
Intellectual disability	Before matching	31	10.19 (2.54)	5.58 (1.96)	35.5%	51.6%	58.1%
	After matching	15	10.00 (2.81)	6.00 (1.84)	20.0%	66.7%	53.3%
			t = -0.01	t = -1.27	χ^2 = 0.53	χ^2 = 0.42	χ^2 = <0.01
			p = 0.18	p = 0.21	p = 0.47	p = 0.52	p = 1.00

		Sample size	Mean age (SD)	Mean self-help score (SD)	Proportion of children with self-injury	Proportion of children with aggression	Proportion of children with destruction of property
			Adj: 0.35	Adj: 0.37	Adj: 0.77	Adj: 0.78	Adj = 1.00
Cornelia de Lang syndrome	Before matching	64	9.00 (3.98)	5.31 (1.87)	64.6%	41.3%	56.5%
	After matching	24	8.38 (3.52	7.13 (1.75)	45.8%	41.7%	58.3%
			t = -0.70	t = 4.24	χ^2 = 1.70	χ^2 = <0.01	χ^2 = <0.01
			p = 0.49	p = <0.01	p = 0.19	p = 1.00	p = 1.00
			Adj: 0.78	Adj: 0.03	Adj: 0.36	Adj:1.00	Adj 1.00
Down syndrome	Before matching	45	9.07 (3.33)	7.00 (1.37)	11.6%	40%	18.6%
	After matching	22	8.59 (3.46)	7.23 (1.57)	4.8%	45.5%	18.2%
			t = -0.53	t = 0.58	χ^2 = 0.04	χ^2 = <0.01	χ^2 = <0.01
			p = 0.60	p = 0.57	p = 0.85	p = 0.93	p = 1.00
			Adj: 0.80	Adj: 0.78	Adj: 1.00	Adj: 1.00	Adj: 1.00
Lowe Syndrome	Before matching	35	9.11 (3.32)	5.91 (1.77)	63.9%	71.4%	57.1%
	After matching	22	8.73 (4.03)	6.77 (1.77)	54.5%	63.6%	54.5%
			t = -0.38	t = 1.78	χ^2 = 0.32	χ^2 = <0.01	χ^2 = <0.01
			p = 0.71	p = 0.08	p = 0.57	p = 0.92	p = 1.00
			Adj: 0.92	Adj: 0.18	Adj: 0.87	Adj: 1.00	Adj 1.00

Note: Adj = adjusted p-valu

Table 3.2 presents an overview of the matching results between each specific group and the CHARGE syndrome group concerning age, gender, and self-help score. Furthermore, it provides a comparative analysis of additional demographic variables, including mobility, vision, hearing, and verbal ability, taken from the background questionnaire and the Wessex Behaviour Scales (Kushllck et al., 1973; refer to the 'Measures' section for further details).

No significant differences were observed between CHARGE syndrome and ID, CdLS, or DS on age. LS is an X-linked syndrome, which exclusively affects boys. As such there was a significant difference between CHARGE syndrome and LS on gender with more males with LS than CHARGE syndrome ($\chi^2 = 13.83$, $p < 0.01$). No significant differences were found between CHARGE syndrome and any of the comparison groups on self-help. Significantly more autistic children and children with DS were fully mobile than children with CHARGE syndrome ($\chi^2 = 6.65$, $p = <0.01$, $\chi^2 = 5.61$, $p = 0.02$). Vision was classified as normal significantly more often in autistic children and children with CdLS than in children with CHARGE syndrome ($\chi^2 = 19.531$, $p < 0.001$, $\chi^2 = 6.75$, $p = <0.01$. Hearing was classified as normal significantly more often in autistic children, children with ID, CdLS and LS than in children with CHARGE syndrome ($\chi^2 = 30.047$, $p < 0.01$, adj $p = 0.03$, $\chi^2 = 8.533$, $p = <0.01$, adj $p = 0.03$, $\chi^2 = 10.154$, $p = <0.01$ adj $p = 0.03$, $\chi^2 = 21.154$, $p < 0.01$, adj $p = 0.03$). Finally, speech was classified as normal significantly normal more often for autistic children and children with DS and LS than children with CHARGE syndrome ($\chi^2 = 2.029$, $p = 0.15$, adj $p = 0.32$, $\chi^2 = 4.492$, $p = 0.03$, adj $p = 0.07$, $\chi^2 = 7.425$, $p = 0.006$, adj $p = 0.03$).

Table 3. 3

Mean age, standard deviation and range, percentage of females and levels of self-help, mobility, speech, and sensory impairment and statistical differences between each clinical group and CHARGE syndrome.

		CHARGE	Autism	ID	CdLS	DS	LS	Comparison	Adj p
N		25	25	15	24	22	22		
Age	Mean	8.12	8.20	10.2	8.38	8.59	8.73	N/S	
	(SD)	3.54	3.54	2.81	3.52	3.46	4.03		
	Range	4-15	4-15	6-15	4-15	4-15	4-17		
Sex	% Female	50	36	47	58	64	0	CS/LS (p = <0.01)	p = 0.03
Self Help	% Partly Able / Able	72	72	73	75	91	73	N/S	
Vision	% Normal	32	96	60	71	68	23	CS/Autism (p = 0.01)	p = 0.03
								CS/CdLS (p = <0.01)	p= 0.03
Hearing	% Normal	20	100	80	71	55	95	CS/Autism (p = <0.01)	p = 0.03
								CS/ID (p = <0.01)	p = 0.03
								CS/CdLS (p = <0.01)	p = 0.03
								CS/LS (p = <0.01)	p = 0.03
Speech	% Normal	32	56	47	46	73	77	CS/Autism (p = <0.001)	p = 0.03

	CHARGE	Autism	ID	CdLS	DS	LS	Comparison	Adj p
							CS/DS (p = 0.03)	p = 0.07
							CS/LS (p = 0.006)	p= 0.03

Note. N/S = No statistically significant differences were observed between the group with CHARGE syndrome and the other clinical groups under study. CS/LS = A significant difference between CHARGE syndrome and Lowe syndrome was found. CS/Autism = A significant difference between CHARGE syndrome and autism was found. CS/DS = A significant difference between CHARGE syndrome and Down syndrome was found. CS/CdLS = A significant difference between CHARGE syndrome and Cornelia de Lange syndrome was found.

Table 3.4 presents the participant characteristics for the CHARGE syndrome group and compares these with the pooled prevalence estimates calculated from the wider CHARGE literature through the meta-analysis in Chapter 2 (see section 2.4.4). Table 3.4 suggests that CHARGE syndrome participants in the present study displayed a similar range and prevalence of physical characteristics to that identified in the wider literature and, therefore, can be considered a representative sample of persons with CHARGE syndrome. Notable differences via visual inspection were lower rates of urinary tract and skeletal or limb abnormalities in the study sample.

Table 3.4

Characteristics of the Study Sample Compared to the Estimated Population Prevalence taken from Chapter 2

Criterion	**Study Sample (N = 26)**	**Estimated Population Prevalence**
Female	13 (52%)	NA
CHD7	25 (100%)	84%
Coloboma	22 (88%)	84%
Choanal Atresia	12 (44%)	51%
Anosmia	8 (28%)	39%
Facial Palsy	11 (44%)	46%
Feeding and Swallowing Difficulties	19 (76%)	80%

Criterion	Study Sample (N = 26)	Estimated Population Prevalence
External Ear Anomalies	19 (76%)	85%
Middle Ear Anomalies	13 (52%)	50%
Inner Ear Anomalies	17 (68%)	75%
Hearing Impairment	22 (88%)	87%
Heart Defects	20 (80%)	75%
Growth Deficiency	15 (60%)	66%
Genital Abnormalities	9 (36%)	20%
Urinary Tract Abnormalities	3 (12%)	54%
Cleft Lip or Palate	5 (20%)	15%
Tracheoesophageal fistula	3 (12%)	25%
Structural Brain Differences	8 (32%)	43%
Skeletal or Limb Abnormalities	3 (12%)	39%

3.3.1.4 Survey Procedure

Parents or caregivers of children with CS completed an online survey created using LimeSurvey or Qualtrics software or a hard copy sent through the post. The survey included an information sheet, consent documentation, and questionnaire measures. Additional questionnaire measures that were absent from the autism, ID, CdLS, DS, and LS datasets were included in the CHARGE Syndrome online survey.

3.3.2 Measures

A copy of each questionnaire is available in Appendix 3C. Measures fall into the following categories: behaviours that challenge and sleep, ability and mobility and putative correlates of behaviours that challenge (namely social communication, executive functioning, anxiety, depression and health).

3.3.2.1 Behaviours that Challenge and Sleep

3.3.2.1.1 Challenging Behaviour Questionnaire (CBQ; Hyman et al., 2002)

The CBQ assesses the severity and occurrence of self-injury, physical aggression, property destruction, and stereotyped behaviour in the past month. The CBQ examines eight types of self-injury adapted from (Bodfish et al., 1995). The severity of each behaviour is calculated by summing answers to the following three questions: 1) Duration of the longest episode in the past month, rated from 1 (less than a minute) to 5 (more than an hour): 2) Need for physical intervention in the past month, rated from 0 (never) to 5 (once an hour): 3) Estimated frequency of the behaviour's recurrence, ranging from 1 (once in the next month) to 5 (within the next 15 minutes). The CBQ shows good inter-rater reliability, with coefficients ranging from .75 to .92 in Cornelia de Lang syndrome (Hyman et al., 2002) and has been used with individuals with intellectual disability (Waite et al., 2017) SATB2 (Shelley et al., 2023) and Down syndrome (Moss et al., 2013). Stereotyped behaviour, characterised by non-goal-oriented repetitive motor movements, is common in individuals with autism and intellectual disabilities (Digennaro Reed et al., 2012). Historically, these behaviours were labelled as "challenging" due to their potential to interfere with learning and social interactions (Digennaro Reed et al., 2012). However, understanding of the functional aspect of stereotyped

behaviours has evolved. Recognising them as potential self-calming or self-stimulating mechanisms suggests that they might be more accurately described as coping strategies rather than “challenging” behaviours (Bolton, 2023). As such, this study did not include the stereotyped behaviour subscale when investigating behaviours that challenge, and instead considered stereotyped behaviours within the Repetitive Behaviour Questionnaire (see 3.3.2.7). In the CHARGE syndrome group the CBQ demonstrated acceptable to good internal consistence for presence (α = 0.79) and severity of behaviour (α = 0.80)

3.3.2.1.2 Modified Simonds and Parraga Sleep Questionnaire (MSPSQ; Simonds & Parraga, 1982)

Simonds and Parraga (1982) and Simonds and Parraga (1984) developed the sleep questionnaire that served as the basis for modifying the MSPSQ. This modified version has been expanded for individuals with intellectual and developmental disabilities (Wiggs & Stores, 1998). The MSPSQ includes 51 items, including qualitative and open-ended questions and ratings on a Likert-scale or yes/no format. The MSPSQ yields seven subscales: Bedtime-Resistance, Sleep onset Delay, Sleep Anxiety, Night Waking, Parasomnia, Sleep Disordered Breathing and Daytime Sleepiness. The MSPSQ has been validated for use with children with autism and children with intellectual disabilities. Sensitivity was .86 and specificity was .89 (Johnson et al., 2012). The MSPSQ has been successfully used in research with individuals with Wiedemann-Steiner syndrome (Bjornsson et al., 2022), Smith-Magenis syndrome, Angelman syndrome and autism (Trickett et al., 2018). The MSPSQ consists of seven subscales: Bedtime Resistance (α = 0.40), Sleep Onset Delay (consisting of one item), Sleep Anxiety (α = 0.33), Night waking (consisting of two items), Parasomnia (α = 0.72), Sleep Disordered Breathing (α = 0.80), Daytime Sleepiness (consists of two items) which showed

unacceptable to good internal consistency. The total score (α =0.75) achieved acceptable internal consistancy based on the CHARGE syndrome sample in the present study.

3.3.2.2 Ability and Mobility

3.3.2.2.1 Wessex Behaviour Scales (Wessex; Kushlick et al., 1973)

The Wessex is a 15-item informant questionnaire that yields five subscales: Continence, Mobility, Self-Help, Speech, and Literacy. The Self-Help subscale was used to measure adaptive functioning as a proxy for intellectual disability. The Wessex has good inter-rater reliability at subscale and item level when used with individuals with intellectual disability (Kushlick et al., 1973; Palmer & Jenkins, 1982) and has been used in research with individuals with severe intellectual disability (Ruddick et al., 2015) and with tuberous sclerosis complex (Eden et al., 2014). The Self-Help subscale, used in the present study, demonstrated good internal consistency (α = 0.84), while the total score showed similarly strong internal consistency (α = 0.89) for CHARGE syndrome.

3.3.2.2.2 Waisman Activities of Daily Living Scale (W-ADL; Maenner et al., 2013)

The W-ADL is a 17-item informant questionnaire designed to assess daily living skills. The W-ADL evaluates independence in three domains: caring for self, caring for the home, and living in the community. Items are rated using three descriptors: 'Independent', 'Does with help' or 'Does not do' scored 2, 1, and 0, respectively. The W-ADL yields a total score with a maximum value of 34. Cronbach's alpha for total scores indicated excellent internal consistency across multiple measurement occasions when assessed with individuals with developmental disabilities (0.90–0.94; Maenner et al., 2013). The W-ADL has been used in

research with individuals with fragile X syndrome (Thurman et al., 2022), attention deficit hyperactivity disorder and autism (Yerys et al., 2022). The total score, the metric used in the present study, achieved excellent (α = 0.94) internal consistence when assessed with the present sample of children with CHARGE syndrome.

3.2.2.3.Behavioural correlates

3.2.2.3.1 The Activity Questionnaire (TAQ; Burbidge et al., 2010)

The 18-item TAQ requires the informant to rate participant behaviours that correlate with overactivity and impulsivity on a five-point scale from 'Never / Almost Never' to 'Always / Almost all the time'. The TAQ yields three subscales: Overactivity, Impulsivity, and Impulsive Speech. Item level inter-rater reliability ranges from .31 to .75 (mean .56), and test-retest reliability ranges from .60 to .90 (mean .75). Inter-rater reliability and test-retest reliability subscale indices and total score exceed .70 when investigated among individuals with intellectual disability (Burbidge et al., 2010). This measure has been successfully used in research with individuals with rare genetic syndromes, including Angelman, Cri du Chat, Cornelia de Lang and Lowe syndromes (Oliver et al. (2011). Of the subscales used in the present study, internal consistency was good (α = 0.89) for the subscale Overactivity, and good for (α = 0.86) for the subscale Impulsivity when assessed with the sample of children with CHARGE syndrome in the present study.

3.2.2.3.2 The Repetitive Behaviour Questionnaire (RBQ; Moss et al., 2009)

The RBQ asks informants to answer 19 questions regarding the frequency of repetitive behaviours observed in the past month. Responses are given on a five-point scale, ranging

from ‘Never’ to ‘More than once a day.’ The RBQ yields five subscales: Stereotyped Behaviour, Compulsive Behaviour, Insistence on Sameness, Restricted Preferences and Repetitive Speech. The RBQ has good inter-rater reliability (range .46 to .80) and test-retest reliability (range .61 to .93) (Moss et al., 2009). Through this process the RBQ was validated for use with Angelman, Cornelia de Lang, Cri du Chat, fragile X, Prader-Willi, Lowe and Smith-Magenis syndromes. The RBQ is appropriate for use with verbal and non-verbal participants and with individuals with autism or with intellectual disability. The RBQ has been used in research with rare genetic conditions including Cornelia de Lang, Fragile X and Lowe syndromes (Moss et al. 2009). For the total score, the metric used in the present study, internal consistency was good ($\alpha = 0.84$) when assessed with the sample of CHARGE syndrome children used in the present study.

3.2.2.4 Social Communication

3.2.2.4.1 The Social Communication Questionnaire – Lifetime Version (SCQ; Berument et al., 1999)

The SCQ is a 40-item informant questionnaire designed to screen for autism. It is based on the Autism Diagnostic Interview and includes questions about the participant’s developmental history (Lord et al., 1994). The questionnaire yields three subscales: Communication, Social Interaction, and Repetitive and Stereotyped Patterns of Behaviour. A score of 15 or higher indicates the presence of autism, while a higher score of 22 differentiates participants with autism from those with other Pervasive Developmental Disorders. The SCQ demonstrates good concurrent validity with the autism Diagnostic Interview and the autism Diagnostic Observation Schedule (Howlin & Karpf, 2004) and adequate sensitivity (.71) and specificity

(.77) with individuals with intellectual disability and intellectual disability and autism (Whitney et al. 2013). The SCQ has been used in research with individuals with Down syndrome (Warner et al. 2017), Cornelia de Lange and Angelman syndromes (Moss et al. 2013). The total score was the metric used for the present study. Internal consistency for the SCQ total score was good (α = 0.89) for verbal children and also good (α = 0.88) for non verbal children when assessed with children with CHARGE syndrome.

3.2.2.5 Executive functioning

3.2.2.5.1 Behaviour Rating Inventory of Executive Function (BRIEF-P; Gioia et al., 2000)

The BRIEF-P is a 63-item questionnaire to assess executive functioning in typically developing children aged 2 to 5.11 years. Informants use a three-point Likert scale ('Never', 'Sometimes', 'Often'), with higher scores indicating greater difficulty. The BRIEF-P demonstrates good internal consistency (0.80 to 0.95) and test-retest reliability (0.78 to 0.90) when used with a sample with Down syndrome (Daunhauer et al., 2014). Although intended for children aged 2 to 5.11 years, the BRIEF-P has been used with children and adults with intellectual disabilities because its items align with developmental age (Daunhauer et al., 2014). The BRIEF-P has been used with children with neurodevelopmental conditions including attention deficit hyperactivity disorder and oppositional-defiant disorder (Ezpeleta et al. 2015) as well as rare genetic syndromes including Cornelia de Lang and Fragile X syndromes (Perry et al. 2022). When assessed using the present sample of children with CHARGE syndrome, internal consistency was excellent (α = 0.95).

3.2.2.5 Anxiety and Depression

3.2.2.5.1 Mood, Interest, and Pleasure Questionnaire – Short Form (MIPQ; Ross & Oliver, 2003)

Using a five-point Likert scale, the 25-item MIPQ requires informants to rate participants on behaviours that correlate with affect. The MIPQ yields two subscales and a total score. The Mood subscale contains 12 items, and the Interest and Pleasure subscale has 13 items. The MIPQ has good to excellent psychometric properties: inter-rater reliability of 0.76, test-retest reliability of 0.87, and intraclass correlation coefficient of 0.94 when used with individuals with severe or profound intellectual disability (Ross & Oliver, 2003). Lower scores indicate lower mood, interest, and pleasure. The MIPQ has been successfully used in research with individuals with Cornelia de Lang syndrome (Nelson et al. 2014) and individuals with severe and profound intellectual disabilities (Hayes et al. 2011). The Mood subscale used in the present study achieved adequate internal consistency ($\alpha = 0.75$) and the Interest and Pleasure achieved good internal consistency ($\alpha = 0.88$) when assessed using the present sample of children with CHARGE syndrome.

3.2.2.5.2 Anxiety Depression and Mood Scale (ADAMS; Esbensen et al., 2003)

The ADAMS is an informant-based measure that assesses 28 behaviours that correlate with anxiety, depression or mood. Behaviours are rated on a scale of 0, “not a problem”, to 3, “severe problem.” The ADAMS produces a total score and five subscale scores: manic/hyperactive behaviour, depressed mood, social avoidance, general anxiety, and compulsive behaviour. The ADAMS has high internal consistency and test retest reliability,

and interrater reliability was satisfactory when assessed with individuals with intellectual disability (Esbensen et al., 2003). The ADAMS has been successfully used in research with individuals with Prader-Willi (Schwartz et al. 2021) and Fragile X (Cordeiro, 2011) syndromes. The metric used in the present study was the total score. Internal consistency for the total score on the ADAMS was excellent (α = 0.91) when assessed with the sample of children with CHARGE syndrome used in the present study.

3.2.2.6 Health

3.2.2.6.1 Gastroesophageal Distress Questionnaire (GDQ; Oliver & Wilkie, 2005)

The 17-item GDQ requires informants to rate behaviours indicative of gastroesophageal reflux over the last two weeks on a 5-point Likert scale ranging from 'does not occur' to 'more than once an hour'. Scores indicating the presence of five daily symptoms of possible gastroesophageal reflux are considered clinically significant. The GDQ has been used with children with Smith-Magenis syndrome, Angelman syndrome, autism and tuberous sclerosis complex (Trickett et al. 2018). No psychometric analyses have been conducted for this measure to date. The metric used for the present study was the GDQ total score. Internal consistency for the total score was acceptable (α = 0.72) when assessed with the sample of children with CHARGE syndrome used in the present study.

3.2.2.6.1 The Health Questionnaire (HQ; Hall et al., 2008)

The HQ is an informant-based measure designed to assess the presence and severity of 15 health problems. The questionnaire asks about the occurrence (yes/no) and severity (0 = 'Never Occurred' to 3 = 'severe problem') of these health problems throughout the

participant's life and the last month. HQ scores are summed to obtain an overall health score and subscale scores for the presence and severity of health problems during the participant's life and the previous month. Mean item-level inter-rater reliability for health problems over the last month was substantial (0.76 (range 0.32-1.00) (Hall et al., 2008). Intraclass correlation coefficient for overall health score and the total number of health problems occurring over the last month was 0.65 and 0.73, respectively (Hall et al., 2008). Intraclass correlation coefficient scores for overall health and the total number of health problems occurring during the participant's life were 0.71 and 0.68, respectively (Hall et al., 2008). All psychometrics were undertaken with individuals with Cornelia de Lang syndrome. The HQ has been used to assess health in Pitt-Hopkins, Angelman and Cornelia de Lange syndromes (Watkins et al. 2019). The metric used in the present study was the presence of health problems ever in the participants life. This subscale had poor internal consistency ($\alpha = 0.50$) when assessed with the present sample of children with CHARGE syndrome.

Data were available for CHARGE Syndrome for all measures and data were available for the Wessex questionnaire and the CBQ for all comparison groups.

3.3.3 Data Analysis

3.3.3.1 Overview

Data were processed and analysed using R version 2023.03.0+386. The distribution of data was assessed using Shapiro-Wilk tests and visual inspection of QQ plots (Appendix 3B). Where data were normally distributed parametric tests were used, and where data was non-

normally distributed non-parametric tests were used. A significance level of < 0.05 was adopted throughout. Multiple comparisons were adjusted for in Objective 1 and 3 due to the detailed, item-level analysis, and multiple tests, increasing the risk of Type I errors. Multiple comparisons were adjusted for each family of tests (grouped by type and specific hypothesis addressed in each objective). Adjusting for multiple comparisons reduces the chance of Type I errors and increases the chance of Type II errors. Type II error may not identify true clinically relevant effects and this can lead to overlooking important findings (Bender & Lange, 2001). However, adjusting for multiple comparisons reduces the risk of false positive results and means that only the more robust effects are detected (Bender & Lange, 2001). The bootstrap correlation matrix (Objective 4) is exploratory and aims to find patterns in the data, not to test specific hypotheses. Therefore, adjusting for multiple comparisons was not necessary.

3.3.3.2 Objective 1, Cross Syndrome Comparison of Behaviours that Challenge

Data for the prevalence of behaviours that challenge (self-injury, aggression, and destruction of property) was taken for CHARGE syndrome and all comparison groups from the CBQ. Statistical analyses used Chi-Square tests, or, when one or more expected frequencies were below 5, Fishers Exact Test. The severity of self-injurious behaviour in children with CHARGE syndrome was compared to other clinical groups using t-tests for parametric data and Mann-Whitney U tests for non-parametric data. Only the severity of self-injurious behaviour was compared across the groups since this was the only severity metric available for autism, ID, CdLS, DS, and LS comparison groups.

3.3.3.3 Objective 2: Exploration of Sleep and Behaviours that Challenge

To detail and quantify the challenges children with CHARGE syndrome experience in relation to sleep, subscale scores from the MSPSQ (night waking, sleep anxiety, bedtime resistance, parasomnia, sleep disordered breathing, daytime sleepiness) and MSPSQ total score were standardised and plotted to facilitate visual comparison. To create standardised z-scores, means were transformed to zero and standard deviations to one. This allows for easier comparison across different subscales. To detail and quantify behaviours that challenge in children with CHARGE syndrome, mean severity scores and prevalence scores were calculated for types of self-injurious behaviour, aggressive behaviour, and destruction of property drawn from the CBQ.

3.3.3.4 Objective 3, Associations Between Ability Level, Sensory and Mobility Level on Sleep and Behaviours that Challenge.

To assess the potential impact of ability level, vision and hearing status, and mobility on sleep and behaviours that challenge for people with CHARGE syndrome, sleep data were sourced from the MSPSQ, data concerning challenging behaviours was taken from the CBQ, whilst data on ability, vision and hearing status, and mobility were drawn from the Wessex. ANOVA or Kruskal-Wallis analysis was employed to evaluate continuous variables. Categorical variables will be analysed using Chi-square test or Fishers Exact test.

3.3.3.5 Objective 4: Bootstrap Correlation Matrix

The study used a Bootstrap correlation matrix to explore associations between variables. The bootstrap correlation matrix was used because it is ideal for exploring data with a small sample size and many variables when there is no predefined hypothesis (Kim, 2002). Traditional correlation estimates can be unstable with small samples, but bootstrapping improves reliability by generating multiple resampled datasets to assess correlation variability.

To minimise the risk of overfitting, the number of variables was reduced by removing variables that likely measure the same underlying construct and prioritising subscales over total scores. Details of excluded variables can be found in Appendix 3D. The included variables are set out in Table 3.5.

Variables, taken from the CBQ, included self-injurious behaviour, aggression, and destruction of property. Sleep parameters were derived from the subscales of the MSPSQ. Further variables included in this matrix were self-help, mobility and speech taken from the Wessex, ability level as indicated by W-ADL, behavioural correlates of behaviours that challenge including repetitive behaviour from the RBQ, hyperactive behaviour derived from the TAQ. Social communication was taken from the SCQ, executive functioning taken from the BRIEF-P and depression and anxiety as taken from the MIPQ and the ADAMS respectively. The matrix also considers the HQ and GDQ health metrics.

Table 3. 5

Variables Included for Bootstrap Correlation Matrix Analysis

Measure	Variable
Wessex	Mobility
	Self-help
	Speech
W-ADL	Total Score
BRIEF-P	Inhibition
	Shift
	Emotional Control
	Working Memory
	Plan Organise
SCQ	Communication
	Restricted, Repetitive and Stereotyped
	Behaviours
	Reciprocal Social Interaction
TAQ	Impulsivity
	Overactivity
CBQ	Severity of Self-Injurious Behaviour
	Severity of Aggressive Behaviour
	Severity of Destruction of Property
RBQ	Stereotyped Behaviour
	Compulsive Behaviour
	Insistence on sameness

Measure	Variable
MIPQ	Mood
	Interest and Pleasure
ADAMS	Social Avoidance
	General Anxiety
GDQ	Total Score
MSPSQ	Bedtime-Resistance
	Sleep onset Delay
	Sleep Anxiety
	Night Waking
	Parasomnia
	Sleep Disordered Breathing
	Daytime Sleepiness
HQ	Severity of Health Problems Ever

Note. WESX = Wessex Behaviour Scales (Kushlicket al., 1973). W-ADL = Waisman Activities of Daily Living Scale (Maenner et al., 2013). BRIEF-P = Behaviour Rating Inventory of Executive Function (Gioia et al., 2000). SCQ = The Social Communication Questionnaire – Lifetime Version (Berument et al., 1999). TAQ = The Activity Questionnaire (Burbidge et al., 2010). Challenging Behaviour Questionnaire (Hyman et al., 2002). RBQ = The Repetitive Behaviour Questionnaire (Moss et al., 2009). MIPQ = Mood, Interest, and Pleasure Questionnaire – Short Form (Ross & Oliver, 2003). ADAMS = Anxiety Depression and Mood Scale (Esbensen et al., 2003). GDQ = Gastro-oesophageal Distress Questionnaire (Oliver & Wilkie, 2005). MSPSQ = Modified Simonds and Parraga Sleep (Simonds &

Parraga, 1982). HQ = The Health Questionnaire (Hall et al., 2008). HADS = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)

Bootstrap Correlation is a robust statistical method that produces multiple bootstrap samples through repeated extraction and replacement of data points from the original dataset. Generating many bootstrap samples enables the construction of correlation coefficient distributions. A correlation coefficient is then calculated for each bootstrap sample. A power analysis was conducted for the bootstrap correlation matrix (Cohen, 1992). A sample size of 30 was chosen with a power of 0.36 to detect medium correlations (0.3) and an alpha level of 0.05 (see Appendix 3E). The sample size of 30 was chosen after consideration of the rarity of CHARGE syndrome and anticipated challenges with recruitment.

3.4 Results

3.4.1 Objective 1: Cross Syndrome Comparison

In line with objective 1, individuals with autism, ID, CdLS, DS and LS were matched by chronological age and self-help score and then compared on the prevalence of self-injury, aggressive behaviour, and destruction of property. CBQ scores were unavailable for six participants with CHARGE syndrome. Final participant numbers for comparison of behaviours that challenge across the five clinical groups are as follows: CHARGE syndrome (20), autism (20), ID (14), CdLS (19), DS (19), LS (19).

3.4.1.1 Comparison of Behaviours that Challenge Across Clinical Groups

Figure 3.1 illustrates a comparison of syndrome profiles of the prevalence of self-injurious behaviour, aggressive behaviour, and property destruction across the syndrome groups. Statistical analyses using Chi-Square Test did not yield sufficient evidence to indicate differences in these behaviours among the groups studied. However, there was a trend for self-injurious behaviour to be more common in individuals with CHARGE syndrome compared to those with Down Syndrome ($p = 0.08$ following adjustment for multiple comparisons).

Figure 3. 1

Prevalence and 5% Error Bars of Behaviours that Challenge Across Clinical Groups: Chi-Squared Comparison with CHARGE Syndrome, Including Pre-Adjustment p-Values for Multiple Comparisons

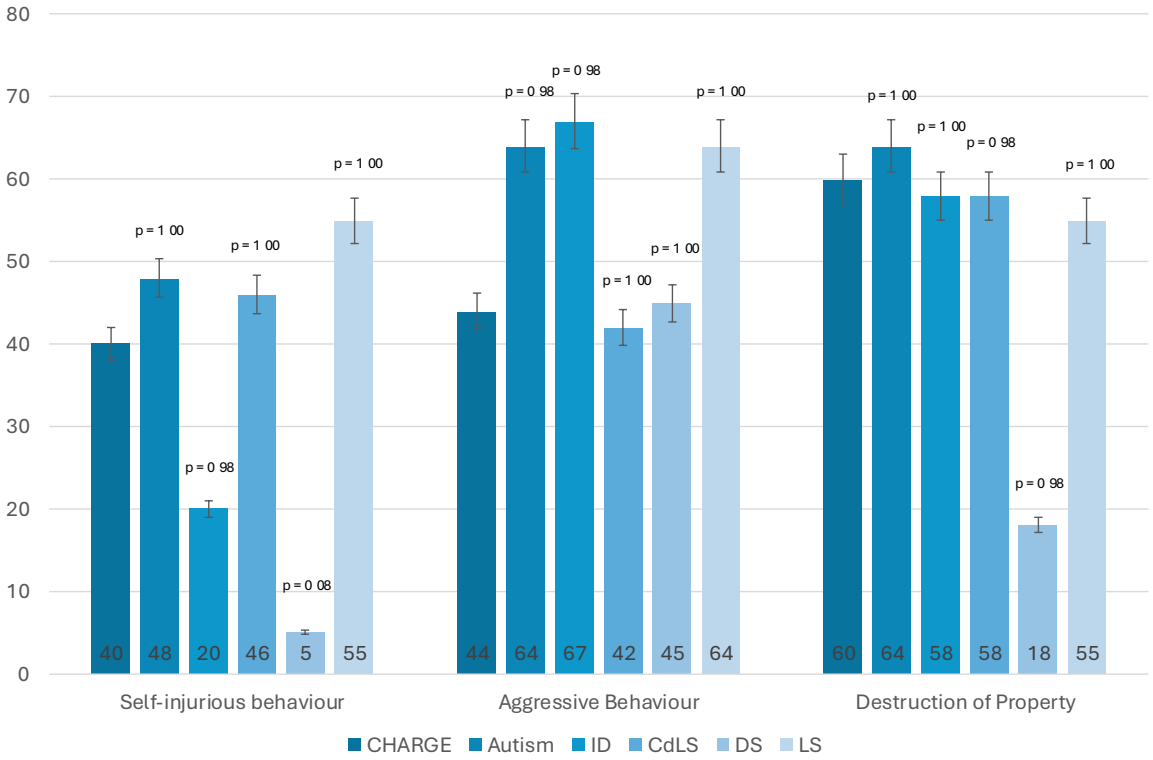


Table 3.6 shows that Mann-Whitney U tests were used to assess differences in the severity of self-injurious behaviour, as measured by the CBQ, between individuals with CHARGE syndrome and each clinical group. When CHARGE syndrome was compared to the other clinical groups (autism, ID, CdLS, DS, and LS), no significant differences were found.

Table 3. 6

Severity of self-injury between CHARGE syndrome and each clinical group

Group mean comparison	Mean Severity Score	Observed Statistic	*p*-value	Adj *p*-value
	CHARGE Syndrome: 15.8			
CHARGE Syndrome and Autism	Autism: 3.8	U = 85.5	0.09	0.45
CHARGE Syndrome and ID	ID: 11.5	U = 17	0.63	0.75
CHARGE Syndrome and CdLS	CdLS: 4.2	U = 47.5	0.43	0.75
CHARGE Syndrome and DS	DS: 12.0	U = 12	0.75	0.75
CHARGE Syndrome and LS	LS: 6.5	U = 65	0.77	0.75

In summary, while statistical analysis did not indicate significant differences between the syndrome profiles of self-injurious behaviour, aggressive behaviour, and destruction of property, or the syndrome profiles of severity of self-injurious behaviour a trend emerged. Specifically, a trend for self-injurious behaviour to be more common in individuals with CHARGE syndrome compared to those with Down Syndrome.

3.4.2 Objective 2.1: Exploration of Behaviour

There was no statistically significant association between age and self-injurious behaviour severity (ρ = 0.09, p = 0.68, adj p = 0.91). There was a significant difference between gender and self-injurious behaviour (U = 7.5, p = 0.40, adj p = 0.80) with females presenting with a higher mean score for self-injury (7.31) than males (5.25). Furthermore, to address the final part of objective 2, prevalence scores were calculated for types of self-injurious behaviour, aggressive behaviour, and destruction of property (see Figure 3.2) for children with CHARGE syndrome.

3.4.2.1 General Characteristics of Self-Injurious Behaviour

The mean severity score for children with CHARGE syndrome with self-Injury was 15.80 ranging from 0 to 60. The most common form of self-injurious behaviour was “Hit Self with Body Part,” shown by every child with CHARGE syndrome that reported self-injurious behaviour in the preceding month.

3.4.2.2 General Characteristics of Aggressive Behaviour

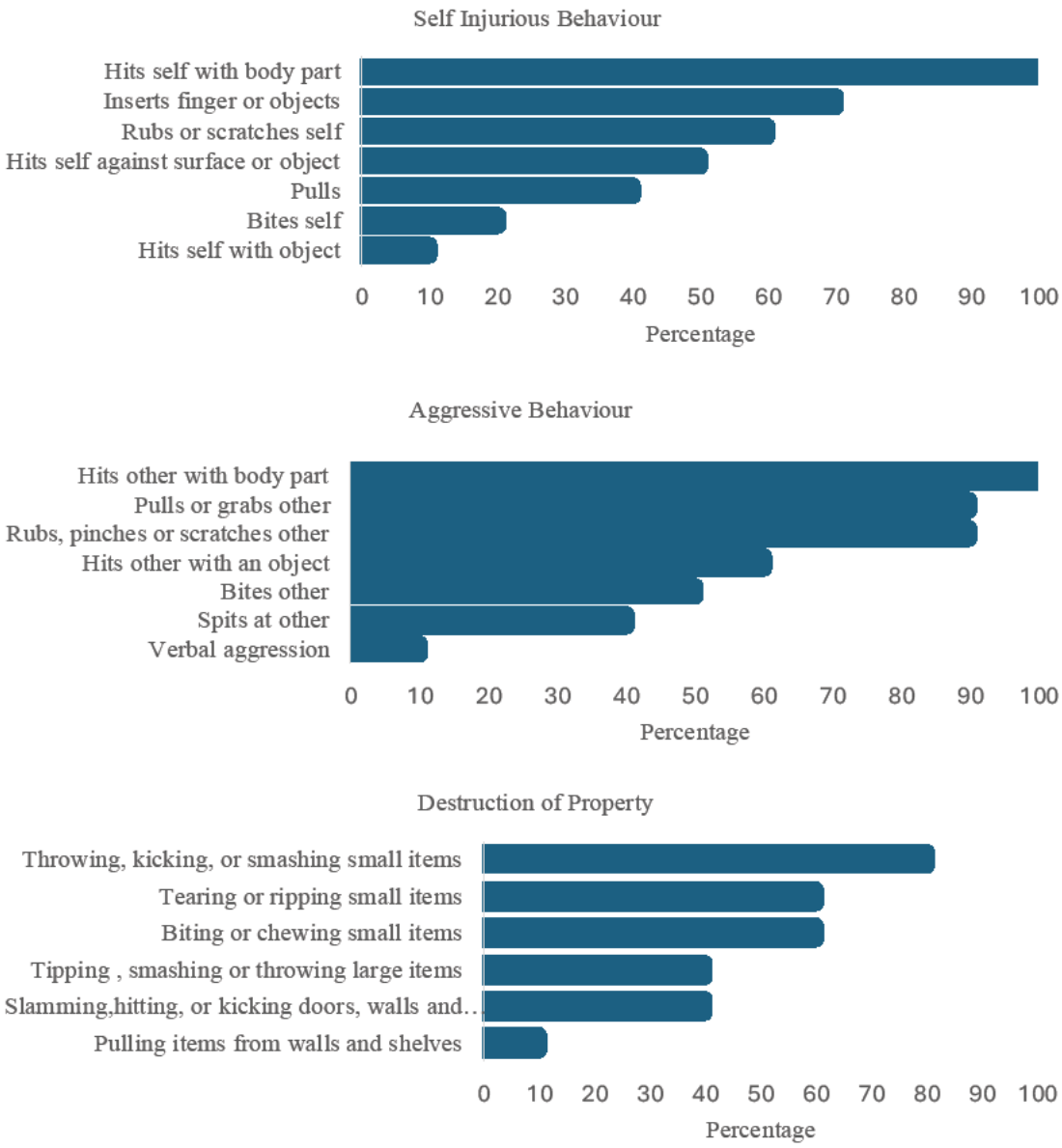
The mean severity score in the CHARGE syndrome cohort for Aggression was 20.09, ranging from 2 to 60. The most common form of Aggressive Behaviour was “Hit other with Body Part,” shown by every participant that reported Aggressive Behaviour in the preceding month.

3.4.2.3 General Characteristics of Destruction of Property

The mean severity score for Destruction of Property was 19.30, ranging from 3 to 45. The most common form of Destruction of Property was “Biting or chewing small items (e.g. books, clothing)” shown by 70% of participants that reported Destruction of Property in the preceding month.

Figure 3.2

Prevalence of behaviour types in CHARGE Syndrome



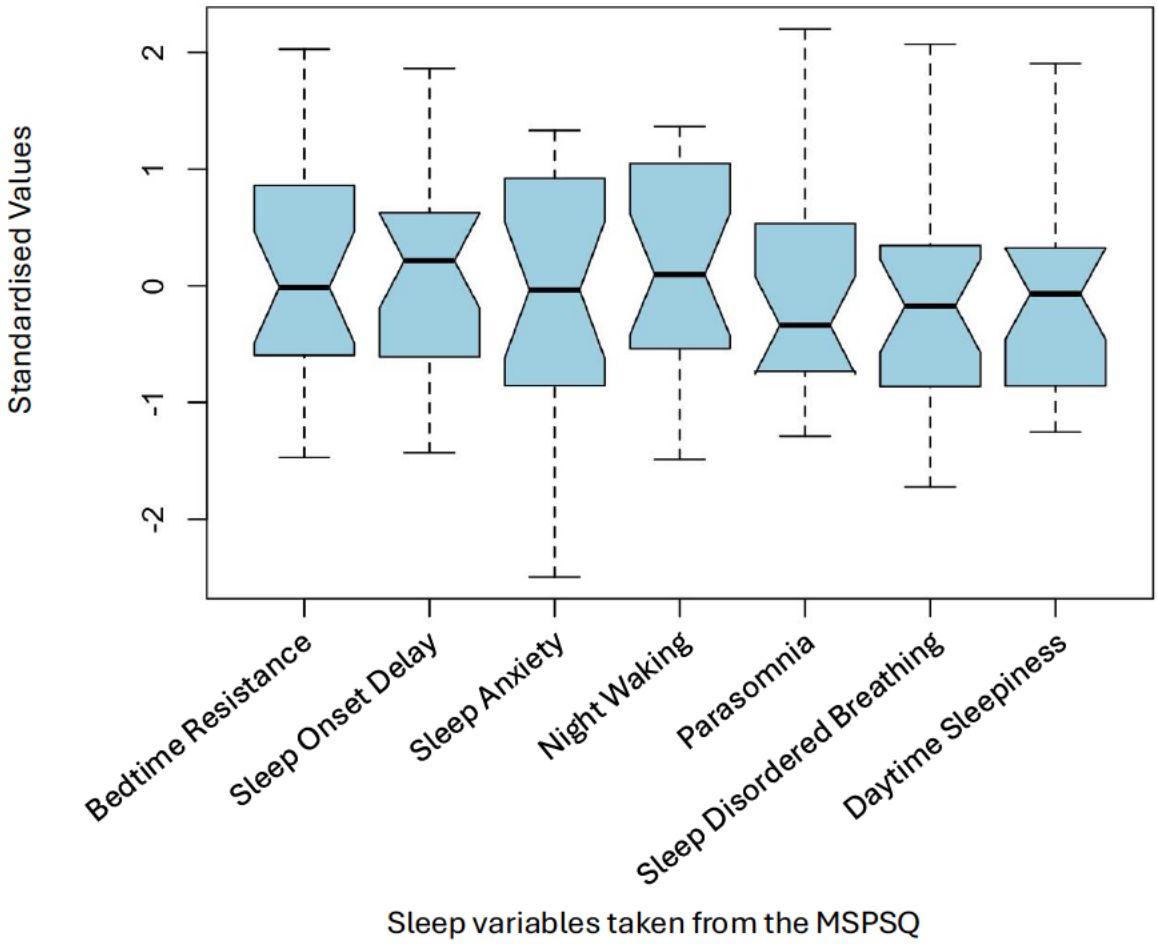
3.4.3 Objective 2.2: Exploration of Sleep

3.4.3.1 General Characteristics of Sleep Scores

There was no statistical association between age and MSPSQ total score (r = -0.01, p = 0.96, adj p = 0.96)) but there was an association between gender and MSPSQ total score (U = 92, p = <0.01, adj.p = 0.04). Males had a higher mean MSPSQ total score than females (78.27 and 67.92). Figure 3.3 illustrates the standardised sleep scores for the seven subscales of the MSPSQ. The highest standardised median score was Sleep Onset Delay (0.21); however, it also had wide confidence intervals (-1.43 to 1.86).

Figure 3. 3

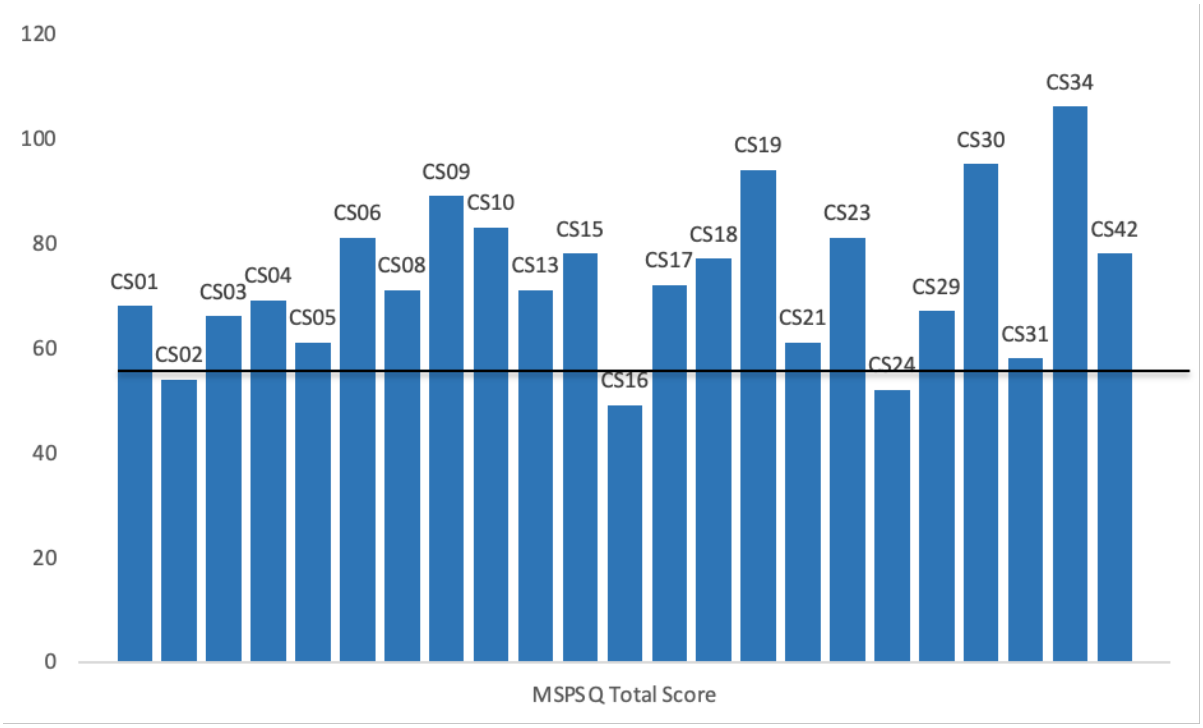
Boxplot of Standardised MSPSQ Sleep Parameter Subscales for the CHARGE syndrome group.



The MSPSQ has a clinical threshold of 56 as the cut-off point for identifying sleep disturbances based on the total MSPSQ score. Figure 3.4 illustrates that 87% of participants scored above this clinically significant range, indicating a high prevalence of sleep disturbances as assessed by the MSPSQ.

Figure 3. 4

Histogram of MSPSQ total scores per participants compared to the clinical cut-off for significant sleep disturbance. Clinical Cut-off of 56 is depicted by a horizontal line



3.4.3.2 Objective 2 Summary

Objective 2 aimed to quantify the challenges faced by children with CHARGE syndrome regarding behaviours that challenge and sleep. Regarding behaviours that challenge, the mean self-injury severity score was 15.8, with the most common behaviour being hits self with body part. Aggressive behaviour had a slightly higher average severity score (20.09), and the most predominant typography was hitting other with body part. For destruction of property, the severity was 19.30 on average, with 80% of participants reporting throwing, kicking or smashing small items. In terms of sleep, the MSPSQ sleep questionnaire revealed the most common sleep problem to be Sleep Onset Delay, with a diverse range of scores and the majority of participants scoring above the clinical cut off. Gender was also an important

factor with a significant difference between gender and severity of self-injury (self-injury was more severe in females) and gender and MSPSQ scores (MSPSQ scores were higher for males).

3.4.4 Objective 3: Associations Between Ability Level, Sensory and Mobility Factors on Sleep And Behaviours That Challenge

3.4.4.1 Sleep

Correlation analysis was used to evaluate objective 3, the potential influence of ability level, sensory and mobility factors on sleep. As presented in Table 3.7 results provided no statistically significant evidence for an association between the seven subscales of the MSPSQ (Night Waking, Sleep Anxiety, Bedtime Resistance, Parasomnia, Sleep Onset Delay, Sleep Disordered Breathing, Daytime Sleepiness), the MSPSQ total score, and the presence of WSX Self-Help, WSX Hearing and Vision Impairment, and WSX Mobility.

Table 3.7

Correlation analysis results for sleep variables across the predictor variables self-help, hearing and vision impairment and mobility

Variable 1	Variable 2	Correlation	p-value	Adj. P-value
Bedtime resistance	Self-help	$\rho = 0.33$	0.13	0.69
	Hearing and vision impairment	$r = 0.13$	0.54	0.93
	Mobility	$\rho = 0.09$	0.68	1.00
Sleep onset delay	Self-help	$\rho = -0.28$	0.20	0.69
	Hearing and vision impairment	$r = 0.19$	0.38	0.74

Variable 1	Variable 2	Correlation	p-value	Adj. P-value
Sleep anxiety	Mobility	ρ = 0.28	0.20	0.69
	Ability level	ρ = 0.22	0.31	0.74
	Hearing and vision impairment	r = -0.10	0.66	1.00
Night Waking	Mobility	ρ = 0.11	0.60	1.00
	Ability level	ρ = 0.34	0.12	0.69
	Hearing and vision impairment	ρ = -0.21	0.33	0.74
Parasomnia	Mobility	ρ = 0.24	0.26	0.73
	Ability level	ρ = -0.26	0.23	0.69
	Hearing and vision impairment	ρ = 0.40	0.06	0.63
Sleep Disordered Breathing	Mobility	ρ = -0.07	0.76	1.00
	Ability level	ρ = -0.26	0.23	0.69
	Hearing and vision impairment	ρ = -0.18	0.42	0.79
Daytime Sleepiness	Mobility	ρ = -0.31	0.14	0.69
	Ability level	ρ = 0.05	0.82	1.00
	Hearing and vision impairment	ρ = 0.17	0.45	0.81
	Mobility	ρ = 0.04	0.84	1.00

3.4.4.2 Behaviours that Challenge

Key findings are presented below for the potential associations between ability level, sensory, mobility factors, sleep and behaviour.

3.4.4.2.1 Self-Injurious Behaviour

Table 3.8 shows the associations between ability level, mobility and self-injurious behaviour. Following adjustment for multiple comparisons, there was a statistical association between ability level and self-injurious behaviour (p = <0.01). This indicates that less able children presented more often with self-injurious behaviour than more able children. Results also indicated that less mobile children were more likley to engage in self-injurious behaviour. However this finding did not hold after adjusting for multiple comparisons. It was not possible to investigate the association between mobility, ability level and hits self with body part because there was not enough variability in the data. Furthermore, a chi squared analysis could not be calculated for combined vision and hearing impairment and any of the self injury variables because all the children in the sample had poor vision and hearing impairment, resulting in no variability in the data.

Table 3.8

Associations between ability, mobility and combined vision and hearing impairment and the prevalence of self-injurious behaviour (SIB)

Variable	Test Statistic	p-value	Adj p-value
Ability level and SIB	Fishers Exact test	<0.01	0.23
Mobility and SIB	Fishers Exact test	<0.01	0.23
Ability level and Hits self with object	Fishers Exact test	1.00	1.00
Ability level and Bites self	Fishers Exact test	0.22	0.69
Ability level and Pulls	Fishers Exact test	1.00	1.00
Ability level and Rubs or scratches self	Fishers Exact test	1.00	1.00

Variable	Test Statistic	p-value	Adj p-value
Ability level and Inserts finger or objects	Fishers Exact test	0.07	0.63
Mobility and Hits self with object	Fishers Exact test	1.00	1.00
Mobility and Bites self	Fishers Exact test	1.00	1.00
Mobility and Pulls	Fishers Exact test	1.00	1.00
Mobility and Rubs or scratches self	Fishers Exact test	1.00	1.00
Mobility and Inserts finger or objects	Fishers Exact test	0.07	0.63

3.4.4.2.2 Aggressive Behaviour

Table 3.9 summarises the associations between ability level, mobility and aggressive behaviour in CHARGE syndrome. It was not possible to investigate the influence of combined vision and hearing impairment with aggression variables, mobility and Hits self with body part, or ability level and hits self with body part because there was not enough variability in this data. The remaining analysis showed no significant association between ability level, mobility and aggressive behaviour. This suggests that ability level and mobility may not influence aggressive behaviour.

Table 3.9

Associations between ability, mobility and combined vision and hearing impairment and aggressive behaviour

Variable	Test Statistic	p-value	Adj p-value
Ability level and aggression	Fishers Exact test	0.35	0.74
Mobility and aggression	Fishers Exact test	0.21	0.69
Ability level and Hits other with object	Fishers Exact test	1.00	1.00

Ability level and Bites other	Fishers Exact test	1.00	1.00
Ability level and Pulls or grabs other	Fishers Exact test	0.36	0.74
Ability level and Rubs, pinches or scratches other	Fishers Exact test	1.00	1.00
Ability level and Spits at other	Fishers Exact test	0.09	0.68
Mobility and Hits other with object	Fishers Exact test	1.00	1.00
Mobility and Bites other	Fishers Exact test	1.00	1.00
Mobility level and Pulls or grabs other	Fishers Exact test	0.36	0.74
Mobility and Rubs, pinches or scratches other	Fishers Exact test	1.00	1.00
Mobility and Spits at other	Fishers Exact test	0.36	0.74

3.4.4.2.3 Destruction of Property

Table 3.10 summarises the association between ability level, mobility, combined vision and hearing impairment, and destruction of property. After adjusting for multiple comparisons there was no significant association between these variables and destruction of property. This suggests that ability level, mobility and combined vision and hearing impairment may not influence destruction of property.

Table 3.10

Associations between ability, mobility and combined vision and hearing impairment and destruction of property.

Variable	Test Statistic	p-value	Adj p-value
Ability level and destruction of property	Fishers Exact test	0.56	1.00
Mobility and destruction of property	Fishers Exact test	0.70	1.00

Variable	Test Statistic	p-value	Adj p-value
Combined vision and hearing impairment and destruction of property	Fishers Exact test	0.70	1.00
Ability level and Biting or chewing small items	Fishers Exact test	0.52	1.00
Ability level and throwing, kicking, or smashing small items	Fishers Exact test	1.00	1.00
Ability level and tearing or ripping small items	Fishers Exact test	1.00	1.00
Ability level and Slamming, hitting, or kicking doors, walls or windows	Fishers Exact test	0.52	1.00
Ability level and Tipping, smashing or throwing large items	Fishers Exact test	0.52	1.00
Mobility and Biting or chewing small items	Fishers Exact test	0.52	1.00
Mobility and throwing, kicking, or smashing small items	Fishers Exact test	1.00	1.00
Mobility and tearing or ripping small items	Fishers Exact test	1.00	1.00
Mobility and Slamming, hitting, or kicking doors, walls or windows	Fishers Exact test	0.52	1.00
Mobility and Tipping, smashing or throwing large items	Fishers Exact test	0.52	1.00
Combined vision and hearing impairment and Biting or chewing small items	Fishers Exact test	0.40	1.00
Combined vision and hearing impairment and throwing, kicking, or smashing small items	Fishers Exact test	0.30	1.00
Combined vision and hearing impairment and tearing or ripping small items	Fishers Exact test	1.00	1.00
Combined vision and hearing impairment and Slamming, hitting, or kicking doors, walls or windows	Fishers Exact test	1.00	1.00

Variable	Test Statistic	p-value	Adj p-value
Combined vision and hearing impairment and Tipping, smashing or throwing large items	Fishers Exact test	1.00	1.00

3.4.4.3 Objective 3 Summary

Objective 3 explored the influence of ability level, sensory, and mobility factors on sleep and behaviours that challenge. The MSPSQ sleep questionnaire revealed no significant associations between these factors and the MSPSQ subscales. More able children were statistically less likely to engage in self-injurious behaviour and there was a significant association in which mobile children were less likely to engage in self-injurious behaviour. However, this association was not statistically significant following adjustment for multiple comparisons. There was no significant association between ability, mobility and combined vision and hearing impairment and aggressive behaviour or destruction of property.

3.4.5 Objective 4: To Explore How Behaviours that Challenge, and Sleep Issues Might be Associated with Other Physical, Behavioural and Sleep Difficulties.

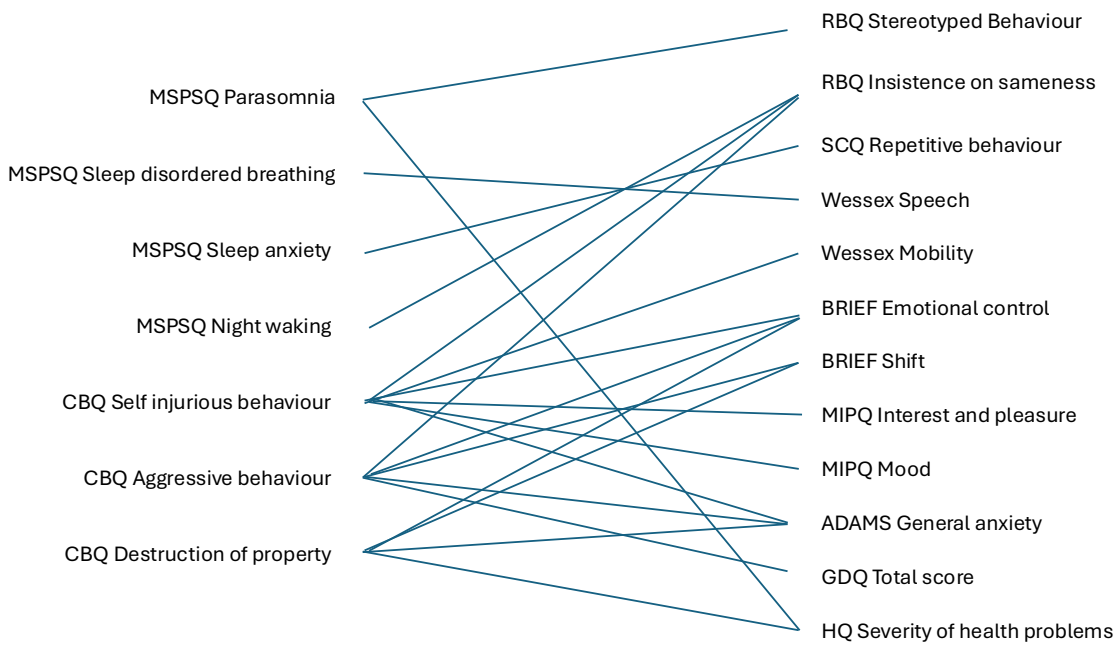
To address objective 4, which is to explore how behaviours that challenge and sleep issues might be associated with other physical, behavioural and sleep difficulties, a bootstrap correlation matrix analysis was run with 1000 replications.

Figure 3.5 displays the significant correlations between different CBQ severity subscale variables and MSPSQ subscales with a correlation coefficient of 0.5 or higher. Each line represents a correlation between two variables. All variables correlated positively with the exception of the following: CBQ self-injurious behaviour and MIPQ mood, Wesex mobility

and CBQ self-injurious behaviour, and self-injurious behaviour and MIPQ interest and pleasure. The most frequent correlates of behaviours that challenge (CBQ severity of aggression, destruction of property and self-injurious behaviour) were difficulties with executive functioning, specifically shift and emotional control in addition to general anxiety and insistence on sameness. Bedtime resistance, night waking and sleep anxiety all correlated positively with restrictive and repetitive behaviour ($r = 0.62$ $p = <0.01$, $r = 0.58$ $p = <0.01$, and $r = 0.58$ $p = <0.01$ respectively). Parasomnia correlated positively with the severity of health conditions over the lifespan ($r = 0.59$, $p = 0.01$) and stereotyped behaviour ($r = 0.50$, $p = <0.01$). Details of the final correlations shown in Figure 3.5 are in Appendix 3F.

Figure 3. 5

Bootstrap Correlation Final Results



3.4.5.1 Objective 5 Summary

While the bootstrap correlation matrix was not adjusted for multiple comparisons, and results should be interpreted with caution. There are a number or statistically significant correlations of moderate or strong strength. There are correlations between behaviours that challenge, anxiety, executive functioning, health variables and mobility. Sleep variables correlate with repetitive and stereotyped behaviour and health. Understanding these correlations can help in identifying and addressing the putative contributionsto behaviours that challenge and sleep problems in children with CHARGE syndrome.

3.5 Discussion

3.5.1 Comparative Analysis of Behaviours that Challenge

The study's first objective was to compare the prevalence and severity of behaviours that challenge. These behaviours include self-injury, aggression, and destruction of property. A comparison was made between CHARGE syndrome, autism, CdLS, DS, LS and ID. There was no statistically significant difference between these groups on the prevalence of self-injurious behaviour, aggressive behaviour or destruction of property, or on the severity of self-injurious behaviour. However, a trend emerged. There was a trend towards self-injurious behaviour being more prevalent for children with CHARGE syndrome than those with DS. This suggests that individuals with CHARGE syndrome may be at a higher risk of self-injurious behaviour than those with DS, and at equivocally high risk to those with CdLS, LS, ID and autism. Given that self-injurious behaviour is similarly prevalent in CdLS (25%-64%; Mulder et al., 2017) autism (42%; Steenfeldt-Kristensen et al., 2020) and CHARGE syndrome (44% section 2.4.7), it is possible that established interventions for CdLS and autism provide

a useful starting point for addressing self-injurious behaviour in children with CHARGE syndrome. More specifically, functionally derived assessments and interventions should be consideredline (Biswas et al., 2023).

3.5.2 Sleep Disturbances in CHARGE Syndrome

Objective 2 sought to detail and quantify the sleep and behavioural challenges experienced by people with CHARGE syndrome. Concordant with Kennert et al.'s (2020) 93% prevalence rate, this study found that 87% of participants scored above the clinical cut-off for significant sleep disturbance on the MSPSQ. The most significant sleep problem was sleep onset delay, indicating that individuals with CHARGE syndrome often experience difficulties falling asleep. This finding aligns with Hartshorne et al. (2009) and Kennert et al. (2020), who highlighted difficulties initiating and maintaining sleep as particularly problematic in CHARGE syndrome. These findings highlight the importance of addressing sleep-related problems in this population. A number of interventions have been successful in supporting sleep onset in people with intellectual disability including the use of melatonin, optimal scheduling, stimulus control and sleep hygiene (Priday et al., 2017).

Furthermore, the MSPSQ total score was independent of age. This is interesting given that sleep requirements vary across developmental stages (Paruthi et al., 2016). It would be of value to explore whether this pattern persists into adulthood, and how early intervention might alter this association. Total MSPSQ scores were higher for males than for females. It is unclear whether there are any gender differences in CHARGE syndrome. Sleep scores may reflect differences in other areas of life, such as hyperactivity, pain, and challenging behavior,

which were beyond the scope of this study. It was also interesting to note that none of the sub sections of the MSPSQ correlated with self-help, vison and hearing, or mobility. While speculation should be approached cautiously, this finding raises the possibility that sleep difficulties may form part of the behavioural phenotype of children with CHARGE syndrome.

3.5.3 Behaviours that Challenge in CHARGE Syndrome

In terms of behaviours that challenge, the study identified common types of self-injurious behaviour, aggressive behaviour, and destruction of property. All informants who reported self-injury endorsed self-hitting with body parts while hitting others with body parts was reported for all participants exhibiting aggressive behaviour. These behaviours differ from the hand biting of Fragile X syndrome or skin picking in Prader–Willi syndrome (Oliver et al., 2013). Understanding the specific behaviours individuals with CHARGE syndrome engage in provides the basis for causal models that can be used to inform targeted interventions and support strategies.

There was a statistically significant association between gender and self-injurious behaviour, suggesting that girls engage in more serious self-injurious behaviour than boys. Among children with intellectual disabilities there has been no difference found between gender and the presence of self-injurious behaviour (Furniss & Biswas, 2012). However, these observations highlight the complex interplay between gender and behaviour. This is likely associated with a combination of factors including biological, social, and psychological factors, however the results should be interpreted cautiously given the small sample. Future research could look into the potentially dynamic factors associated with gender in children

with CHARGE syndrome that are not seen in children with intellectual disability of heterogeneous aetiology.

Additionally, no statistically significant differences were identified between the severity of self-injurious behaviour and age. This is concerning given that such behaviours can be extremely persistent in other neurodevelopmental conditions (Laverty et al., 2020). There could be several reasons for why age and severity of self-injurious behaivour do not correlate. For example, it could be that environmental triggers are consistent, or that self-injurious behaviour could be part of the CHARGE syndrome childhood phenotype. However, it is essential to interpret these findings cautiously due to the limited sample size. Future research involving larger cohorts of children with CHARGE syndrome is necessary to validate these results.

3.5.4 Impact of Ability Level, Vision and Hearing Status and Mobility on Sleep and Behaviour

Objective 3 aimed to assess how ability level, vision and hearing status, and mobility could impact sleep patterns and challenging behaviours. The study revealed that self-injurious behaviour was less common in children with higher ability scores than those with lower self-help scores . This supports section 1.7.2, where challenging behaviours are more typically associated with more severe levels of intellectual disability (Hill & Furniss, 2006; McClintock et al., 2003). However, there were no further associations between self-injurious behaviour, aggressive behaviour, destruction of property, and ability, mobility or combined vision and hearing impairment.

3.5.5 Correlation Matrix

Furthermore, objective 4 used a correlation matrix to examine potential associations between challenging behaviours, sleep difficulties, and other physical and behavioural difficulties. While the study did uncover several correlations, these findings should not be overinterpreted.

Behaviours that challenge were associated with challenges in executive functioning. More specifically, self-injurious behaviour, aggressive behaviour and destruction of property correlate with BRIEF emotional control and aggressive behaviour and destruction of property correlate positively with BRIEF shift. This supports the work of Hartshorne et al. (2007) whose data suggested that executive functioning difficulties may be associated with behaviours that challenge. Hartshorne et al. (2017) suggest supporting children with CHARGE syndrome with emotional regulation can improve behaviours that challenge.

Furthermore, self-injurious behaviour in the present study correlated negatively with Wessex mobility. As such, the less mobile a child were more likely to engage in self-injurious behaviour. This finding supports the work of Hartshorne and Cypher (2004) who found an association between later age of walking and more behaviours that challenge. This result highlights a potentially important area for future research, and it would be valuable for other researchers to explore this relationship further.

Behaviours that challenge correlated positively with ADAMS general anxiety. This finding is interesting given that Hartshorne et al. (2017) suggests that behavioural challenges in CHARGE syndrome may be caused by a combination of pain, sensory issues and anxiety that can be improved through interventions targeted at behaviour regulation. Interventions aimed at improving executive functioning could be beneficial, leading to broader positive outcomes for children with CHARGE syndrome.

An interesting finding from the correlation matrix was that sleep disordered breathing positively correlated with Wessex speech. As both sleep disordered breathing (MacLean, et al. 2009) and delayed speech (Timmons et al., 2001) are associated with cleft lip, listed as a characteristic of CHARGE syndrome (Blake 1998) cleft lip may be the latent variable.

It is notable that parasomnia correlated positively with health difficulties across the lifetime and stereotyped behaviour. It is possible that there is an association with health difficulties causing pain and pain impacting sleep (Stratton & Hartshorne, 2019). However, as greater intellectual disability is associated with increased stereotyped behaviour (Moss et al., 2009) and increased health burden (Liaoi et al., 2021) and poorer sleep quality (Surtees et al., 2018) the underlying latent factor with both of these associations might be severity of intellectual disability. While the present study was not sufficiently powered to examine these potential associations, future studies with larger samples might usefully investigate this.

Sleep anxiety, night waking and parasomnia correlated positively with SCQ repetitive behaviour, RBQ insistence on sameness and RBQ stereotyped behaviour respectively. All of

these are associated with CHARGE syndrome, deaf-blindness and autism (Hartshorn et al. 2005). This suggests that some of the sleep interventions used for autistic or deaf-blind children may be suitable for children with CHARGE syndrome. For example, melatonin therapy, behavioral interventions, parent education programs.

3.5.6 Limitations

The sample for the present study consisted of only children. The decision to only recruit children was pragmatic. Recruiting children led to a more harmonious group without compromising the sample with adults. I note that the most recent update to the diagnostic criteria was in 2005 (Verloes 2005). As such, if the study was undertaken in 2024, participants who were 19 or older would have been diagnosed using one of the earlier algorithms. While these algorithms are not incorrect, they do vary, and this introduces variability. Also of note is the behaviour and sleep variables in the present study were independent of age. It is important to find out whether this pattern persists into adulthood.

The matching process shaped the samples used in the study. For instance, the Down syndrome group had a higher proportion of children that engaged in behaviours that challenge, and the Cornelia de Lange group had higher self-help scores after matching took place. The CHARGE syndrome group were also affected by the matching process. Matching saw the exclusion of younger children, those with higher self-help scores and those who engaged in behaviours that challenge. Ultimately, the matching process may have affected the generalisability of the study.

Additionally, the matching process may have influenced the internal consistency of each group and the observed differences between the CHARGE syndrome and respective comparison groups. The groups were matched on the variables age and self-help. Matching to these variables meant that the autism group showed higher rates of property destruction in the final sample, and the Down syndrome group showed elevated self-help scores. Seeing how the matching process can bias sample composition it is important not to draw broad conclusions about the behavioural and sleep variables of interest.

There were also differences when matching children with CHARGE syndrome with children from other clinical groups on the variable's mobility, vision, hearing and speech. Significantly more children with autism and DS than children with CHARGE syndrome were fully mobile. Delayed mobility in CHARGE syndrome is associated with vestibular difficulties, increased number of medical conditions, poorer vision, delayed speech development, and increasing frequency of behaviours that challenge (Hartshorne and Cypher, 2004; Hartshorne, Grialou and Parker (2005); Hartshorne, Hefner & Davenport, 2005; Salem-Hartshorne and Jacob, 2005). This highlights the additional challenges faced by children with CHARGE syndrome in achieving full mobility, which are less common or less severe in children with autism or children with DS.

As expected, children with CHARGE syndrome had significantly poorer vision than autistic children or children with DS. Children with CHARGE syndrome also had poorer hearing than autistic children, children with CdLS, LS and ID. Increasing vision and hearing impairment are associated with poorer outcomes, including a heightened risk of behaviours

that challenge (Brown 2005). As such, the group with CHARGE syndrome may have been at a greater risk of behaviours that challenge than autistic children, children with DS, CdLS, LS and ID. However, it is notable that differences in behaviours that challenge between these groups, other than self-injury in DS, were not statistically different.

It is noteworthy that due to transparency in recruitment materials parents were aware that the study was a study of behaviour in CHARGE syndrome. Given this, parents whose children were experiencing behavioural challenges were likely be more motivated to participate in the study. This, therefore, should be considered when interpreting the findings. The studies that the comparison groups were initially recruited to had a similarly transparent recruitment process and were subject to the same bias. It is also notable that the questionnaires used were validated for individuals with intellectual disability. However, after assessing the questionnaires for internal validity it was found that two-thirds demonstrated good to excellent internal validity.

There were potential limitations in the recruitment of participants. The study was conducted from December 2020 to November 2021. This corresponds with the COVID lockdown in the UK of March 2020. COVID restrictions varied in terms of restrictions and duration for individuals who were medically vulnerable and those who were not. The pandemic caused considerable anxiety for parents whose children faced a potentially life-threatening disease when their immune system is already compromised (Theodoropoulos, 2003). Children with neurodevelopmental conditions can find change difficult and this may have been compounded by COVID restrictions (Masi et al., 2021). As such, it is probable that

the CHARGE syndrome group in the present study were experiencing disproportionally more challenges that families in the other five groups. This is likely to have impacted all of the questionnaires, with higher scores for behaviour, anxiety, depression, health variables, executive and social functioning.

A correlation matrix was used in objective 4 to examine potential associations between challenging behaviours, sleep issues, and other physical and behavioural difficulties. While the study revealed several correlations, it is crucial to note that correlation does not imply causation. Despite this, the comparison of CHARGE syndrome in this study is one of the most comprehensive and is an important starting point for understanding CHARGE syndrome. The use of questionnaires tailored for individuals with intellectual disabilities adds to its overall quality.

Regarding the bootstrap correlation matrix, a decision was made not to adjust for multiple comparisons. By not adjusting for multiple comparisons the chance of Type I error is increased. This can lead to misleading results and over-reporting. This limits the reliability of individual findings and means results should be interpreted cautiously, focusing on broader patterns rather than specific values.

A sample size of 30 with a power of 0.36 was chosen for the study. This was a practical decision given that CHARGE is a rare syndrome, and we anticipated challenges with recruitment given the COVID pandemic. While the proposed sample size left the study

underpowered, it was noted that the study was exploratory and that the results would offer an initial insight into this rare genetic syndrome. A correlation matrix was used to handle the small sample size and the non-parametric nature of the data, allowing for more flexible analysis. However, the sample used in this chapter of the thesis was 25, and this further reduced the power of the analysis. As such results should be interpreted with caution. However there have been a number of influential studies that have used small studies investigating rare genetic syndromes including KGB (Murray et al. 2017), Smith-Magenis (Martin et al. 2006) and Angelman syndromes (Agar et al. 2020). Future studies with larger samples are essential to validate these preliminary findings and better understand the relationships between sleep and behaviour in CHARGE syndrome.

Psychometric properties were available for all measures for intellectual disability, but only internal consistency was available for CHARGE syndrome. It is notable that the internal consistency for the MSPSQ subscales, Bedtime Resistance and Sleep Anxiety, were poor and inadequate respectively. While the MSPSQ is validated with children with intellectual disabilities, the heterogeneity in CHARGE syndrome may not align with constructs assessed in the general intellectual disability population. A sample of children with intellectual disability are likely to be more homogenous than a sample with CHARGE syndrome leading to higher internal consistency for the same measure. Furthermore, questionnaires designed for children with intellectual disability may not be suitable for children with CHARGE syndrome because of their sensory differences. Children with CHARGE syndrome may interact differently with their environment. As such, this can lead to inconsistency in responses and lower internal consistency. Finally, children with CHARGE syndrome face unique stressors and this may be reflected in qualitatively different behaviours when compared to children

with intellectual disability. As such, items on a questionnaire may behave differently for these two groups.

3.5.7 Conclusion

In conclusion, this study provided valuable insight into the severity and prevalence of behaviours that challenge. The study focuses on comparing the prevalence and severity of self-injurious behaviour between CHARGE syndrome, autism, CdLS, DS and LS. There was no statistical association between CHARGE syndrome, CdLS, DS or LS on the severity or prevalence of self-injurious behaviour. This finding is important because it means that CHARGE syndrome has an equivocal prevalence and severity of self-injurious behaviour to autism and CdLS in whose self-injurious behaviour is prevalent (Steenfeldt-Kristensenand et al., 2020; Oliver et al., 2009). The study also explored sleep, and the results reaffirmed that disturbed sleep is problematic for children with CHARGE syndrome. The correlations observed between behaviours that challenge and sleep disturbances, and executive functioning, repetitive behaviour, anxiety, mood, repetitive behaviour, health, mobility and speech provide a starting point for understanding the complex interplay between these variables in CHARGE syndrome.

CHAPTER FOUR

SLEEP IN CHILDREN WITH CHARGE SYNDROME

4.1 Preface

Sleep in CHARGE syndrome was examined in Chapters 2 and 3. Chapter 2 used meta-analysis to delineate a 45% prevalence of sleep disturbances in CHARGE syndrome. However, studies predominantly used unvalidated questionnaires or single-question assessments within questionnaires. Chapter 3 addressed this limitation using a validated questionnaire designed for persons with an intellectual disability. Results indicated 87% of participants with CHARGE scored above the clinical cut-off for significant sleep disturbances. Chapter 4 uses subjective and objective methods to better understand sleep in CHARGE syndrome. Subjective methods include the use of sleep diaries and questionnaires, whereas objective assessments include the use of wrist-worn activity monitors. The term "subjective methods" refers to assessments that rely on the perspective of the informant, rather than reflecting the experiences or perceptions of the individual being reported on.

4.2 Introduction

Sleep incorporates behavioural and physiological processes. Behaviourally, sleep is a reversible, recurrent state of reduced cognitive function, mobility, and responsiveness to external stimuli (Siegel, 2005). Physiologically, sleep is monitored and assessed through the use of electroencephalogram (EEG), electrooculography (EOG), and electromyography (EMG) measurements (Helfand et al., 1986). These tools classify sleep into two main phases:

non-rapid eye movement and rapid eye movement. These sleep phases alternate in cycles during sleep (Aserinsky & Kleitman, 1955). To understand sleep, it is also important to understand the circadian rhythm. The circadian rhythm is an internal process that regulates the sleep-wake cycle and is controlled by a "master clock" located in the suprachiasmatic nuclei (Chokroverty, 2010). The requirement for sleep changes as the central nervous system matures, and it is also shaped by neurological, environmental, and genetic factors and co-morbid conditions. These factors contribute to the dynamic nature of sleep patterns throughout a person's life (Chokroverty, 2010).

The requirement for sleep varies across the lifespan, particularly during childhood. The American Academy of Sleep Medicine (AASM) has developed consensus recommendations about the amount of sleep needed for optimal health at different ages (see Table 4.1; Paruthi et al., 2016). These guidelines show the changing sleep needs as children grow and develop. They highlight the complexity and significance of sleep across the lifespan and emphasise the importance of adopting a developmental perspective when studying sleep, as sleep needs follow a predictable developmental trajectory at a population level.

Table 4. 1

The American Academy of Sleep Medicine consensus recommendations for children's sleep

Age group	Age range	Recommended hours of sleep including any naps
Infants	4-12 months	12 to 16 hours
Toddlers	1-2 years	11 to 14 hours
Preschool	3-5 years	10 to 14 hours
Children	6-12 years	9 to 12 hours
Teenagers	13-18 years	8 to 10 hours

Age group	Age range	Recommended hours of sleep including any naps

4.2.1 Sleep disorders and sleep disturbances

Sleep research includes research on sleep disorders and research on sleep disturbances. Sleep disorders are a taxonomy of conditions that affect sleep quality, timing, and duration (American Academy of Sleep Medicine, 2023). Medical, psychological, or environmental issues can cause sleep disorders. Examples of sleep disorders include insomnia, restless legs syndrome, parasomnias, and bruxism (Tooth grinding; American Academy of Sleep Medicine, 2023). Conversely, sleep disturbance is an umbrella term for any interruption or disruption to the typical sleep pattern. This may include the behavioural outcome of a sleep disorder or short-term disturbances in sleep patterns or parameters (Chokroverty, 2009). Sleep disorders and disturbances can result in sleep deprivation. This can lead to short- and long-term consequences, such as impaired concentration, heart disease risk, and memory problems (Chokroverty, 2010).

The growing field of sleep disorder research is increasingly looking at how poor sleep may affect people with intellectual disabilities. Individuals with intellectual disabilities experience more intense and enduring sleep disturbances than those without intellectual disabilities (Surtees et al., 2018), with the prevalence of sleep disturbance in intellectual disabilities ranging from 13% to 86% (Didden & Sigafoos, 2001; see section 1.1.4). The heightened prevalence of sleep disturbance is likely driven by multiple factors, including behaviours that challenge, physical health and undiagnosed pain and concomitant sensory and psychiatric conditions (see sections 1.1.2 to 1.1.7).

In addition to research on sleep disturbance, a greater consideration of circadian rhythm abnormalities is crucial in children with intellectual disabilities. For example, in Smith-Magenis syndrome, known shifts in circadian rhythm can lead to daytime sleepiness, which affect mood and behaviour (Trickett et al., 2020), demonstrating that circadian rhythm alteration may be a viable and effective intervention target to affect mood and behaviour. For people with intellectual disabilities, already facing challenges with co-occurring neurodevelopmental and mental health diagnosis (section 1.1.14.6), physical conditions and pain experiences (section 1.14.2-3), atypical sleep-wake patterns and subsequent daytime sleepiness can exacerbate these problems (Trickett et al., 2020). As such, understanding and addressing circadian rhythm abnormalities could lead to targeted treatments that improve the lives of affected individuals.

4.2.2 Methods for Assessing Sleep in People with Intellectual Disabilities

Sleep assessment for individuals with intellectual disabilities requires a combination of objective and subjective methods, each providing unique perspectives on various aspects of sleep (O'Sullivan et al., 2023). Objective methods for assessing sleep quality include polysomnography, electrocardiography and actigraphy. Polysomnography (PSG) uses an electroencephalogram (EEG) to measure brain activity, an electrooculogram (EOG) to monitor eye movements, and an electromyogram (EMG) to assess muscle activity. It also records oxygen saturation and heart rate (Xu & Lian, 2022). Similarly, electrocardiography captures heart rate, rhythm, and other cardiac electrical activities, including possible arrhythmias and ischemia (Xu & Lian, 2022).

While PSG thoroughly evaluates sleep quality, the method can be invasive as it involves the placement of multiple sensors and electrodes on the patients body which can be uncomfortable and disrupt normal sleep patterns. This invasiveness can make PSG particularly challenging for children with intellectual disabilities to tolerate (Lanzlinger et al., 2023). Additionally, PSG tends to be limited in duration, typically spanning 1-2 nights in a clinical environment. This temporal constraint can fail to capture naturalistic habitual sleep patterns, essential for understanding an individual's sleep behaviours in their day-to-day life (Toon et al., 2016). Furthermore, PSG alone does not provide enough data for the comprehensive examination of circadian rhythms, as such analyses require more extensive recordings of sleep-wake cycles over extended periods (Hofstra & De Weerd, 2008). In contrast, actigraphy is a less invasive alternative that can capture sleep/wake variability objectively over a longer period in a home environment (Cheung et al., 2018). Actigraphy uses accelerometers to monitor body movement to indicate wakefulness and sleep. Accelerometers are worn around the wrist or ankle, allowing for objective sleep assessment in a naturalistic environment over an extended period (recommended minimum of 5 days, Acebo et al., 1999). Actigraphy has proven effective in describing sleep patterns in children with genetic syndromes associated with intellectual disabilities (Agar et al., 2020; Trickett et al., 2020).

Complimentary to these objective methods, subjective methods such as sleep diaries and questionnaires offer nuanced insights into the individual experience of sleep. These methods can elucidate patterns and experiences that physiological measures cannot capture. However, questionnaires are generally less concordant with objective measurements than sleep diaries (O'Sullivan et al., 2023). This suggests that questionnaire responses may be more prone to

subjective bias and/or capture unique, global aspects of sleep phenomena that are not measured through objective tools and diaries. Moreover, objective methods are vital for generating robust data on sleep duration and night-time awakenings because they offer continuous monitoring and are less susceptible to errors that could result from caregivers' limited awareness or recall biases (O'Sullivan et al., 2023). Therefore, a well-validated method for assessing sleep in children involves the combination of actigraphy with sleep diaries and questionnaires (O'Sullivan et al., 2023). This combined approach merges objective physiological data with subjective experiences, providing a comprehensive view of sleep patterns.

4.2.3 Sleep in CHARGE Syndrome

Building on the discussion outlined in section 1.1.9 about behavioural phenotypes and the importance of research in specific aetiologies of intellectual disability, emphasis is now placed on sleep in a specific genetic syndrome associated with intellectual disability: CHARGE syndrome. CHARGE syndrome is a rare genetic condition characterised by coloboma, heart defects, choanal atresia, and developmental delays. Hearing loss and vision impairment are also common to CHARGE syndrome (see section 2.4.4).

Visual impairment can influence circadian rhythm, as light and dark are environmental cues for melatonin production (Chokroverty, 2010). This potential pathway to sleep disturbance may be compounded by the meta-analytic findings from Chapter 2, which indicated a high prevalence of behavioural issues and painful medical conditions in CHARGE syndrome. Results suggest that, in samples of people with CHARGE syndrome, 48% exhibit aggressive behaviour, 44% engage in self-injurious behaviour, 58% suffer from gastro-

oesophageal reflux, and 74% experience frequent ear infections (otitis media) (section 2.4.2 to 2.4.7). These conditions are often linked to sleep disturbances (Stratton & Hartshorne, 2019). Developing comprehensive models to explore the bidirectional relationships among sleep, pain, and behaviour can offer a more nuanced understanding of the challenges faced by individuals with CHARGE syndrome. Such insights can then be used to create more effective intervention strategies.

Research on sleep disturbances and circadian rhythm abnormalities in individuals with CHARGE syndrome is limited. Existing studies primarily consist of case reports and questionnaire-based investigations leaving a gap in understanding these issues (Hartshorne et al., 2009; Kennert et al., 2020). This limited research has hindered the development of accurate interventions and support strategies for individuals with CHARGE syndrome. To date, comprehensive investigations into circadian rhythm abnormalities in CHARGE syndrome are also lacking. Instead, the existing body of research includes few cohort studies that use questionnaires to explore sleep quality. Using questionnaires, Trider and Blake (2012) found a 65% prevalence of obstructive sleep apnea in CHARGE syndrome. Additionally, using the Sleep Disturbances Scale for Children (SDSC), Hartshorne et al. (2009) and Kennert et al. (2020) reported that 58% and 93% of participants, respectively, scored at or above the clinical cut-off for sleep disturbances. These studies identified common sleep issues, including sleep initiation and maintenance difficulties, sleep-wake transitions, excessive somnolence and sleep disordered breathing. Moreover, Hartshorne et al. (2009) reported a correlation between sleep disturbances and behaviours that challenge. A limitation of these studies if that they do not provide any objective data or provide data about sleep parameters.

Despite these findings, the current research on sleep in individuals with CHARGE syndrome still needs to be improved. Approximately 45% of individuals with CHARGE syndrome experience disturbed sleep (see section 2.4.7). However, this analysis is based on a few studies, highlighting the need for further research to validate these conclusions. Future research must employ methodologies specifically validated for individuals with intellectual disabilities, as emphasized in section 1.1.14.8. Building on the insights from Hartshorne et al.'s (2009) study, exploring potential connections between sleep patterns and challenging behaviours could significantly enhance understanding of CHARGE syndrome and mechanisms that connect clinical difficulties. These findings can pave the way for more effective interventions and support strategies.

Given the vulnerabilities children already experience (see section 4.1.1), focusing on describing sleep in children with CHARGE syndrome is crucial. Sleep is essential for cognitive and physical development, and sleep disturbances during childhood can exacerbate existing health and developmental challenges (Paruthi et al., 2016). Furthermore, comparing sleep patterns to an age-matched, typically developing control group is imperative. Given that sleep follows a developmental trajectory comparison with chronologically age matched typically developing children allows investigation of any divergence of this trajectory that might be caused by CHARGE syndrome.

4.2.4 Summary

Sleep is a complex phenomenon that encompasses behavioural and physiological processes. Sleep needs change over the lifetime, particularly during childhood. Sleep

disturbances are prevalent among individuals with intellectual disabilities, exacerbated by various factors, including physical health, sensory issues, and psychiatric conditions. Specific syndromes like Smith-Magenis syndrome show unique sleep-related challenges associated with shifts in circadian rhythm that can affect mood and behaviour. Sleep assessment for individuals with intellectual disabilities requires objective and subjective methods. Although limited, current research suggests that sleep assessment techniques, including actigraphy, sleep diaries, and questionnaires used with typically developing children likely have a similar outcome to those with intellectual disabilities. As such, researchers can incorporate age-matched control groups of typically developing children as a reference point for evaluating the specific sleep-related challenges of children with genetic syndromes. The prevalence of sleep difficulties in CHARGE syndrome, a genetic syndrome associated with intellectual disability, is estimated to be 45%. Individuals with CHARGE syndrome often engage in behaviours that challenge and have visual impairments related to circadian rhythm abnormalities. These behaviours may be exacerbated by sleep deprivation, coupled with the potential for frequent pain experiences that can adversely affect both sleep and behaviour. This highlights the urgent need for further research, specifically objective sleep assessments that are non-invasive and provide information about sleep parameters. Given the importance of sleep for cognitive and physical development, focusing on sleep in children with developmental vulnerabilities like CHARGE syndrome is crucial.

4.2.5 Study Aims

This study aims to elucidate sleep-wake patterns and disruption among children with CHARGE syndrome. It further aims to investigate the interconnectedness between sleep, pain, and challenging behaviours in this population. Building on previous research, this study

will use a combination of objective and subjective sleep measures, including actigraphy, sleep diaries and sleep questionnaires. Additionally, caregivers will provide information about the pain their child experiences using observational assessment tools appropriate for children with few to no words. Parents will complete corresponding behavioural assessment scales to rate behaviours that challenge. It is important to note here that the term "subjective" refers to the perspective of the informant, rather than reflecting the experiences or perceptions of the individual being reported on.

4.2.6 Research Questions

1. What are the subjectively experienced and objectively measured characteristics of sleep for children with CHARGE Syndrome?
2. How do the subjective and objective sleep and objectively measured circadian rhythm profiles of children with CHARGE syndrome differ from those of typically developing children?
3. How are subjective and objective measures of sleep, pain and behaviour related in CHARGE?

4.3 Methods

4.3.1 Participants

Parents and carers of seven children with CHARGE Syndrome were recruited for the 10-day sleep assessment between May 2022 and December 2022. The mean age of the CHARGE syndrome group was 8 years 5 months (SD 3.47). A parent or carer reported all children to have presented with any form of behaviours that challenge in the preceding month. Children with CHARGE syndrome were matched on age and sex to typically developing children

(mean age 8 years 3 months, SD 3.77). Children with CHARGE syndrome were recruited through an existing database, developed for the study in Chapter 3, of families who had consented to be contacted about research studies and through social media and relevant charities. Typically developing children were selected by age and sex from a historical dataset held at the University of Birmingham (initially recruited to Trickett et al., 2020). There were no specific expectations for sample size, as all eligible families were contacted from a restricted database. Additionally, data collection occurred during the COVID restrictions (see Appendix 1A for a timeline), which likely reduced the number of families willing to engage in such an intensive study.

Table 4.2 presents the demographic information of children with CHARGE syndrome and typically developing children. Groups were well matched on age (t = 0.118, p = 0.91) and sex (z -0.557, p = 0.58).

Table 4. 2

Demographic Information for the CHARGE syndrome and Typically Developing cohort taken from the background questionnaire

	CHARGE Syndrome (n = 7)	Typically Developing (n = 7)	*t*/Fishers Exact Test
Mean age (SD)	8:14 years (3.67)	8:29 years (3.77)	t (12) -0.07 p = 0.94
Males (%)	57.14	71.43	p = 1.00
Mean age of diagnosis (SD)	12 days (18.37)	NA	
Diagnosing professional: % (N)	Paediatrician: 43% (3) Clinical Geneticist: 29% (2) Other: 29% (2)	NA	
Verbal: % (N)	71% (5)	100% (7)	

	CHARGE Syndrome (n = 7)	Typically Developing (n = 7)	*t*/Fishers Exact Test
Mobile: % (N)	75% (6)	100% (7)	
Parent mean age (SD)	41.14 years (6.52)	38.57 years (6.48)	*t*(12) 0.74 *p* = 0.47
Parents highest level of education % (N)	3 or more ,A or O Levels, NVQ 3, BTEC National, or equivalent: 14% (1) Polytechnic/University degree, NVQ 4, or equivalent: 57% (4) Masters/Doctoral degree, NVQ 5, or equivalent: 29% (2)	3 or more ,A or O Levels, NVQ 3, BTEC National, or equivalent: 29% (2) Polytechnic/University degree, NVQ 4, or equivalent: 57% (4) Masters/Doctoral degree, NVQ 5, or equivalent: 14% (1)	
Family Annual Income: % (N)	£25,001 - £35,000: 14% (1) £35,001 - £45,000: 14% (1) £45,001 - £55,000: 14% (1) £55,001 - £65,000: 14% (1) £65,001 or more: 43% (3)	£15,001 - £25,000: 29% (2) £35,001 - £45,000: 14% (1) £45,001 - £55,000: 14% (1) £55,001 - £65,000: 14% (1) £65,001 or more: 29% (2)	

Table 4.3 presents the participant characteristics for the CHARGE syndrome group and compares these with prevalence estimates from the meta-analysis in Chapter 2. Although this sample of only 7 participants is compared for demonstration purposes, caution is needed in assuming representativeness due to the small sample size and purpose of descriptive exploration.

Table 4. 3

Participant characteristics and estimated population characteristics taken from Chapter 2

Criterion	Study Sample (n = 7)	Estimated Population prevalence
CHD7	6 (86%)	84%
Coloboma	5 (71%)	84%
Choanal Atresia	4 (57%)	51%
Anosmia	2 (29%)	39%
Facial Palsy	5 (71%)	46%
Feeding and Swallowing Difficulties	7 (100%)	80%
External Ear Anomalies	5 (71%)	85%
Middle Ear Anomalies	5 (71%)	50%
Inner Ear Anomalies	5 (71%)	75%
Hearing Impairment	7 (100%)	87%
Heart Defect	5 (71%)	75%
Growth Deficiency	4 (57%)	66%
Cleft Lip or Pallet	1 (14%)	20%
Genital Abnormalities	4 (57%)	54%
Tracheoesophageal fistula	1 (14%)	15%
Urinary tract problems	0 (0%)	25%
Structural Brain Anomalies	2 (29%)	43%
Skeletal of limb abnormalities	2 (29%)	39%

4.3.2 Ethics

As documented in Appendix 4A, ethical approval was granted by the Science, Technology, Engineering and Mathematics Ethical Review Committee at the University of Birmingham (ERN _18-1805).

4.3.3 Procedure

Participants wore an Actiwatch 2 (Philips Respironics) on their wrist for up to ten consecutive days to gather objective data. For subjective data collection, parents completed questionnaires detailing family demographics, child characteristics, and sleep patterns. Additionally, parents participated in the Vineland Adaptive Behavior-III Interview (VABS-III; Sparrow et al., 2016) conducted over the phone.

4.3.3.1 Subjective Measures

A copy of each of the subjective measures is available in Appendix 4B

4.3.3.1.1 Background Questionnaire

The Background questionnaire gathered information regarding the parents' age, level of education and income, children's age, genetic or clinical diagnoses, sex, and living arrangements.

4.3.3.1.2 Vineland Adaptive Behavior Scales - III (VABS: Sparrow et al., 2016)

The VABS provides a suitable estimate of adaptive functioning for research purposes in children with CHARGE syndrome, as a proxy for intellectual disability where standardised IQ assessments might be confounded, for example, by hearing and visual impairment (Sparrow et al., 1984). The VABS is a semi-structured interview that yields standardised scores for communication, daily living skills, socialisation, and motor skills, along with an adaptive behaviour composite score (ABC) used to estimate intellectual disability. The VABS demonstrates excellent internal consistency, ranging from 0.94 to 0.99, and test-retest reliability, ranging from 0.64 to 0.94 (Pepperdine & McCrimmon, 2018).

4.3.3.1.3 Modified Simonds and Parraga Sleep Questionnaire (Simonds & Parraga, 1984; Wiggs & Stores, 1998)

Simonds and Parraga (1982, 1984) developed the sleep questionnaire that served as the basis for the modified MSPSQ. This modified version was expanded for individuals with intellectual and developmental disabilities (Wiggs & Stores, 1998). The MSPSQ includes 51 items, including qualitative and open-ended questions and ratings on a Likert-scale or yes/no format. The MSPSQ yields seven subscales: Bedtime Resistance, Sleep onset Delay, Sleep Anxiety, Night Waking, Parasomnia, Sleep Disordered Breathing and Daytime Sleepiness. Maas et al. (2011) reported good inter-class correlation (0.80) and good convergent validity between the MSPSQ and the Sleep Disturbance Scale for Children ($r = 0.79$, $p < 0.001$). Elevated MSPSQ scores suggest greater sleep issues and a threshold score of 56 is recommended to identify individuals as “poor sleepers,” according to Johnson et al. (2012).

4.3.3.1.4 Research Diary

Participants were provided with an information booklet and research diary. In the diary they were asked to record ratings of behaviours indicative of pain, the presence and severity of behaviours that challenge, and sleep-wake patterns. Sleep wake characteristics were collected using the research diary to aid in actigraphy cleaning. Participants recorded specific information about their children's sleep habits, including the time they went to sleep, the time they woke up, instances of actiwatch removal, their sedentary behaviour throughout the day, and any instances and reasons for waking during the night.

4.3.3.1.4.1 The Behavioural Indicators of Pain Observation

The FLACC (Face, Legs, Activity, Crying, Consolability) scale (Voepel-Lewis et al., 1997) is a pain assessment tool commonly used in pediatric healthcare settings to evaluate pain in infants and young children who may not be able to communicate their pain effectively. Parents watched an information video provided by the researchers on how to use the FLACC. The FLACC scale involves a ten-minute observation of pain-related behavioural cues, including facial expressions, leg movements, activity levels, crying, and consolability. Each indicator is rated on a scale of 0 to 2, allowing for a maximum composite score of 10 (0 relaxed and comfortable, 1-3 mild discomfort, 4-6 moderate pain, 7-10 severe discomfort or pain or both). The FLACC was conducted once in the morning and again in the evening.

4.3.3.1.4.2 Behaviours that Challenge

Parents rated the severity of behaviours that challenge twice daily, once in the morning and once in the evening, on a scale of 0 (did not occur) to 5 (severe). Behaviours assessed

included self-injury, aggression, property destruction, irritability, overactivity, and impulsivity.

4.3.3.2 Objective Measures of sleep: Actigraphy

Participants were given a wrist actigraph, Philips Respironics 2 (AW2; Philips Respironics, Eindhoven, Netherlands), recording accelerometric activity for 10 consecutive days. Data were sampled in 30-second epochs and digitally stored for subsequent analysis. Data were cleaned using the protocol developed by Trickett et al. (2017; see Appendix 4C). The AW2 system is widely used in research, and the default settings used in the present study have been validated against polysomnography (Lambiase et al., 2014; Toon et al., 2016; van Alphen et al., 2021). The parameters estimated are summarised in Table 4.4 and illustrated in Figure 4.1.

Table 4. 4

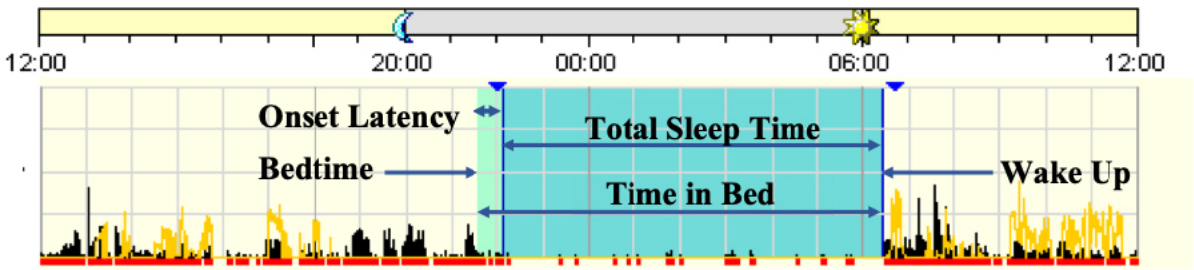
Actigraphy sleep parameters

Sleep Parameter	Description
Bedtime	The summation of epochs between the Start Time and the End Time of a given Sleep multiplied by the Epoch Length in minutes
Get Up Time	The summation of epochs between the Start Time and the End Time of a given Wake interval multiplied by the Epoch Length in minutes.
Time in Bed (hours)	The summation of hours between Bedtime and Get Up Time
Total Sleep Time (hours):	The summation of sleep epochs within the designated sleep period.
Onset Latency (minutes):	The time between the Start Time of a given Rest Interval and the following Sleep Start Time, in minutes
Sleep Efficiency (%)	Total Sleep Time divided by a given Rest Interval multiplied by 100
WASO (minutes)	The summation of wake epochs between Bedtime and Get Up Time

Note. WASO (wake after sleep onset)

Figure 4. 1

One Night Example of Actigraph data.



Parametric and non-parametric methods were used to estimate rest–activity circadian rhythm parameters. The R package Extract Circadian Rhythms Metrics from Actigraphy Data (ActCR) was used to fit a sine wave to the actigraphy data (see Figure 4.2), computing the Midline Estimating Statistic of Rhythm (MESOR) and Amplitude detailed in Table 4.5. The R package Non-Parametric Measures of Actigraphy Data 'nparACT' was used to quantify Interdaily Stability, Intradaily Variability, and Relative Amplitude (Table 4.5).

Figure 4. 2

Definition of parametric rhythm characteristics: MESOR and Amplitude

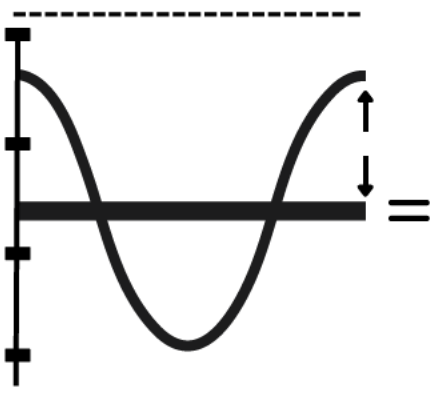


Table 4. 5

Parametric and non-parametric circadian parameters

Parametric / Non-Parametric	Measure	Description
Parametric	MESOR	Rhythm-adjusted mean activity level, approximation of the mean activity level.
Parametric	Amplitude	The peak-to-nadir difference, with higher amplitudes indicating a more robust rhythm.
Non-Parametric	Interdaily stability	Measure the variability of rest-activity patterns across all days. Higher values indicate a higher level of stability between days.
Non-Parametric	Intradaily variability	Assesses the fragmentation and magnitude of transitions between rest and activity within a day. Higher values indicate a higher frequency of transitions between rest and activity, such as frequent naps or increased awakenings during the night.
Non-Parametric	Relative amplitude (RA)	A measure of the normalised mean difference in activity between the most active 10 hours and the least active 5 hours. Higher values indicate decreased night-time activity and increased daytime activity, indicating a stronger rest-activity rhythm.

4.3.4 Data Analysis

All analysis was completed in R version 2023.03.0+386.

Data from all participants met the minimum requirements for actigraphy: five days of valid actigraphy data for circadian parameters (Berkemeyer et al., 2016), and 80% wear time over each 24-hour period for calculating actigraphy parameters (Li et al., 2021).

Bayesian independent samples t-tests were used to explore associations between participants with CHARGE syndrome and an age and sex-matched typically developing group. The Jeffreys-Zellner-Siow prior (JZS; Jeffreys, 1961) is used for these analyses, with the Midline Estimating Statistic of Rhythm (MESOR), Amplitude, Interdaily Stability, Intradaily Variability, M10, L5 and Relative Amplitude as the key parameters. The ttest.tstat function of the BayesFactor package (Morey et al., 2015) was used to calculate the BF JZS (Jeffreys, 1961) default prior distribution (Rouder et al., 2009) was used to model the alternative hypothesis. This Cauchy distribution is two-tailed and it is cantered on zero with a scaling factor of 0.707 (Rouder et al., 2009). The strength of the Null hypothesis was based on Jefferys'(1961) criteria, BF between 0.33 and 3 are considered week evidence, between 3 and 10 suggest moderate evidence and larger than 10 constitutes strong evidence in favour of the null hypothesis. If BF_{10} is greater than one, H_1 has stronger support than H_0; if BF_{10} is less than 1, H_0 has stronger evidence than H_1 (Jefferys, 1961). The JZS prior was chosen for its ability to reduce the influence of extreme values and provide a more robust estimate of the population parameters (Rouder et al., 2009). The JZS prior has been specifically designed for small samples (Jefferys, 1961). It works by balancing the information in the data with reasonable assumptions about the population (Jefferys, 1961). Due to this methodology the JZS prior is particularly well suited to heterogeneous samples. However, the use of a small case series used here limits the generalisability of the findings, which increases the risk of

Type I and II errors, and reduces statistical power, making it difficult to detect meaningful effects or draw definitive conclusions about the broader population.

Pearson's correlation tests examined the relationship between objective sleep parameters (taken from actigraphy) and subjectively defined behaviour and pain ratings. The aim was to evaluate whether there was an association between pain, behaviour, and sleep parameters. The non-parametric Spearman's Rank Correlation test was applied if the data were not normally distributed. R^2, the square of the correlation coefficient, was calculated for each correlation. R^2 ranges from 0 to 1, signifying the proportion of variability in the dependent variable that the independent variable can explain. Benjamini-Hochberg adjustments for multiple tests were applied to help account for type I errors (Benjamini & Hochberg, 1995).

The Chapter uses a combination of group level and participant level analysis. Participant level analysis is useful for understanding variability within participants. Whereas group level statistics are better for recognising trends. Inferential and Bayesian statistics in research questions 1 and 2 are at the subject level and the correlations in research question 3 are participant level. Using a combination of participant and group level analysis allows for a nuanced interpretation of the data, supporting individual outcomes while ensuring robust comparisons at the group level.

4.4 Results

4.4.1 Evaluation of Sleep Patterns in Participants with CHARGE Syndrome: Subjective and Objective Analysis

To address the first research question regarding the subjective and objective characteristics of sleep among children with CHARGE Syndrome, subjective and objective sleep data in CHARGE syndrome were analysed.

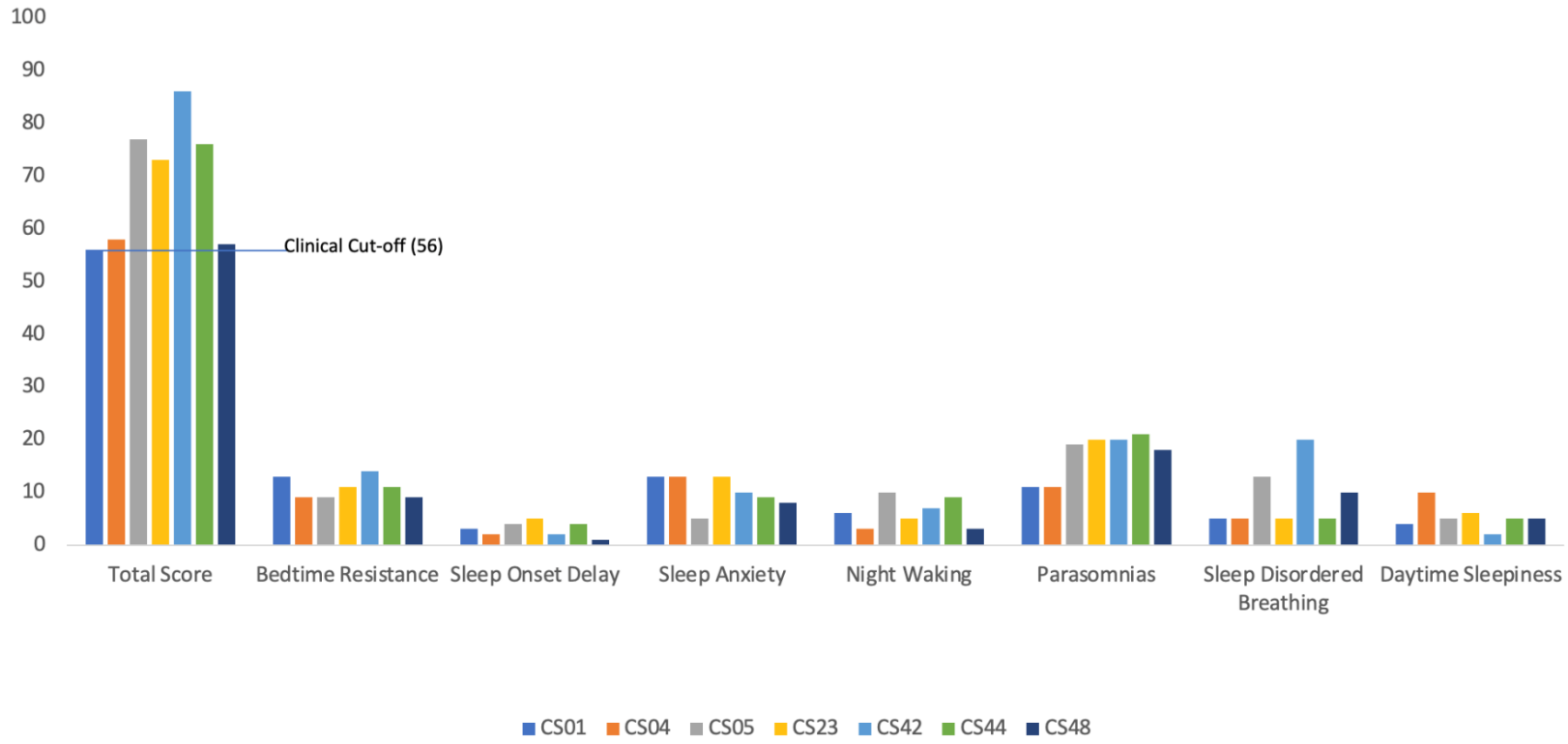
4.4.1.1 Subjective Sleep Parameters: MSPSQ

Figure 4.3 presents the subscale results of the MSPSQ.

All participants experienced disturbed sleep. Participants CS01, CS04 and CS23 scored higher on sleep anxiety than the other participants. CS04 scored higher than the other participants on daytime sleepiness, and CS05 and CS42 experienced heightened rates of sleep disordered breathing.

Figure 4. 3

MSPSQ Scores for CHARGE Syndrome Participants



Participants adaptive behaviour composite (ABC) scores, taken from the VABS were as follows: CS01(79), CS04(67), CS05(22), CS23(84), CS42(51) CS44(35), CS48(84). To explore potential associations between ABC scores and subjective sleep parameters, correlations were conducted between actigraphy and MSPSQ variables.

The distribution of each variable was visually assessed using QQ-plots and tested for normality using Shapiro-Wilk tests (Appendix 4D). Pearson's correlation was conducted for variables with an approximate normal distribution. A Spearman's rank test was performed for variables showing a non-normal distribution.

As shown in Table 4.6, there were no statistically significant correlation between subjective sleep variables and ABC scores.

Table 4.6

Correlations Between ABC Scores and Subjective Sleep Parameters for Children with CHARGE syndrome

	Correlation with ABC Scores	$\mathbf{r^2}$	***p***	$\boldsymbol{p}^{\textbf{adjusted}}$
Bedtime Resistance	r = 0.08	0.01	0.86	0.91
Sleep Onset Delay	r = -0.29	0.08	0.53	0.91
Sleep Anxiety	r = 0.69	0.48	0.09	0.42
Night Waking	r = -0.87	0.75	0.01	0.14
Parasomnias	ρ = -0.32	0.10	0.48	0.91

Sleep Disordered Breathing	$\rho = -0.35$	0.12	0.44	0.91
Daytime Sleepiness	$r = 0.18$	0.03	0.69	0.91

4.4.1.2 Objective Sleep Measures: Actigraphy Sleep Parameters

Table 4.7 presents the mean and standard deviation for sleep characteristics captured using actigraphy. The earliest to bed and earliest to rise were CS42 and CS48. These participants also experienced the most effective sleep. CS05 was the latest to go to bed and had the latest get up time. Sleep efficiency for each participant is presented in Table 4.7.

Table 4.7

Actigraphy-Based Sleep Metrics Across Participants

ID		Bedtime (HH:MM:SS)	Get Up Time (HH:MM:SS)	Time in Bed (HH:MM:SS)	Total Sleep Time (HH:MM:SS)	Onset Latency (mins)	Sleep Efficiency (%)	WASO (mins)
CS01	μ	20:47:27	08:59:48	08:26:03	08:36:00	4.38	73.95	23.13
	SD	00:29:10	06:03:52	01:53:57	00:47:47	6.39	39.11	5.79
CS04	μ	20:47:48	09:28:46	08:49:10	08:42:53	28.55	76.64	22.89
	SD	00:19:58	06:25:23	01:20:33	00:40:07	27.26	30.10	7.11
CS05	μ	22:01:06	10:02:54	8:32:15	7:51:09	15.86	75.70	47.67
	SD	00:58:34	06:35:54	01:26:55	01:08:08	19.85	25.30	29.33
CS23	μ	21:25:43	09:29:20	10:18:23	08:25:33	74.85	75.06	18.31
	SD	00:39:08	04:50:42	02:01:23	01:49:17	45.31	8.91	8.43
CS42	μ	19:11:37	05:18:26	10:16:48	8:47:26	7.19	86.53	39.25
	SD	00:22:09	01:41:52	01:43:08	01:48:58	5.38	7.55	42.92
CS44	μ	20:24:56	04:43:10	8:18:13	7:19:26	15.17	79.73	18.06
	SD	00:26:51	01:29:33	01:49:06	01:44:11	15.71	22.96	7.17
CS48	μ	18:37:12	05:20:21	10:43:09	9:17:27	8.45	86.72	63.05
	SD	00:43:36	01:00:41	01:00:16	01:02:35	10.45	5.91	37.77

Furthermore, actigraphy sleep parameters did not correlate with participants' ABC scores (Table 4.8). The distribution of each variable was visually assessed using QQ-plots and tested for normality using Shapiro-Wilk tests. Pearson's correlation was conducted for variables adhering to an approximate normal distribution. A Spearman's rank test was performed for variables showing a non-normal distribution.

Table 4.8

Correlations Between Objective Sleep Parameters and ABC Scores for Children with CHARGE syndrome

	Correlation with ABC Scores	**r^2**	***p***	***p* adjusted**
Bedtime	r = -0.33	0.11	0.47	0.91
Get Up Time	r = 0.09	0.01	0.85	0.91
Time in bed	r = 0.54	0.29	0.22	0.77
Total Sleep Time	r = 0.74	0.06	0.06	0.42
Onset Latency	r = 0.32	0.11	0.48	0.91
Sleep efficiency	ρ = -0.05	<0.01	0.91	0.91
WASO	r = -0.05	<0.01	0.91	0.91

Note. WASO = Wake after sleep onset

4.4.2 Bayesian Analysis of Sleep as Measured Using Objective and Subjective Methods in CHARGE Syndrome Compared to Typical Development

This section addresses the second research question regarding subjective and objective sleep and objectively measured circadian rhythm profiles of children with CHARGE syndrome compared to typically developing children. Detailed results for each circadian rhythm parameter are presented below.

4.4.2.1 Subjective Measures

Table 4.7 shows Bayesian independent t-tests that were conducted to examine differences in means between the CHARGE Syndrome group and the typically developing group across sleep variables taken from the MSPSQ. Across the sleep variables, the Bayes factor indicated there was weak evidence for the null hypothesis (no difference between means) and the alternative hypothesis (a difference between means) between the CHARGE syndrome group and the typically developing group. This indicates that there was not strong enough evidence to suggest that the sample means were different or the same.

Table 4. 6

Bayesian independent t-test of MSPSQ results for CHARGE Syndrome and Typically Developing participants

Variable	Charge Syndrome Group μ(SD)	Typically Developing Group μ(SD)	Factor (*d*)	Model Favoured	Strength of evidence
Bedtime Resistance	10.86 (2.04)	12.00 (4.32)	0.53 (-0.38)	Null	Weak

Variable	Charge Syndrome Group μ(SD)	Typically Developing Group μ(SD)	Factor (*d*)	Model Favoured	Strength of evidence
Sleep Onset Delay	3.00 (1.41)	1.86 (1.07)	1.09 (0.91)	Alternative	Weak
Sleep Anxiety	10.14 (3.08)	10.00 (2.94)	0.45 (0.05)	Null	Weak
Night Waking	6.14 (2.73)	4.00 (1.53)	1.20 (0.97)	Alternative	Weak
Parasomnias	17.14 (4.30)	14.86 (3.03)	0.68 (0.62)	Null	Weak
Sleep Disordered Breathing	9.00 (5.80)	5.57 (1.13)	0.93 (0.82)	Null	Weak
Daytime Sleepiness	5.29 (2.43)	2.71 (1.50)	0.93 (0.82)	Null	Weak

4.4.2.2 Objective Measures

Bayesian independent t-tests examined mean differences in actigraphy parameters between the CHARGE Syndrome and the typically developing groups. Across the actigraphy variables, the Bayes factor BF_{10} indicated weak evidence for the null hypothesis (no difference between means) and the alternative hypothesis (a difference between means) between the CHARGE syndrome and the typically developing group (Jeffreys, 1961). This suggests insufficient evidence to support the conclusion that the sample means were different or the same.

Table 4. 7

Bayesian independent t-test of actigraphy parameters for CHARGE Syndrome and Typically Developing participants

Variable	Charge Syndrome Group, μ (SD)	Typically Developing Group, μ (SD)	Factor (*d*)	Model Favoured	Strength of evidence
Bedtime	20:10:03 (01:12:23)	19:57:35 (02:14:36)	0.49 (0.29)	Null	Weak
Get Up Time	06:05:16 (01:06:25)	07:12:00 (00:49:40)	1.69 (-1.14)	Alternative	Weak
Time in Bed (Hours)	09:37:41 (00:55:48)	10:04:24 (01:00:41)	0.57 (-0.46)	Null	Weak
Total Sleep Time (hours)	08:14:34 (00:46:31)	08:18:38 (00:57:59)	0.45 (-0.08)	Null	Weak
Onset Latency (minutes)	29.68 (30.03)	21.90 (11.24)	0.51 (0.34)	Null	Weak
Sleep Efficiency (%)	84.48 (5.30)	85.30 (1.75)	0.47 (-0.21)	Null	Weak
WASO (minutes)	38.73 (18.31)	47.40 (15.61)	0.90 (-0.80)	Null	Weak

Note. WASO = wake after sleep onset

Bayesian independent t-tests were conducted to examine differences in means between the CHARGE Syndrome group and the typically developing group across circadian rhythm parameters extracted from participants' actigraphy data. For the variables MESOR,

Amplitude, M10, L5, and Relative Amplitude showed Bayes Factors BF_{10} supporting a null model, suggesting no significant differences between the groups; however, the evidence was weak, indicating that neither the null nor the alternative hypothesis was strongly supported (Jeffreys, 1961). Similarly, for the variables Interdaily Stability and Intradaily Variability the Bayes Factors BF_{10} supported an alternative model, indicating evidence for a difference between the CHARGE syndrome group and the typically developing group (Jeffreys, 1961) suggesting that the CHARGE syndrome group was less stable. However, the evidence was weak, and therefore no definitive conclusions could be drawn (see Table 4.9).

Table 4. 8

Bayesian independent t-test of circadian rhythm parameters for CHARGE Syndrome and Typically Developing participants

Variable	Charge Syndrome Group, μ (SD)	Typically Developing Group, μ (SD)	Factor	Model Favoured	Strength of evidence
MESOR	145.43 (73.69)	161.37 (31.39)	0.49	Null	Weak
Amplitude	154.42 (92.08)	173.39 (38.93)	0.48	Null	Weak
Interdaily Stability	0.29 (0.08)	0.36 (0.05)	1.37	Alternative	Weak
Intradaily Variability	0.50 (0.10)	0.42 (0.04)	1.28	Alternative	Weak
M10	276.76 (146.92)	315.52 (67.48)	0.51	Null	Weak
L5	6.01 (4.24)	5.00 (2.17)	0.49	Null	Weak
Relative Amplitude	0.93 (0.07)	0.97 (0.01)	0.87	Null	Weak

4.4.3. Sleep, Pain and Behaviour Associations

This section addresses the final research question regarding whether measures of sleep correlate with pain and behaviour. Due to the number of comparisons, a Benjamini-Hochberg correction was used for Table 4.10 and again for Table 4.11.

4.4.3.1 Objective Sleep Parameters and Subjective Behaviour Measures

There were no statistically significant correlations between objective sleep measures and subjective behaviours reported for any participant when analysing within-subject night-by-night data (Table 4.10).

Table 4. 9

Sleep and behaviour correlations

	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (%)	WASO (minutes)
CS01	r = -0.15, $r^2 = 0.31$ $p = 0.59$ $p^{adjusted} = 0.99$	ρ = -0.41 $r^2 = 0.21$ $p = 0.13$ $p^{adjusted} = 0.99$	ρ = 0.11 $r^2 = 0.06$ $p = 0.69$ $p^{adjusted} = 0.99$	ρ -0.07 $r^2 = 0.04$ $p = 0.81$ $p^{adjusted} = 0.99$
CS04	ρ = 0.17 $r^2 = 0.03$ $p = 0.53$ $p^{adjusted} = 0.99$	ρ = -0.36 $r^2 = 0.13$ $p = 0.17$ $p^{adjusted} = 0.99$	ρ = 0.44 $r^2 = 0.19$ $p = 0.09$ $p^{adjusted} = 0.99$	ρ = 0.20 $r^2 = 0.04$ $p = 0.46$ $p^{adjusted} = 0.99$
CS05	ρ = 0.14 $r^2 = 0.02$ $p = 0.59$ $p^{adjusted} = 0.99$	ρ = -0.19 $r^2 = 0.04$ $p = 0.44$ $p^{adjusted} = 0.99$	ρ = -0.04 $r^2 = 0.01$ $p = 0.89$ $p^{adjusted} = 0.99$	ρ = 0.10 $r^2 = 0.01$ $p = 0.70$ $p^{adjusted} = 0.99$
CS23	ρ = -0.17 $r^2 = 0.03$ $p = 0.57$ $p^{adjusted} = 0.99$	ρ = 0.09 $r^2 = 0.01$ $p = 0.75$ $p^{adjusted} = 0.99$	ρ = -0.11 $r^2 = 0.01$ $p = 0.71$ $p^{adjusted} = 0.99$	ρ = -0.11 $r^2 = 0.01$ $p = 0.71$ $p^{adjusted} = 0.99$

	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (%)	WASO (minutes)
CS42	ρ = -0.01 r^2 = <0.01 *p* = 0.99 *p* adjusted = 0.99	r = 0.12 r^2 = 0.02 *p* = 0.64 *p* adjusted = 0.99	ρ = 0.02 r^2 = <0.01 *p* = 0.94 *p* adjusted = 0.99	ρ = 0.14 r^2 = 0.02 *p* = 0.59 *p* adjusted = 0.99
CS44	ρ = -0.01 r^2 = <0.01 *p* = 0.99 *p* adjusted = 0.99	ρ = -0.41 r^2 = 0.17 *p* = 0.08 *p* adjusted = 0.99	ρ = 0.31 r^2 = 0.09 *p* = 0.20 *p* adjusted = 0.99	ρ = 0.10 r^2 = 0.01 *p* = 0.68 *p* adjusted = 0.99
CS48	ρ = 0.05 r^2 = <0.01 *p* = 0.85 *p* adjusted = 0.99	ρ = -0.17 r^2 = 0.03 *p* = 0.48 *p* adjusted = 0.99	ρ = 0.37 r^2 = 0.14 *p* = 0.12 *p* adjusted = 0.99	ρ = -0.39 r^2 = 0.15 *p* = 0.10 *p* adjusted = 0.99

Note. WASO = wake after sleep onset. Adjustment for multiple comparisons was completed using the Benjamini-Hochberg (1988) method.

4.4.3.2 Objective Sleep Parameters and Subjective Pain Measures

There were no statistically significant correlations between objective sleep measures and subjective pain reported for any participant when analysing within-subject night-by-night data (Table 4.11).

Table 4. 10

Pain and behaviour correlations

	Total Sleep Time (hours)	**Onset Latency (minutes)**	**Sleep Efficiency (%)**	**WASO (minutes)**
CS04	ρ = 0.17 r^2 = 0.03 *p* = 0.53 *p* adjusted = 0.99	ρ = -0.36 r2 = 0.13 *p* = 0.17 *p* adjusted = 0.99	ρ = 0.44 r^2 = 0.19 *p* = 0.09 *p* adjusted = 0.99	ρ = 0.20 r^2 = 0.04 *p* = 0.46 *p* adjusted = 0.99
CS05	ρ = 0.09	ρ = 0.36	ρ = -0.07	ρ = -0.20

	Total Sleep Time (hours)	Onset Latency (minutes)	Sleep Efficiency (%)	WASO (minutes)
	$r^2 = 0.01$ $p = 0.77$ $p^{adjusted} = 0.90$	$r^2 = 0.13$ $p = 0.25$ $p^{adjusted} = 0.85$	$r^2 = 0.01$ $p = 0.84$ $p^{adjusted} = 0.90$	$r^2 = 0.04$ $p = 0.53$ $p^{adjusted} = 0.85$
CS23	$\rho = -0.32$ $r^2 = 0.10$ $p = 0.28$ $p^{adjusted} = 0.85$	$\rho = -0.06$ $r^2 = 0.00$ $p = 0.84$ $p^{adjusted} = 0.90$	$\rho = -0.25$ $r^2 = 0.06$ $p = 0.41$ $p^{adjusted} = 0.85$	$\rho = -0.35$ $r^2 = 0.12$ $p = 0.24$ $p^{adjusted} = 0.85$
CS42	$\rho = 0.07$ $r^2 = 0.01$ $p = 0.80$ $p^{adjusted} = 0.90$	$r = -0.14$ $r^2 = 0.02$ $p = 0.60$ $p^{adjusted} = 0.87$	$\rho = -0.01$ $r^2 = <0.01$ $p = 0.99$ $p^{adjusted} = 0.99$	$\rho = -0.18$ $r^2 = 0.03$ $p = 0.49$ $p^{adjusted} = 0.85$

Note. WASO = wake after sleep onset. No pain data was available for participant CS01. Adjustment for multiple comparisons was completed using the Benjamini-Hochberg (1988) method.

4.4.3.3 Post Hoc Pawer analysis

To ensure scientific rigor, a post hoc power test was conducted for the correlations (Table 4.1) and the Bayesian analysis (Table 4.7). These tables were selected because they contained the largest sets of statistics measuring either correlations or Bayesian information. The power analysis for the Bayesian analysis was 0.16. And power analysis for the correlation analysis was run, and this was 0.10.

4.5 Discussion

The primary aim of the current study was to provide a comprehensive description of the sleep profile of children with CHARGE syndrome. This included examining subjectively reported and objectively measured sleep characteristics and comparison with those observed

in typically developing children. The study also described circadian rhythms in CHARGE syndrome and delineated differences in these rhythms between CHARGE syndrome and the typically developing comparison group. Additionally, it explored the relationships between sleep, levels of pain, and behaviours that challenge in this cohort.

Using a multi-method approach, the present study incorporated objective and subjective sleep assessments, including actigraphy, sleep diaries and questionnaires. To account for potential communication limitations in children with CHARGE syndrome, caregiver-reported observational assessment was used to assess experiences of pain. Input from parents was also gathered through ratings of behaviours that challenge. This is the first objective sleep study in a sample of children with CHARGE syndrome.

4.5.1 Research Question 1: Sleep Characteristics in Individuals with CHARGE Syndrome

The first research question explored subjective and objective sleep characteristics in children with CHARGE syndrome. The results revealed pervasive sleep disturbance across all participants, substantiating the high prevalence of sleep issues outlined in Chapter 2 as well as those reported by Hartshorne et al. (2009) and Kennert et al. (2020). Interestingly, actigraphy sleep parameters and MSPSQ scores did not correlate with ABC scores, which may imply that sleep disturbances in CHARGE syndrome are not directly associated with adaptive behaviour abilities. Instead, they might constitute a separate challenge requiring specialised attention, irrespective of a child's ability level.

CS01, CS04, and CS23 exhibited higher sleep anxiety levels than others. Anxiety surrounding sleep could exacerbate existing sleep-related issues and might necessitate

targeted interventions (Willis & Gregory, 2015). This highlights the need for a multifaceted approach to treating sleep disturbances, potentially including behavioural or psychological therapies and medical treatments. Participant CS04 experienced the highest score for daytime sleepiness, which could have broad implications for daily functioning, including social interactions and educational performance (Chokroverty, 2010).

Similarly, participants CS05 and CS42 reported heightened rates of sleep disordered breathing, which could have long-term health consequences (Chokroverty, 2010). Hartshorne et al. (2009) and Kennert et al. (2020) also reported sleep breathing difficulties as a common feature of CHARGE syndrome. CS42 and CS48 were identified as the earliest to go to bed and wake up, yet CS48 also experienced the most awakenings after sleep onset. This could suggest disrupted sleep cycles or possible sleep maintenance issues that may necessitate further investigation. Indeed, difficulties with initiating and maintaining sleep were among the most prevalent sleep disturbances reported by Hartshorne et al. (2009) and Kennert et al. (2020). CS23 had the most prolonged sleep onset latency but also had one of the the longest times in bed. Participant CS01 was found to have the least efficient sleep. Inefficient sleep could harm overall health and well-being (Chokroverty, 2010).

These findings highlight the complexity of sleep disturbances for individuals with CHARGE syndrome and the individual differences in the profile of sleep parameters and sleep disturbance in children with CHARGE syndrome. With no significant correlation with ABC scores, sleep disturbances are a distinct area of concern that warrant independent investigation and intervention.

4.5.2 Research Question 2: Comparative Sleep and Circadian Profiles in CHARGE Syndrome and Typically Developing Children

The study's second research question explored how sleep and circadian rhythm profiles differ between children with CHARGE syndrome and those typically developing. To assess these differences, subjective measures taken from the MSPSQ and objective measures extracted from actigraphy data were analysed using Bayesian independent t-tests. The study found weak evidence for the null and alternative hypotheses in the Bayesian t-tests comparing children with CHARGE syndrome to typically developing children. This suggests that children with CHARGE syndrome are similar to typically developing children on subjective measures, objective measure and cycadean rhythm measures.

This finding is surprising, particularly because children with CHARGE syndrome experience several painful health conditions (Trider et al. 2017). This would be likely to cause disturbed sleep, for example poor sleep efficiency when it is difficult for the child to maintain sleep because of pain (Stratton et al., 2019). Similarly, sleep apnoea associated with choanal atresia can lead to disturbed sleep, contributing to early waking (Trider et al. 2017). One reason for these results could be that parents of typically developing children were more motivated to take part in the study if their child had sleep difficulties. This may have biased the sample.

4.5.3 Research Question 3: Interconnections Between Sleep, Pain, and Behaviour

The third section aimed to examine associations between objective sleep parameters and the subjective behaviour and pain ratings. The data did not yield any statistically significant correlations between objective sleep measures and subjective behaviour measures for any of the participants. This finding differs from the existing literature, which posits a relationship between sleep quality and behavioural outcomes (Trickett et al., 2020). The lack of significant findings may be attributable to the small sample size. Further, subjective behaviour measures were recorded by parents and caregivers twice daily and this may not have been sensitive enough to detect nuanced changes that may have correlated with sleep parameters. However, this is the first study to have looked at objective sleep parameters and associations with daytime behaviour in CHARGE syndrome.

The study found no significant associations between objective sleep parameters and subjective pain measures (Table 9). These results do not align with the CHARGE syndrome literature suggesting that poor sleep exacerbates pain experiences (Stratton & Hartshorne, 2019). The lack of significant correlations may result from the small sample size or other factors such as medication use or medical conditions that could affect sleep or cause pain. Alternatively, the lack of correlations could be due to limited variability in the sample if all participants have poor sleep and high pain.

There is a need for a more refined methodology to further understand these associations. Given how complex these associations are, future research might employ a longitudinal design using more refined and sensitive methods with a larger sample size that is powered to

detect putative differences. In conclusion, while aim 3 sought to uncover the interconnectedness of sleep, pain, and behaviour, the findings suggest that any association could be more complex and warrants further investigation.

4.5.4 Strengths and Limitations

This study had several strengths. One of the primary strengths of the study was its multi-method approach that integrated both subjective and objective sleep assessments, thereby offering a comprehensive view of sleep patterns in children with CHARGE syndrome. To account for potential communication limitations, the study used caregiver-reported assessments for measuring experiences of pain. The study was more reliable because of this. The study effectively compared children with CHARGE syndrome to typically developing children using Bayesian independent t-tests, helping to contextualise the sleep and circadian rhythm profiles unique to CHARGE syndrome. Finally, the objective measures of circadian rhythm parameters are also a strength, as this is an often-overlooked aspect of sleep quality that could have implications for treatment (Chokroverty, 2010). However, it is notable that subjective methods refer to the subjective experience of the questionnaire's informant and not the subjective experience of the child with CHARGE syndrome. Future research should aim to capture the experiences of children with CHARGE syndrome.

The study also had limitations. Families were recruited between May and December 2022, during which the COVID pandemic continued to affect daily life, including local lockdowns that began in June and a four-week lockdown from November to December 2022 (Appendix 1.A; Institute for Government, 2022). While many people in the country were beginning to

experience some freedom from the COVID restrictions, parents of children with CHARGE syndrome, particularly those who were medically vulnerable, may have continued to isolate to protect their children (Sanders, 2020). As such, the families that took part likely had children with fewer medical complications, who were no longer isolated and had greater access to resources, allowing them to participate in research (Theodoropoulos, 2003). These children may have fewer sleep problems. However, it is notable that the present research was advertised as a sleep study. Given the disruption of COVID many children may have experienced sleep difficulties. It is the parents of these children that would be the most motivated to take part to gain insight into these challenges.

It's important to highlight that the sample in the present study were highly educated and affluent. Here 85% of parents were educated to degree level of above, and 43% earned over £65,000 annually. As noted in section 1.3, parents who have more money and therefore resources are more likely to belong to a parent support group (Zeutenhorst, 2017). As the majority of participants were contacted through parent support groups this may explain this bias in the data.

Recruitment for the study was limited to children aged 4 to 15 years, and thus, no direct inferences can be made about adults with CHARGE syndrome. However, it is important to study sleep in children with CHARGE syndrome because sleep patterns in this population are likely linked to developmental stages. As sleep is associated with cognitive, physical and emotional characteristics throughout development, it is important to study how CHARGE

syndrome affects sleep during childhood. Sleep is a particular concern for parents and sleep research can provide insight and practical support for families.

An a priori power analysis was not conducted for the present study. The sample was drawn from a database developed for the study in Chapter 3. There was no expectation for sample size given that the database was considered to be a comprehensive resource, and all eligible participants were contacted. To address scientific rigor, a post hoc power analysis was subsequently conducted. The power analysis was conducted for the Bayesian t-test analysis to understand the sensitivity of the study given the observed effect size. Frequentist power analysis, based on Cohen's *d* was conducted. Frequentist power analysis can provide a measure of sensitivity for Bayesian statistics based on sample and effect size (Wagenmakers, 2016). The power for the Bayesian t-test was 0.16, with an effect size of 0.08 and a sample size of 7. A post-hoc test was also conducted for the correlations that were run. The power was 0.10 based on the mean effect size of 0.08 and a sample size of 7. It is, therefore, notable that the study was considerably underpowered. However, the study is pioneering and investigate an under researched subject area. The present study will provide the groundwork for larger studies in this area: provoking new research questions and new hypothesis. The use of a small sample enabled the use of detailed analysis and the study of nuanced difference between children that larger studies would likely overlook. The level of detail adds to a more comprehensive understanding of sleep. Furthermore, this work is directly relevant to clinicians and families who can use this information to inform practice, therapeutic approaches and individualised care plans.

Because the study used a cross-sectional design it was not possible to make causal inferences between sleep disturbances, pain and behaviours that challenge. Future research might use a longitudinal design. Use of a diary that was completed twice daily may not have been sufficient to capture changes related to sleep parameters. Finally, the study did not account for potential confounding variables like medication use or other medical conditions that could affect sleep or pain, which could limit the interpretability of the findings.

4.5.5 Conclusion

In collusion, this pioneering study provided the first multi-modal study of sleep in CHARGE syndrome. By using subjective and objective measures and by comparing children with CHARGE syndrome to typically developing children, this research provides a unique perspective on sleep and circadian rhythms. Despite its strengths, the study also had limitations such as small underpowered sample, reduced generalisability, sample bias, and confounding variable that may not have been unaccounted for. Future research should use larger longitudinal samples that may lend themselves to causal interpretations. This pioneering study paves the way for future research with new research questions and new hypothesis. Ultimately, such research may lead to targeted sleep interventions for children with CHARGE syndrome.

CHAPTER FIVE

INVESTIGATING BEHAVIOURS THAT CHALLENGE IN CHILDREN WITH CHARGE SYNDROME

5.1 Preface

Behaviours that challenge were examined in Chapter 2. Chapter 2 used meta-analysis to delineate a 48% prevalence of aggressive behaviour and 44% prevalence of self-injurious behaviour. However, studies predominantly used unvalidated questionnaires or single-question assessments within questionnaires. Chapter 3 overcame some of these limitations, using validated questionnaires to investigate behaviours that challenge. However, knowing the function of behaviour is essential to develop effective interventions and this was not covered. Chapter 5 addresses this limitation, using validated assessments to understand the form and function of behaviours that challenge. This approach is not only suitable but also invaluable for research and clinical application.

5.2 Introduction

5.2.1 The Impact of Behaviours that Challenge on Children and their Social Environment

Children with neurogenetically determined conditions associated with intellectual disability, such as CHARGE syndrome, often show behaviours that challenge. As outlined in section 1.1.7.1, a behaviour is defined as challenging if it is culturally abnormal and so intense, frequent, or long-lasting that it is likely to severely compromise the safety of the individual or others. Self-injury, aggression, and destruction of property are reported by parents and care providers to be the most concerning forms of behaviours that challenge

(Griffith & Hastings, 2014). Prevalence rates for self-injurious and aggressive behaviour vary between 10% and 20% for individuals with intellectual disability (Emerson et al., 2001; Emerson & Bromley, 1995; Kiernan & Kiernan, 1994; Lowe et al., 2007). Behaviours that challenge can be extremely persistent, particularly in clinical groups associated with intellectual disability (Laverty et al., 2020). Both pharmacological and non-pharmacological interventions are used to address behaviours that challenge, however, these interventions yield relatively small effects (Groves et al., 2023). Behaviours that challenge can physically harm the child and those around them and can lead to increasing social isolation and decreasing social support (Hastings et al., 2013). Therefore, addressing and managing these behaviours is essential to ensure the positive well-being and quality of life of the child and their family.

5.2.2 Research Priorities: CHARGE Syndrome and Behaviours that Challenge

The genetic syndrome of interest in the present research is CHARGE syndrome. CHARGE syndrome is a rare multisystem genetic condition characterised by vision and hearing impairment with associated intellectual disability and communication difference (outlined in section 1.1.14). While there is limited research on behaviours that challenge in this population, the meta-analysis conducted in Chapter 2 indicated a high prevalence of aggressive behaviour (48%) and self-injurious behaviour (44%) (section 2.4.7). Additionally, Chapter 3 revealed a 45% prevalence of self-injurious behaviour, a 50% prevalence of aggressive behaviour and a 45% prevalence of destruction of property (section 3.4.1.1). These estimates are considerably higher than the 5.1% and 4.1% prevalence in intellectual disability reported by Ruddick et al. (2015). This disparity suggests an increased risk for persons with CHARGE syndrome beyond that conferred by intellectual disability. However, it is notable that this disparity was not supported in Chapter 3. It is a research priority to investigate and

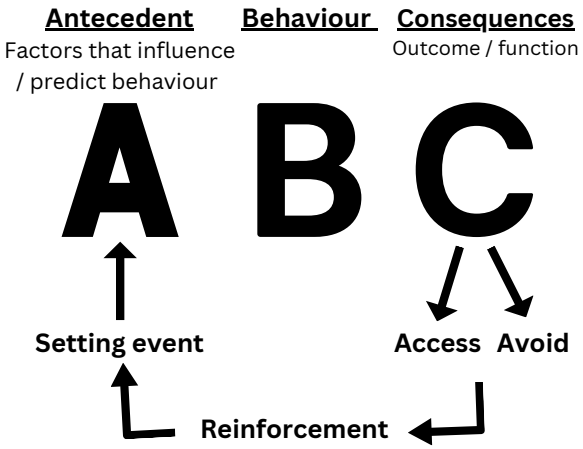
elucidate factors that could be maintaining challenging behaviours in CHARGE syndrome with a view to future efforts focusing on the design of appropriate interventions.

5.2.3 The ABC Model: Understanding Behaviour Functions

Psychological models can help identify factors associated with behaviour and the factors that reinforce or modify behaviour. The ABC (Antecedent, Behaviour, Consequence) or behavioural model, illustrated in Figure 5.1, serves as a tool for elucidating potential functions of behaviours that challenge. In the ABC model, the "Antecedent" is what happens immediately before the behaviour takes place, this is the condition that establishes the motivating properties of the consequence, followed by the "Behaviour", and finally the "Consequence" that directly follows the behaviour and serves to increase or decrease the likelihood of the behaviour occurring again in the future in the presence of the same antecedent. This process of increasing or decreasing the likelihood of behaviour based on its consequences is known as "reinforcement". Reinforcement can be negative, positive, or automatic. Positive reinforcement promotes or sustains a behaviour through rewards, negative reinforcement encourages behaviour by removing something undesirable, and automatic reinforcement is behaviour that is maintained by sensory or internal stimuli that are not socially mediated. Successful interventions for behaviours that challenge rely heavily on determining the function of behaviours (Matson et al., 2012). Indeed, the NICE guidelines recommend identifying the function of behaviour to develop effective intervention (National Institute for Health and Care Excellence, 2015). Understanding what drives behaviours that challenge and how the contingencies surrounding a behaviour may be maintaining it can guide the development of an effective framework for modifying or managing the behaviour (Moreno, 2010).

Figure 5. 1

The Antecedent, Behaviour Consequence (ABC) model



5.2.4 The ABC Model in Functional Behaviour Analysis

The ABC model is used in Functional Behaviour Analysis. Functional Behaviour Analysis is a systematic approach used to understand the functions of behaviours, enabling effective interventions to be developed. Several methods can be used to ascertain functions of behaviours including questionaries (Durand & Crimmins, 1988), interviews, descriptive naturalistic observations and experimental functional analysis (Gresham et al., 2001). Each method has associated strengths and weaknesses. Standardised questionnaires and interviews efficiently gather data from various sources, they are brief to administer and are amenable for larger cohort studies, but they may not capture less common behaviours and may be subject to informant bias. Naturalistic observations identify idiosyncratic behaviours, but results, as for questionaries and interviews, are limited as they are correlational. Experimental analysis reveals causal relationships between behaviours and associated contingencies but is a lengthy and therefore often an impractical process which demands extensive training. Ethically, there are concerns around eliciting behaviours that challenge and managing the risk of that

behaviour. Functional behaviour analysis is recommended for persons of all ages with CHARGE syndrome, including children, who engage in behaviours that challenge (Smith et al., 2010).

Common functions of behaviours that challenge for persons with an intellectual disability include gaining social attention, escape from aversive stimuli, easing physical discomfort and acquiring tangibles (Matson et al., 2012). There is also evidence to suggest that functions of behaviour may vary by age, adaptive behaviour, and clinical presentation (Grey & Hastings, 2005; Medeiros et al., 2014). For example, autistic individuals, or individuals with high autistic characteristics, may be more likely to show behaviours reinforced by social escape rather than social attention, or they may have sensory sensitivity, experiencing certain sounds, light, or touch to be aversive and therefore may show more behaviours that are negatively reinforced by the removal of sensory stimuli (Barrera & Graver, 2009). Individuals with fragile X syndrome sometimes display behaviours that challenge as a result of heightened responsiveness to discriminative stimuli associated with escalating social demands within their environment. This is because social anxiety forms part of the behavioural phenotype and social anxiety can significantly impact how individuals with fragile X syndrome respond to social learning and reinforcement (Hall et al., 2006). Similarly, in Cornelia de Lange syndrome environmental variables, including social interactions, can play a significant role in shaping behaviours, particularly self-injurious behaviours (Arron et al., 2006).

Lewis and Lowther (2001) recommend functional assessment as part of the strategy for effective intervention planning in CHARGE syndrome. Based on the profile of CHARGE syndrome Bernstein & Denno (2005) emphasize the significance of escape from social

attention, sensory sensitivity, and pain and discomfort as important factors to consider in understanding the functions of behaviours that challenge in individuals with CHARGE syndrome. Specific characteristics in CHARGE syndrome may also influence behaviour function. These characteristics include sensory impairment (Bernstein & Denno, 2005) and the experience of painful health conditions (as outlined in section 2.4.5). Sensory sensitivity and chronic pain are associated with social avoidance (Asmundson et al., 1999; Ludlow et al., 2023). It is also worth noting that due to the high prevalence of autism (28%; section 2.4.7), and intellectual disability (64%; 2.4.7), there is a possibility of shared functions among individuals with CHARGE syndrome, intellectual disability, and autism.

One approach to explore the functions of behaviours that challenge in CHARGE syndrome would be to focus on the most common forms of behaviour identified in the syndrome. The meta-analysis (section 2.4.7) and the syndrome profile comparison study (section 3.4.1.1) revealed that aggressive behaviour was the most prevalent behaviour reported in CHARGE, and therefore delineating common functions of aggression in CHARGE will likely yield the most significant benefits. Thus far, the literature on behaviours that challenge in CHARGE syndrome has primarily consisted of case studies that employ experimental functional behavioral analysis (Bernstein & Denno, 2005; Smith et al., 2022). This type of analysis, in addition to being ethically questionable, is only able to provide results about the case series under investigation. As such, given the limitations of using experimental functional behaviour analysis for larger sample sizes and a need for future research to compare participants within groups, it is advisable to employ standardised questionnaires or interviews as more suitable alternatives. Such measures are quick and cost effective to administer, they are less invasive and can be administered by multiple sources.

5.2.5 Summary

In summary, behaviours that challenge, particularly self-injurious and aggressive behaviour are prevalent in CHARGE syndrome. When these behaviours are present in clinical groups associated with intellectual disability, they can be extremely persistent, and it is therefore crucial to address these behaviours to ensure the well-being and quality of life of the individual and their family. Functional behaviour analysis is a recommended method for assessing behaviours that challenge in individuals with CHARGE syndrome. However, to date, there has been a lack of large-scale studies dedicated to investigating the underlying functions of these behaviours in CHARGE. Existing research has primarily consisted of individual case studies. Functions of behaviour may vary in CHARGE syndrome by age, intellectual ability, by the presence of autism characteristics, degree of sensory impairment and pain and discomfort. It is a priority to identify the common functions of behaviour in CHARGE syndrome to refine further research and build a greater understanding of behaviours that challenge in CHARGE syndrome and inform intervention strategies.

Therefore, the research aims for the present study are:

1. To describe the severity of aggression and behaviours of most concern to parents / caregivers in children with CHARGE.

2. To identify the functions of behaviours that challenge in children with CHARGE syndrome.

5.3 Methods

5.3.1 Ethical Review

The Science and Technology (STEM) Ethics Review Committee, University of Birmingham provided ethical review and approval (ERN_18-1805; ethical approval details can be found in Appendix 5A).

5.3.2 Recruitment

Parents/Caregivers of children with CHARGE syndrome were recruited between November 2021 and January 2023 primarily from an existing participant database held by the research team. The database included the details of parents/caregivers of children with CHARGE syndrome from the UK and the USA who had taken part in the study in Chapter 3 and agreed to be contacted about future studies. There was no recruitment target for the present study as the database was considered to be a comprehensive resource and all parents/caregivers were contacted and all that responded took part. Ethical approval for the ongoing use of this database (IRAS: 20638, Appendix 3A), including GDPR-compliant procedures for storing and treating data, was adhered to in the present study. Participants were initially contacted by email with details of the study and were then followed up by telephone within seven days. If parents/caregivers could not be contacted by telephone, an email invitation was sent inviting parents/caregivers to complete online consent forms.

Additional parents/caregivers of a child with CHARGE syndrome were also recruited through an advert posted to social media groups affiliated with the USA and UK family support groups. Parents/caregivers were included if they had a child with CHARGE

syndrome, aged 4 to 15 years, diagnosed by a medical professional who had engaged in any form of behaviours that challenge in the preceding month.

5.3.3. Participants

5.3.3.1. Demographic Characteristics

Participants with CHARGE syndrome included 8 females and 5 males, age range 4.11 to 14.8 years. The majority of participants were from the UK, with one male and one female from the USA. Demographic characteristics are presented in Table 5.1

Table 5. 1

Demographic Characteristics of the CHARGE Syndrome Sample

Category	Values
	CHARGE Syndrome (n = 14)
Median age (IQR range)	9.9 years (6.45)
Males (%)	36.71
Mean age of diagnosis (SD)	7.08 months (13)
Diagnosing professional: % (N)	Paediatrician: 4/13 Clinical Geneticist: 8/13 Endocrinologist: 1/13
Parents/caregivers mean age (SD)	44.38 years (6.28)
Parents/caregivers highest level of education % (N)	No formal qualifications 8% (1)
	Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC 15% (2)
	3 or more ,A or O Levels, NVQ 3, BTEC National, or equivalent: 8% (1)
	Polytechnic/University degree, NVQ 4, or equivalent: 31% (4)

Category	Values
	Masters/Doctoral degree, NVQ 5, or equivalent: 38% (5)
Family Annual Income: % (N)	£15,000 – 25,000: 15% (2) £25,001 - £35,000: 8% (1) £35,001 - £45,000: 14% (2) £45,001 - £55,000: 23% (3) £65,001 or more: 38% (5)

5.3.3.2. Physical Characteristics

Medical characteristics of CHARGE syndrome reported by parents/caregivers in the present study are presented in Table 5.2. A copy of the questionnaire containing the medical characteristics can be seen in Appendix 5B. While the number of participants in the current sample is low, characteristics were broadly similar to the estimated population prevalence obtained through the meta-analysis reported in Chapter 2.

Table 5. 2

Participant characteristics and estimated population characteristics taken from meta-analytic data in Chapter 2.

Criterion	Study Sample % with each characteristic (n = 13) %(n)	Estimated Population prevalence
CHD7	92% (12)	84%
Coloboma	92% (12)	84%
Choanal Atresia	38% (5)	51%
Anosmia	46% (6)	39%
Facial Palsy	62% (8)	46%
Feeding and Swallowing Difficulties	85% (11)	80%
External Ear Anomalies	69% (9)	85%
Middle Ear Anomalies	62% (8)	50%
Inner Ear Anomalies	69% (9)	75%
Hearing Impairment	85% (11)	87%
Heart Defect	77% (10)	75%
Growth Deficiency	69% (9)	66%
Cleft Lip or Pallet	31% (4)	20%
Tracheoesophageal fistula	23% (3)	15%
Urinary tract problems	15% (2)	25%
Structural Brain Anomalies	31% (4)	43%
Skeletal or limb abnormalities	38% (5)	39%

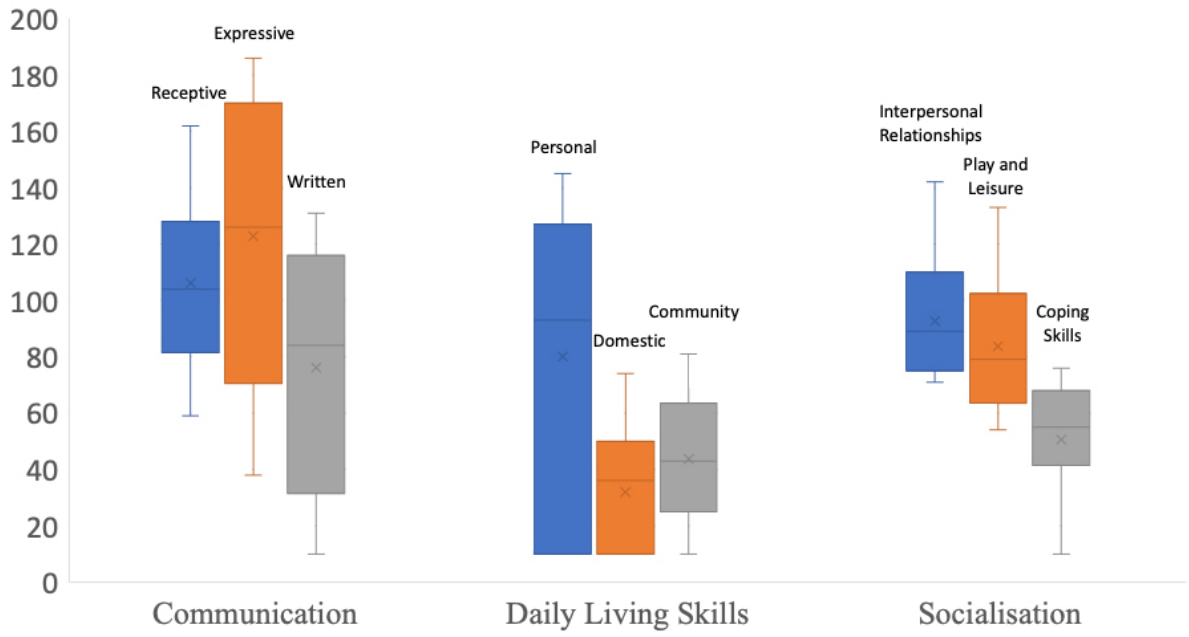
Note. Number of participants is low, however, percentages are used for the purpose of contrast

5.3.3.3 Adaptive behaviour

VABS adaptive behaviour growth scale values are illustrated in Figure 2. The VABS measure is available in Appendix 5C. The highest scores were achieved for the Expressive Communication domain (μ = 122.85, SD = 52.25) and the lowest scores were achieved for the Domestic subscale of the Daily Living Skills domain (μ = 32, SD = 23.24). The median ABC score for the sample was 42 (IQR 46) ranging from 22 to 88. Details of the VABS can be found in section 5.3.4.1.

Figure 5. 2

Growth Scale Scores and Error Bars for the Communication, Daily Living and Socialisation Scores of the VABS. Lines Inside Boxes Represent Mean Scores and Crosses Represent the Median Score



Note. N = 13

5.3.4. Measures

Three informant interviews formed the core measures for the study: the Vineland Adaptive Behavior Scales – III (VABS; Sparrow et al., 2016), the Challenging Behaviour Interview (CBI; Oliver et al., 2003) and the Questions About Behavioural Function (QABF; Matson & Vollmer, 1995). A copy of all measures can be found in Appendix 5B

5.3.4.1 Vineland Adaptive Behavior Scales - III (VABS: Sparrow et al., 2016)

The VABS was developed to support the diagnosis of intellectual and developmental disabilities, as poor adaptive functioning is one component of intellectual disability (Sparrow et al., 1984). Hence, the VABS provides a proxy estimate of intellectual disability for research purposes in children with CHARGE syndrome, where standardised IQ assessments might be confounded by hearing and/or visual impairment. The VABS is a semi-structured interview suitable for carers of individuals with an intellectual disability. It generates standard and growth scale values for communication, daily living skills, socialisation, and motor skills, along with an adaptive behaviour composite score (ABC) used to estimate adaptive functioning, which can be used as a proxy for intellectual disability.

The norm-referenced scores of the VABS are less reliable at the extreme ends of the score distribution, leading to floor effects and increased measurement error for individuals with intellectual disability (Farmer et al., 2020). Therefore, where possible, the present study used growth scale values (GSV) that serve as an index of ability derived from item response theory. GSVs are available at the subdomain level. The Vineland-3 was calibrated using the Andrich rating scale model (Daniel & Vannier, 2022). To convert ability scores to GSVs, a

coefficient of 9.1024 was applied along with a subdomain-specific constant (determined through joint maximum likelihood) to ensure a minimum GSV of 10 (Daniel & Vannier, 2022). The maximum GSV varies from 110 to 197 based on the specific subdomain. It is therefore not possible to compare across scales. These values can be obtained through a lookup table corresponding to raw subdomain scores, which is publicly accessible. Therefore, there are several benefits of using a GSV. Unlike norm referenced scores which can show ceiling and floor effects, GSVs provide a more accurate account of an individual's abilities over a broader range (Daniel & Vannier, 2022). GSVs offer a continuous scale that can be used to accurately track change over time. Furthermore, the GSV provides a way of taking a nuanced and reliable look at adaptive behaviour. This is particularly useful for samples where results tend to cluster at extremes. The Vineland-3 demonstrates excellent internal consistency, ranging from 0.94 to 0.99, and test-retest reliability, ranging from 0.64 to 0.94 (Pepperdine & McCrimmon, 2018).

5.3.4.2 The Challenging Behaviour Interview (CBI: Oliver et al., 2003)

The CBI (see Appendix 5E) consists of two parts: Part 1 asks parents/caregivers whether their child has presented with any of thirteen types of challenging behaviour over the previous month. Part 2 investigates two behaviours identified in Part 1 in more detail. These behaviours include aggression (if selected) and the behaviour the parent/caregiver felt was most concerning (if not aggression). Part 2 includes fourteen questions exploring the frequency, duration, and impact of both behaviours on the child and their environment. The cumulative scores for both behaviours can be added to calculate an overall severity score, although this approach combines scores across different dimensions. Higher scores indicate a higher level of severity. The CBI is psychometrically robust when used with individuals with

intellectual disability: Inter-rater reliability: 0.69; test–retest reliability: Pearson's r = 0.90 (Oliver et al., 2003).

5.3.4.3 Questions About Behavioural Function (QABF: Matson & Vollmer, 1995)

The QABF (see Appendix 5D) is a functional assessment questionnaire to explore a clearly operationalised behaviour's potential function or functions. The present study used the QABF as an interview with parents and caregivers to allow for any questions to be easily addressed. The behaviour of interest in the present study was aggressive behaviour, as determined by the findings of Chapter 2, which revealed it to be the most prevalent behaviour (48%). This pragmatic approach, a focus on aggressive behaviour, was taken as the results are likely to yield the most benefit to understanding behaviour in CHARGE syndrome. Aggression was operationalised based on the description of aggression in the Challenging Behaviour Interview "A non-accidental, physical act involving physical contact with another person likely to result in pain or distress" (CBI: Oliver et al., 2003). Parents were asked if there were any other behaviours of concern. This second behaviour is based on the parent/caregiver's choice of topographical class of behaviour. In cases where participants did not exhibit aggressive behaviour, the parent/caregiver's identified behaviour of concern was used. Conversely, if the parent/caregiver solely reported aggressive behaviour as their concern, the interview solely focused on aggressive behaviour.

The fundamental premise of the QABF (the evaluation of associations between behaviour and environmental consequences) is analogous to that of experimental functional behavioural analysis. Twenty-five interview questions pertain to five potential functions of behaviour: accessing social attention, escape from demands, accessing tangibles, sensory sensitivity and

reinstatement of routine or repetitive behaviour. There are five questions related to each subgroup, and questions are scored on a four-point Likert scale: *Never* (0), *Rarely* (1), *Some* (2), *Often* (3) with an option for *Does not Apply*. The function of a behaviour is inferred by the endorsement (score of 1-3) of at least four questions in a single subgroup. Behaviours may have more than one function or may have secondary functions. A severity score (from 0-15) can be calculated for each subscale by adding the scores (0-3) given for each of the five questions within that subgroup.

Internal consistency for the QABF ranges from .79-.99, and test-retest reliability is good, ranging from .64 to 1.0 (Paclawskyj et al., 2000). The QABF has been extended to include fifteen additional questions related to three well-documented functions of behaviour reported in children with neurodevelopmental conditions, including escape from social attention, reinstatement of routine/repetitive behaviour, and pain (Richards, 2012).

5.3.4.4 CBI Triage Algorithm

An algorithm was developed for the present study to triage CBI scores to provide severity ratings useful for research and practice. The algorithm gives participants one rating for frequency of behaviours that challenge and one for Impact of behaviours that challenge. Impact and frequency can be rated as either Mild, Moderate or Severe. Intervention statements are then applied to these ratings. Participants receive two ratings, one for urgency (1-3) and one for need (1-3). Additionally, a statement is made regarding whether a function and therefore the basis of a targeted intervention has been identified. The triage algorithm is set out below.

The Triage Algorithm

The aim is to triage the CBI scores for any behaviour or person in a way that is clinically meaningful and easily understood. The triage algorithm simplifies assessment, prioritises interventions, facilitates communication, targets behaviours, optimises resources, and supports data-driven decisions.

Participants receive two ratings, one for frequency [low, moderate, high] and one for impact [low, moderate high].

Frequency

The frequency of challenging behaviour is rated as follows.

Frequency is rated **low** if:

- if the person shows the behaviour weekly or monthly (score of 1 or 2 on frequency)

Frequency is rated **moderate** if:

- if the person shows the behaviour daily (score of 3 on frequency)

Frequency is rated **high** if:

- if the person shows the behaviour every 15 minutes or every hour (score of 4 or 5 on frequency)

Impact

The impact of challenging behaviour is rated **low** when the outcome is no more than the following:

- Duration of less than 5 minutes (score of 2 or less for duration)
- Response of verbal discouragement or nothing (score of 1 or 0 for response)
- Minor or no effect on physical health (score of 1 or 0 for physical health)
- Disruption or mild damage or no damage to the environment (score of 1 or 0 for environment)

The impact of challenging behaviour is rated as **moderate** when the outcome meets the following:

- Duration of between 5 and 15 minutes (score of 3 for duration)
- Response of informal physical intervention (score of 2 for response)
- Moderate effect on physical health (score of 2 for physical health)
- Moderate damage to the environment (score of 2 for environment)

The impact of challenging behaviour is rated as **high** when the following outcomes are met:

- Duration of more than 15 minutes (score of 4 or 5 for duration)
- Response of a physical intervention by more than one person or seclusion (score of 3 or 4 for response
- Significant effect on physical health (score of 3 for physical health)
- Significant or extreme damage to the environment (score of 3 or 4 for environment)

Intervention Statements

The objective is to provide clear intervention statements based on triage scores, which can effectively determine the level of urgency and necessary actions required in each situation.

These intervention statements serve as tools for establishing intervention priorities and defining targets for clinical settings.

Participants receive two statements, one for urgency [1,2,3] and one for need [1,2,3]. Additionally, a statement is made regarding whether a function and therefore the basis of a targeted intervention has been identified.

Urgency

Urgency is rated **1** (watchful waiting) if:

- If frequency is rated low

Urgency is rated **2** (assessment required) if:

- If frequency is rated moderate

Urgency is rated **3** (immediate intervention) if:

- If frequency is rated high

Need

Need is rated **1** (watchful waiting) if:

- If impact is rated low

Need is rated **2** (assessment required) if:

- If impact is rated moderate

Need is rated **3** (immediate intervention) if:

- If impact is rated high

Function

Rated as identified if:

- If the function of the behaviour has been identified

Rate as not identified if:

- If no function of behaviours has been identified

5.3.5 Data analysis

The present study was a case series. Because of the limited sample size, it was not appropriate to apply inferential statistics, and therefore a power analysis, that require a larger sample to draw broader conclusions. To address the first aim, the severity of aggression and the behaviour of most concern to parents and caregivers was described using the triage algorithm. To address the second research objective, analysis described the function of behaviours that challenge using the QABF.

5.3.6 Procedure

Participants first completed consent forms and background information on the platform Qualtrics. Secondly, participants completed the CBI and then the QABF over the phone or through video conferencing. Interviews took approximately two to three hours in total to complete, and participants could split the interviews over two or more days as required. Information and consent forms and interview forms are available in Appendix 5C.

5.4. Results

5.4.1. Challenging Behaviour Interview

The first aim of this study was to describe the severity of aggression and behaviours of most concern to parents/caregivers. The results from the challenging behaviour interview are summarised to address this aim.

5.4.1.1 Aggression

All 13 parents and caregivers reported that their child had engaged in aggressive behaviour the month before the research interview. The primary concern for three parents and caregivers (CS01, CS41, CS44) was their child's aggression. As presented in Table 5.3, two children received the maximum score of high frequency, high impact, and one child received the minimum score of low frequency, low impact.

Table 5. 3

Severity Ratings Taken from the Challenging Behaviour Interview (CBI) and the Triage Algorithm. Cells in the Table Contains Symbols (+, -) Representing the Severity of Each Category from the CBI

	Frequency	Duration	Response	Physical Health	Environment	Frequency	Impact
Aggression							
CS01	+	++++	++	+	-	Low	**High**
CS04	++	++	++	-	-	Low	Moderate
CS05	+++	+++++	++	++	-	Moderate	**High**
CS09	+++++	++	+++	++	+	**High**	**High**
CS18	++	++++	+++	+	++	Low	**High**
CS23	+++	+++++	+++	++	+++	Moderate	**High**
CS30	+++	++++	++	+	+	Moderate	**High**
CS31	++	+	++	+	+	Low	Moderate
CS34	+++++	+++++	+++	++	++++	**High**	**High**
CS40	+++	++	++	+	+++	Moderate	**High**

	Frequency	Duration	Response	Physical Health	Environment	Frequency	Impact
CS41	++	++++	++	-	-	Low	**High**
CS44	++	++	++	+	-	Low	Moderate
CS48	++	+	+	-	-	Low	Low
Self-Injurious Behaviour							
CS05	+++	+++++	++	++	-	Moderate	**High**
CS09	+++++	++	++	++	+	**High**	Moderate
CS18	+++	+	+++	++	++	Moderate	**High**
CS23	+++	+++	++	++	-	Moderate	Moderate
CS30	+++	+++	++	++	-	Moderate	Moderate
CS31	+++	+	++	++	-	Moderate	Moderate
CS40	++++	+++	++	++	-	**High**	Moderate
CS48	++	+	+	+	-	Low	Low
Destruction of property							
CS04	+	++	++	-	-	Low	Moderate

	Frequency	Duration	Response	Physical Health	Environment	Frequency	Impact
Inappropriate Vocalisations							
CS34	+++++	+++++	+	++	++++	**High**	**High**

Frequency: + = By this time next month. ++ = By this time next week. +++ By this time tomorrow. ++++ In the next hour +++++ In the next 15 minutes. Duration: + = Less than a minute. ++ = Less that 5 minutes. +++ = Less than 15 minutes. ++++ = Less than an hour. +++++ = More than an hour. Response: - = Nothing. + = Verbal discouragement or reminder. ++ = Informal physical intervention by one member of staff. +++ = Informal physical intervention by more than one member of staff. Formal restraint procedure. Protective or restrictive devices employed. ++++ = Seclusion. PRN medication. Legal involvement or legal advice has been sought. Section of mental health act invoked. Physical health: - = No effect at all. + = Minor, temporary injury. ++ = Moderate injury. +++ = Significant injury. Environment: - = No damage or loss at all. + = Disruption or mild damage. ++ = Moderate damage. +++ = Significant damage. ++++ = Extreme damage.

5.4.1.2 Self injurious behaviour

Another behaviour that concerned eight parents and caregivers was self-injurious behaviour. As presented in Table 5.3, two children received a high frequency, moderate impact score, three received moderate frequency high impact scores, and three received moderate frequency moderate impact. One child received the score low-frequency low impact.

5.4.1.3 Destruction of property

CS04 was reported to exhibit destruction of property, the most concerning behaviour for this child, approximately once a month. As presented in Table 5.3, this child achieved a score of low frequency, moderate impact.

5.4.1.4 Inappropriate Vocalisations

CS34 was reported to show inappropriate vocalisations, the most concerning behaviour for this child, approximately every 15 minutes. As presented in Table 5.3, this child achieved the highest score: high frequency high impact.

5.4.1.5 Summary

Two of the thirteen children in the analysis received at least one high-frequency, high-impact score. Nine of thirteen children engaged in at least one behaviour that scored high impact. Eight children engaged in behaviours that occurred with at least moderate frequency, and twelve children engaged in behaviour that was scored as at least moderate impact.

5.4.1.6 Severity Ratings

Table 5.3 presents the severity of each type of behaviour assessed. The severity score was drawn from the scoring algorithm. Three participants received the highest rating of high-frequency, high impact. The most common rating was moderate frequency and high impact and the least common ratings were low-frequency, low impact, and high-frequency moderate impact.

5.4.1.7 Intervention Recommendations

Based on the scoring Algorithm, Urgency was rated 1 [watchful waiting] for seven participants, 2 [assessment needed] for five children, and 3 [immediate intervention] for three children. Regarding Need, one child was rated 1 [watchful waiting], three children were rated 2 [assessment needed] and nine children were rated 3 [immediate intervention].

5.4.2 Function of Behaviour

To address the second research objective, the analysis investigated the function of behaviours that challenge (see Table 5.4). The most endorsed function of aggressive behaviour was the reinstatement of routine or repetitive behaviour. This was a primary (the only) function for only one participant. The next most endorsed functions of aggressive behaviour were sensory sensitivity and pain and discomfort. The most endorsed function of self-injurious behaviour was the reinstatement of routine or repetitive behaviour followed by escape from demands and pain and discomfort. The function endorsed for inappropriate vocalisations was sensory sensitivity and this was a primary function. No function of

behaviour was endorsed for the parent who reported destruction of property as a concern. The most commonly endorsed function of behaviour was reinstatement of routine (n = 14), followed by sensory sensitivity (n = 12) and pain and discomfort (n = 12).

Table 5. 4

Functions of Aggressive and Self-Injurious Behaviour, Destruction of Property and Inappropriate Vocalisations Taken from the QABF.

Cells in the Table Contain Symbols (+/-) representing the presence or absence of behavioural function

	Communication Functions					Sensory Functions				
	Attention	**Escape from Attention**	**Escape from Demands**	**Access to Tangibles**	**Reinstatement of Routine**	**Self-Stimulation**	**Sensory Sensitivity**	**Pain / Discomfort**	**Any Communication Function**	**Any Sensory Function**
Aggression										
CS01	-	-	-	-	-	-	-	-	-	-
CS04	-	-	+	-	+	-	-	+	+	-
CS05	-	+	-	-	+	-	+	+	+	+
CS09	-	+	+	+	+	-	+	-	+	+
CS18	-	+	+	-	+	-	-	+	+	-
CS23	+	+	+	+	+	-	+	+	+	+
CS30	-	-	+	+	+	-	+	+	+	+
CS31	-	-	-	-	-	-	-	-	-	-
CS34	-	-	+	-	-	-	+	-	+	+
CS40	-	-	-	-	-	-	+	+	-	+
CS41	-	-	-	-	+	-	-	-	+	-
CS44	+	-	-	+	+	-	+	+	+	+
CS48	-	-	-	-	-	-	-	-	-	-
Total	**2**	**4**	**6**	**4**	**8**	**0**	**7**	**7**	**9**	**7**
Self-Injurious Behaviour										

	Communication Functions					Sensory Functions				
	Attention	**Escape from Attention**	**Escape from Demands**	**Access to Tangibles**	**Reinstatement of Routine**	**Self-Stimulation**	**Sensory Sensitivity**	**Pain / Discomfort**	**Any Communication Function**	**Any Sensory Function**
CS05	-	+	-	-	+	-	+	+	+	+
CS09	-	+	+	+	+	-	+	-	+	+
CS18	-	+	+	-	+	-	-	+	+	-
CS23	+	+	+	-	+	+	-	+	+	+
CS30	-	-	+	-	+	-	+	+	+	+
CS31	-	-	-	-	-	-	-	-	-	-
CS40	-	-	+	-	+	+	+	+	+	+
CS48	-	-	-	-	-	-	-	-	-	-
Total	**1**	**4**	**5**	**1**	**6**	**2**	**4**	**5**	**6**	**5**
Destruction of Property										
CS04	-	-	-	-	-	-	-	-	-	-
Total	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Inappropriate Vocalisations										
CS34	-	-	-	-	-	-	+	-	-	+
Total	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**1**
All behaviour										
Total Sum	**3**	**8**	**11**	**5**	**14**	**2**	**12**	**12**	**15**	**13**

Note. + = function of behaviours. - = no function of behaviour

5.4.3 Summary

As presented in Table 5.5, two children scored the highest severity rating (high, high) for their most difficult behaviour, and one participant scored the lowest (low, low). The function of behaviour for ten of the thirteen children was communicative, and the function was sensory for seven of the thirteen children. Pain and discomfort were the function of behaviour for seven of thirteen children, and for three of thirteen children, there was no identifiable function for the behaviours assessed. The functions of behaviour were primary for two participants.

Table 5. 5

Summary table of child level data

	Age (years)	ABC score	Most difficult behaviour	Severity of most difficult behaviour	Highest Intervention Statement	Communication Function	Sensory Function	Pain Function
CS01	4.11	74	Aggression	Low/**High**	Immediate intervention	-	-	-
CS04	10.0	66	Aggression	Low/Moderate	Assessment required	+	-	+
CS05	13.6	22	Aggression	Moderate/**High**	Immediate intervention	+	+	+
CS09	9.10	40	Aggression	**High**/**High**	Immediate intervention	+	+	-
CS18	14.0	22	Self-injurious behaviour	Moderate/**High**	Immediate intervention	+	-	+
CS23	9.9	84	Aggression	Moderate/**High**	Immediate intervention	+	+	+
CS30	7.5	31	Aggression	Moderate/**High**	Immediate intervention	+	+	+

	Age (years)	ABC score	Most difficult behaviour	Severity of most difficult behaviour	Highest Intervention Statement	Communication Function	Sensory Function	Pain Function
CS31	5.9	39	Self-injurious behaviour	Moderate/Moderate	Assessment required	-	-	-
CS34	14.8	61	Aggression	**High**/**High**	Immediate intervention	+	+	-
CS40	12.7	42	Aggression	Moderate/**High**	Immediate intervention	+	+	+
CS41	11.7	88	Aggression	Low/**High**	Immediate intervention	+	-	-
CS44	10.2	35	Aggression	Low/Moderate	Assessment required	+	+	+
CS48	5.2	84	Aggression	Low/Low	Watchful waiting	-	-	-

Note. The most difficult behaviour is the behaviour selected as the highest frequency and impact. If the frequency and impact were rated the same for two forms of behaviour, aggression was considered the most difficult behaviour.

5.5 Discussion

The current study adds to the limited body of research on behaviour in children with CHARGE syndrome. A strength of this research lies in its use of validated measures tailored for individuals with intellectual disabilities. This represents a notable strength because a substantial portion of the existing literature has relied on single questions or unvalidated questionnaires.

Having examined the form and function of behaviours that challenge in children with CHARGE syndrome, this chapter will now explore the implications of these findings. This section will discuss insights into these behaviours and outline future research directions.

5.5.1 The Triage Algorithm

The triage algorithm was created to help rate the severity of behaviours that challenge behaviours for use in research and practice. This has several benefits for clinical use. Firstly, it provides a structured and consistent assessment process, assigning ratings for frequency and impact across participants. Participants are assessed using the same criteria facilitating communication between practitioners. Secondly, by using frequency and impact scores to develop urgency and need outcomes the algorithm given practitioners clean intervention priorities. This is particularly important in practices with limited resources. Thirdly, the algorithm, along with the Function of Behaviour questionnaire, can be used to guide practitioners regarding the function of behaviour. This can form the basis for targeted interventions such as applied behaviour analysis. Finally, the triage algorithm can be used to monitor the need for intervention over time. For example, practitioners can monitor the effectiveness of intervention strategies.

5.5.2 Severity and Characteristics of Challenging Behaviours

5.5.2.1 Aggressive Behaviour

All 13 participants presented with varying degrees of aggressive behaviour, each exhibiting different frequencies and levels of impact. For two participants, aggressive behaviour was of high frequency and high impact (occurring approximately every 15 minutes and resulting in moderate injuries). Nine participants' ratings met level 3 intervention for either urgency or need, suggesting the requirement for immediate intervention. Three children's ratings met level 2 intervention based on moderate scores for impact, suggesting the requirement for assessment. One child's rating met level 1 intervention, suggesting a watchful waiting approach. Trider et al. (2017) suggest behaviour management is monitored from three years of age and adjunct therapies are recommended for behaviours that challenge, including music and pet therapies. Understanding the diverse range of aggressive behaviours exhibited by these children is essential for tailoring effective interventions.

Aggression is part of the behavioural phenotype of genetic syndromes associated with intellectual disability including fragile X syndrome. Given the 48% prevalence of aggressive behaviour outlined in section 2.4.7 aggressive behaviour may also form part of the behavioural phenotype of CHARGE syndrome.

5.5.2.2 Self-Injurious Behaviour

Eight out of thirteen parents and caregivers expressed concerns about their child's self-injurious behaviour. None of the participants reported self-injurious behaviour as having a

high frequency and high impact. However, for two participants, self-injurious behaviour was characterised by a high frequency and moderate impact. In these cases, the behaviour occurred either every hour or every 15 minutes, resulting in moderate injuries and requiring informal physical intervention. Ratings for four of the eight children suggested a level 3 immediate intervention. This was based on urgency for two of these children, and for two, it was based on need. Three participant's ratings met level 2 for intervention, suggesting the requirement for an assessment. One participant's ratings met level 1 for intervention, suggesting watchful waiting.

As discussed in section 5.1.1, in line with the findings of this chapter, self-injurious behaviour is consistently identified as one of the most distressing issues for parents and care providers (Griffith & Hastings, 2014). Such behaviours can devastate physical health and increase social isolation (Hastings et al., 2013). Therefore, addressing and effectively managing self-injurious behaviour is essential to ensure the child and their family's well-being and overall quality of life. This should be considered an urgent research priority.

5.5.2.3 Summary

Nine of thirteen children assessed using the CBI presented with behaviours that required immediate intervention. Three of thirteen children presented with behaviour requiring assessment, and one child presented with behaviour that required watchful waiting.

5.5.3 Functions of Behaviours that Challenge

5.5.3.1 Functions of Aggressive Behaviour

The most endorsed function of aggressive behaviour was the reinstatement of routine, followed by sensory sensitivity and pain and discomfort. Reinstatement of routine is commonly associated with autism, and autism is reported in 28% of individuals with CHARGE syndrome (see section 2.4.7). This prevalence is considerably higher than for individuals with intellectual disability (18%) or the general population (0.6 to 1.11%) (Tonnsen et al., 2016). However, reinstatement of routine could also be associated with obsessive-compulsive behaviour, which is seen in 36% of individuals with CHARGE syndrome (see section 2.4.7). Therefore, conducting a thorough clinical investigation exploring autism and obsessive-compulsive disorders as well as closely related conditions such as anxiety is essential to elucidate the causal mechanisms involved in these associations.

Similarly, sensory sensitivity is a characteristic associated with autism (Robertson & Simmons, 2013). However, CHARGE syndrome is primarily characterised by multisensory impairment, suggesting a potential connection between sensory issues and this syndrome. Indeed, in their assessment of 'autistic-like' behaviour in CHARGE syndrome Hartshorne et al. (2005) reported more sensory characteristics in CHARGE syndrome than in their autism or deafblind cohort. The third most frequent function of aggressive behaviour was pain and discomfort, endorsed by seven of thirteen parents and caregivers. Understanding the underlying causes of behaviour can guide intervention strategies, but it is challenging to identify pain in children who have a limited ability to communicate their discomfort (section 1.1.14.3). Given the substantial prevalence of pain and discomfort among individuals with

CHARGE syndrome (section 1.1.14.3) and the notable number of parents and caregivers who have identified these as potential triggers for aggressive behaviour in this study, practitioners should consider the possibility of pain and discomfort when addressing instances of aggressive behaviour. In particular, pain and discomfort should be excluded before lengthy functional assessments of external contingencies are undertaken.

5.5.3.2 Functions of Self-Injurious Behaviour

The most endorsed function of self-injurious behaviour was the reinstatement of routine, followed by pain and discomfort and escape from demands. Notably, reinstatement of routine and pain and discomfort are common functions for aggressive and self-injurious behaviour. This emphasises the importance of clinicians considering these as possible functions across behaviours as certain functions can serve multiple functions.

5.5.3.3 Functions of Other Behaviours that Challenge

Sensory sensitivity was endorsed for inappropriate vocalisations, while no specific function could be identified for property destruction. There are several reasons why a function was not identified for property destruction. Firstly, property destruction may not have been severe enough to identify a clear function of behaviour given that it was a relatively infrequent and moderately impactful behaviour. Secondly, the QABF assesses common, and not all, functions of behaviour. Therefore, the QABF may not be sensitive enough to capture potentially nuanced functions of behaviour in this instance. Thirdly, while most behaviours can be understood from a behavioural perspective not all behaviours have a specific function; some may be less problematic for various reasons, such as occurring intermittently.

5.5.4 Limitations

The study has several limitations. The findings are based on a case series of 13 children with CHARGE syndrome. These children may not be representative of the CHARGE syndrome population for several reasons. The sample was recruited during the COVID pandemic. The pandemic was an extremely anxiety provoking situation for parents who would have been concerned about their child contracting a life-threatening disease, particularly given their compromised immune system (Theodoropoulos, 2003). Restrictions imposed varied by country, region and medical status, with individual's considered as medically vulnerable facing the most stringent conditions (Sanders 2020). As such, it is possible the parents that took part in the study had more resources giving them time to take part in this time intensive research, and that the children involved in the research had less medical challenges. However, it is notable that Children with CHARGE syndrome may have experienced more behavioral challenges during the COVID pandemic. Using an operant learning paradigm, the COVID pandemic can be conceptualised as an aversive stimulus that provokes anxiety. The anxiety-inducing nature of the pandemic likely exacerbated existing behavioural dynamics, reinforcing certain behaviours and potentially intensifying behaviours that challenge. This is particularly notable in CHARGE syndrome where multiple environmental influences may be present. Results should be interpreted with this in mind.

There was no power analysis conducted for the present study. The study was descriptive and did not have a sample size large enough for inferential statistics. In the context of this case series the emphasis was on descriptive and exploratory analysis. inferential statistics allow for

results to be generalised to the populations whereas descriptive statistics cannot be generalised past the sample in the study. Larger studies have statistical power which gives the study an increased chance of identifying a true effect, reducing the risk of Type II errors. The larger sample will likely be a more homogenous sample, with less opportunity for outliers. It is possible to be more confident in the findings, especially when dealing with small effect sizes or complex associations. However, small samples with descriptive statistics, as used in the present study, also have their strengths. The present study has provided preliminary insight and an in-depth examination of behaviour in a rare, complex genetic syndrome that would be difficult to capture in a larger study. The descriptive statistics used help explain patterns in individual variability. Furthermore, initial data collection from case series can lead to hypothesis generation for future research. Case series studies are simpler to conduct and less expensive than a cohort or case control study. Case series are particularly useful for conditions like CHARGE syndrome where few participants are available. Despite its limitations, this study offers a primary insight into behaviors that challenge in children with CHARGE syndrome. Case series studies, while limited, are useful for rare conditions, allowing initial data collection and hypothesis generation for future research.

It is also important to compare groups of individuals that are similar to CHARGE syndrome to better understand how CHARGE syndrome affects behaviour. Use of a well thought out comparison group in future studies can help highlight the unique behavioural characteristics linked to this condition.

It was also a limitation that the study only recruited children with CHARGE syndrome as the results cannot be generalised to adults with the condition. The small sample would also have been larger if adults were included. However, the decision was deliberate and pragmatic. The function of behaviour is likely to be different for adults than it is for children. This is because children's behaviours are plausibly driven by exploring and learning about their environment and learning to communicate. Because of this, the functions of behaviour are likely to be gaining attention, sensory stimulation and escape from demands. The function of behaviour may be different for adults who may have learned certain skills to deal with environmental stressors and whose communication is more developed.

There were several limitations in the triage algorithm that require consideration. As noted, in section 5.2.1 regarding RCT trials, pharmacological and non-pharmacological interventions yield relatively small effects (Groves et al., 2023). The knowledge base is small and underpowered and reporting of behaviours requires greater precision (Groves et al., 2023). The present study is indeed underpowered and behaviours are reported at a gross level with no reference to the typology of behaviour.

The triage algorithm relies on subjective reports and provides limited contextual information. The triage algorithm is based on a subjective report, the Challenging Behaviour Interview, rather than direct observation of behaviour. Subjective measures can be compromised on consistency and reliability by the informant's expectations or personal beliefs (Durand & Crimmins, 1988). The triage algorithm also provides little information about contextual factors. Factors may include changes in the child's environment, personal

history or environmental triggers. As such the triage algorithm may lead to misinterpretation of the severity and cause of the behaviour.

Additional limitations should be considered regarding the Function of Behaviour Questionnaire. The function of behaviour questionnaire is quick and easy to administer, it is cost effective and facilitates communication between practitioners. However, the Functional Behaviour questionnaire relies on data reported by parents which can be biased or inaccurate. It lacks depth and detail to allow investigation of multifaceted behaviours and unlike Functional behavioural analysis, the Function of Behaviour Questionnaire cannot be used to test hypothesis and therefor identify causal mechanisms. The Function of Behaviour Questionnaire is based on the principles of operant learning theory, the process where behaviour is shaped by consequences, using positive or negative reinforcement. There are several limitations with operant learning theory that should also be considered. Operant learning theory simplifies complex behaviours by reducing them to stimulus response outcomes. It does not take account of the role of social and cultural contexts on behaviour, or alternative learning strategies such as observational learning. It cannot account for genetic differences and biological factors and there are ethical concerns about its application, for example, where a child's behaviour issues may be stimulated for experimental purposes. However, operant learning theory is supported by a large body of empirical research and is widely accepted by practitioners (Hanley et al., 2003). It focuses on observable behaviours and so is amenable to measurement. It explains how behaviour is shaped through reinforcement (positive and negative) and punishment. This leads to precise interventions through, for example, positive behaviour supports.

Furthermore, due to the scope of this study, not all behaviours and functional aspects of behaviour could be comprehensively examined. Therefore, it is essential to recognise that the analysis was not exhaustive, and additional behaviours and functional dimensions may warrant investigation. For example, there may be an interaction between factors. Pain could be a setting event that means that on a certain day the person is much less likely to want to shift from routine and ritualised behaviour. Conversely, pain could be a motivating operation in which the person achieves some alleviation from their symptoms through routine and ritualised behaviour. Subsequent research should explore these unexamined aspects to understand CHARGE syndrome-related behaviours and functions comprehensively. A multifaceted assessment incorporating observation measures may improve future research. The findings from the present study provide a foundation for such investigations.

5.5.5 Conclusion

In conclusion, this chapter has provided valuable insight into the severity and function of behaviours that challenge for children with CHARGE syndrome. Addressing these issues will enhance the overall well-being and quality of life for children with CHARGE syndrome and their families. The severity and characteristics of aggressive behaviour among the participants highlight the need for further research into whether this behaviour forms part of the behavioural phenotype of CHARGE syndrome. Conducting syndrome profile comparisons, as suggested, can help identify underlying causal mechanisms and shed light on the unique behavioural characteristics associated with this condition. However, as demonstrated in the triage algorithm, the frequency, impact, and function of the behaviour for the individual and

the decision to actively treat is important regardless of whether the behaviour forms part of the phenotype. It is notable that self-injurious behaviour was a concern for parents and caregivers in this study. It is crucial to develop support strategies and interventions to address this behaviour given the potentially negative impact on health and wellbeing. The various functions of behaviours that challenge, including reinstatement of routine, sensory sensitivity, and pain and discomfort highlight the potential overlap of different behaviours. It is important for clinicians and researchers to consider these functions when designing interventions for persons with CHARGE syndrome.

CHAPTER SIX

GENERAL DISCUSSION

6.1 Preface

In this chapter, the findings of all empirical chapters are discussed in the context of the existing literature. Throughout this discussion, the strengths, limitations, and implications of these findings will be explored as well as their relevance to clinical applications, future research, and the behavioural phenotype of CHARGE syndrome.

6.2 Introduction

CHARGE syndrome is a multisystem congenital disorder with an estimated prevalence of 1 in 8,500 births. CHARGE Syndrome belongs to a class of rare conditions called neurocristopathies (see section 2.2.2). Neurocristopathies are characteristically heterogeneous and phenotypically complex conditions affecting cardiac, vagal, trunk and sacral development (Bérubé-Simard & Pilon, 2019). As such, all associated characteristics vary from severe to absent in CHARGE syndrome, manifesting in different combinations across individuals. This heterogeneous phenotype is thus challenging to predict and is typically managed through multidisciplinary clinics. Therefore, conducting a comprehensive meta-analysis in Chapter 2 was beneficial to elucidate the phenotypic variability in CHARGE syndrome. This approach allowed for a more precise outline of clinical manifestations and the potential for therapeutic insights. As such, Chapter 2 addressed the first aim of the thesis: To identify and estimate the prevalence of behavioural, cognitive, and physical characteristics and conditions among persons with CHARGE syndrome and to explore putative associations between these characteristics.

While the physical phenotype of CHARGE syndrome has been extensively documented (see section 2.2.4), more research was needed into the behavioural phenotype of CHARGE. Research to date consisted of poor-quality large N studies or high-quality small N studies that did not use representative samples. CHARGE syndrome is characteristically heterogeneous, but when considering the partial specificity model, certain behaviours are likely more prevalent in individuals with CHARGE syndrome than those without the condition: the behavioural phenotype. Chapter 3 investigated the behavioural phenotype of CHARGE syndrome and addressed the second research aim: To explore the profile of behaviours, skills and challenges in children with CHARGE syndrome and describe how this profile compares to children without CHARGE syndrome.

The results of Chapters 2 and 3 highlighted the high prevalence of sleep disturbance in CHARGE syndrome. Previous sleep research in CHARGE syndrome has predominantly used subjective measurements such as questionnaires. Research had typically used single questions or unvalidated questionnaires leading to poor quality research. The most valid approach to research sleep assessment in neurodevelopmental conditions is to combine objective and subjective measures that capture different aspects of sleep (O'Sullivan et al., 2023). Chapter 4 used this approach to address the third aim of the thesis: to examine the profile of sleep in CHARGE syndrome and investigate possible associations between sleep quality, behaviour, and behavioural indicators of pain. Furthermore, as outlined in section 1.1.11.2, an age-matched, typically developing control group should be used to delineate developmental effects of sleep in CHARGE syndrome. For this reason, Chapter 4 compared objective and subjective sleep parameters between children with CHARGE syndrome and an aged matched

typically developing control group on subjective and objective sleep parameters, addressing the fourth aim: to compare sleep quality between children with CHARGE syndrome and typically developing children.

Finally, the meta-analytic findings in Chapter 2 highlighted a concerningly high prevalence of behaviours that challenge in CHARGE syndrome, specifically aggressive behaviour (48%) and self-injurious behaviour (44%). Based on these findings, Chapter 5 focused on aggressive behaviour and a second behaviour chosen by parents to be of concern. Chapter 5 addressed the final aim of the thesis: to explore common functions of behaviours that challenge in CHARGE syndrome.

6.3 Main Findings

Given the broad aims of this thesis, to facilitate integration and discussion, key findings are synthesised into three themes: phenotypic variability in CHARGE syndrome, behaviours that challenge in CHARGE syndrome and sleep in CHARGE syndrome.

6.3.1 Phenotypic variability in CHARGE syndrome

Chapter 2 presented the first comprehensive meta-analysis of phenotypic characteristics and variability in CHARGE syndrome. The observed heterogeneity in the data was substantial. For instance, the prevalence of intellectual disability ranged from 18% (Dammeyer, 2012) to 100% in the primary data included in the meta-analysis (Asher et al., 1990; Davenport et al., 1986; Hittner et al., 1979; Shoji et al., 2014; Smith et al., 2005). This variability is considerable when compared to other syndromes associated with intellectual disability, for example in 'classical' Cornelia de Lange syndrome and fragile X syndrome in

males where intellectual disability forms part of the diagnostic criteria (Basile et al., 2007; Ciaccio et al., 2017). Since a full understanding of the genetic phenotype is yet to be uncovered (van Ravenswaaij-Arts & Martin, 2017) it is possible that genotype-phenotype correlations may, in the future, be used to describe some of this variability.

There are three reasons why this variability confirms that CHARGE syndrome should be researched independently of intellectual disability. Firstly, the heterogeneity in cognitive profiles of individuals with CHARGE syndrome ranges from no intellectual disability to severe and profound intellectual disability. As such, treating CHARGE syndrome as a synonymous with intellectual disability loses this variability. Secondly, intellectual disability in CHARGE syndrome has a distinct aetiology. When intellectual disability is present, it is only one part of this complex syndrome. Thirdly, the variability of intellectual disability is likely influenced by sleep, pain and behaviour unique to CHARGE syndrome. This may mean that supports and interventions developed for individuals with intellectual disability may not be appropriate for individuals with CHARGE syndrome.

Similarly, the range for autism diagnosis in the meta-analysis papers varied from 6% (Hartshorne & Cypher, 2004) to 60% (Smith et al., 2005). These findings were reflected in the meta-analytic data where autism was reported in 28% of individuals with a wide 95% confidence interval of 16-41%. Such variability has been reported in other genetic syndromes associated with intellectual disability (Richards et al., 2015), for example Cornelia de Lange syndrome where autistic-like behaviour has been reported in between 53% (Berney et al., 1999) and 89% (Bhuiyan et al., 2005). There are several reasons why there may be variability

in reports of prevalence estimates in CHARGE syndrome. Firstly, it is notable that there are no diagnostic tests for Autism that have been validated for use in CHARGE syndrome (Smith et al., 2005). As noted in Chapter 2, there was a wide range of measures used, some of better quality than others. Secondly, variability can be introduced by the researchers' level of experience. CHARGE is a unique syndrome, and few researchers have expertise in working with this population.

Rates of aggression and self-injurious behaviour presented a similar pattern, ranging from 38% (Hartshorne & Cypher, 2004) to 68% (Johansson et al., 2006) for aggression and from 34% (Hartshorne & Cypher, 2004) to 54% (Johansson et al., 2006) for self-injury. Given the small sample sizes and the poor methodological quality identified in Chapter 2, it would be wrong to draw definitive conclusions on prevalence rates from the meta-analysis of these samples. Chapter 3 (Section 3.4.5) indicates that some of the variability in self-injury could be explained by other factors, including mobility, low mood, anxiety and executive function. Similarly, the variability in aggression may be explained by executive functioning, anxiety and gastrointestinal reflux (Section 3.4.5). These associations are likely complex and bidirectional, making them challenging to capture through the simple, two-variable analysis used in the majority of this thesis. However, the work presented in this thesis provides a critical step forward by first robustly describing variability in CHARGE syndrome through meta-analytic techniques and second providing initial exploration of sources of variability through the behavioural phenotype survey correlations.

The variability reported in CHARGE syndrome has important implications for understanding the behavioural phenotype. The heterogeneity in the meta-analysis in Chapter 2

was not well explained by study methods, suggesting that heterogeneity is likely to be explained at the population level. This heterogeneity poses substantial challenges for clinicians when attempting to make predictions regarding the quality of life experienced by individuals with CHARGE syndrome. It also complicates the decision-making process regarding the most effective strategies for providing preventative interventions and counselling families on what to expect in the future for their child. Further research is required to understand the variability in CHARGE syndrome, and this will aid in predicting outcomes and refining the behavioural phenotype. For example, there are factors that have been beyond the scope of this thesis but could explain some of the variability reported, such as social support, or medical or clinical interventions. Further research should explore these factors.

This substantial variability also has implications for the overarching thesis. Using a small data set, stemming from the rarity of CHARGE syndrome, raises concerns about the appropriateness of such a limited dataset. For this reason, the thesis has taken the opportunity to look at averages as well as individual level data where possible. Additionally, there is an increased risk of recruitment bias due to the inherent heterogeneity within the CHARGE syndrome population. These factors should be taken into consideration when interpreting the results from this thesis.

In summary, this thesis has made a considerable contribution to the existing literature. Using a comprehensive meta-analysis, it was possible to advance what is known about the phenotypic variation in CHARGE syndrome. By emphasising key characteristics such as intellectual disability, autism, aggressive and self-injurious behaviour, it shows the complex

interplay of cognitive, behavioural, and medical factors unique to CHARGE syndrome. Results can be used to advocate for more nuanced, syndrome-specific approaches.

6.3.2 Behaviours that challenge

6.3.2.1 Aggression

The prevalence of aggression, as taken from the meta-analysis conducted in Chapter 2, was 48% (see section 2.4.7). However, the variability was considerable (95% CI 40%-57%). This high prevalence was replicated in Chapter 5, where all participants who engaged in challenging behaviours in the preceding month engaged in aggressive behaviour (N=13). This 100% prevalence rate for aggressive behaviour was higher than that reported for other genetic syndromes associated with intellectual disability (Powis & Oliver, 2014). However, while a 100% prevalence is noteworthy, it is important to consider the role of sample size. Future research should investigate whether this finding is generalisable to the CHARGE syndrome population, in other contexts and environmental factors.

When asked about behaviours of most concern, three of thirteen parents or caregivers referenced aggressive behaviour. Aggressive behaviour was rated as high frequency and high impact for two children, suggesting a need for immediate intervention. As such, while aggression was the most prevalent behaviour for parents and caregivers it was not always the most concerning. When aggressive behaviour is preset, there is a need for immediate intervention. Aggressive behaviour is deeply challenging for children and their families. It affects family dynamics, causing emotional strain and isolation (Cooper et al., 2009; Holden & Gitlesen, 2006). Aggressive behaviour can impact a child's ability to engage in social and educational settings, reducing opportunities to grow and learn. Practitioners should focus on

developing tailored support and interventions that foster inclusion and positive social interactions.

There were different typologies of aggressive behaviour, with “Hit other with Body Part” being the most prevalent in chapter 3. “Hit others with Body Part” was shown by every participant who reported aggressive behaviour in the preceding month. These are novel findings as this level of detail has not been assessed in previous research. Furthermore, it is important to differentiate the typology of aggressive behaviour as comparing behaviours between syndrome groups can help uncover underlying causal mechanisms (Oliver, 2017).

The most endorsed function of aggressive behaviour, identified in Chapter 5, was reinstatement of routine or repetitive behaviour. This finding also supports the work of Bernstein and Denno (2005) who demonstrated reinstatement of routine or repetitive behaviour as a function of behaviours that challenge in an educational setting. Furthermore, Bernstein and Denno (2005) posited that repetitive behaviour may be part of the behavioural phenotype of CHARGE syndrome. Antecedent interventions that increase the availability of the reinforcer (repetitive behaviour) may reduce aggression in teaching sessions. However, this requires further research.

In summary, this thesis provides novel insights into aggressive behaviour in children with CHARGE syndrome. It highlights the prevalence, typologies and functions of aggressive behaviour. Specifically, it looked at prevalence and typologies of aggressive behaviour such as hit other with body part. This adds valuable depth to the existing literature and a provides a starting point for understanding aggression if children with CHARGE syndrome.

6.3.2.2 Self-injurious behaviour

Based on the meta-analysis conducted in Chapter 2, the prevalence of self-injurious behaviour in CHARGE syndrome was 44%. Self-injurious behaviour was the behaviour of most concern in Chapter 5 for eight of thirteen parents and caregivers. As such, self-injurious behaviour was the most concerning behaviour, despite being lower prevalence than aggression. This may be because self-injury has an immediate impact on the child and there is a real risk of long-term physical consequences. Compared to other behaviours, self-injury is particularly difficult to whatness and presents a unique challenge because of the potential for serious injury and need for constant supervision. The presence of self-injurious behaviour is a risk factor for psychiatric hospitalisation, reactive physical intervention and poor quality of life (Richards et al., 2016) indicating that research looking at interventions should be a priority.

The most endorsed function of self-injurious behaviour in Chapter 5 was the reinstatement of routine or repetitive behaviour. Bernstein and Denno (2005) suggest that the requirement for reinstatement of routine and repetitive behaviour may be a manifestation of Obsessive Compulsive Disorder (OCD) in CHARGE syndrome. They suggest that sometimes it is only possible to diagnose OCD when a behavioural intervention for reinstatement of routine and repetitive behaviour has been unsuccessful. This is an important consideration for research and clinical practice. Furthermore, as reinstatement of routine or repetitive behaviour was commonly endorsed for self-injurious behaviour and aggressive behaviour it is plausible that some children with CHARGE syndrome may show clusters of behaviours that share the same

function. If this is the case, prioritising intervention research around one specific function, in this case reinstatement of routine or repetitive behaviour, might be beneficial.

Chapter 3 revealed that the severity of self-injurious behaviour was statistically increased for participants who were more able compared to those classified as not able. This was an unexpected finding, given that self-injury is positively correlated with intellectual disability (Hill & Furniss, 2006; McClintock et al., 2003; section 1.1.7.2). Not able status may reflect the severity of combined sensory impairment rather than intellectual disability. However, it is important to consider the limitations of this analysis, particularly the small sample size which may have limited the power to identify certain associations. Multiple comparisons were adjusted for to limit the risk of Type I errors. However, this approach may be too conservative.

It is notable that there was no statistical difference between the CHARGE syndrome group and the CdLS, autism, LS, DS or ID groups on self-injurious behaviour in Chapter 2. However, it is notable that individuals with CdLS and ID are at heightened risk for self-injury (Davies & Oliver, 2016; Kline et al., 2018). A more fine-grained analysis should be conducted to investigate the role of other factors across syndrome groups, for example environmental or social factors on different typographies of self-injurious behaviour. Such an approach, using a same-but-different methodology (see section 1.1.11.3) can be used to identify causal mechanisms that are invaluable for developing clinical interventions.

This thesis offers a contribution to the understanding of self-injurious behaviour in children with CHARGE syndrome. It emphasises its prevalence and putative correlations with

ability level. The findings indicate that there are unique and immediate challenges that impact the child and their family. Comparative analysis with other syndromes and the call for nuanced investigation lay the groundwork for future cross-syndrome research and clinical strategies.

6.3.2.3 Destruction of property

One parent reported destruction of property in Chapter 5 to be the behaviour of most concern. This behaviour occurred at low frequency and had a moderate impact, suggesting that assessing the behaviour is advisable. The most common form of Destruction of Property in Chapter 3 was “Throwing, kicking or smashing small items”. Unlike aggression and self-injury, which affect the individual and those directly involved, destruction of property has the potential to disrupt the whole family. Destruction of property can be unpredictable and anxiety provoking. For families that may already be experiencing financial and emotional strain destruction of property may be overwhelming. In the context of CHARGE syndrome, “Throwing, kicking or smashing small items” could potentially be a sign of sensory overload or frustration over communication differences. Children with CHARGE syndrome may begin by engaging in minor property destruction such as knocking over or lightly hitting objects. Over time, this behaviour may be shaped into more specific actions, such as throwing, kicking, or smashing small items. Such behaviour may be shaped by an aversive stimulus such as sensory overload. The consequence could be a parent intervening to sooth the child and to prevent further destruction or distress. As such the child learns there is an association between sensory overload and destruction of property such that the behaviour becomes part of a functional strategy for the child. It is important to note that neither the child or the adult should be viewed as being to blame for the situation and ultimately the behaviour.

Understanding the dynamic association between the child's condition and the parent's efforts to provide support enables more compassionate personalised interventions.

In summary, this thesis adds to the limited body of research into destruction of property in children with CHARGE syndrome. Recognising that these behaviours come from sensory overload or frustration shifts the focus from blame to understanding. Further research should work on developing interventions that are compassionate and promote positive behavioural outcomes.

6.3.3 Sleep

The prevalence of sleep difficulties in CHARGE syndrome in the meta-analysis was 45%. However, this may be an underestimate because different studies have different criteria for sleep difficulties (Section 2.4.7). In the thesis, the prevalence of sleep difficulties seems to be even more pronounced. Here, 87% of participants scored above the clinical cutoff for disturbed sleep on the MSPSQ in Chapter 3, and in Chapter 4, this percentage rose to 100%. While it is notable that these are small samples, these results suggest that these samples are considerably higher than the prevalence in the meta-analysis. These could be several reasons for this. Firstly, specific characteristics could be common to the samples in Chapter 3 and 4 that were not common in the meta-analysis. These could include level of sensory difference and pain, both of which potentially affect sleep. Secondly, the use of parent support measures may have skewed the results for example through recall bias. Thirdly, parents that took part in the studies in Chapters 3 and 4 were experiencing restrictions due to COVID. This was an extremely anxious time for parents and their families and it likely had an impact on sleep.

In Chapter 3, the MSPSQ questionnaire revealed the most prevalent sleep problem: Sleep Onset Delay. However, there was considerable variability in scores. The variability may be, in part, associated with the small sample size that limits the generalisability of the results. Furthermore, the study was conducted during the COVID pandemic, a time when families were affected in different ways (see Apendix 1A). This adds a layer of complexity when interpreting the data. It is also possible that variability was introduced by unmeasured variables such as environmental, physiological or cultural differences. A more comprehensive study including more nuanced aspects of the CHARGE syndrome phenotype may explain sleep problems in this population.

Chapter 4 revealed no significant correlation between actigraphy parameters and children's ABC scores, suggesting no association between sleep and adaptive behaviour as measured by the VABS. This finding appears to contradict the intellectual disability literature, where individuals with intellectual disability exhibit more persistent and severe sleep disturbances than individuals without intellectual disability (Browne et al., 2023; Surtees et al., 2018). However, given the heterogeneity in CHARGE syndrome (see section 1.1.14.1) and the small sample size in Chapter 4, the participants with CHARGE syndrome may not have presented with high enough levels of intellectual disability to be associated with sleep disturbances. Furthermore, differences in sleep between individuals with and without an intellectual disability are driven by the presence of syndrome group (Browne et al., 2023). As such future research might also investigate the type of sleep difficulties experienced in more detail.

As outlined in section 4.2.3, the assessment of sleep requires a combination of objective and subjective methods. Although objective methods were used, no significant results were found after adjusting for multiple comparisons where necessary. There was weak evidence for a difference between typically developing children and children with CHARGE syndrome, based on Bayesian t-tests, suggesting that the two groups may exhibit similar objective parameters (e.g., actigraphy). The child who went to sleep the earliest, had the longest total sleep time, had the greatest sleep efficiency and the longest wake after sleep onset. This child was also one of the youngest in the study, which may explain the need for more sleep. Regarding subjective measurement outcome this child reached the threshold for the clinical cut-off for sleep disturbance. They had the lowest score for sleep onset delay and night waking. Thus, taken together, findings from objective and subjective measures give an overall picture of sleep in children with CHARGE syndrome. The lack of significant objective associations between children with CHARGE syndrome and typically developing children suggests that both groups are similar on sleep measures. Overall the results show the complexity of measuring sleep in neurodevelopmental conditions. These findings are clinically important because the typically developing group can serve as a benchmark for assessing developmental challenges related to sleep in the CHARGE syndrome group. This comparison enables a more comprehensive understanding of equity. Further more, these findings strengthen the argument made by O'Sullivan et al. (2023) for the importance of using a combination of subjective and objective measures when assessing sleep in individuals with intellectual disability.

When examining circadian rhythm parameters, there was weak evidence of an association between typically developing children and those with CHARGE syndrome, suggesting that

there may not be a significant difference between the two groups in this area. This is consistent with the lack of strong evidence for differences in subjective or objective sleep measures. These findings are surprising given that previous studies have reported poor sleep in CHARGE syndrome (Hartshorne et al., 2009; Kennert et al., 2020). Howeverthese studies did not use a controle group, which limits direct comparison. Given the developmental nature of sleep, it was a strength of the study in Chapter 4 that it matched children with CHARGE syndrome with typically developing children by age. However the sample used in the study in Chapter 4 was smaller than used by Hartshorne et al. (2009) and Kennert et al. (2020), meaning the sleep data may be less reliable due to the small sample and the variability in CHARGE syndrome.

In summary, this thesis adds the understanding of sleep in CHARGE syndrome using a combination of subjective and objective methods and comparing them with an age matched typically developing cohort. Findings highlight the complex nature of sleep in this population. Results support the need for further research involving larger, well-matched samples and a combination of assessment methods to better characterise sleep disturbances in children with CHARGE syndrome.

6.4 Limitations

While the findings in this thesis are robust, several limitations must be acknowledged, particularly the fact that the research focuses exclusively on children with CHARGE syndrome. Findings are likely not applicable to adults with CHARGE syndrome as developmental stages can significantly influence outcomes associated with behaviour, cognition and sleep. Without collecting information about adults, the study has missed invaluable data about how behaviour manifests, persists or worsens over time. Furthermore,

adults with CHARGE syndrome experience different health conditions to children. Including adults with CHARGE syndrome in the research would have provided information on how the syndrome interacts with aging and health outcomes.

While recruiting children has limitations, it also has strengths. By focusing on the developmental years this thesis provides a nuanced understanding of childhood in CHARGE syndrome. Early identification of developmental patterns may lead to early intervention and favourable long-term outcomes. Given the complexity of CHARGE syndrome, recruiting participants can be challenging. By be recruiting children aged 4 to 15 years, the thesis benefits from a more homogenous sample, which ensures that the data gathered is rich and focused. This research offers practical information for families and practitioners on sleep difficulties and behaviours that challenge. However, the age range used (4-15 years) for children was broad, particularly for the study in Chapter 4 that had only 7 participants. In this case, it is difficult to claim that the sample is representative. In Chapters 3, 4, and 5, the studies strike a balance between the depth of data and the size of the sample. For instance, conducting the actigraphy sleep study on a larger cohort would not have been practical, given the complexity and detail involved in this type of data collection.

A notable challenge of research with CAHRGE syndrome is the variability with which individuals are diagnosed. Unlike other genetic syndrome such as Cornelia de Lange syndrome or Down syndrome, CHARGE syndrome does not have one universally accepted set of diagnostic criteria, and this is challenging for research and clinical practice. In Chapters 3, 4, and 5 inclusion criteria asked only for a diagnosis of CHARGE syndrome. This ensured

that children that took part in the study had the majority of characteristics of CHARGE syndrome, but this did not account for the variability in diagnostic criteria. Some individuals may have fewer clinical characteristics of CHARGE syndrome but have the CHD7 variant, whereas other children may have more of the typical characteristics of CHARGE syndrome but not have undergone genetic testing. As a result, this variability introduces a considerable degree of heterogeneity into the data, which may affect the generalisability of the findings. Future research should use more stringent diagnostic criteria to reduce variability and improve the consistency and comparability of research outcomes across studies.

Given the variability in CHARGE syndrome, it could be questioned whether it is worthwhile to study it in isolation or whether it would be more appropriate to investigate it as part of broader intellectual disability research. The extent of this variability suggests that detecting significant patterns would require a very large sample size. A size that may not be feasible given the rarity of CHARGE syndrome. However, as noted in Section 1.1.14, intellectual disability is a highly heterogeneous group, including many neurodevelopmental conditions. Other rare genetic syndromes have demonstrated distinct behavioural typologies; for example, skin picking in Prader-Willi syndrome or hand biting in Fragile X syndrome. Such behaviours may be unique to a specific syndrome or shared with only a few others. These behaviours have distinct aetiologies which lead to specific consequences and trajectories requiring quite specific support. Identifying a tendency for a unique pattern of behaviour can also help with genetic counselling. In this thesis, for example, 100% of participants displaying self-injurious behaviour were reported to "hit self with body part," while 100% of those showing aggression "hit others with body part." Furthermore, 80% of children who engaged in destruction of property presented with throwing, kicking, or

smashing objects. These behaviours could be part of the behavioural phenotype of CHARGE syndrome, but determining this would require comparison of behaviours across syndrome groups using a same-but-different methodology.

The COVID pandemic likely had a considerable impact on the thesis as a whole. Since families with CHARGE syndrome were disproportionately affected by the pandemic this adds complexity to the data. There are four key implications for this thesis. Firstly, fewer families are likely to have taken part in the studies because anxiety and concerns about the pandemic meant they had less time and resources to take part in research. Secondly, the anxiety and isolation of the COVID pandemic likely had an influence on sleep and behaviour. As such, the thesis likely reports on atypical pandemic-related outcomes when compared to pre-pandemic conditions. Thirdly, some parents may have been more motivated to take part in the research because their child was experiencing behavioural or sleep difficulties. This could potentially skew the sample towards children with greater behavioural issues. Finally, the social and emotional context of COVID described in Chapters 3, 4 and 5 is essential for understanding how the pandemic has impacted families with children with CHARGE syndrome, making these chapters interdependent. In the behaviour and sleep data collected the COVID pandemic needs to be considered as a crucial variable and not background noise.

As mentioned in Chapter 4, families participating in the research were generally affluent and well-educated. This may be because the sample was drawn, primarily, from a parent support group. Parents who attend parent support groups tend to be more affluent (Zeutenhorst, 2017). However, it is notable that being a carer is typically associated with a

higher risk of poverty (Emerson, 2007). As such it is not clear how representative the sample in the thesis is. Nonetheless, it is crucial to recognise that, despite the potential affluence and education of the sample, their struggles are no less valid than those of less privileged families. Thus, while this thesis may include a subsample of families of children with CHARGE syndrome, it remains a valid and valuable contribution to the literature.

The study was underpowered primarily due to the small sample size, limiting the generalisability of the results. This is particularly disheartening as parents have invested precious time in the research. However, it is essential to highlight that this study is pioneering. It is the first to conduct a meta-analysis of the most reported characteristics of CHARGE syndrome. It is also the first to administer a series of validated questionnaires specifically for individuals with CHARGE syndrome and to test their internal consistency using a sample from this population. It was also the first to use objective sleep assessments with children with CHARGE syndrome and to develop and use the triage algorithm. As such this research is a valuable resource for further research questions and new hypothesis.

6.5 Conclusion

This thesis has provided valuable insight into the behavioural phenotype of children with CHARGE syndrome, shedding light on its phenotypic variability, behaviours that challenge and sleep disturbances.

Findings highlight the heterogeneity in CHARGE syndrome and the requirement for further, more nuanced research to improve overall well-being and quality of life. The diverse

characteristics and conditions identified in CHARGE syndrome highlight its phenotypic variability. This variability poses challenges for research, given that research is based on small sample sizes and the potential for recruitment bias. However, this variability serves as a reminder of each person's unique experience with the syndrome.

Aggressive and self-injurious behaviours were prevalent concerns regarding behaviours that challenge in CHARGE syndrome. This thesis highlighted the need for further research to explore the typologies and functions of challenging behaviour. Executive functioning difficulties were identified as critical correlates of these behaviours, emphasising the importance of addressing these cognitive challenges in intervention strategies.

Sleep disturbances were also a prevalent issue in CHARGE syndrome, with up to 100% of participants experiencing disturbed sleep. The combined use of objective and subjective sleep patterns highlighted the value of multimethod approaches.

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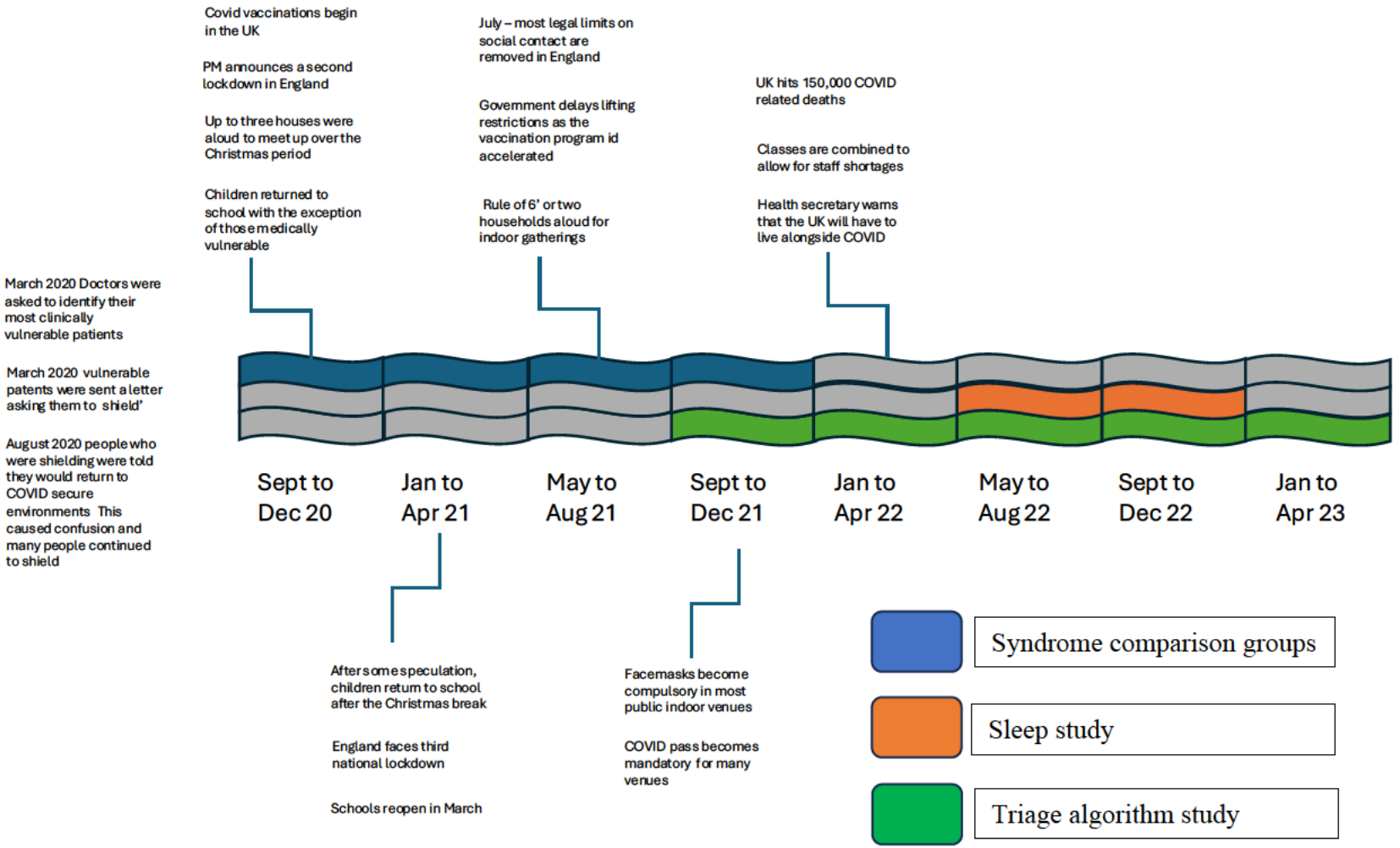
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APPENDICES

Appendix 1A: COVID Timeline



British Foreign policy group https //bfpg co uk/2020/04/covid-19-timeline/

Appendix 2A: Detailed Search Strategy

Databases

Database: Pubmed; Date of search: 12-01-2021

Search: ((((((("CHARGE Syndrome*") OR "CHARGE Association*") OR (((((Coloboma) AND Heart anomaly) AND Choanal Atresia) AND Genital Anomalies) AND Ear Anomalies)) OR "Hall-Hittner Syndrome*") OR CHD7) OR SEMA3A)

("charge syndrome*"[All Fields] OR "charge association*"[All Fields] OR (("coloboma"[MeSH Terms] OR "coloboma"[All Fields] OR "colobomas"[All Fields]) AND ("heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("heart"[All Fields] AND "anomaly"[All Fields]) OR "heart anomaly"[All Fields]) AND ("choanal atresia"[MeSH Terms] OR ("choanal"[All Fields] AND "atresia"[All Fields]) OR "choanal atresia"[All Fields]) AND (("genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields] OR "genitals"[All Fields] OR "genitally"[All Fields]) AND ("abnormalities"[MeSH Subheading] OR "abnormalities"[All Fields] OR "anomalies"[All Fields] OR "anomalie"[All Fields] OR "anomaly"[All Fields])) AND (("ear"[MeSH Terms] OR "ear"[All Fields]) AND ("abnormalities"[MeSH Subheading] OR "abnormalities"[All Fields] OR "anomalies"[All Fields] OR "anomalie"[All Fields] OR "anomaly"[All Fields]))) OR "hall hittner syndrome*"[All Fields] OR "CHD7"[All Fields] OR ("semaphorin 3a"[MeSH Terms] OR "semaphorin 3a"[All Fields] OR "sema3a"[All Fields]))

Translations

- Coloboma: "coloboma"[MeSH Terms] OR "coloboma"[All Fields] OR "colobomas"[All Fields]
- Heart anomaly: "heart defects, congenital"[MeSH Terms] OR ("heart"[All Fields] AND "defects"[All Fields] AND "congenital"[All Fields]) OR "congenital heart defects"[All Fields] OR ("heart"[All Fields] AND "anomaly"[All Fields]) OR "heart anomaly"[All Fields]
- Choanal Atresia: "choanal atresia"[MeSH Terms] OR ("choanal"[All Fields] AND "atresia"[All Fields]) OR "choanal atresia"[All Fields]
- Genital: "genitalia"[MeSH Terms] OR "genitalia"[All Fields] OR "genital"[All Fields] OR "genitals"[All Fields] OR "genitally"[All Fields]
- Anomalies: "abnormalities"[Subheading] OR "abnormalities"[All Fields] OR "anomalies"[All Fields] OR "anomalie"[All Fields] OR "anomaly"[All Fields]
- Ear: "ear"[MeSH Terms] OR "ear"[All Fields]
- Anomalies: “abnormalities”[Subheading] OR “abnormalities”[All Fields] OR “anomalies”[All Fields] OR “anomalie”[All Fields] OR “anomaly”[All Fields]
- SEMA3A: "semaphorin-3a"[MeSH Terms] OR "semaphorin-3a"[All Fields] OR "sema3a"[All Fields]

Sort by: Best Match

Number of hits: 2,346

Publication dates: no restrictions

Database: Embase, through Ovid®; Date of search: 12-01-2021

Search: ("CHARGE Syndrome*" or "CHARGE Association*" or (Coloboma and Heart anomaly and Choanal Atresia and Genital Anomalies and Ear Anomalies) or "Hall-Hittner Syndrome*" or CHD7 or SEMA3A).af

Number of hits: 2,641

Publication dates: no restrictions

Database: Medline, through Ovid®; Date of search: 12-01-2021

Search: ("CHARGE Syndrome*" or "CHARGE Association*" or (Coloboma and Heart anomaly and Choanal Atresia and Genital Anomalies and Ear Anomalies) or "Hall-Hittner Syndrome*" or CHD7 or SEMA3A).af

Number of hits: 1,936

Publication dates: no restrictions

Database: PsycInfo, through Ovid®; Date of search: 12-01-2021

Search: ("CHARGE Syndrome*" or "CHARGE Association*" or (Coloboma and Heart anomaly and Choanal Atresia and Genital Anomalies and Ear Anomalies) or "Hall-Hittner Syndrome*" or CHD7 or SEMA3A).af

Number of hits: 838

Publication dates: no restrictions

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Appendix 2B: Additional Details for Methods Used in the Synthesis of Results

The Funnel Plot

The funnel plot is used to detect systematic heterogeneity resulting from small study bias. The funnel plot is a scatter plot of standard error by prevalence estimates for each of the studies included in the meta-analysis. Where bias is not present, studies with high precision are plotted near the centre (representing the meta-analytic synthesis) and studies with less precision present in equal numbers on either side with data following a symmetric inverted funnel shape. Visual inspection of the funnel plot is supplemented by Egger's regression test for which the standard error is regressed against the prevalence estimate (Egger et al., 1997).

The Trim and Fill procedure

The trim and fill method (Duval & Tweedie, 2000) is designed to address the effect of deviations from the symmetric inverted funnel shape plot. This procedure uses an iterative algorithm to remove outlying effect size values identified on the side of the funnel plot that indicates positive effects. The algorithm then adds the original studies back into the analysis and imputes a mirror image for each on the side associated with negative effects to retain symmetry.

The fail-safe N (Rosenthal, 1979)

The fail-safe N (Rosenthal, 1979) provides an estimation of how many zero effect size studies could be added to the omnibus test before the associated p-value is no longer

significant. If the fail-safe N is greater than the number of effects included than the omnibus test can be considered robust to publication bias.

Leave-one-out procedure

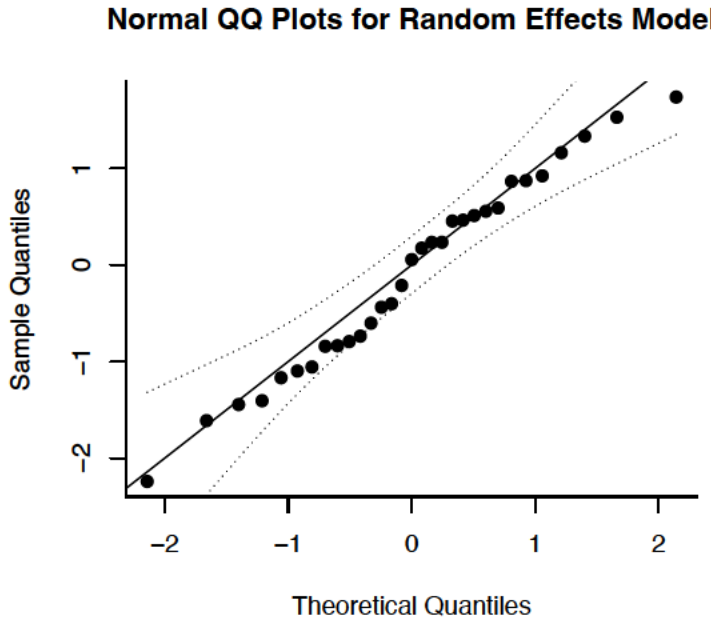
The leave-one-out procedure is the process of iteratively omitting one study at a time from the meta-analysis and recalculating the omnibus test. Results can then be evaluated to assess whether the pooled prevalence estimate is driven by the effect of any single study.

Appendix 2C: Forest Plots and Sensitivity Analysis for Clinical Features

2C.1 Coloboma

Appendix 2C. Figure 1a

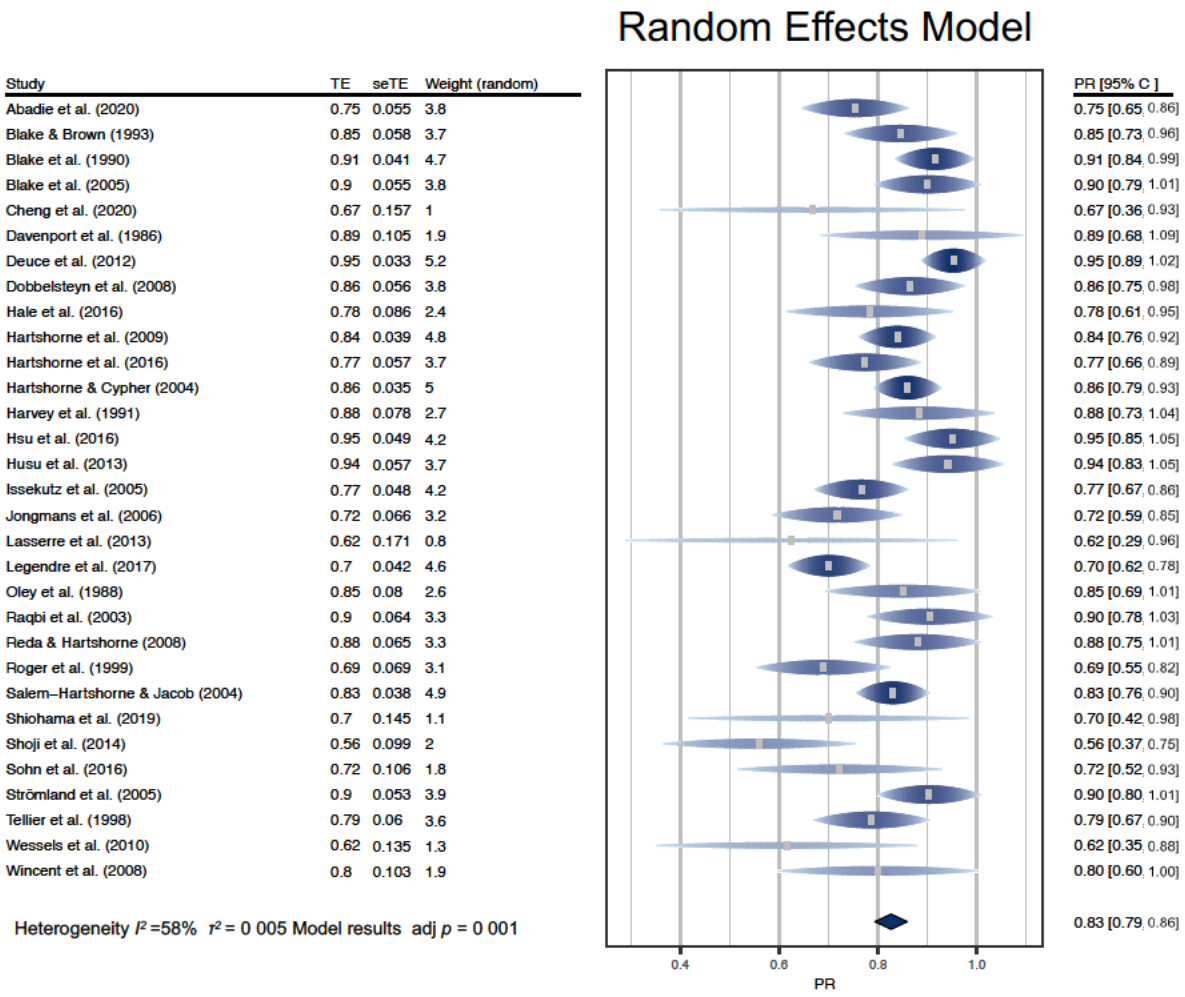
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Coloboma



Note. Visual inspection of the QQ plot suggests an approximate normal distribution of study effects for the 31 studies reporting coloboma in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model

Appendix 2C. Figure 1b

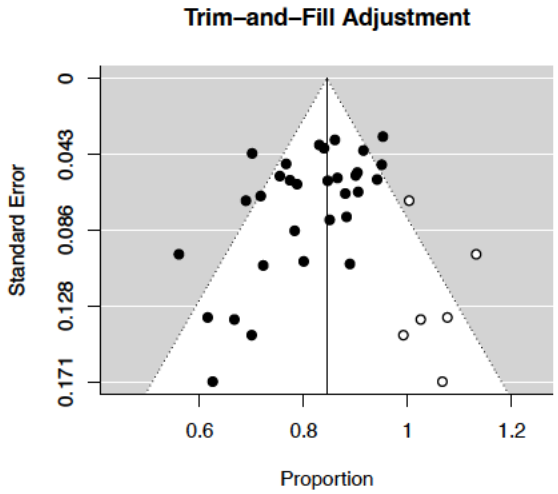
Random Effects Models of The Pooled Prevalence Estimate for Coloboma in CHARGE Syndrome



Note. The pooled prevalence estimate for coloboma in CHARGE syndrome is 83% (95% CI, 74-86%; permuted *p*-value = 0.001; *k* = 31) with moderate heterogeneity (I^2 = 58%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 64553 suggests that the observed effect is robust to potential publication biases

Appendix 2C. Figure 1c

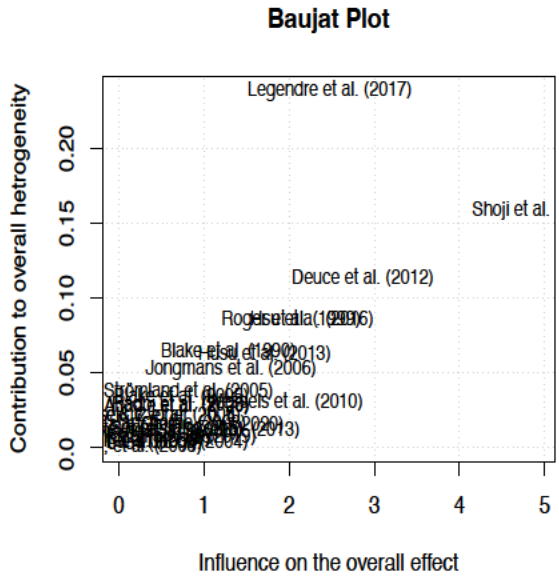
Funnel Plot of Standard Error by Prevalence of Coloboma Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.011). Using the trim and fill procedure it was estimated that 6 (SE = 3.71) studies were missing on the right side. Adjusted estimate = 84%, (95% *CI* = 81-89%, *p* = <.001; $\tau^2 = 0.076$, $I^2 = 61\%$)

Appendix 2C. Figure 1d

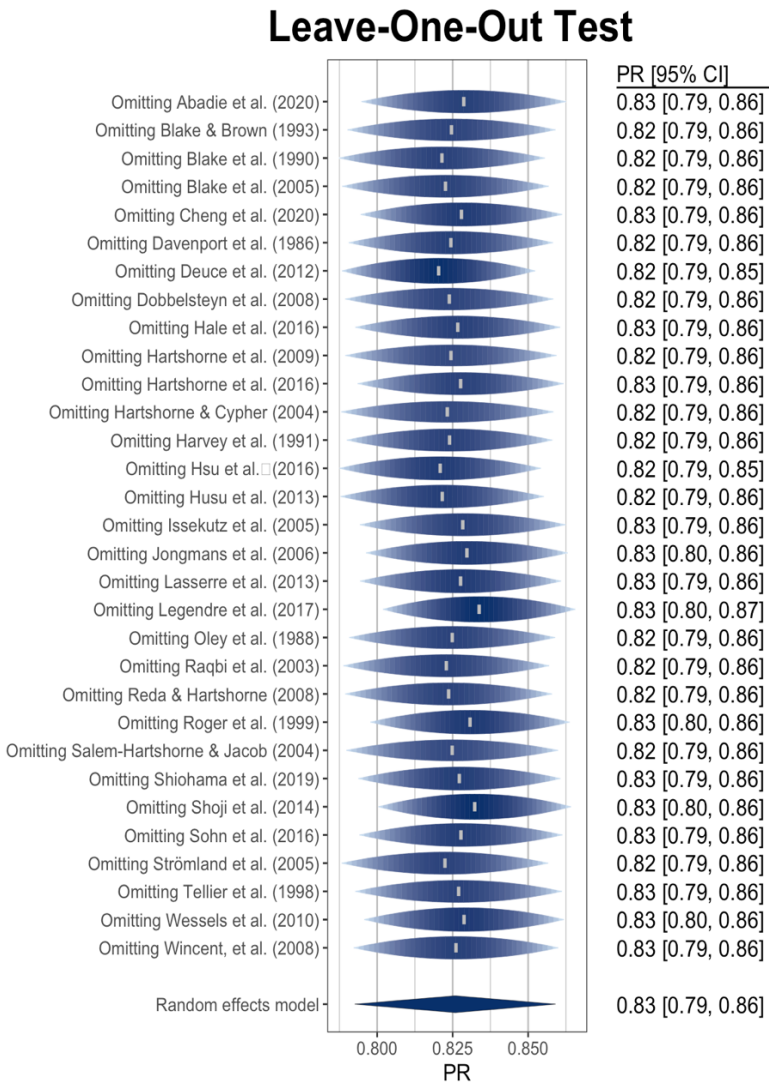
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Coloboma



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Legendre et al. (2017) had the greatest contribution to overall heterogeneity and Shoji et al. (2014) had the greatest influence on the overall effect

Appendix 2C. Figure 1e

Leave-One-Out Random Effects Model for Studies Reporting Coloboma

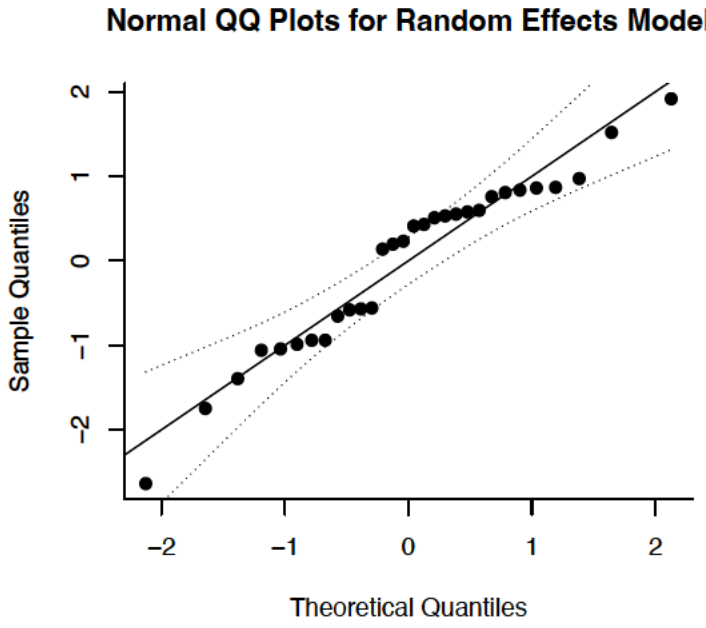


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Choanal Atresia

Appendix 2C. Figure 2a

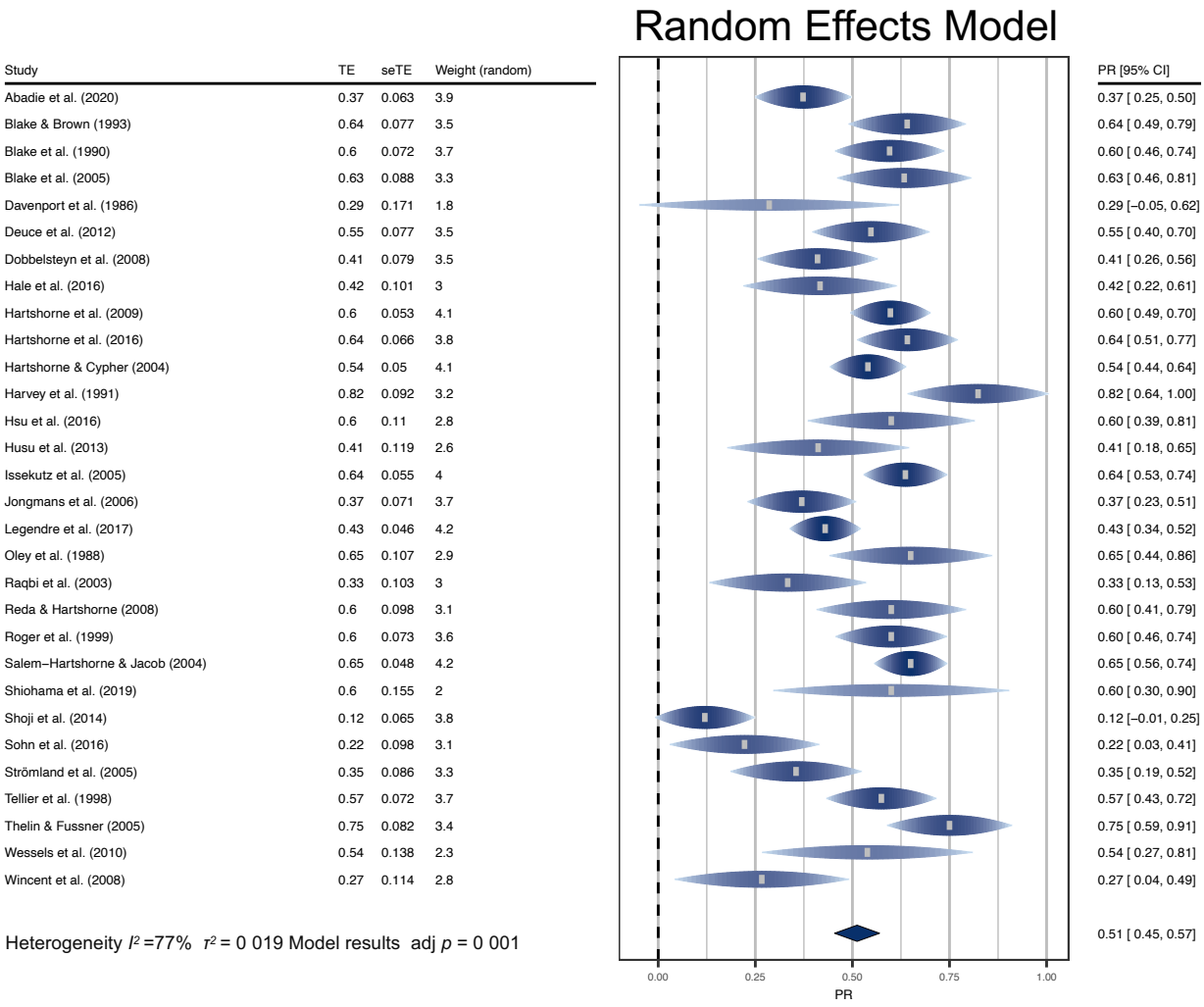
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Choanal Atresia



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 30 studies reporting choanal atresia in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model

Appendix 2C. Figure 2b

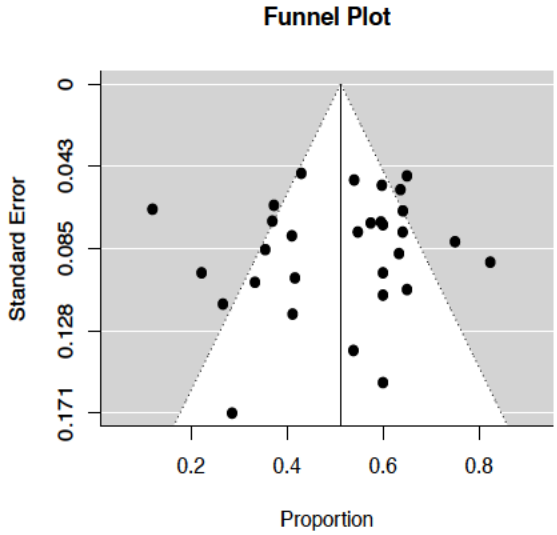
Random Effects Models of The Pooled Prevalence Estimate for Choanal Atresia in CHARGE Syndrome



Note. The pooled prevalence estimate for choanal atresia in CHARGE syndrome is 51% (95% CI, 45-57%; permuted *p*-value = 0.001; *k* = 30) with high heterogeneity (I^2 = 77%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 14252 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 2c

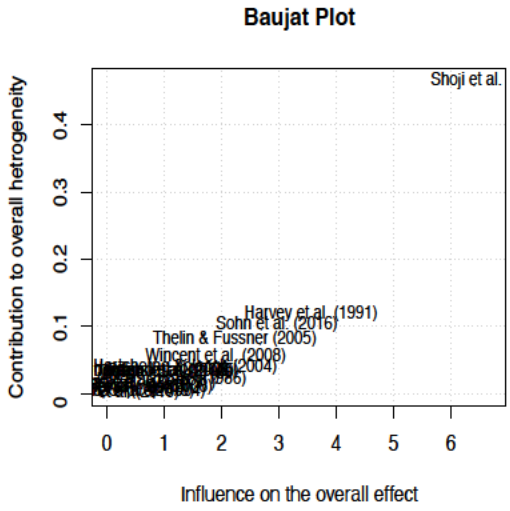
Funnel Plot of Standard Error by Prevalence of Choanal Atresia



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.528)

Appendix 2C. Figure 2d

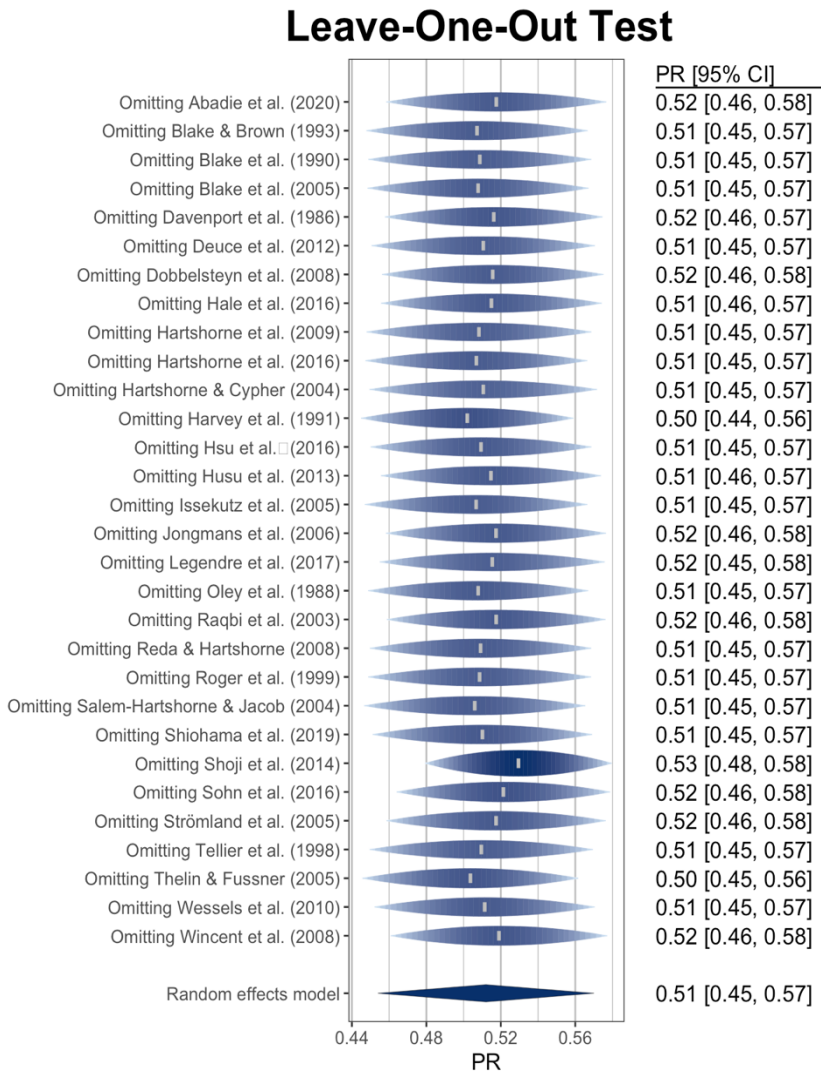
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Choanal Atresia



Note. Shoji et al. (2014) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 2e

Leave-One-Out Random Effects Model for Studies Reporting Choanal Atresia

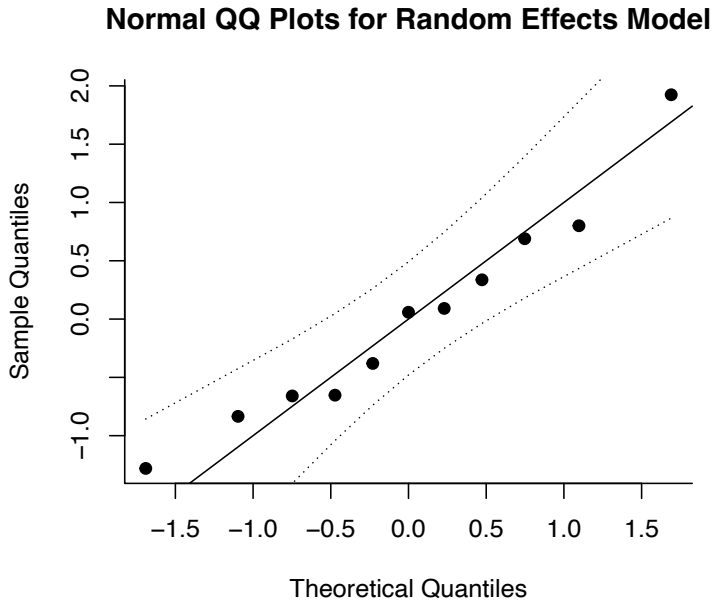


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Anosmia

Appendix 2C. Figure 3a

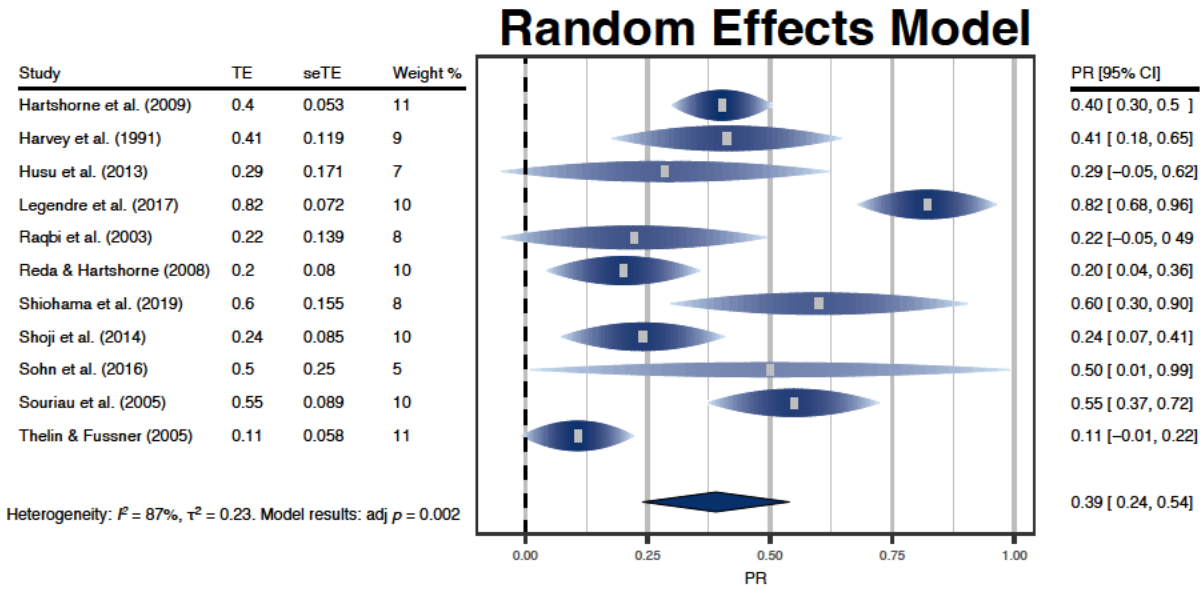
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Anosmia



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting Anosmia in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 3b

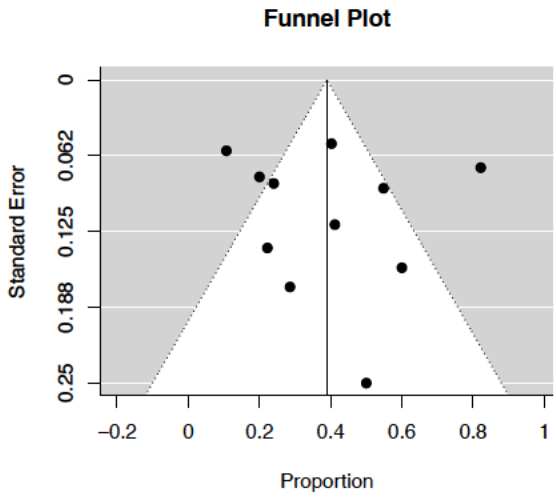
Random Effects Models of The Pooled Prevalence Estimate for Anosmia in CHARGE Syndrome



Note. The pooled prevalence estimate for anosmia in CHARGE syndrome is 39% (95% CI, 24-54%; permuted *p*-value = 0.002; *k* = 11) with high heterogeneity (I^2 = 87%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 734 suggests that the observed effect is robust to potential publication biases

Appendix 2C. Figure 3c

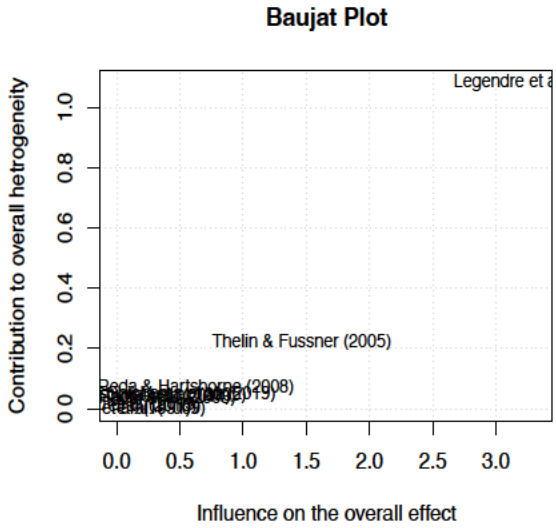
Funnel Plot of Standard Error by Prevalence of Anosmia



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.741)

Appendix 2C. Figure 3d

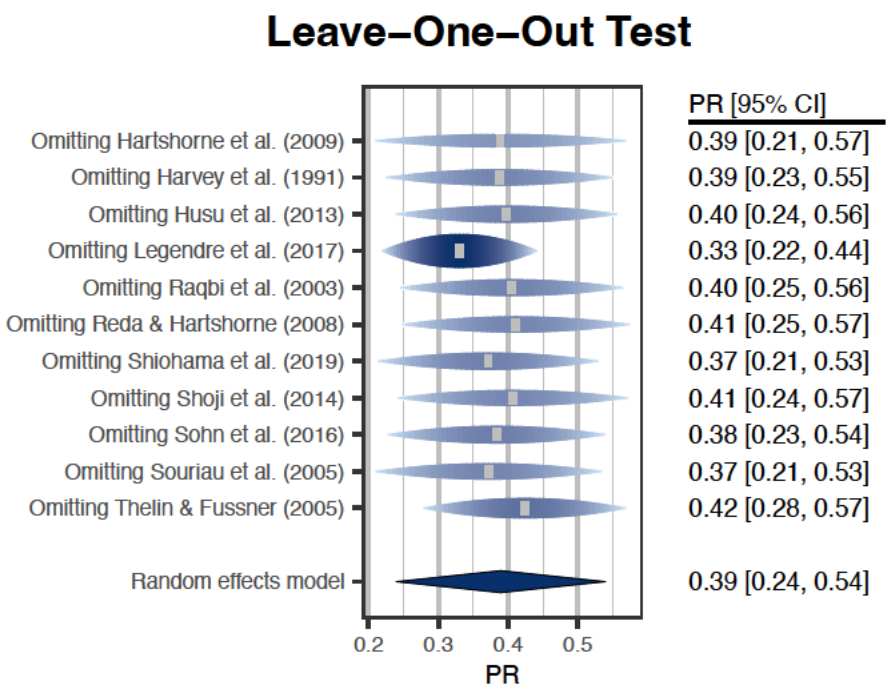
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Anosmia



Note. Legendre et al. (2017) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 3e

Leave-One-Out Random Effects Model for Studies Reporting Anosmia

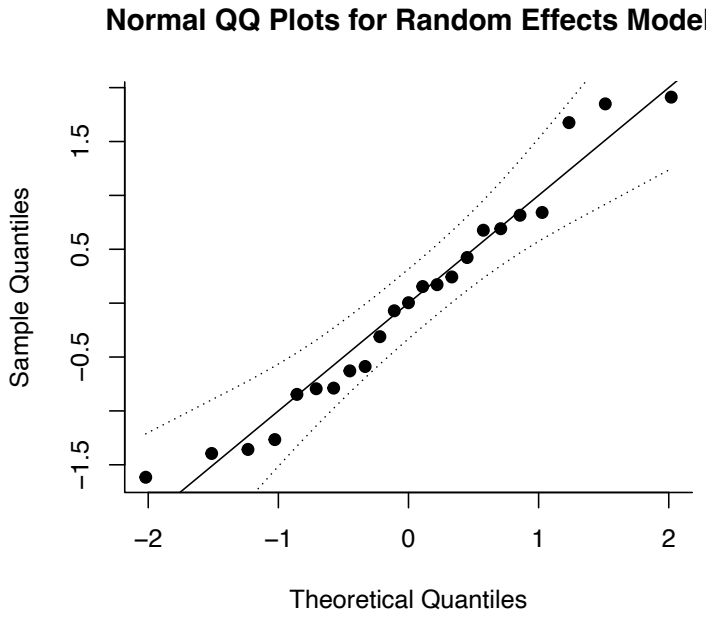


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Facial Palsy

Appendix 2C. Figure 4a

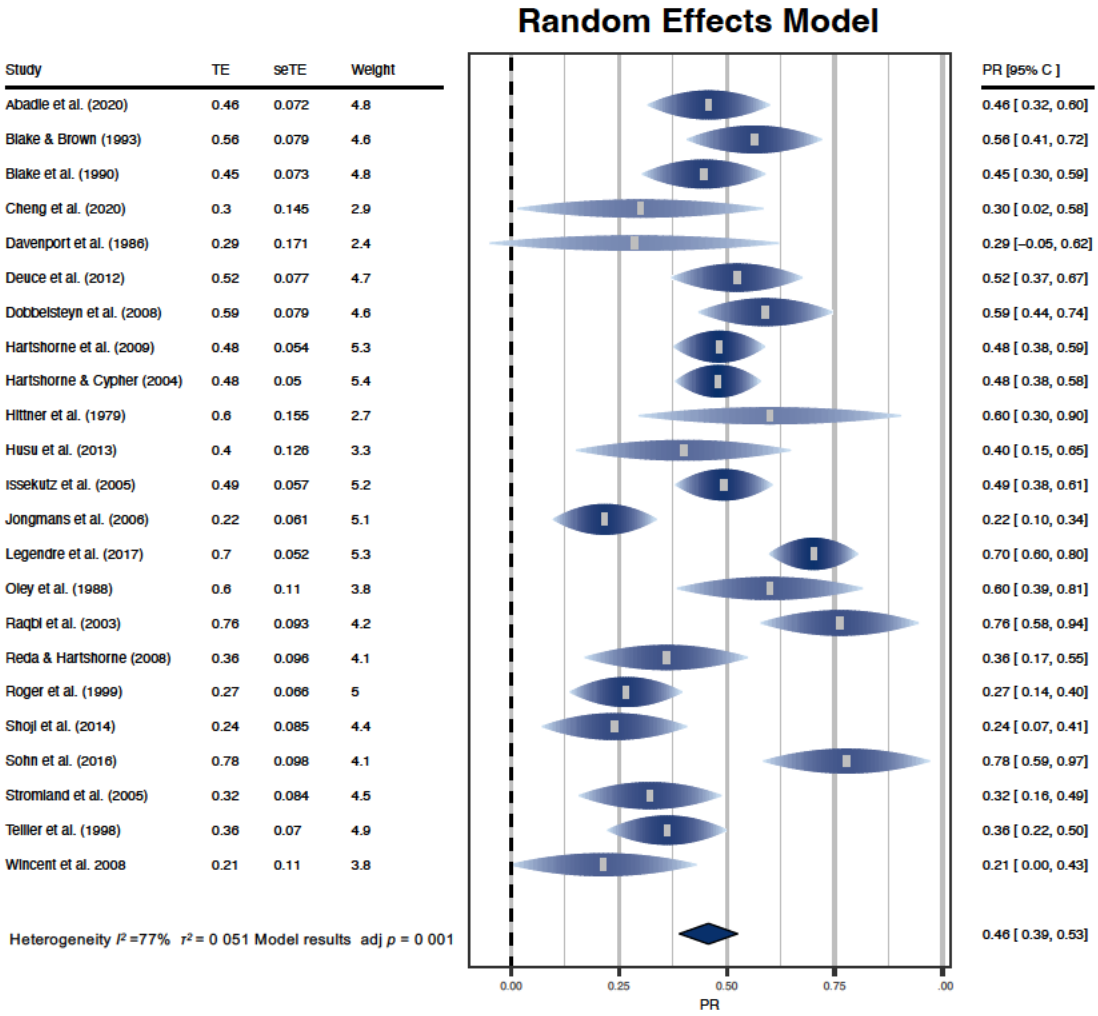
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Facial Palsy



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 23 studies reporting facial palsy in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 4b

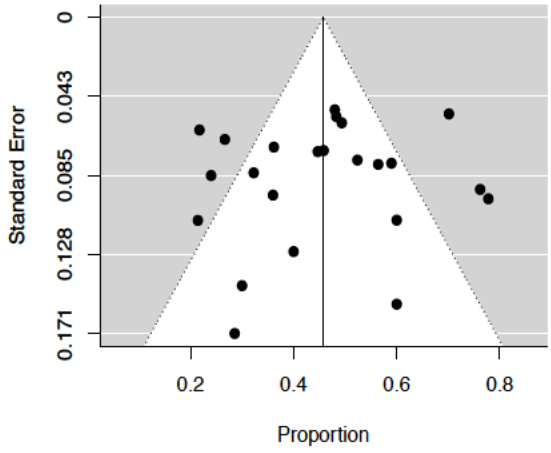
Random Effects Models of The Pooled Prevalence Estimate for Facial Palsy in CHARGE Syndrome



Note. The pooled prevalence estimate for facial palsy in CHARGE syndrome is 46% (95% CI, 39-53%; permuted *p*-value = 0.001; *k* = 23) with high heterogeneity (I^2 = 77%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ2. Rosenthal Fail-safe N = 6435 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 4c

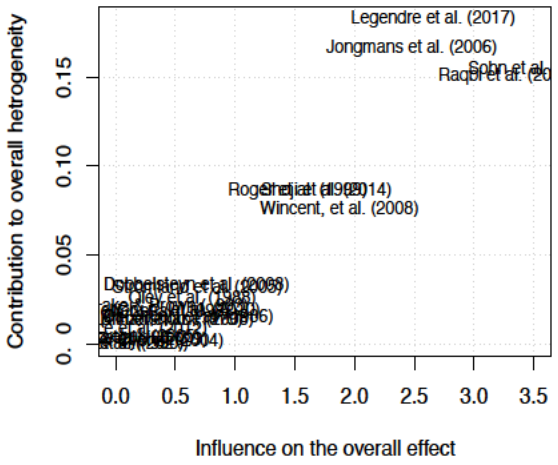
Funnel Plot of Standard Error by Prevalence of Facial Palsy



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.655)

Appendix 2C. Figure 4d

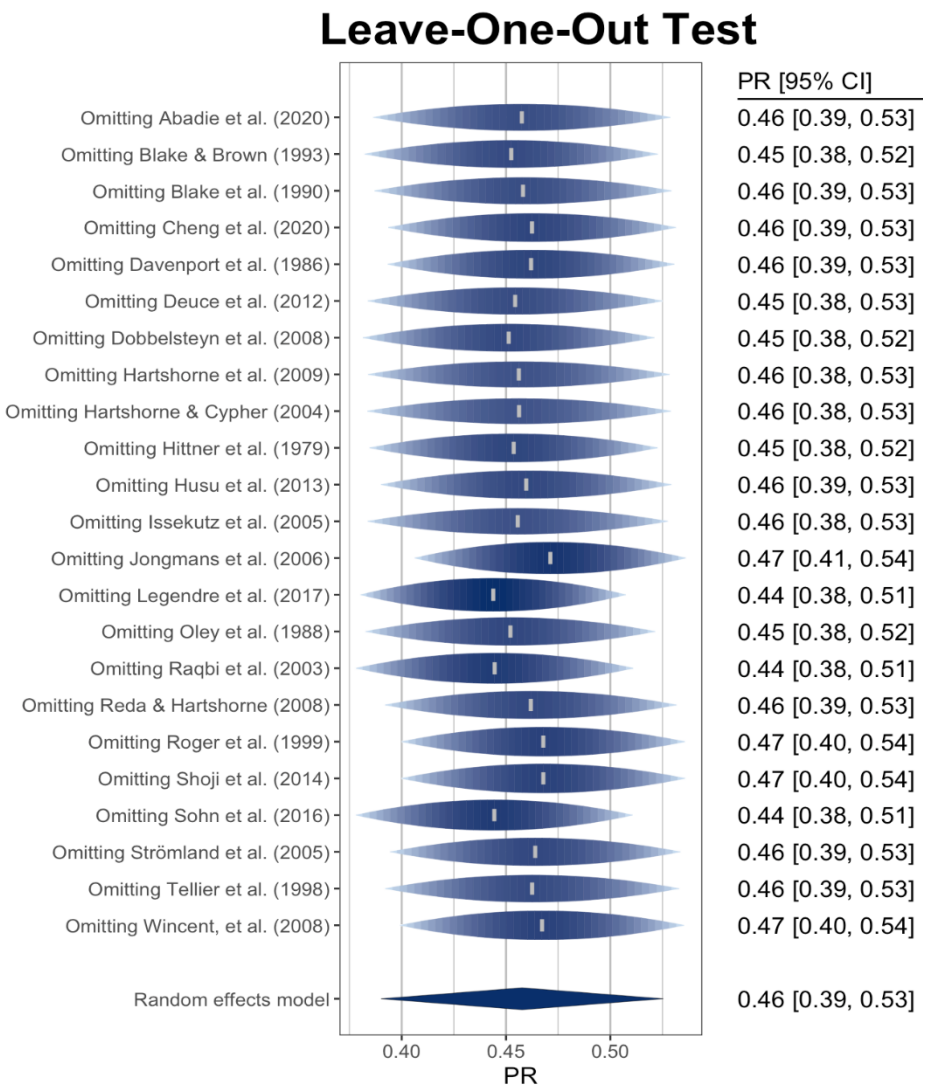
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Facial Palsy



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Legendre et al. (2017) had the greatest contribution to overall heterogeneity. Sohn et al. (2016) had the greatest influence on the overall effect.

Appendix 2C. Figure 4e

Leave-One-Out Random Effects Model for Studies Reporting Facial Palsy

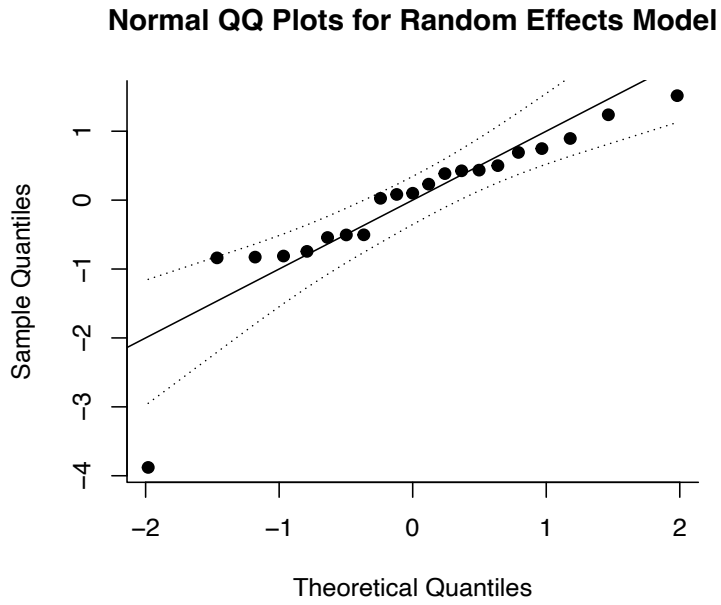


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Feeding and Swallowing Difficulties

Appendix 2C. Figure 5a

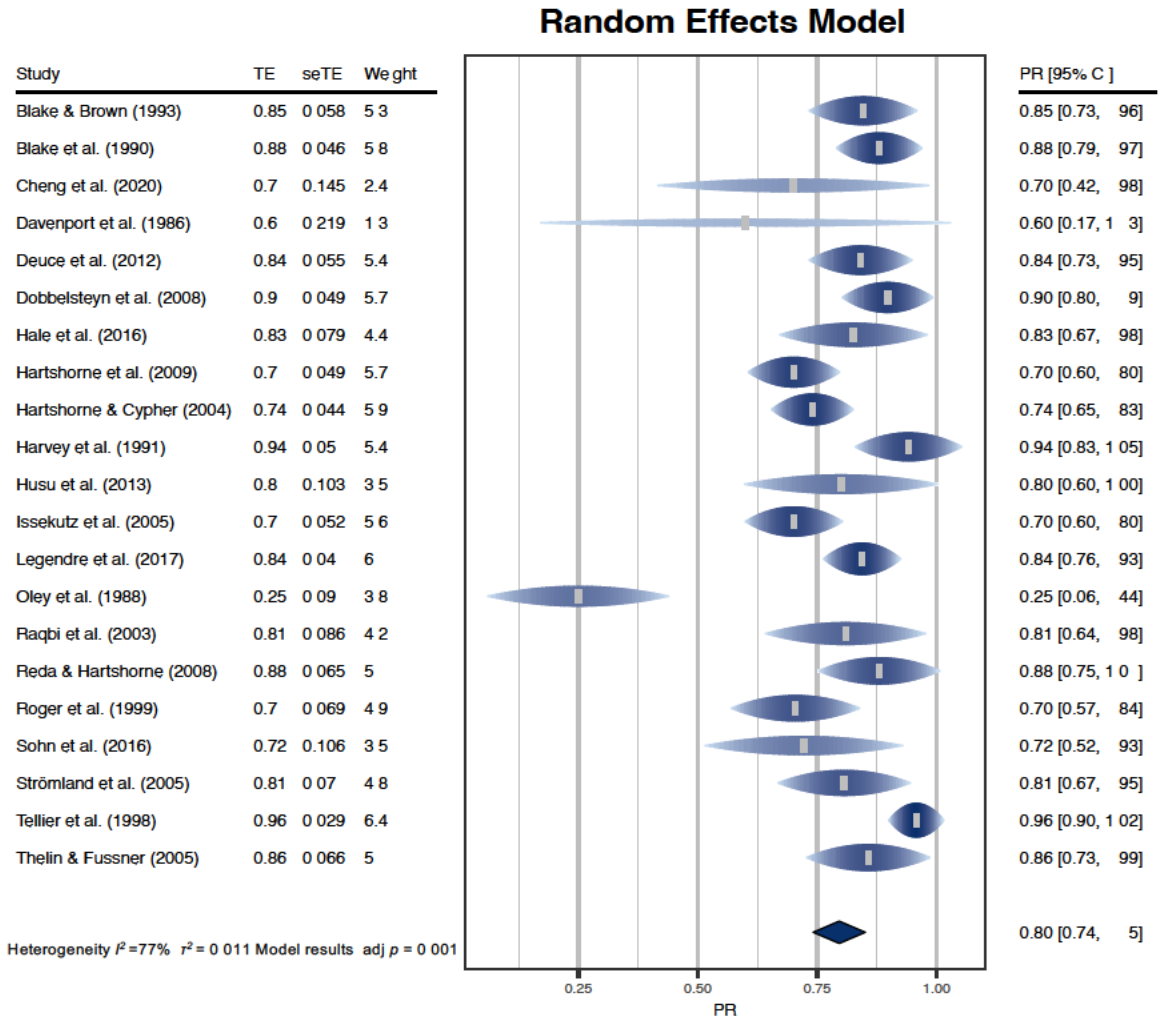
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Feeding and Swallowing Difficulties



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 21 studies reporting feeding and swallowing difficulties in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 5b

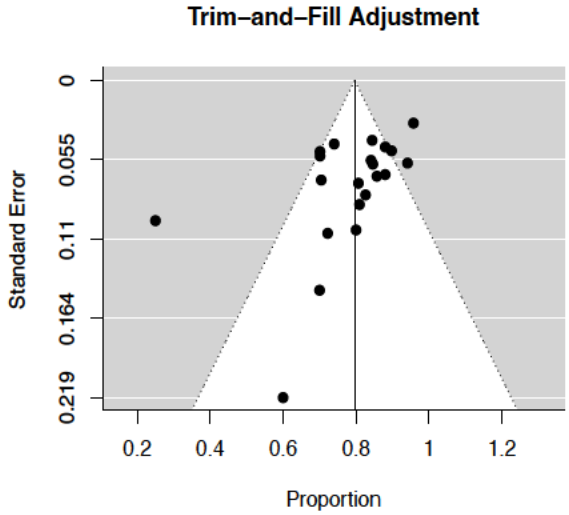
Random Effects Models of The Pooled Prevalence Estimate for Feeding and Swallowing Difficulties in CHARGE Syndrome



Note. The pooled prevalence estimate for feeding and swallowin0g difficulties in CHARGE syndrome is 80% (95% CI, 74-85%; permuted p-value = 0.001; k = 21) with high heterogeneity (I^2 = 77%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ2. Rosenthal Fail-safe N = 27790 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 5c

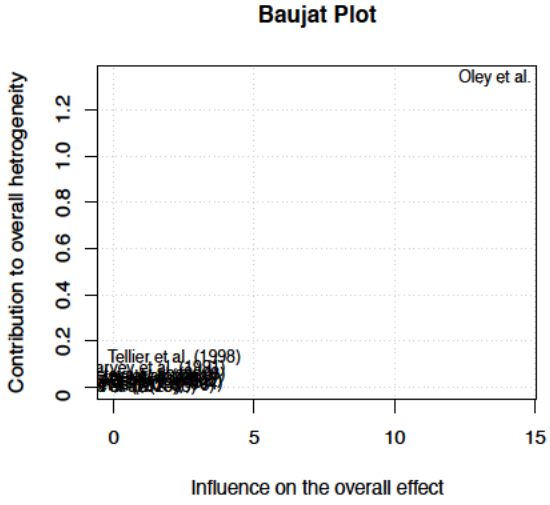
Funnel Plot of Standard Error by Prevalence of Feeding and Swallowing Difficulties



Note. Publication bias [small study effect] was identified (Egger's test p = 0.018). The trim and fill procedure did not impute any missing studies

Appendix 2C. Figure 5d

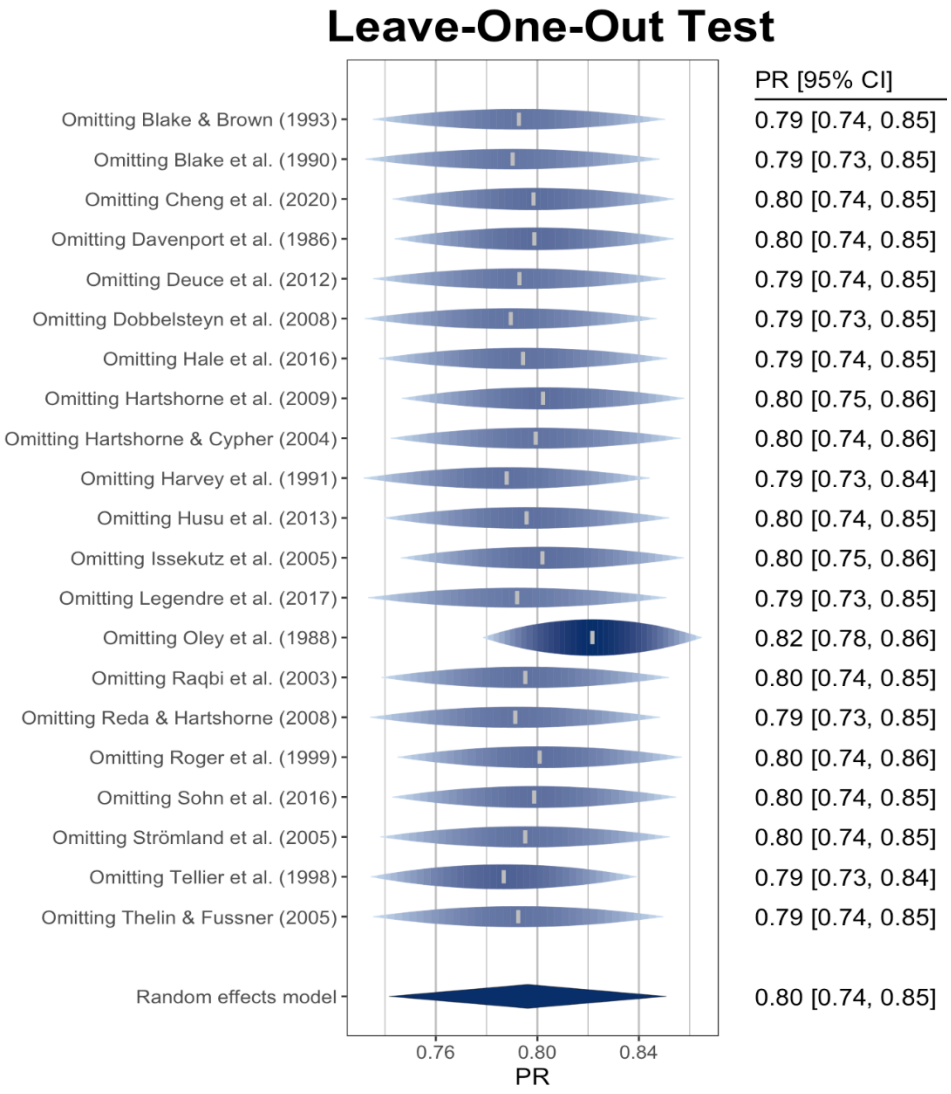
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Feeding and Swallowing Difficulties



Note. Oley et al. (1988) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2C. Figure 5e

Leave-One-Out Random Effects Model for Studies Reporting Feeding and Swallowing Difficulties

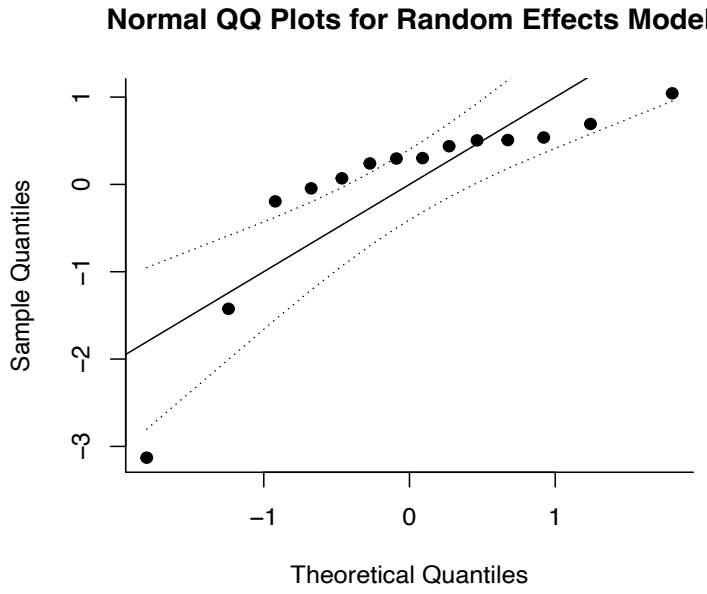


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

External Ear Anomalies

Appendix 2C. Figure 6a

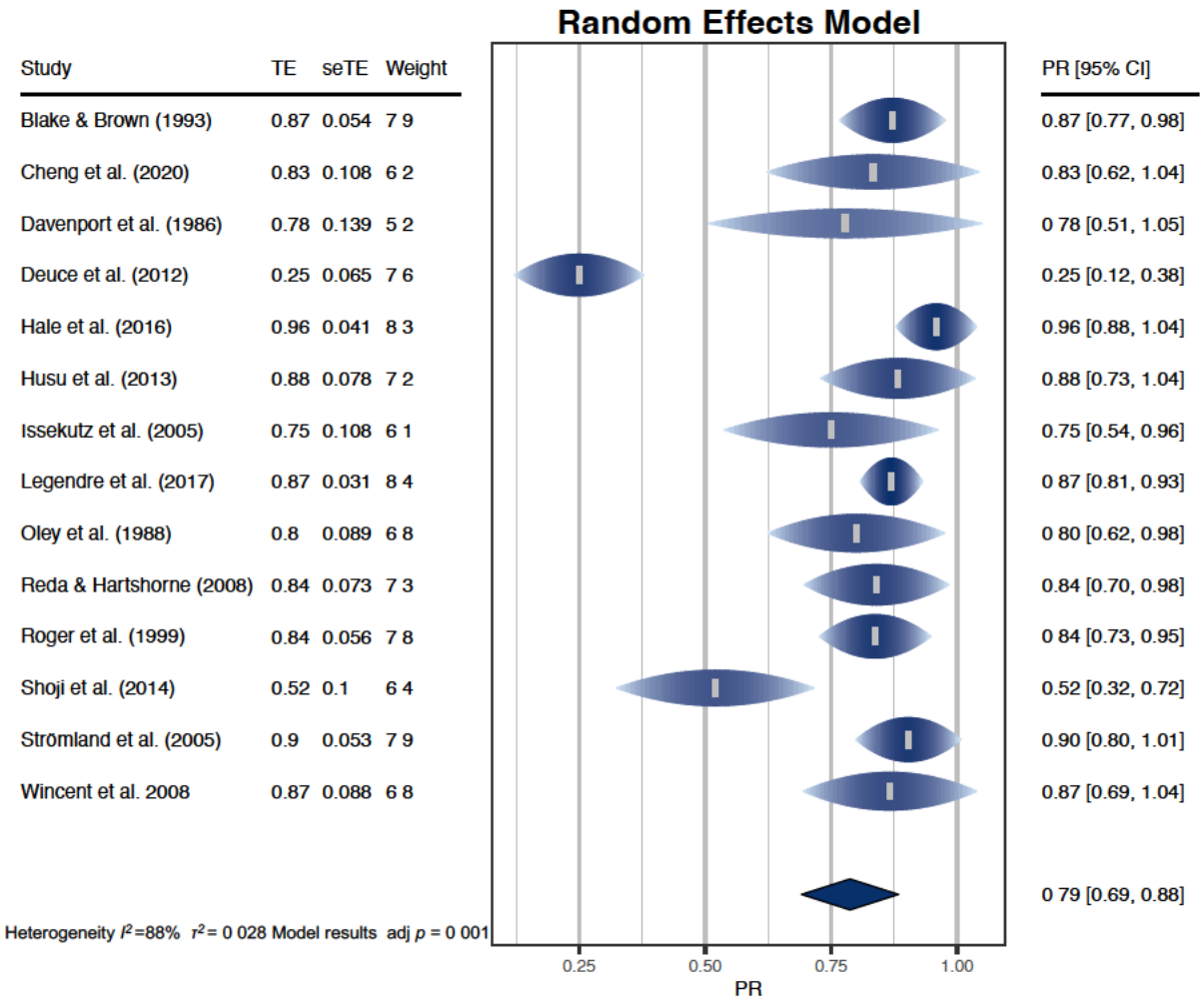
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting External Ear Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 14 studies reporting external ear anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 6b

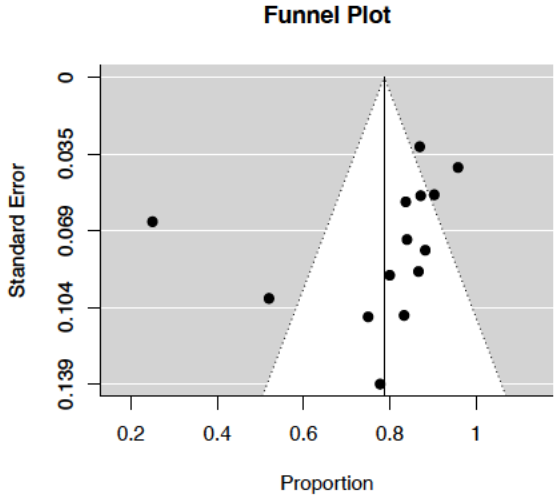
Random Effects Models of The Pooled Prevalence Estimate for External Ear Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for external ear anomalies in CHARGE syndrome, based on above model, is 79% (95% CI, 69-88%; permuted p-value = 0.001; k = 14) with high heterogeneity (I^2 = 88%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 10698 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 6c

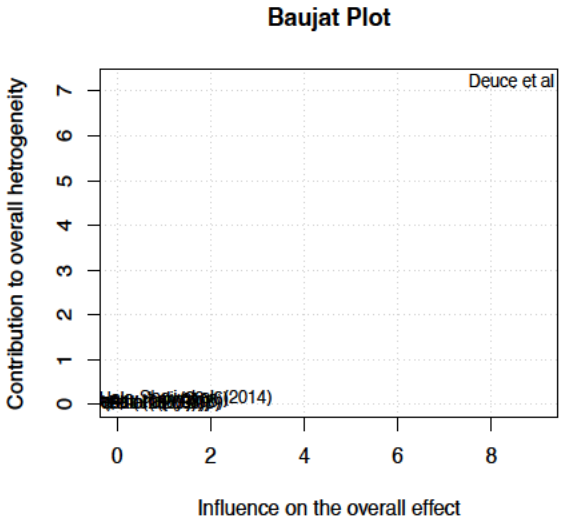
Funnel Plot of Standard Error by Prevalence of External Ear Anomalies



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.227)

Appendix 2C. Figure 6d

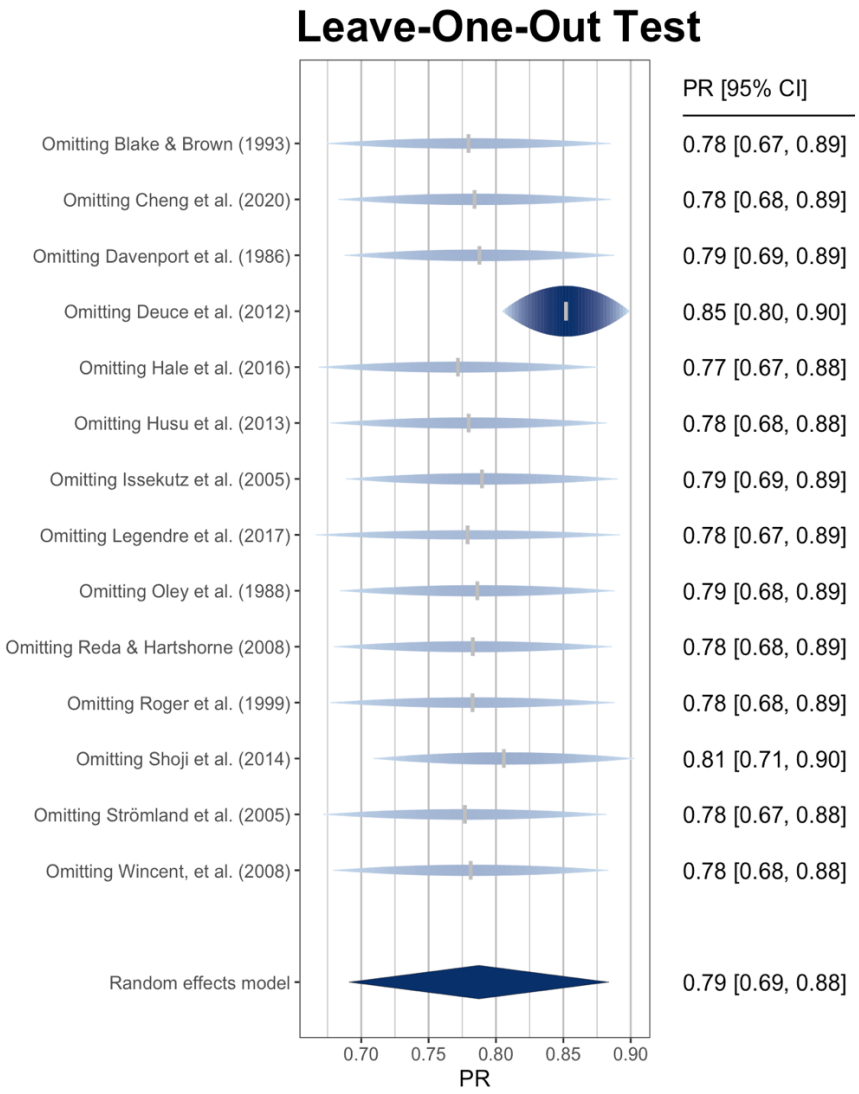
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting External Ear Anomalies



Note. Deuce et al. (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 6e

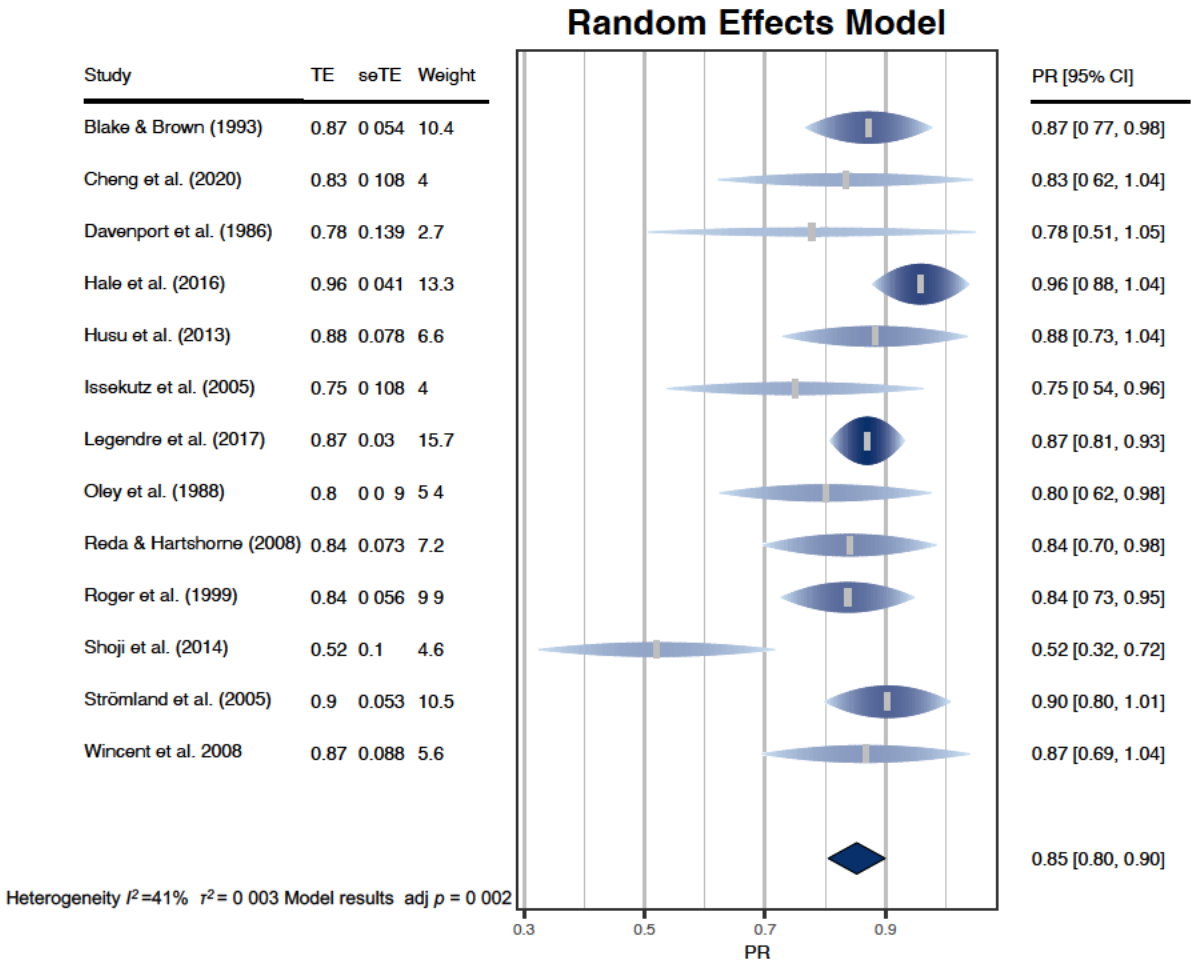
Leave-One-Out Random Effects Model for Studies Reporting External Ear Anomalies



Note. Leave one out analysis indicating that the Deuce et al. (2012) study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2C. Figure 6f

Random Effects Models of The Pooled Prevalence Estimate for External Ear Anomalies in CHARGE Syndrome

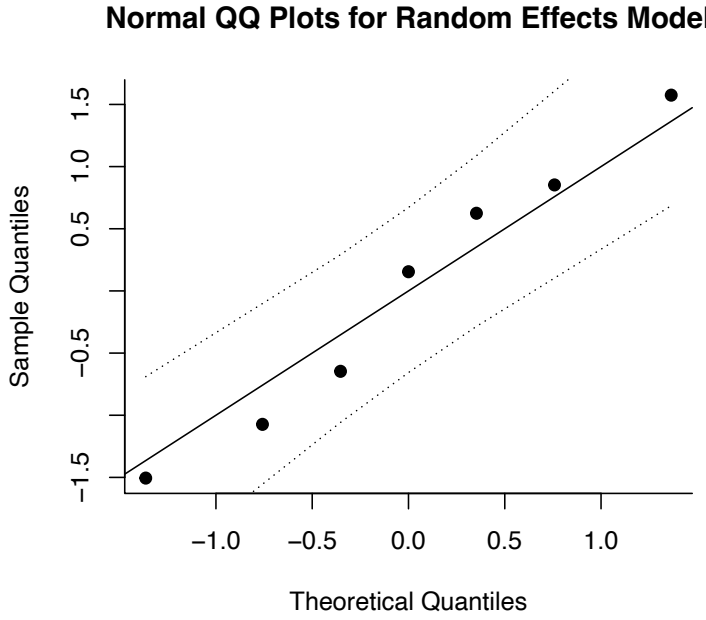


Note. Based on the results of the sensitivity analysis Deuce *et al* (2012) was removed from the final model. The pooled prevalence estimate for external ear anomalies in CHARGE syndrome is 85% (95% CI, 80-90%; permuted p-value = 0.002; k = 13) with moderate heterogeneity (I^2 = 41%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2.

Middle Ear Anomalies

Appendix 2C. Figure 7a

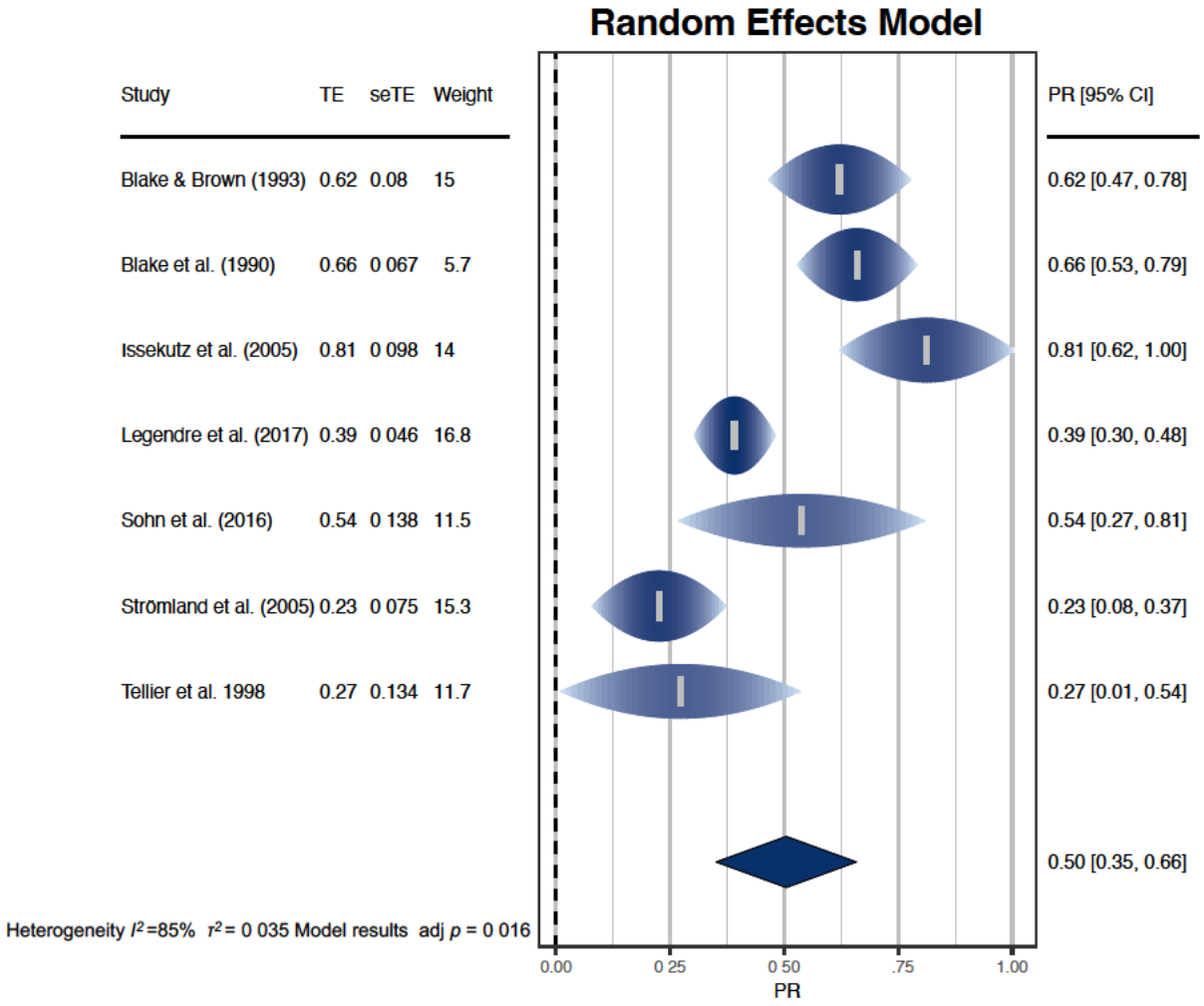
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Middle Ear Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 7 studies reporting middle ear anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 7b

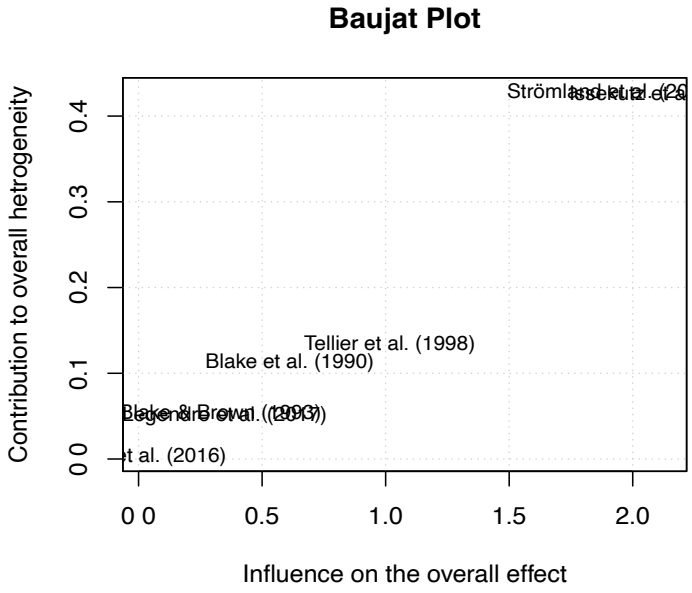
Random Effects Models of The Pooled Prevalence Estimate for Middle Ear Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for middle ear anomalies in CHARGE syndrome is 50% (95% CI, 35-66%; permuted p-value = 0.016; k = 7) with high heterogeneity (I^2 = 85%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2.

Appendix 2C. Figure 7c

Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Middle Ear Anomalies



Note. Issekutz et al. (2005) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2C. Figure 7d

Leave-One-Out Random Effects Model for Studies Reporting Middle Ear Anomalies

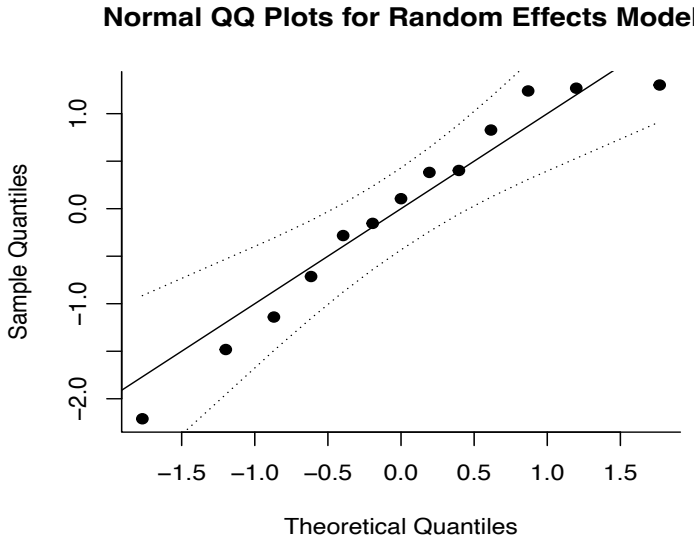


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Inner Ear Anomalies

Appendix 2C. Figure 8a

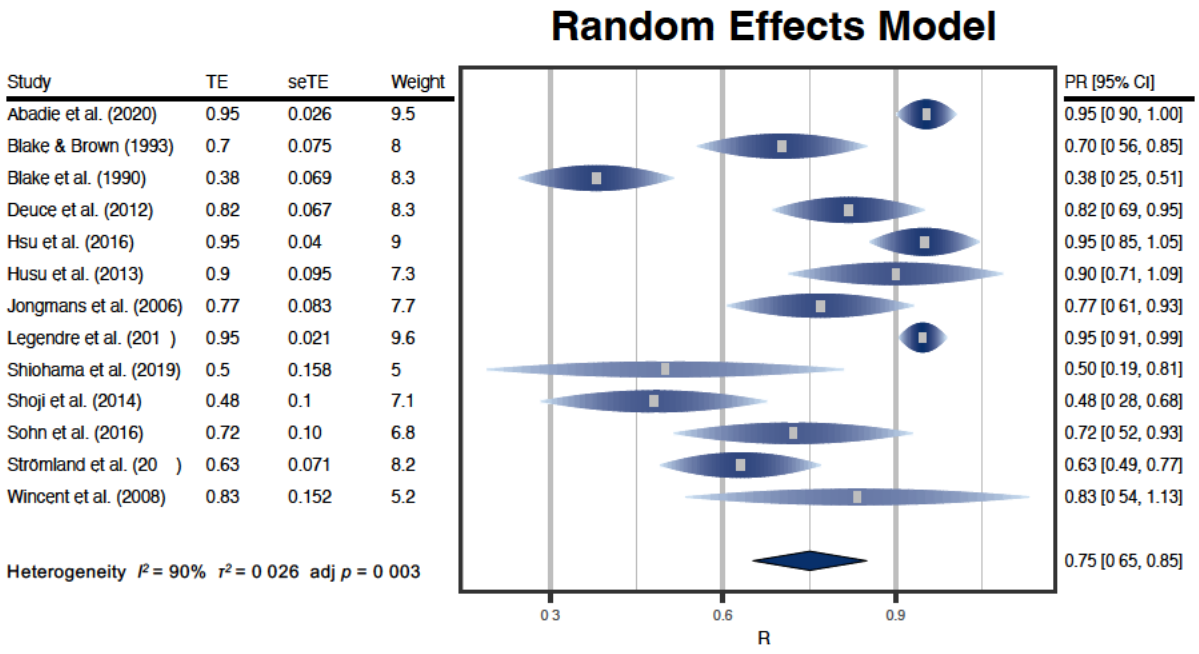
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Inner Ear Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 13 studies reporting inner ear anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 8b

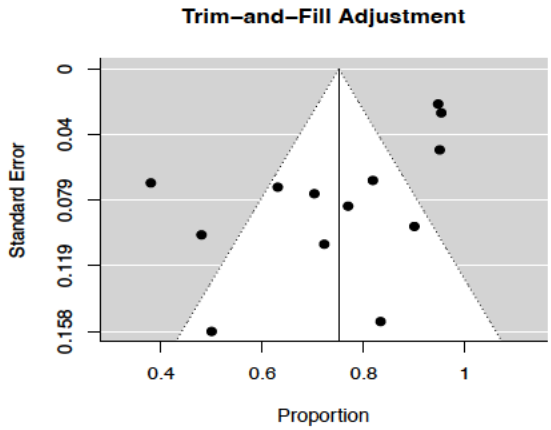
Random Effects Models of The Pooled Prevalence Estimate for Inner Ear Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for inner ear anomalies in CHARGE syndrome is 75% (95% CI, 65-85%; permuted p-value = 0.003; k = 13) with high heterogeneity (I^2 = 90%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 11368 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 8c

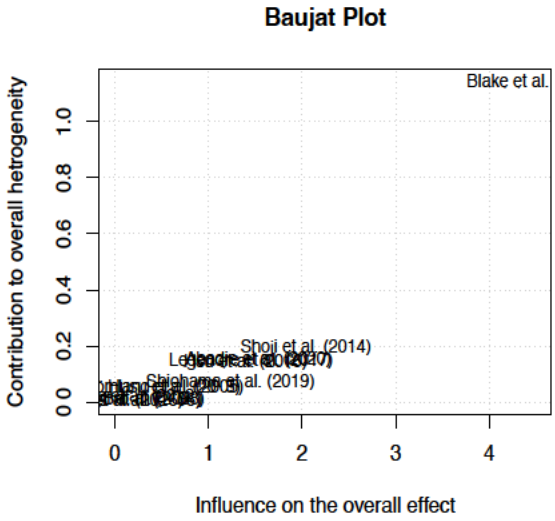
Funnel Plot of Standard Error by Prevalence of Inner Ear Anomalies Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.006). The trim and fill procedure did not impute any missing studies.

Appendix 2C. Figure 8d

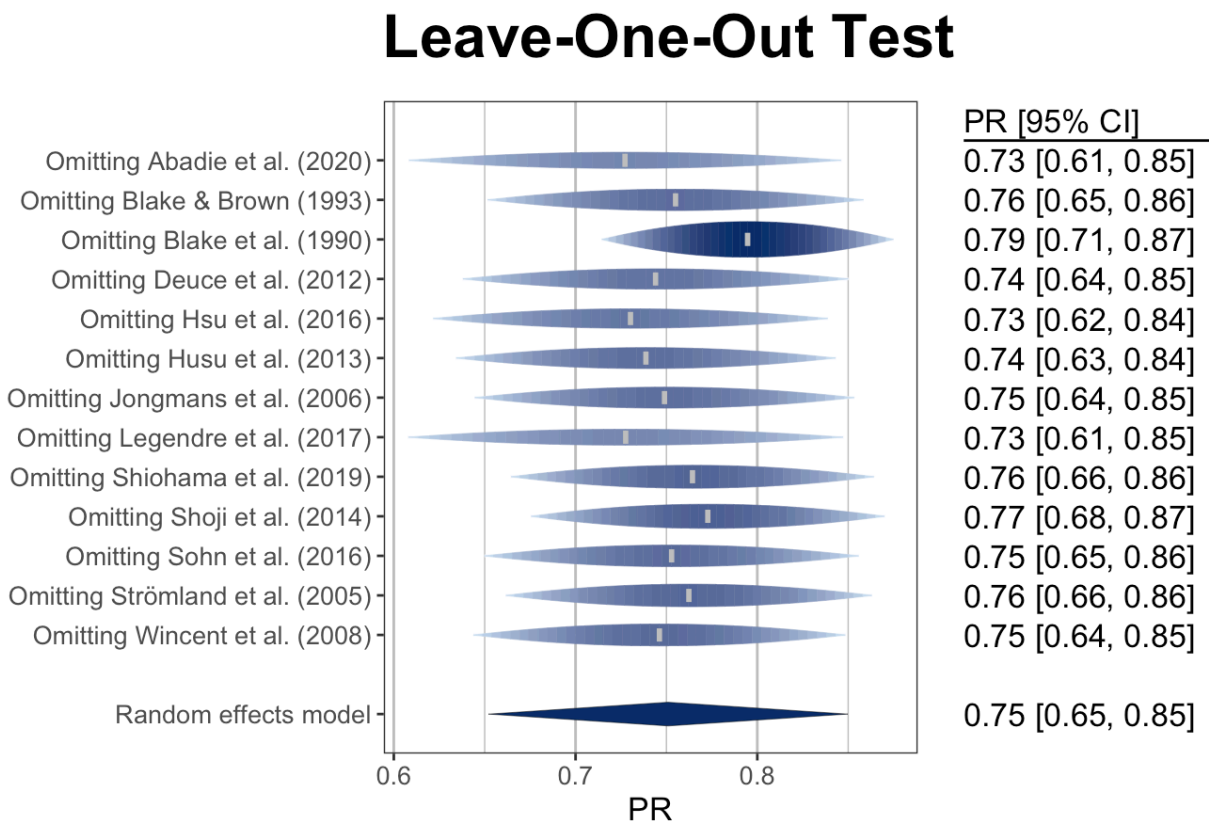
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Inner Ear Anomalies



Note. Blake et al. (1990) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 8e

Leave-One-Out Random Effects Model for Studies Reporting Inner Ear Anomalies

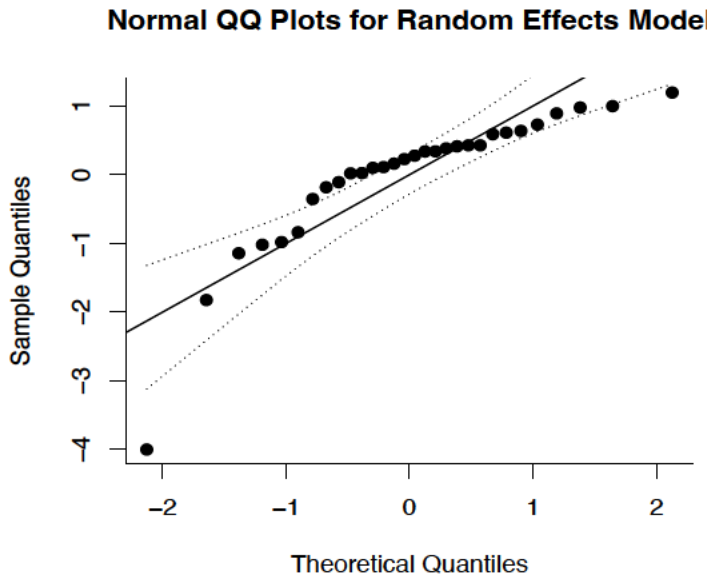


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Heart Defects

Appendix 2C. Figure 9a

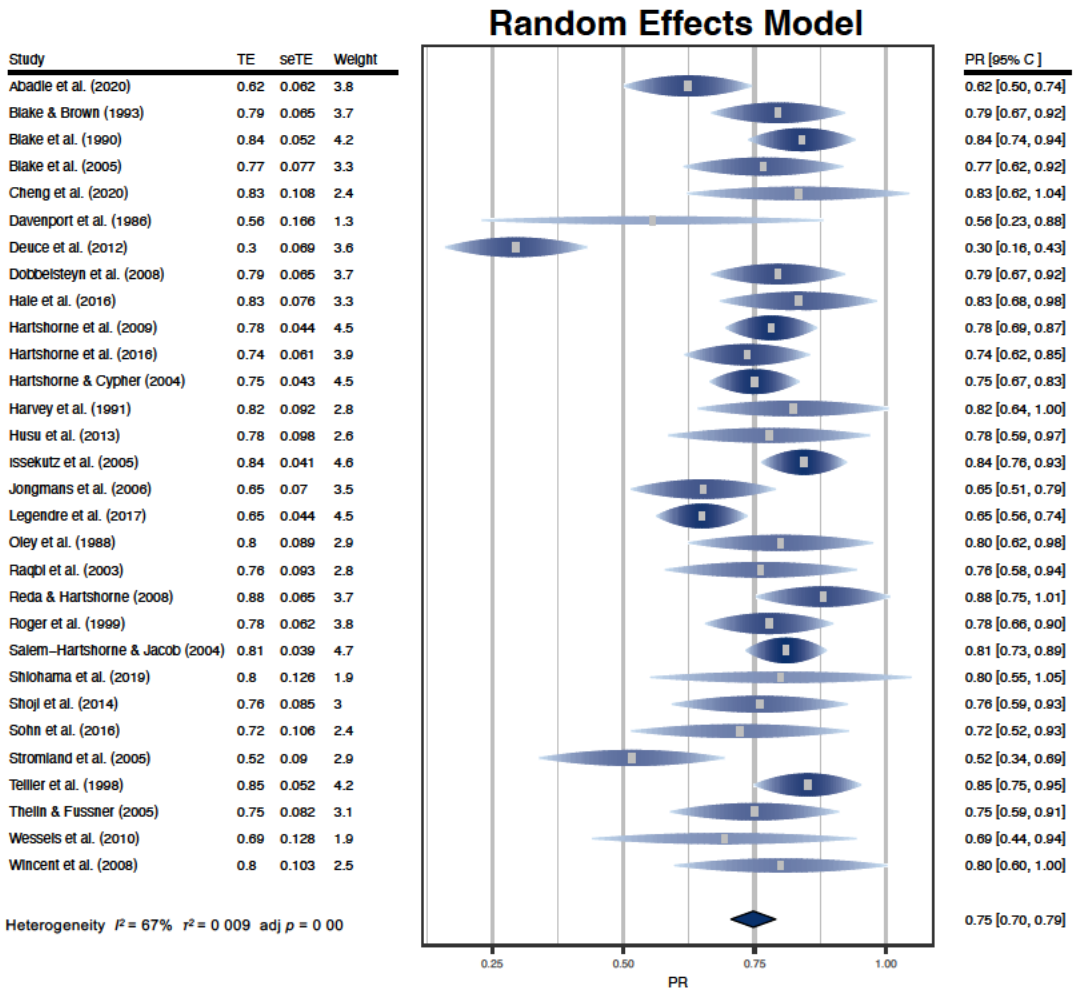
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Heart Defects



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 30 studies reporting heart defects in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 9b

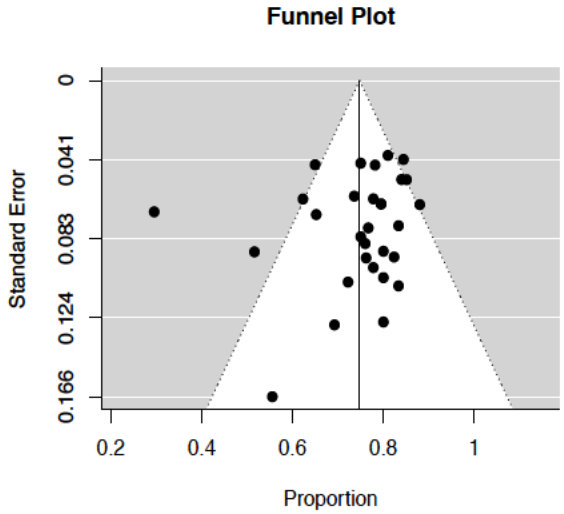
Random Effects Models of The Pooled Prevalence Estimate for Heart Defects in CHARGE Syndrome



Note. The pooled prevalence estimate for heart defects in CHARGE syndrome is 75% (95% CI, 70-79%; permuted p-value = 0.001; k = 30) with moderate heterogeneity (I2 = 67%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 39228 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 9c

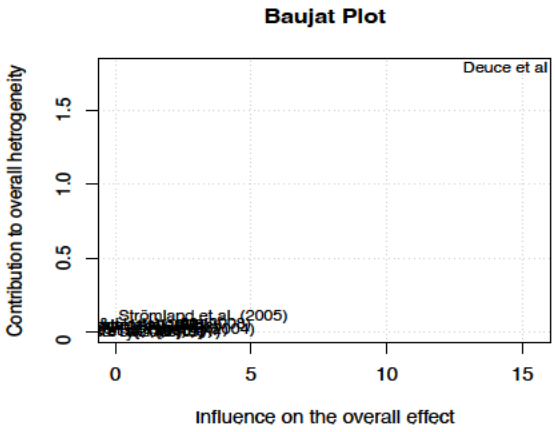
Funnel Plot of Standard Error by Prevalence of Heart Defects



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.348)

Appendix 2C. Figure 9d

Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Heart Defects



Note. Deuce et al. (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 9e

Leave-One-Out Random Effects Model for Studies Reporting Heart Defects

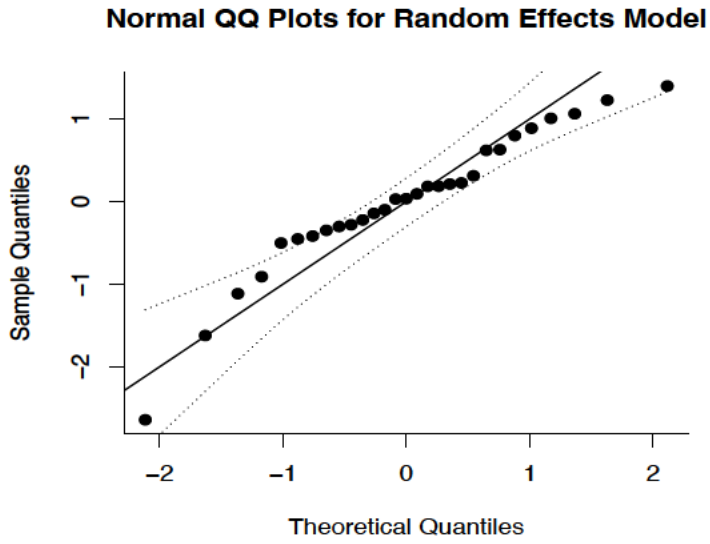


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Growth Deficiency

Appendix 2C. Figure 10a

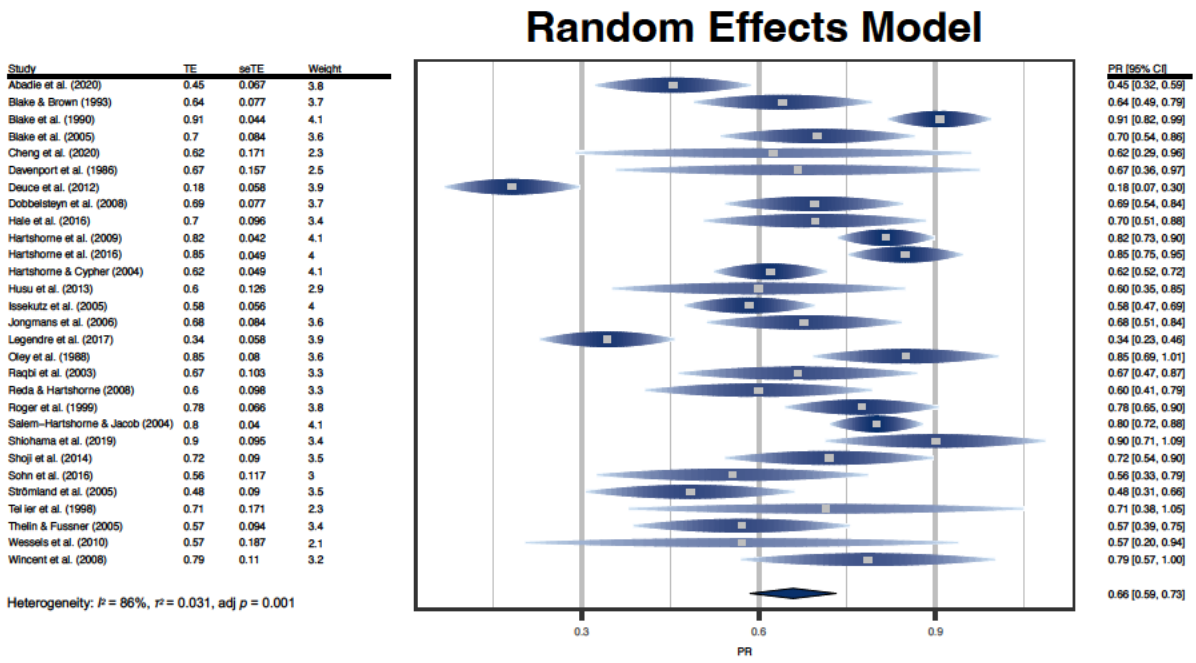
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Growth Deficiency



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 29 studies reporting growth deficiency in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 10b

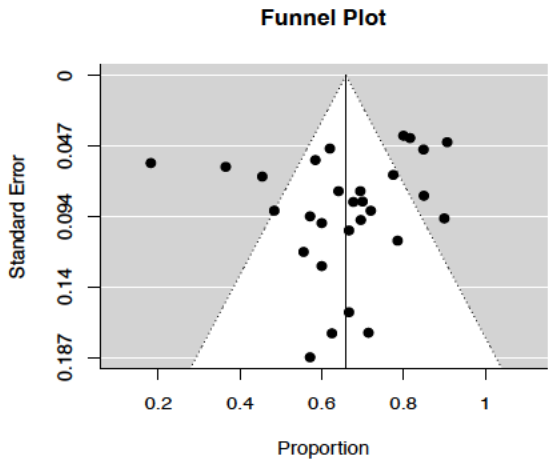
Random Effects Models of The Pooled Prevalence Estimate for Growth Deficiency in CHARGE Syndrome



Note. The pooled prevalence estimate for growth deficiency in CHARGE syndrome is 66% (95% CI, 59-73%; permuted p-value = 0.031; k = 29) with high heterogeneity (I^2 = 86%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 23693 suggests that the observed effect is robust to potential publication biases

Appendix 2C. Figure 10c

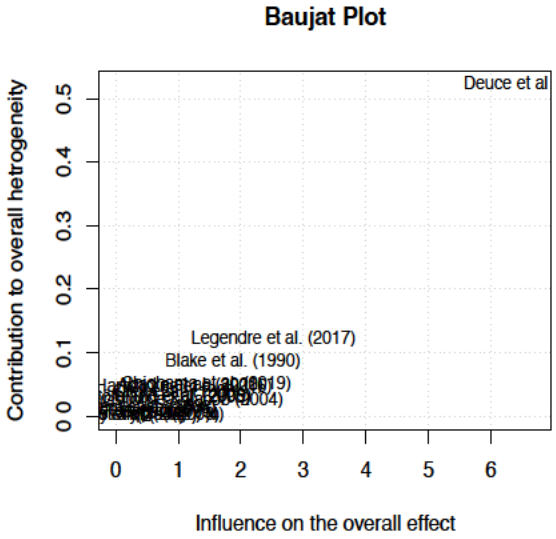
Funnel Plot of Standard Error by Prevalence of Growth Deficiency



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.267)

Appendix 2C. Figure 10d

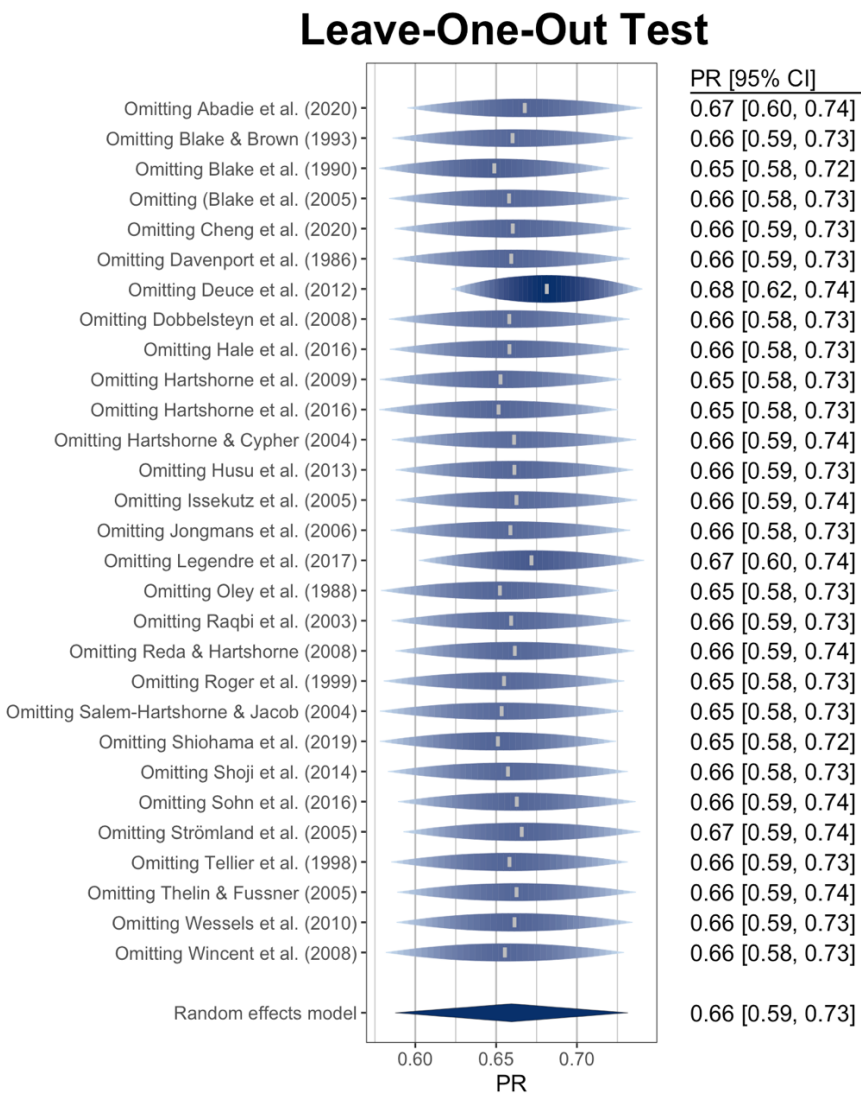
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Growth Deficiency



Note. Deuce et al. (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 10e

Leave-One-Out Random Effects Model for Studies Reporting Growth Deficiency

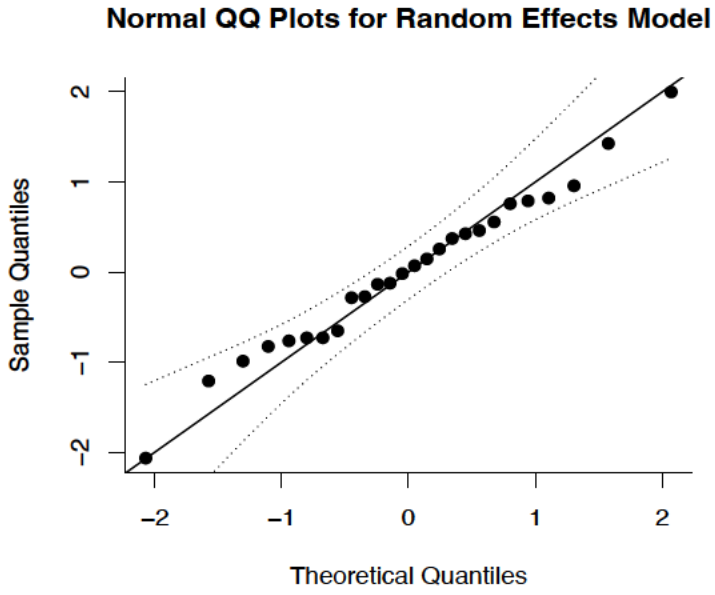


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Genital Hypoplasia

Appendix 2C. Figure 11a

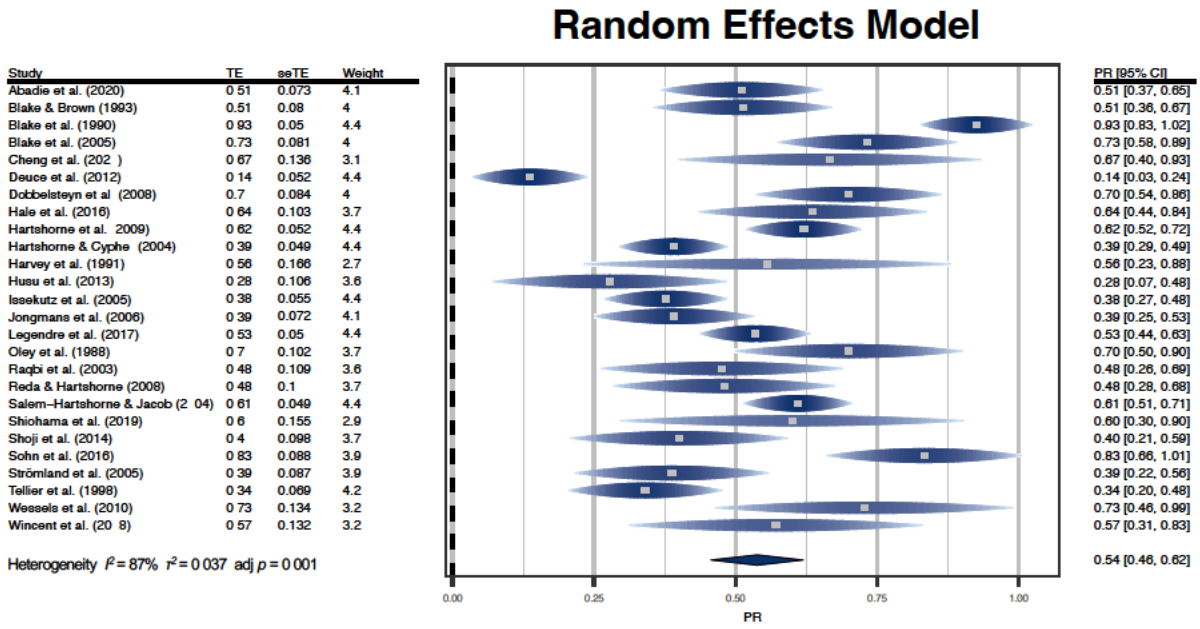
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Genital Hypoplasia



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 26 studies reporting genital hypoplasia in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 11b

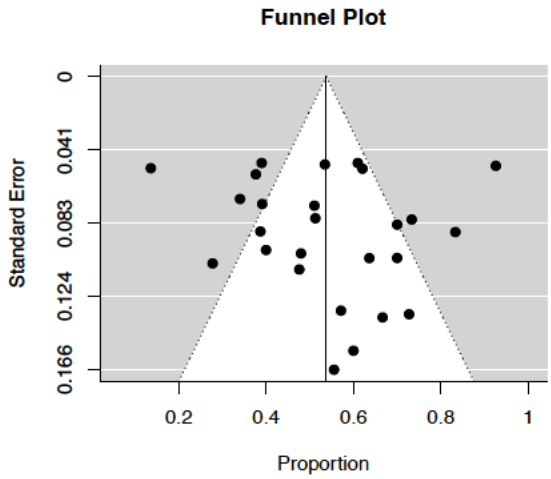
Random Effects Models of The Pooled Prevalence Estimate for Genital Hypoplasia in CHARGE Syndrome



Note. The pooled prevalence estimate for genital hypoplasia in CHARGE syndrome is 54% (95% CI, 46-62%; permuted p-value = 0.037; k = 26) with high heterogeneity (I^2 = 87%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 11548 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 11c

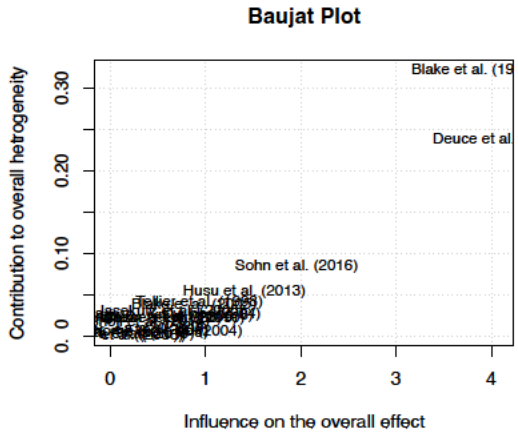
Funnel Plot of Standard Error by Prevalence of Genital Hypoplasia



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.654).

Appendix 2C. Figure 11d

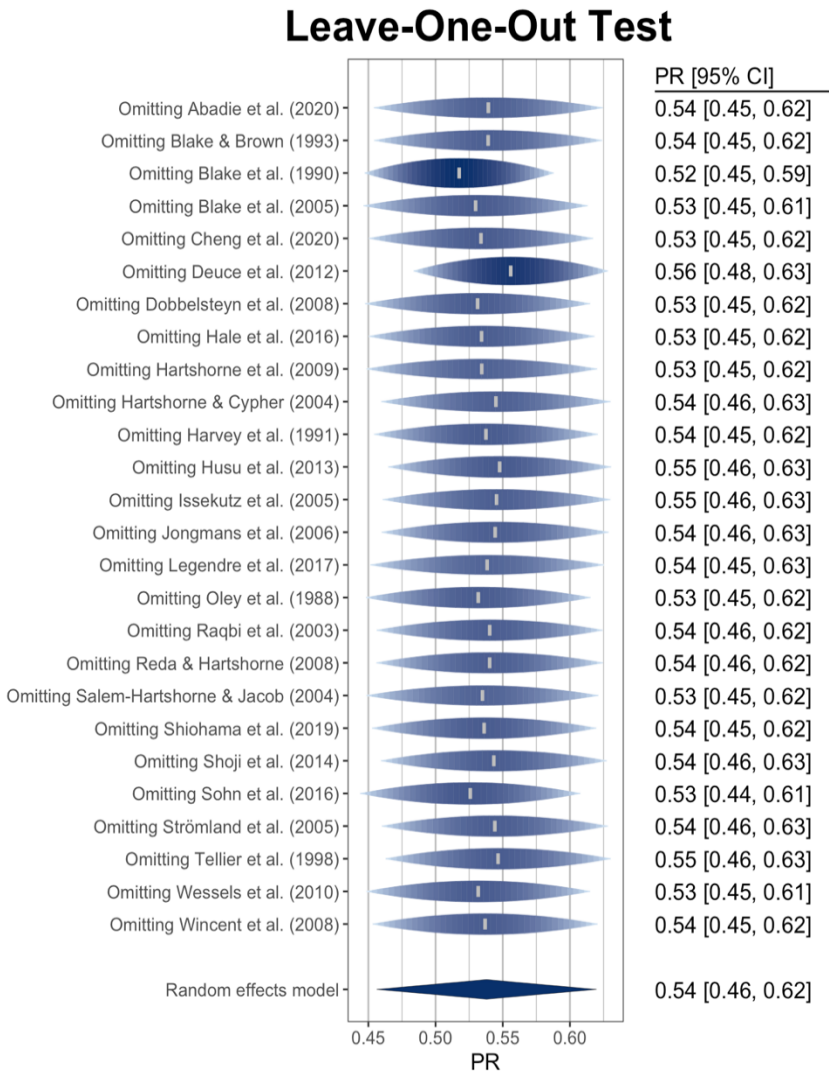
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Genital Hypoplasia



Note. Blake et al. (1990) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 11e

Leave-One-Out Random Effects Model for Studies Reporting Genital Hypoplasia

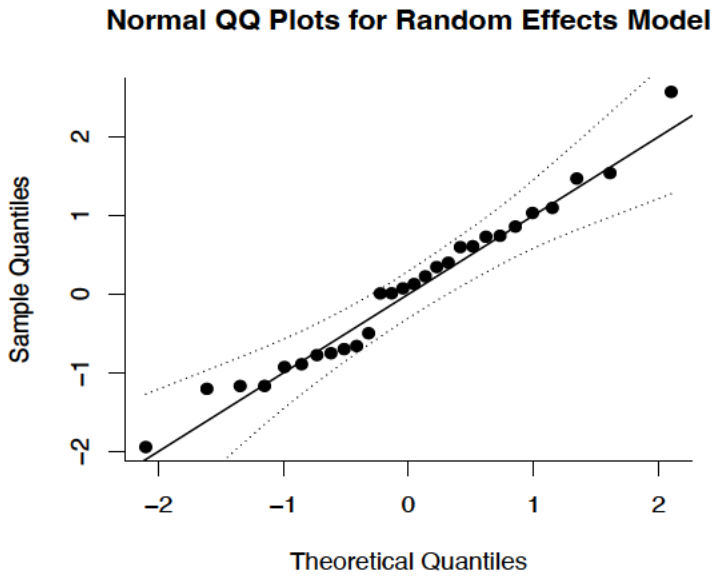


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Cleft Lip or Palate

Appendix 2C. Figure 12a

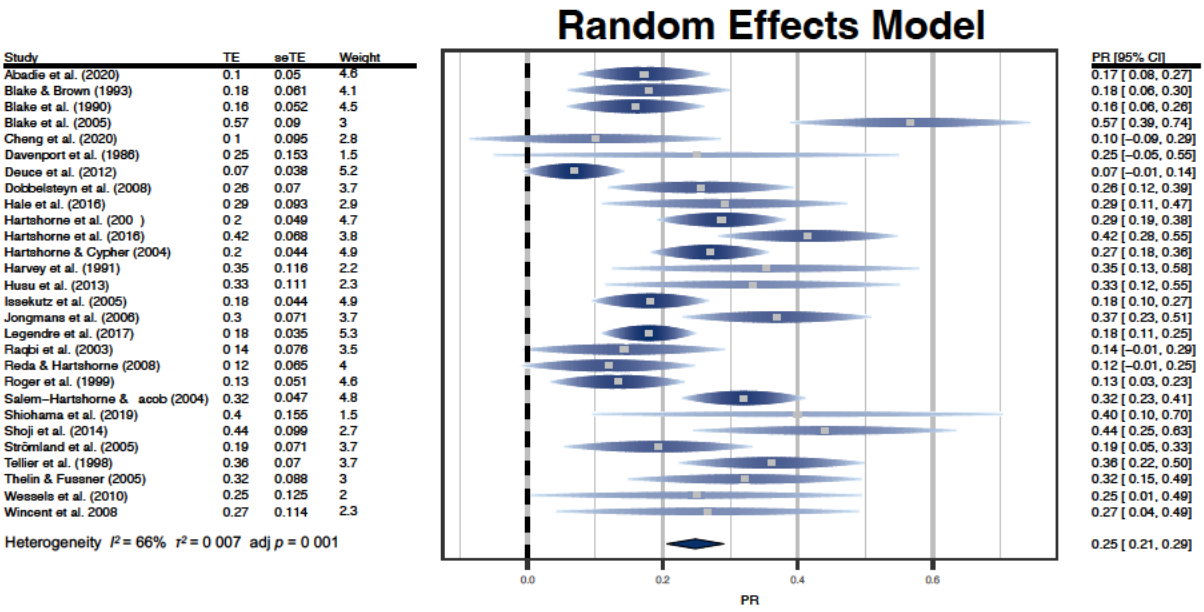
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Cleft Lip or Palate



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 28 studies reporting cleft lip or palate in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 12b

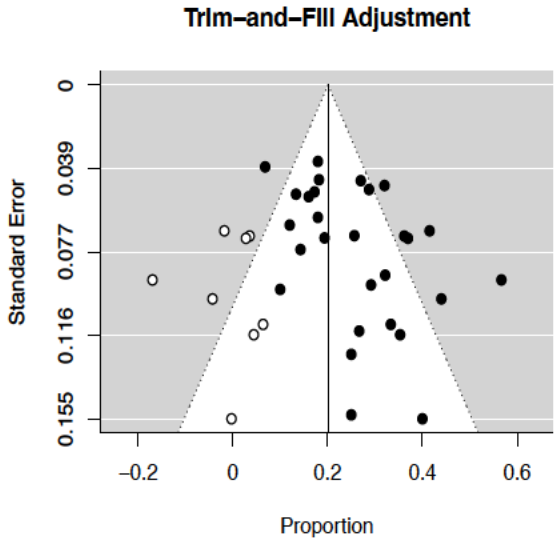
Random Effects Models of The Pooled Prevalence Estimate for Cleft Lip or Palate in CHARGE Syndrome



Note. The pooled prevalence estimate for cleft lip or palate in CHARGE syndrome is 25% (95% CI, 21-29%; permuted p-value = 0.001; k = 28) with moderate heterogeneity (I^2 = 66%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 3795 suggests that the observed effect is robust to potential publication biases

Appendix 2C. Figure 12c

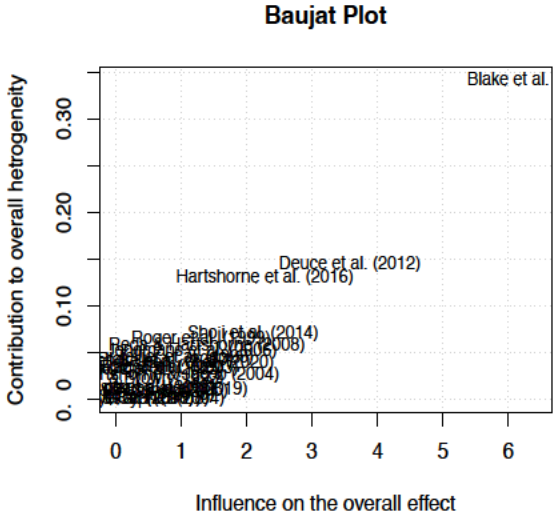
Funnel Plot of Standard Error by Prevalence of Cleft Lip or Palate Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.013). Using the trim and fill procedure it was estimated that 8 (SE = 3.47) studies were missing on the left side. Adjusted estimate = 20%, (95% CI = 16-25%, p = <.001; τ2 = 0.111, I2 = 74%).

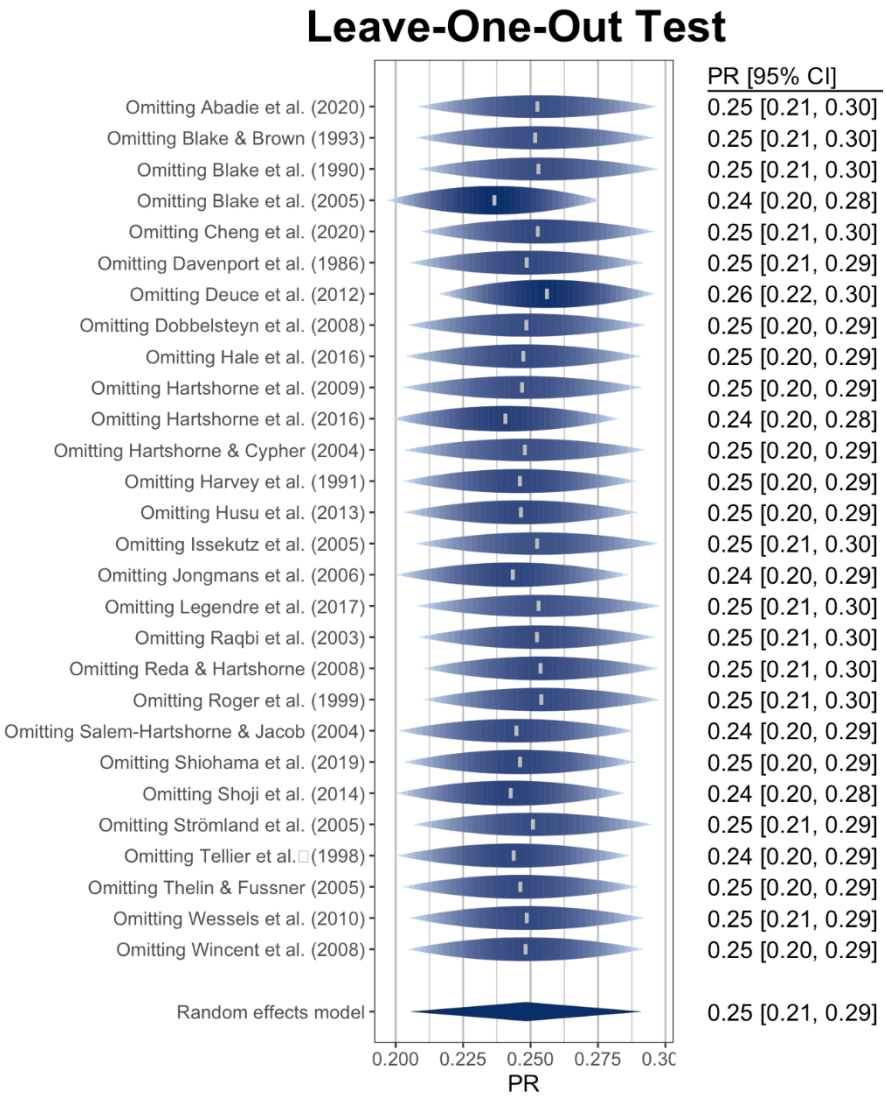
Appendix 2C. Figure 12d

Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Cleft Lip or Palate



Note. Blake et al. (1990) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 12e Leave-One-Out Random Effects Model for Studies Reporting Cleft Lip or Palate

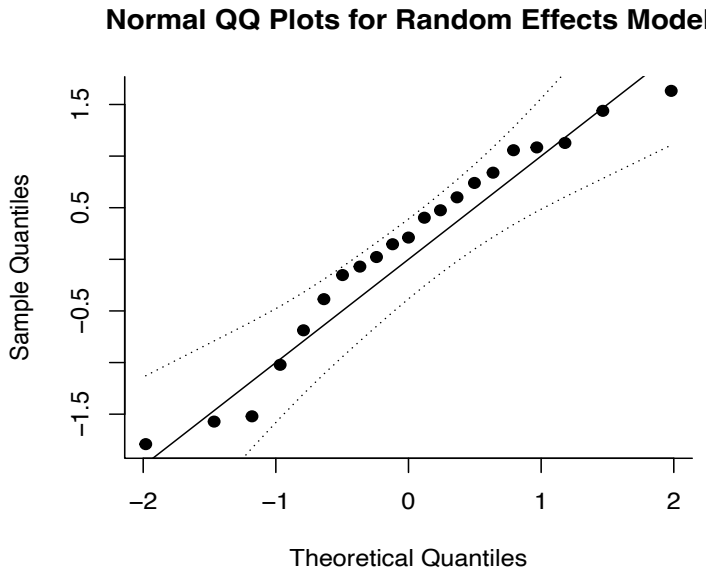


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Tracheoesophageal Fistula

Appendix 2C. Figure 13a

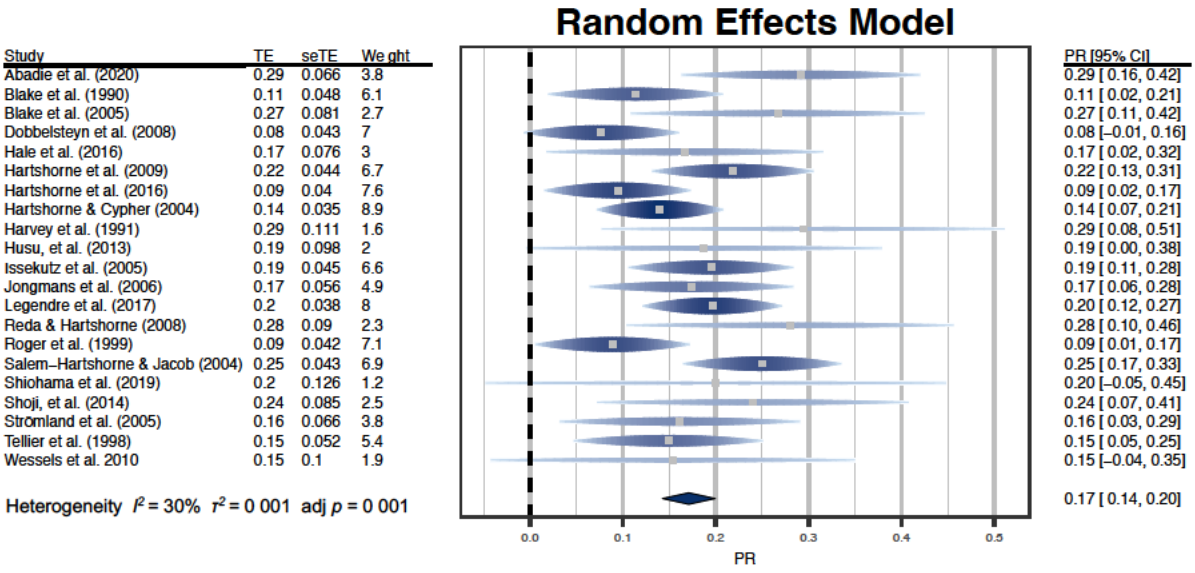
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Tracheoesophageal Fistula



Note. Visual inspection of the QQ plot suggests an approximate normal distribution of study effects for the 21 studies reporting tracheoesophageal fistula in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 13b

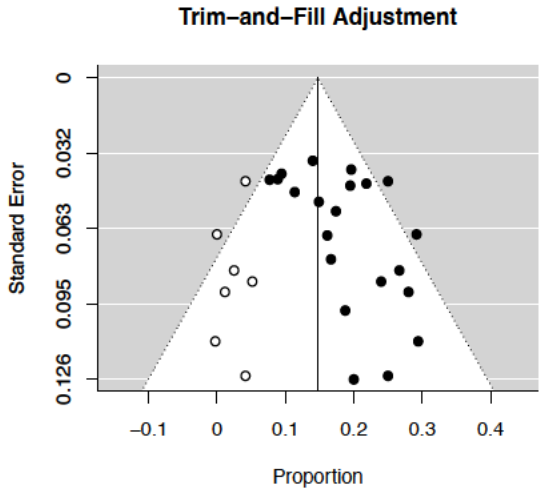
Random Effects Models of The Pooled Prevalence Estimate for Tracheoesophageal Fistula in CHARGE Syndrome



Note. The pooled prevalence estimate for tracheoesophageal fistula in CHARGE syndrome is 17% (95% CI, 14-20%; permuted p-value = 0.001; k = 21) with low heterogeneity (I2 = 30%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ2. Rosenthal Fail-safe N = 1553 suggests that the observed effect is robust to potential publication biases

Appendix 2C. Figure 13c

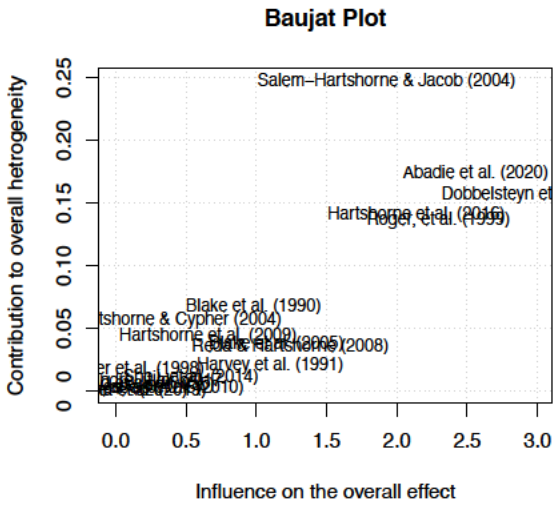
Funnel Plot of Standard Error by Prevalence of Tracheoesophageal Fistula Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.035). Using the trim and fill procedure it was estimated that 7 (SE = 2.95) studies were missing on the left side. Adjusted estimate = 15%, (95% *CI* = 12-18%, *p* = <.001; τ^2 = 0.003, I^2 = 47%).

Appendix 2C. Figure 13d

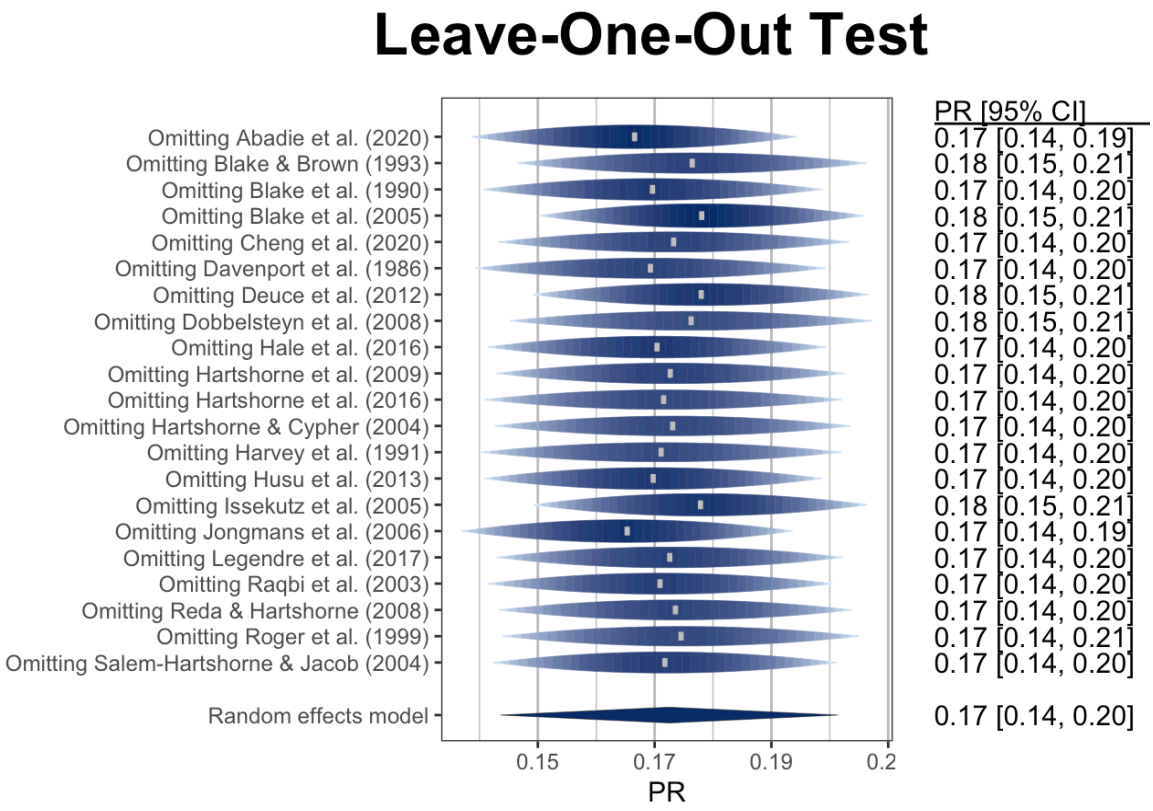
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Tracheoesophageal Fistula



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Salem-Hartshorne & Jacob (2004) had the greatest contribution to overall heterogeneity and Dobbelsteyn et al. (2008) had the greatest influence on the overall effect.

Appendix 2C. Figure 13e

Leave-One-Out Random Effects Model for Studies Reporting Tracheoesophageal Fistula

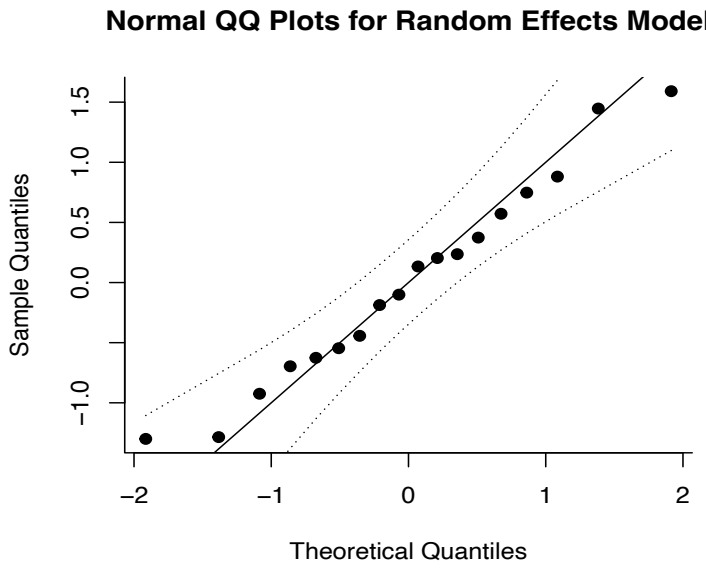


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Brain Anomalies

Appendix 2C. Figure 14a

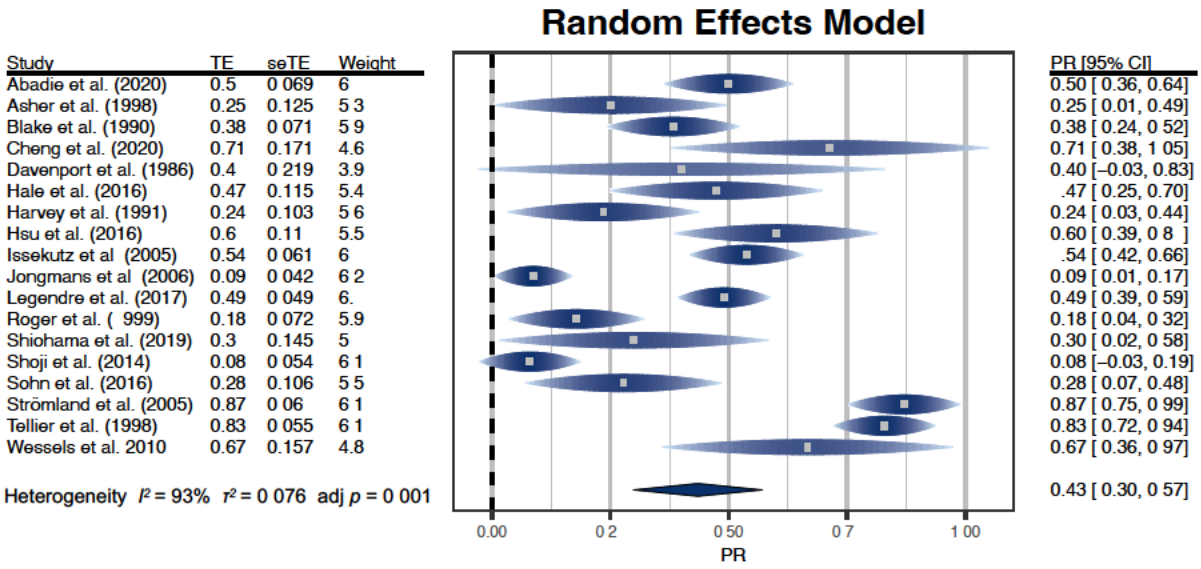
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Brain Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 18 studies reporting brain anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 14b

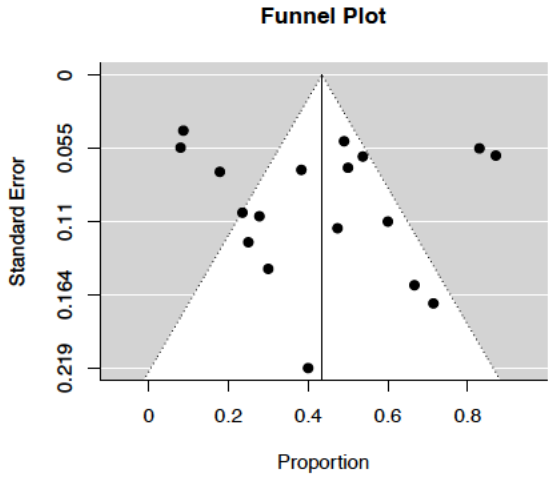
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Brain Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for brain anomalies in CHARGE syndrome is 43% (95% CI, 30-57%; permuted p-value = 0.001; k = 18) with high heterogeneity (I^2 = 93%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 3377 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 14c

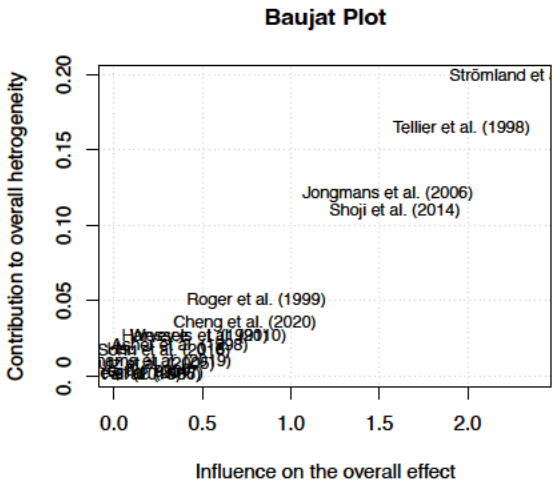
Funnel Plot of Standard Error by Prevalence of Brain Anomalies



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.61).

Appendix 2C. Figure 14d

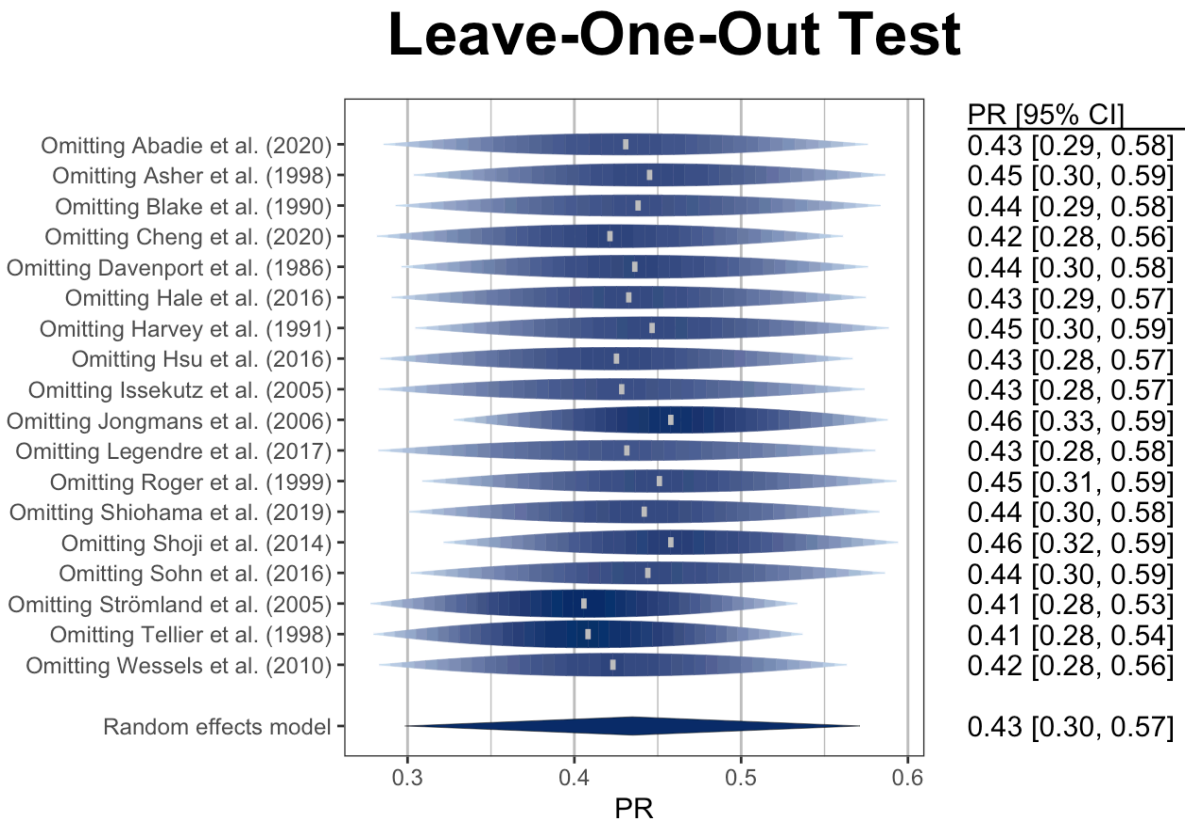
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Brain Anomalies



Note. Strömland et al. (2005) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 14e

Leave-One-Out Random Effects Model for Studies Reporting Brain Anomalies

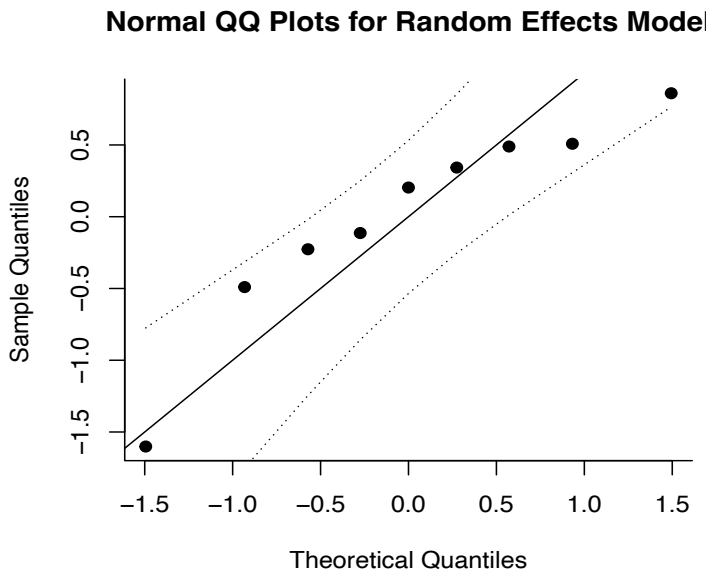


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Characteristic Face

Appendix 2C. Figure 15a

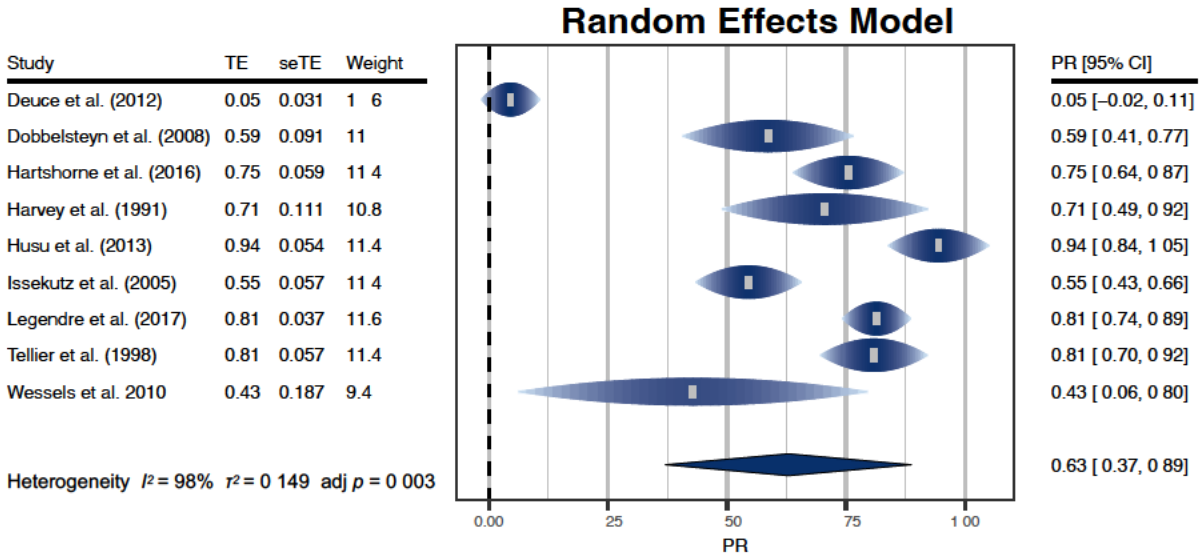
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Characteristic Face



Note. Visual inspection of the QQ plot suggests an approximate normal distribution of study effects for the 9 studies reporting characteristic face in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 15b

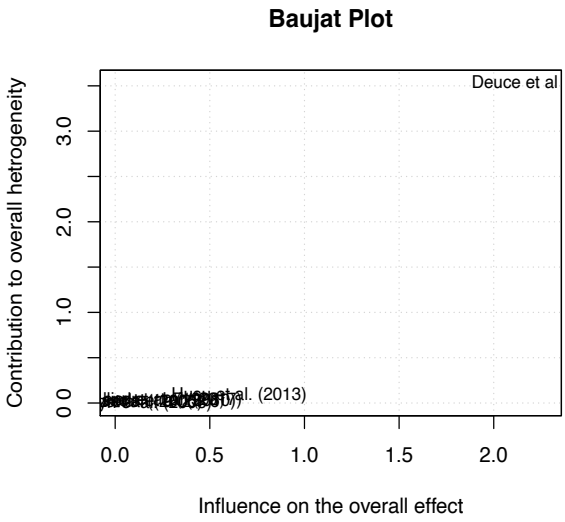
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Characteristic Face in CHARGE Syndrome



Note. The pooled prevalence estimate for characteristic face in CHARGE syndrome, based on the model above, is 63% (95% CI, 37-89%; permuted p-value = 0.003; k = 9) with high heterogeneity (I^2 = 98%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2

Appendix 2C. Figure 15c

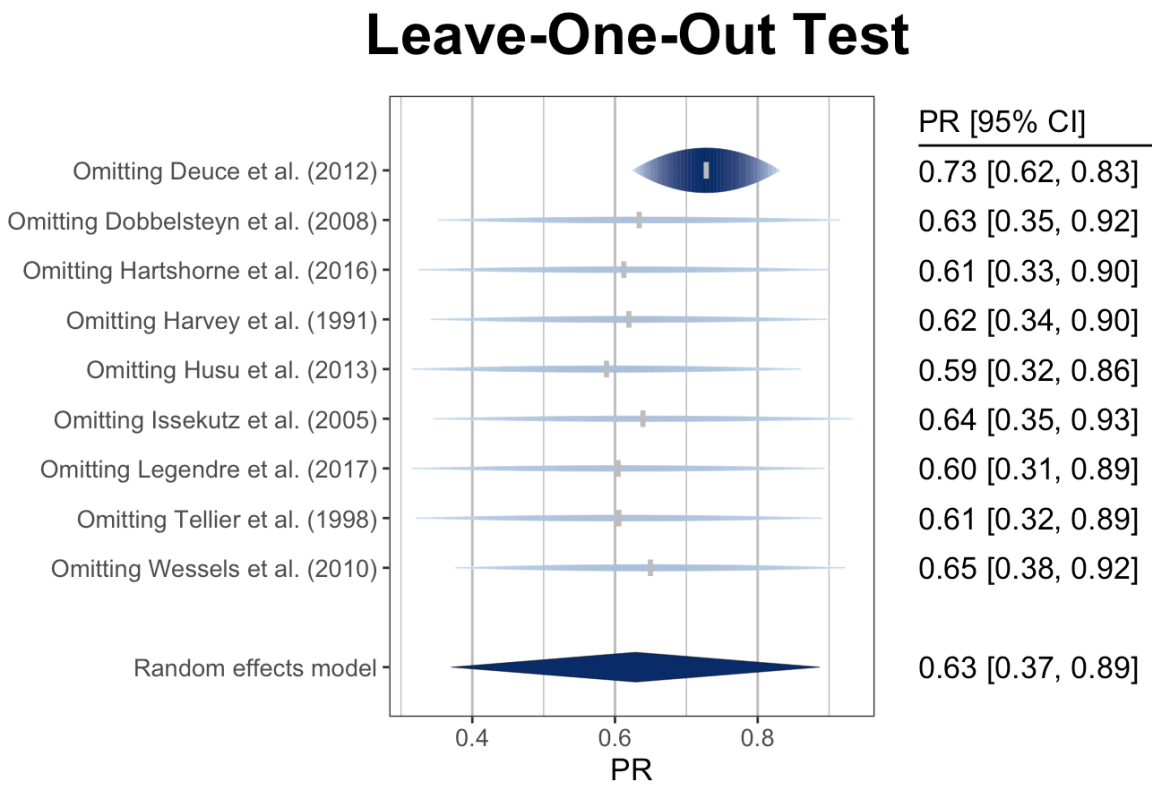
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Characteristic Face



Note. Deuce et al. (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 15d

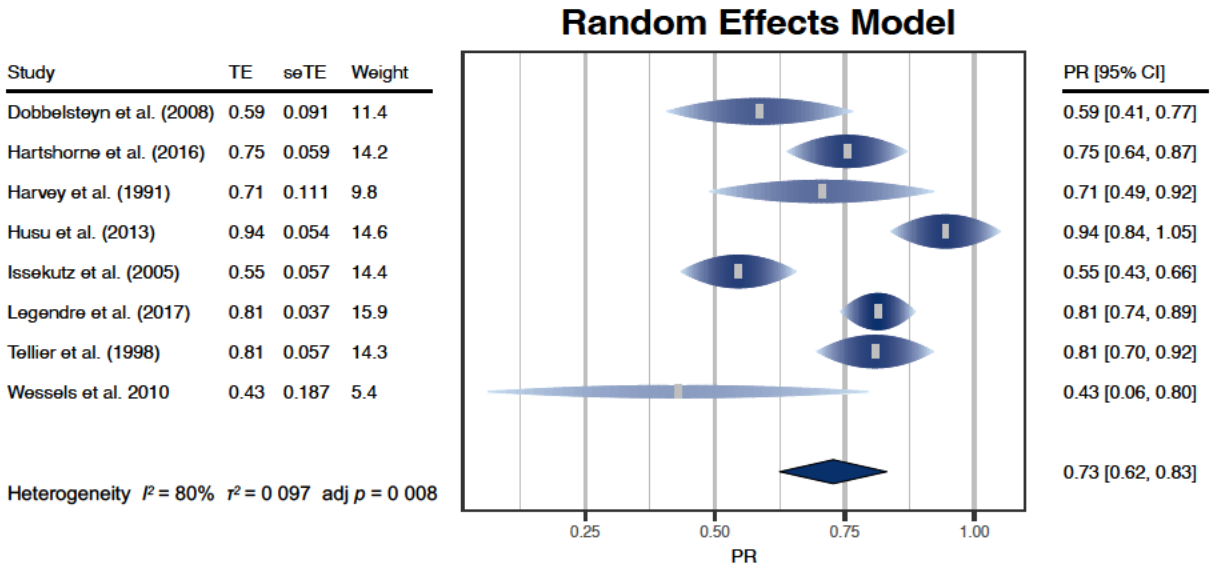
Leave-One-Out Random Effects Model for Studies Reporting Characteristic Face



Note. Leave one out analysis indicating that the Deuce et al. (2012) study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2C. Figure 15e

Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Characteristic Face in CHARGE Syndrome

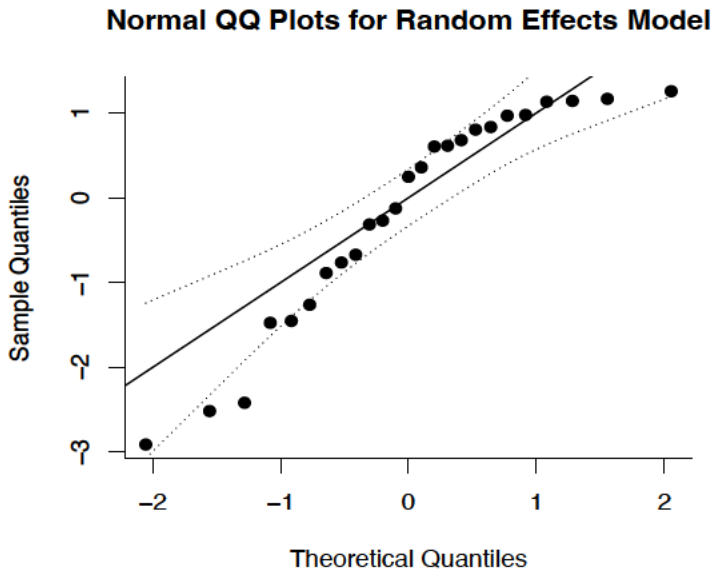


Note. Based on the results of the sensitivity analysis Deuce *et al* (2012) was removed from the final model. The pooled prevalence estimate for characteristic face in CHARGE syndrome is 73% (95% CI, 62-83%; permuted p-value = 0.008; k = 8) with high heterogeneity (I^2 = 80%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2.

Hearing Impairment

Appendix 2C. Figure 16a

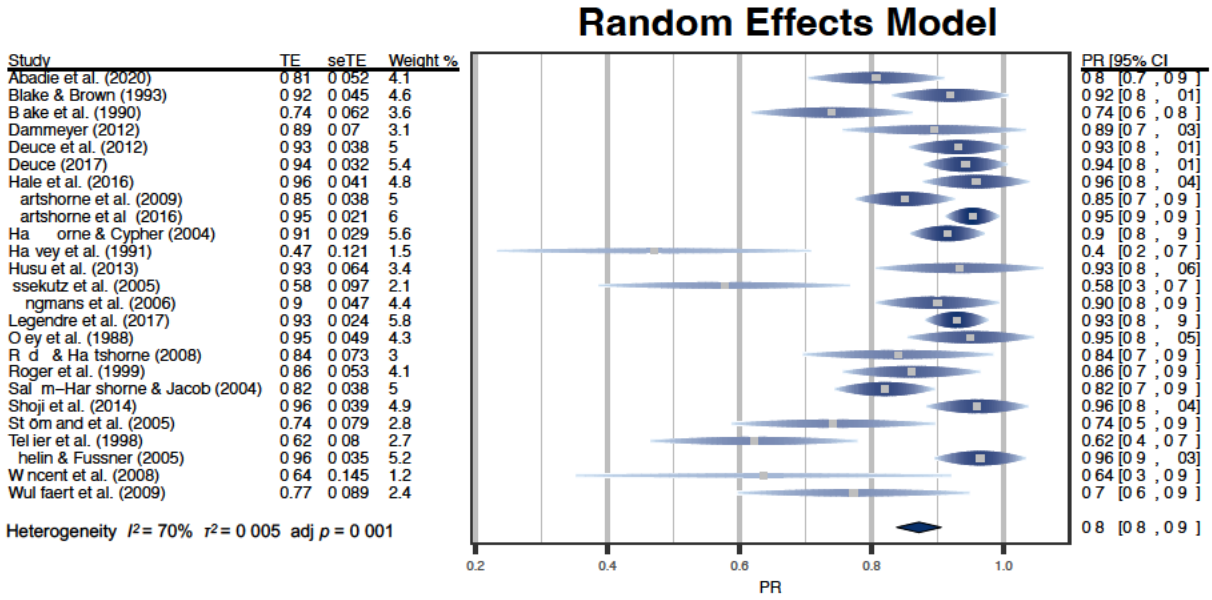
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Hearing Impairment



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 25 studies reporting hearing impairment in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 16b

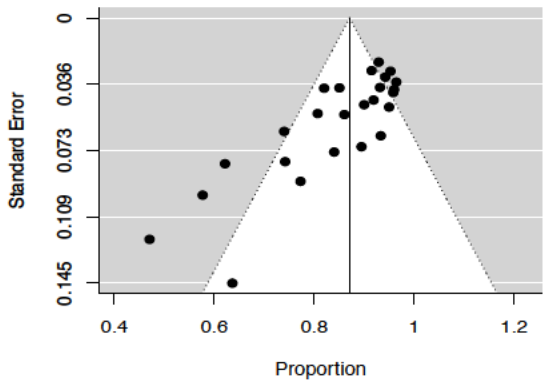
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Hearing Impairment in CHARGE Syndrome



Note. The pooled prevalence estimate for hearing impairment in CHARGE syndrome is 87% (95% CI, 84-91%; permuted p-value = 0.001; k = 25) with moderate heterogeneity (I^2 = 70%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 77214 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 16c

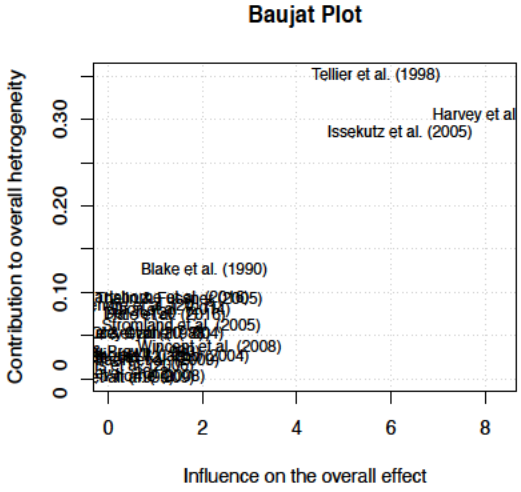
Funnel Plot of Standard Error by Prevalence of Hearing Impairment



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 2.018)

Appendix 2C. Figure 16d

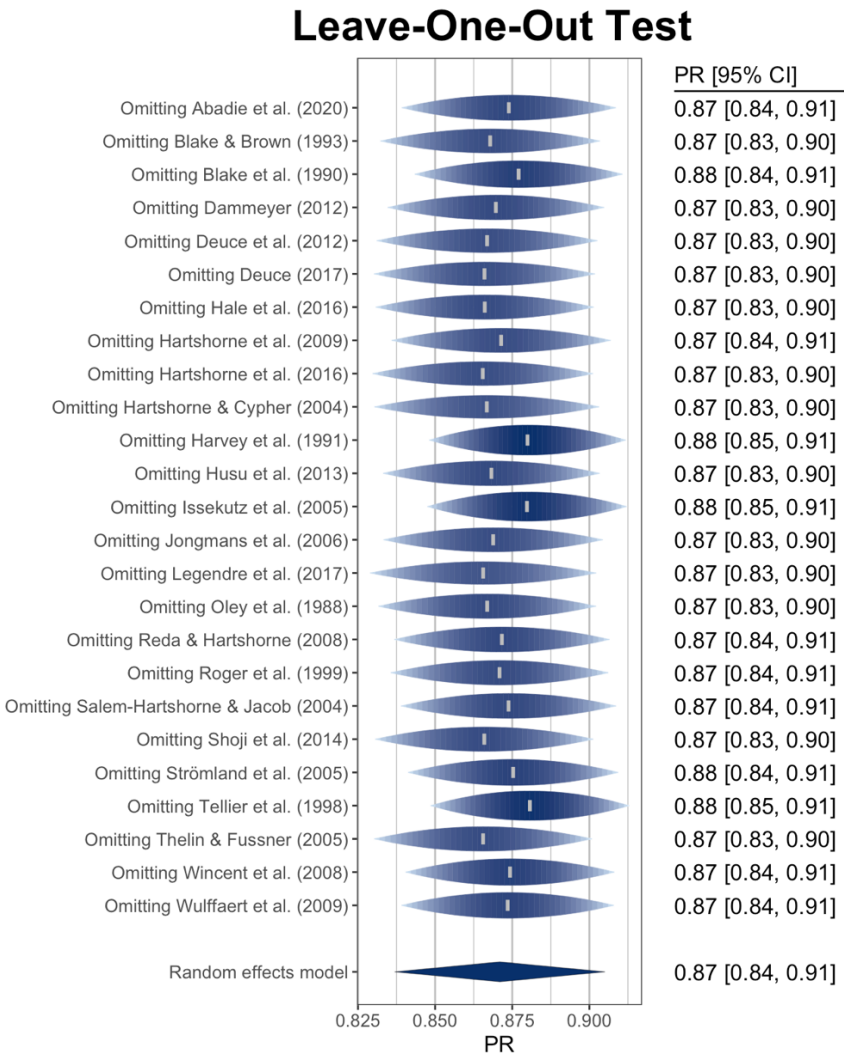
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Hearing Impairment



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Tellier et al. (1998) had the greatest contribution to overall heterogeneity and Harvey et al. (1991) had the greatest influence on the overall effect.

Appendix 2C. Figure 16e

Leave-One-Out Random Effects Model for Studies Reporting Hearing Impairment

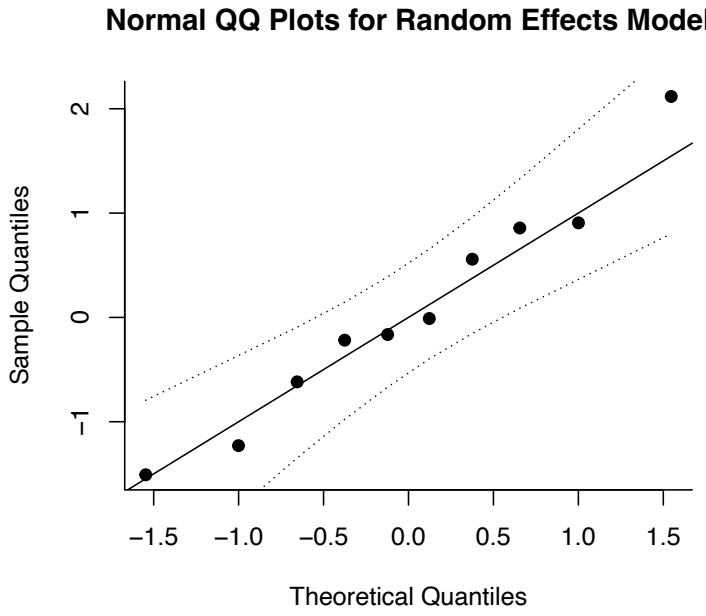


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Iris Coloboma

Appendix 2C. Figure 17a

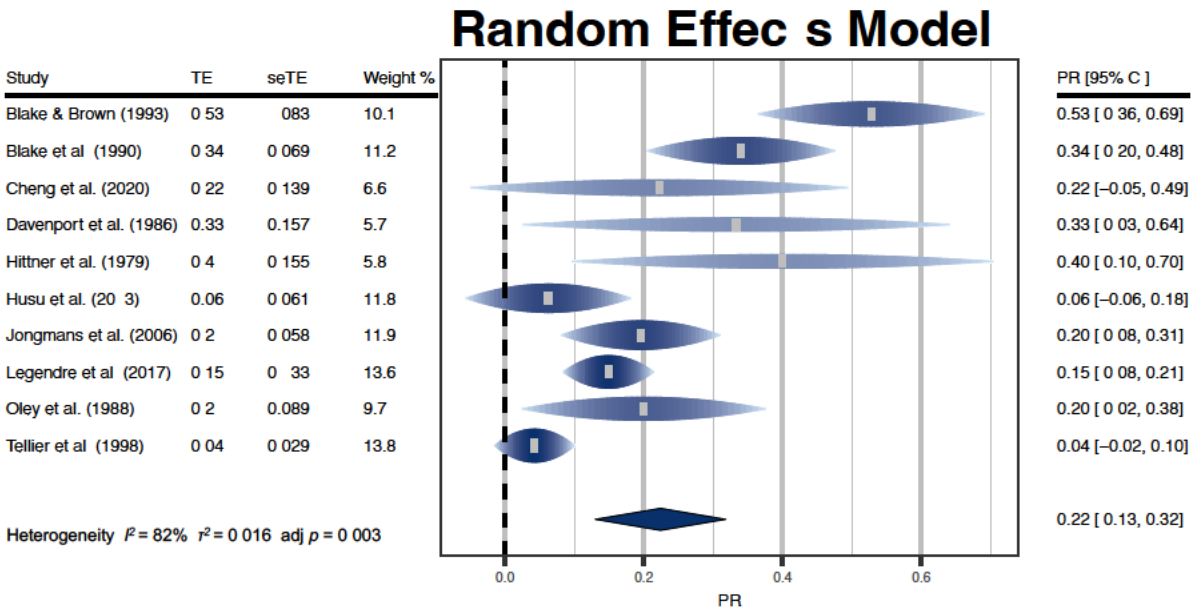
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Iris Coloboma



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 10 studies reporting iris coloboma in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 17b

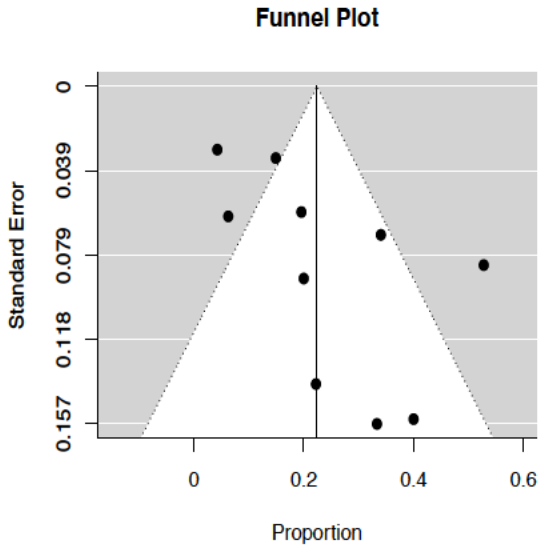
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Iris Coloboma in CHARGE Syndrome



Note. The pooled prevalence estimate for iris coloboma in CHARGE syndrome is 22% (95% CI, 13-32%; permuted p-value = 0.003; k = 10) with high heterogeneity (I^2 = 82%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 325 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 17c

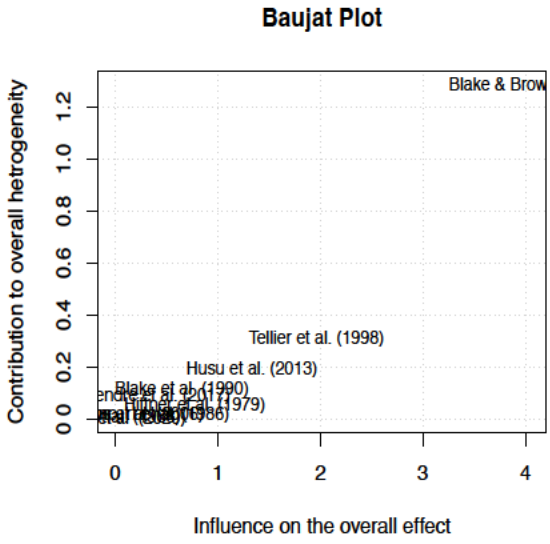
Funnel Plot of Standard Error by Prevalence of Iris Coloboma



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.034)

Appendix 2C. Figure 17d

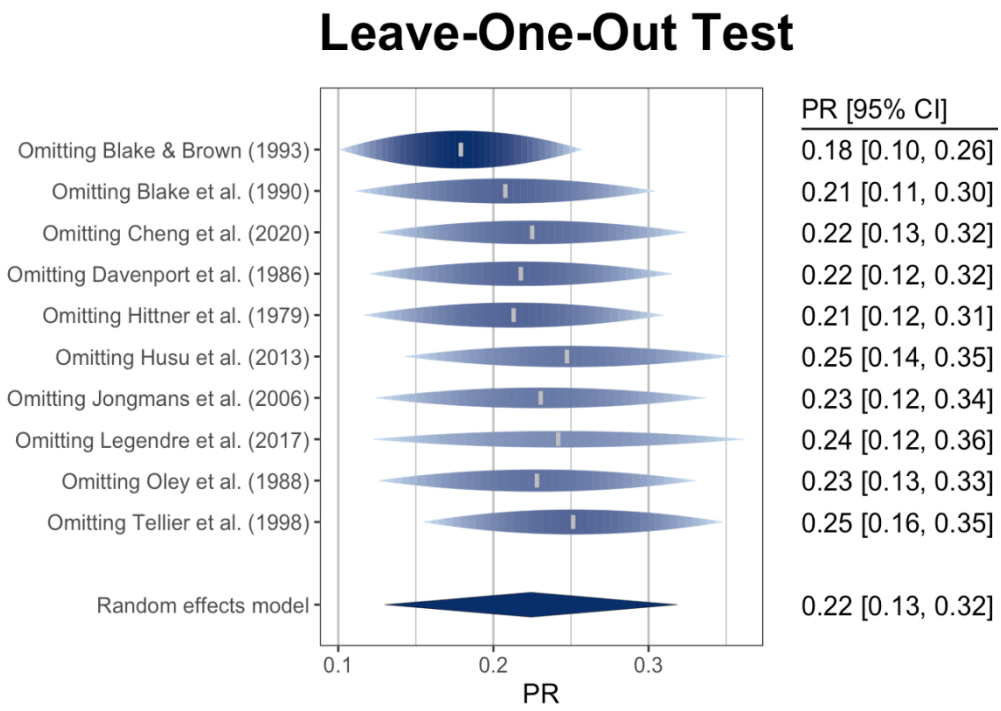
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Iris Coloboma



Note. Blake and Brown (1993) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 17e

Leave-One-Out Random Effects Model for Studies Reporting Iris Coloboma

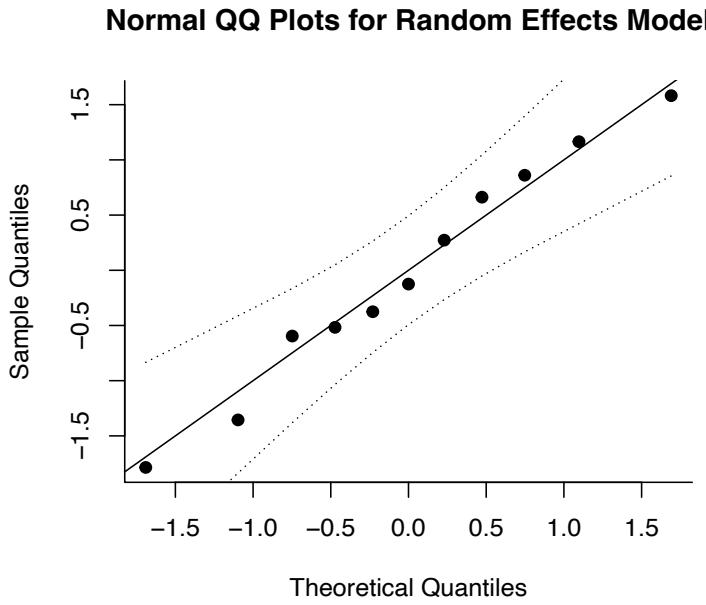


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Posterior segment coloboma

Appendix 2C. Figure 18a

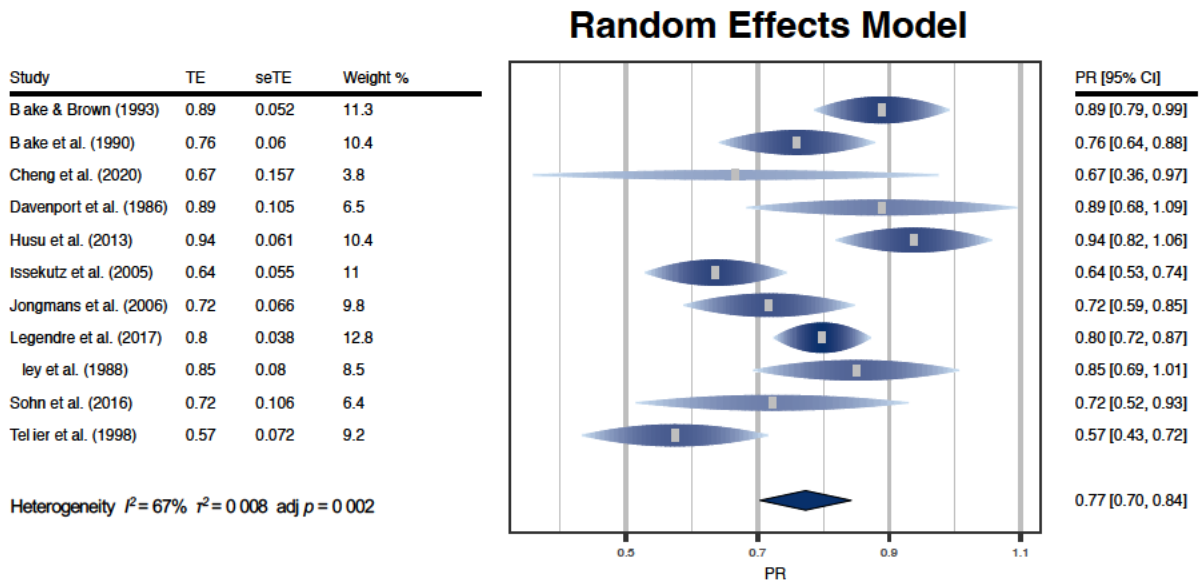
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Posterior Segment Coloboma



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting posterior segment coloboma in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 18b

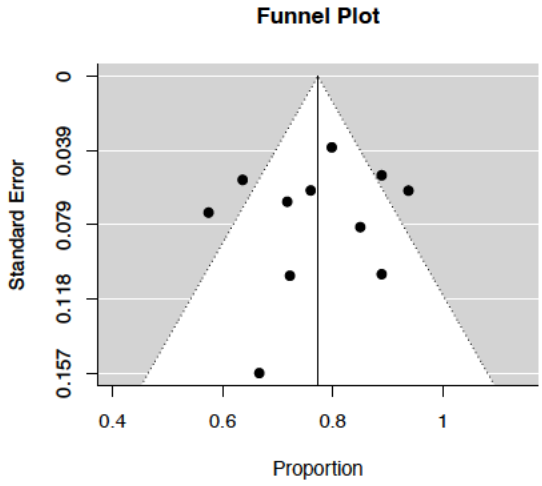
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Posterior Segment Coloboma in CHARGE Syndrome



Note. The pooled prevalence estimate for posterior segment coloboma in CHARGE syndrome is 77% (95% CI, 70-84%; permuted p-value = 0.002; k = 11) with moderate heterogeneity (I^2 = 67%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 5940 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 18c

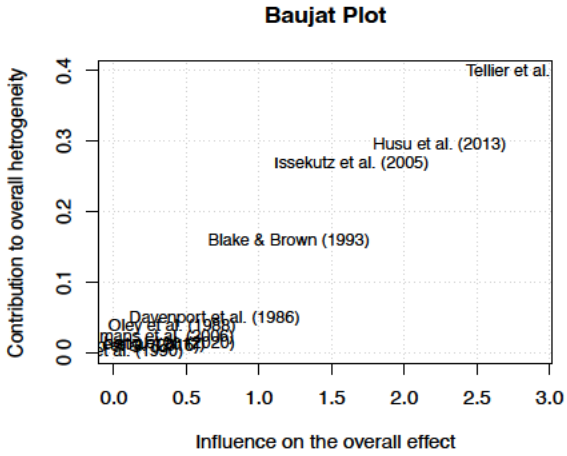
Funnel Plot of Standard Error by Prevalence of Posterior Segment Coloboma



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.659)

Appendix 2C. Figure 18d

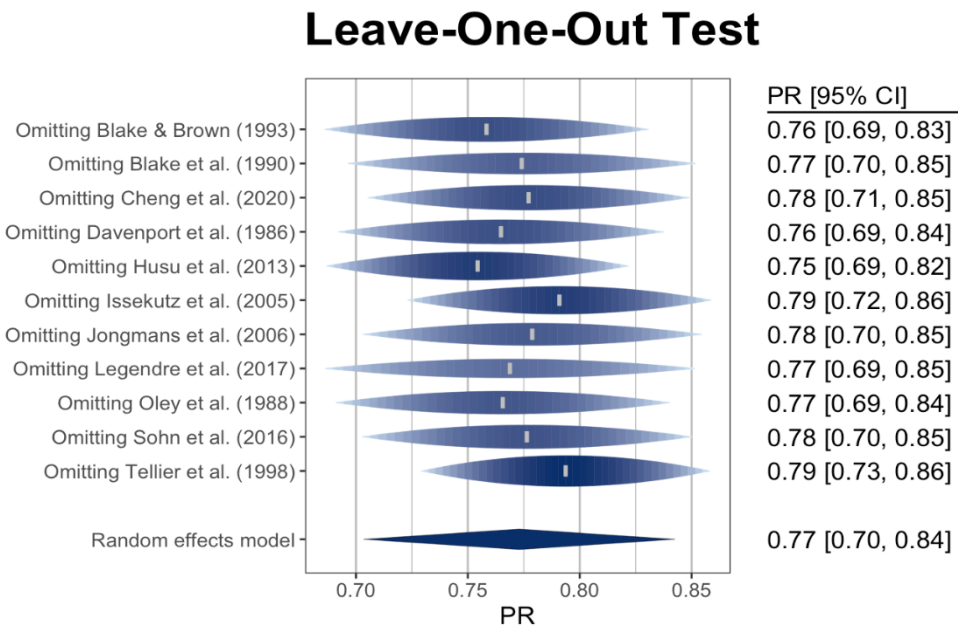
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Posterior Segment Coloboma



Note. Tellier et al. (1998) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 18e

Leave-One-Out Random Effects Model for Studies Reporting Posterior Segment Coloboma

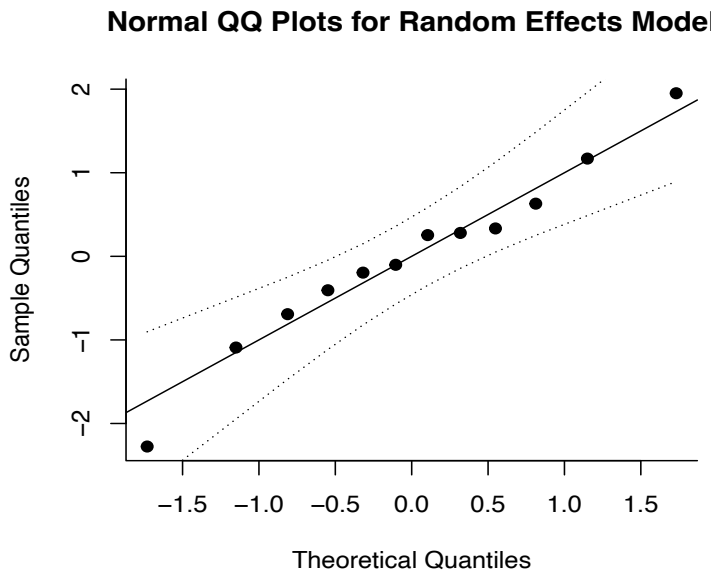


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Bilateral Coloboma

Appendix 2C. Figure 19a

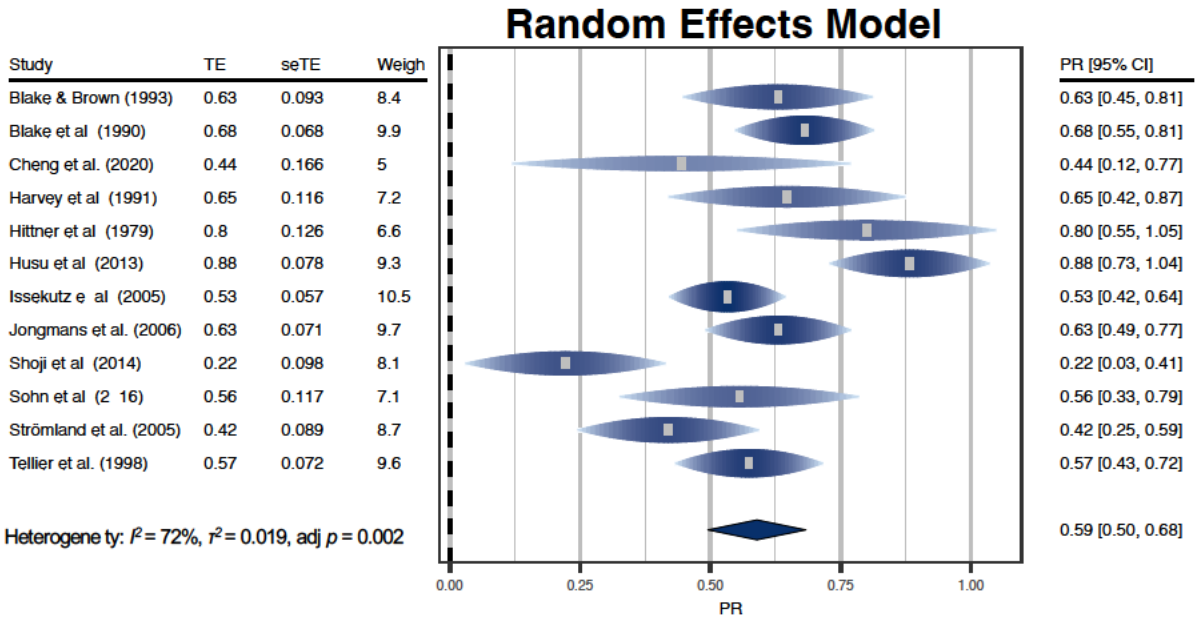
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Bilateral Coloboma



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 12 studies reporting bilateral coloboma in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 19b

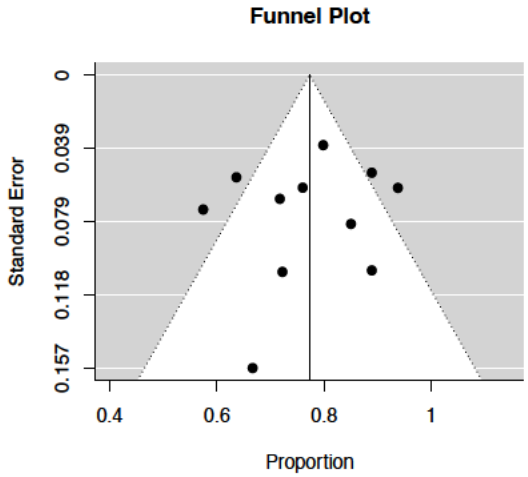
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Bilateral Coloboma in CHARGE Syndrome



Note. The pooled prevalence estimate for bilateral coloboma in CHARGE syndrome is 59% (95% CI, 50-68%; permuted p-value = 0.002; k = 12) with moderate heterogeneity (I^2 = 72%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 2390 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 19c

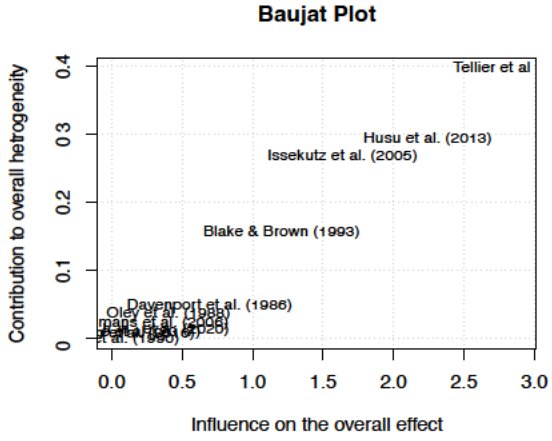
Funnel Plot of Standard Error by Prevalence of Bilateral Coloboma



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.761

Appendix 2C. Figure 19d

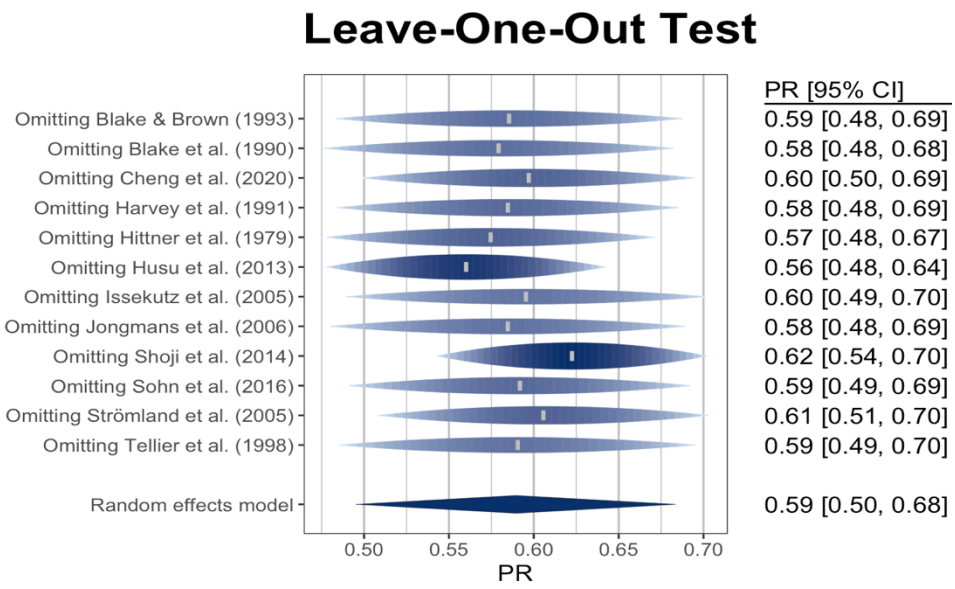
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Bilateral Coloboma



Note. Shoji et al. (2014) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2C. Figure 19e

Leave-One-Out Random Effects Model for Studies Reporting Bilateral Coloboma

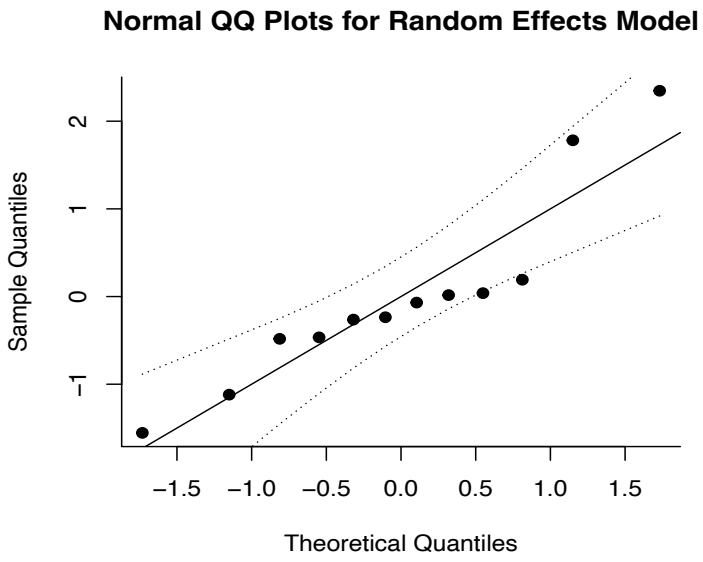


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Bilateral Choanal Atresia

Appendix 2C. Figure 20a

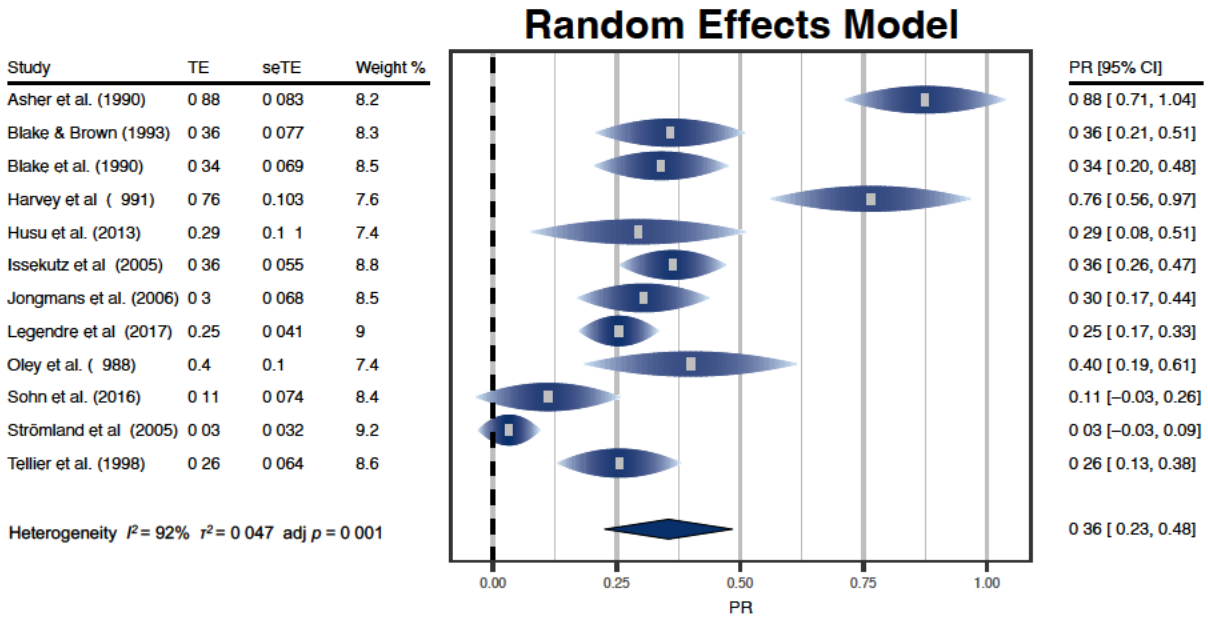
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Bilateral Choanal Atresia



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 12 studies reporting bilateral choanal atresia in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 20b

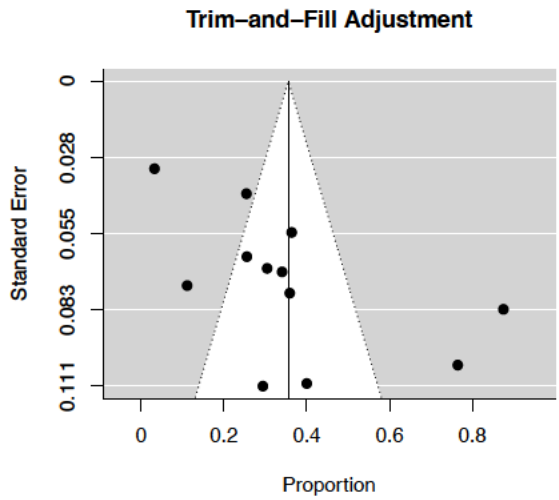
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Bilateral Choanal Atresia in CHARGE Syndrome



Note. The pooled prevalence estimate for bilateral choanal atresia in CHARGE syndrome is 36% (95% CI, 23-48%; permuted p-value = 0.001; k = 12) with high heterogeneity (I^2 = 92%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 1224 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 20c

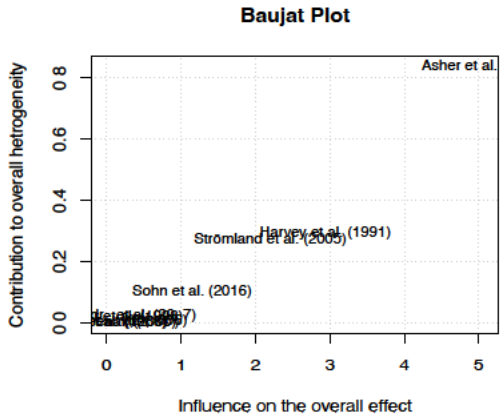
Funnel Plot of Standard Error by Prevalence of Bilateral Choanal Atresia Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.011). The trim and fill procedure did not impute any missing studies.

Appendix 2C. Figure 20d

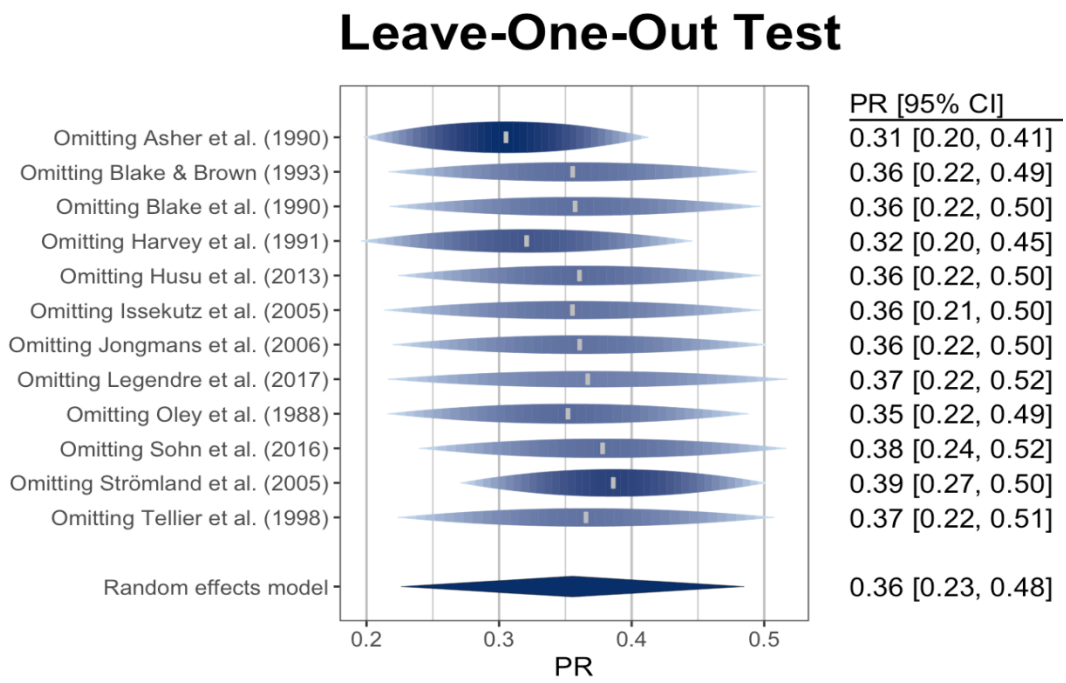
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Bilateral Choanal Atresia



Note. Asher et al. (1990) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2C. Figure 20e

Leave-One-Out Random Effects Model for Studies Reporting Bilateral Choanal Atresia

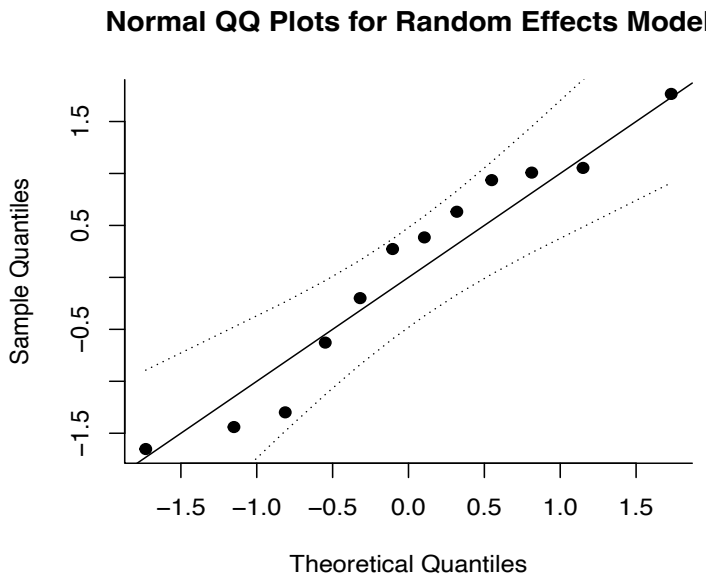


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Patent Ductus Arteriosus

Appendix 2C. Figure 21a

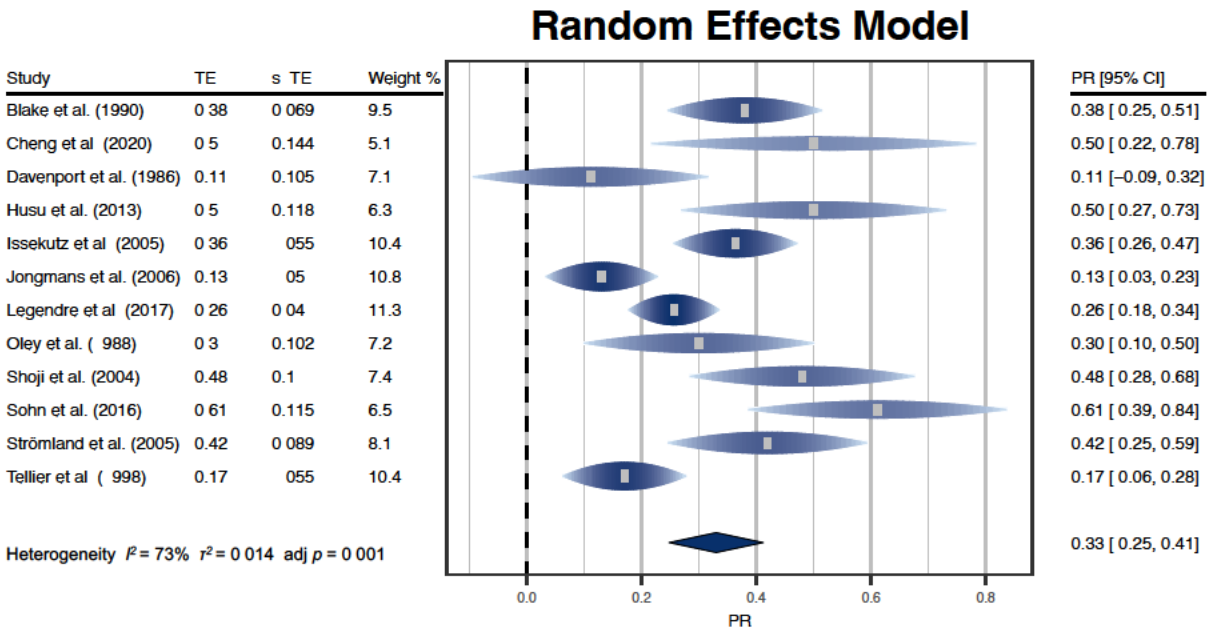
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Patent Ductus Arteriosus



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 12 studies reporting patent ductus arteriosus in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 21b

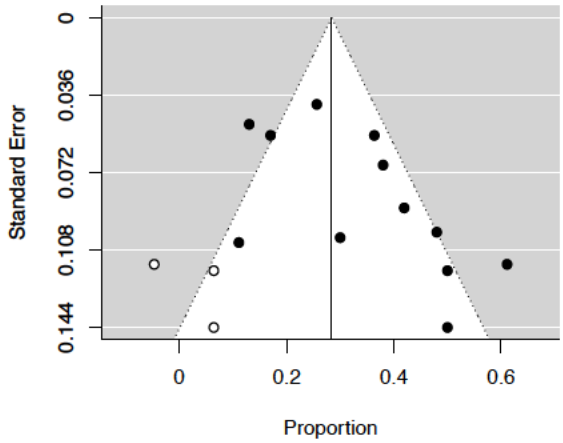
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Patent Ductus Arteriosus in CHARGE Syndrome



Note. The pooled prevalence estimate for patent ductus arteriosus in CHARGE syndrome is 33% (95% CI, 25-41%; permuted p-value = 0.001; k = 12) with moderate heterogeneity (I^2 = 73%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 942 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 21c

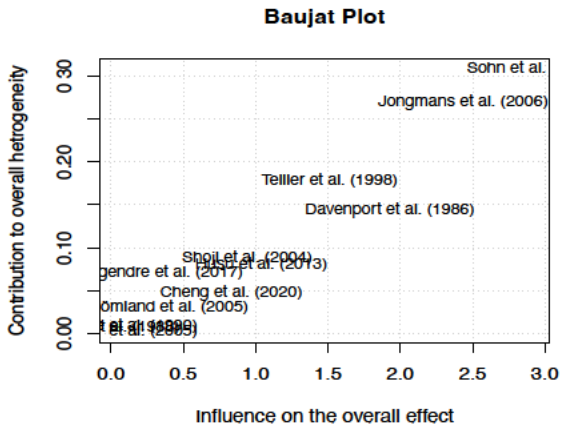
Funnel Plot of Standard Error by Prevalence of Patent Ductus Arteriosus Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.041). Using the trim and fill procedure it was estimated that 3 (SE = 2.37) studies were missing on the left side. Adjusted estimate = 28%, (95% CI = 20-37%, p = <.001; τ2 = 0.017, I2 = 74%).

Appendix 2C. Figure 21d

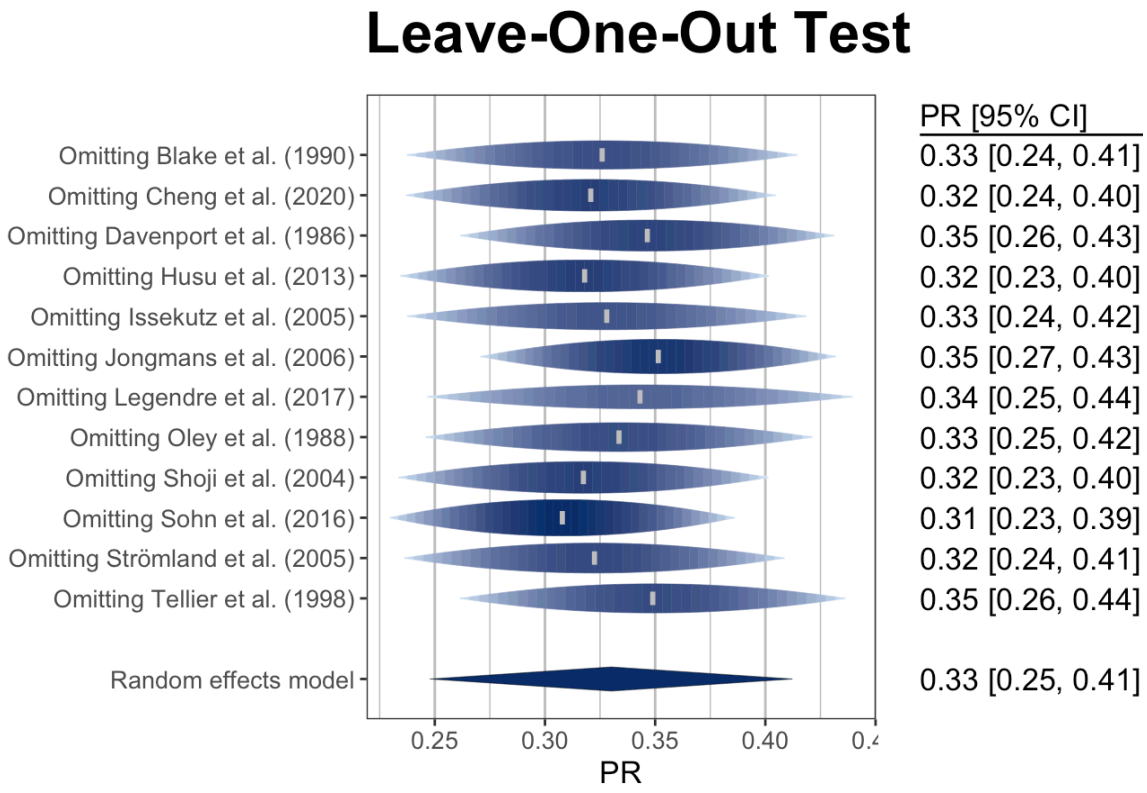
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Patent Ductus Arteriosus



Note. Sohn et al. (2016) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2C. Figure 21e

Leave-One-Out Random Effects Model for Studies Reporting Patent Ductus Arteriosus

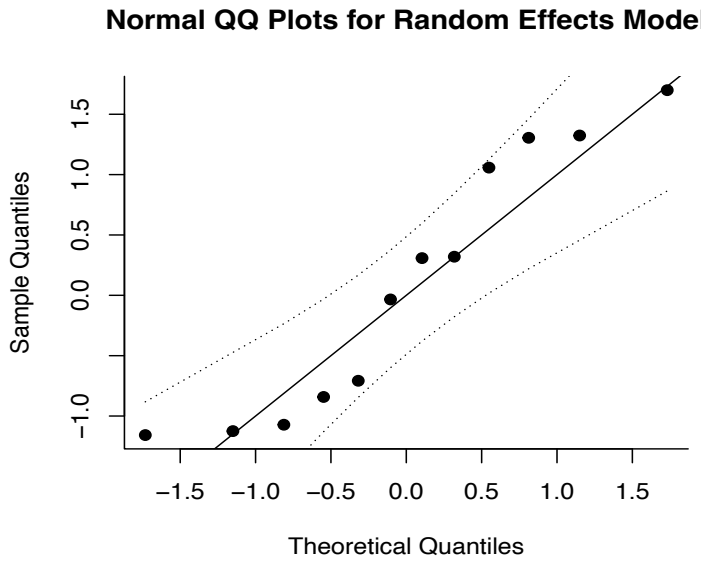


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Atrial Septal Defect

Appendix 2C. Figure 22a

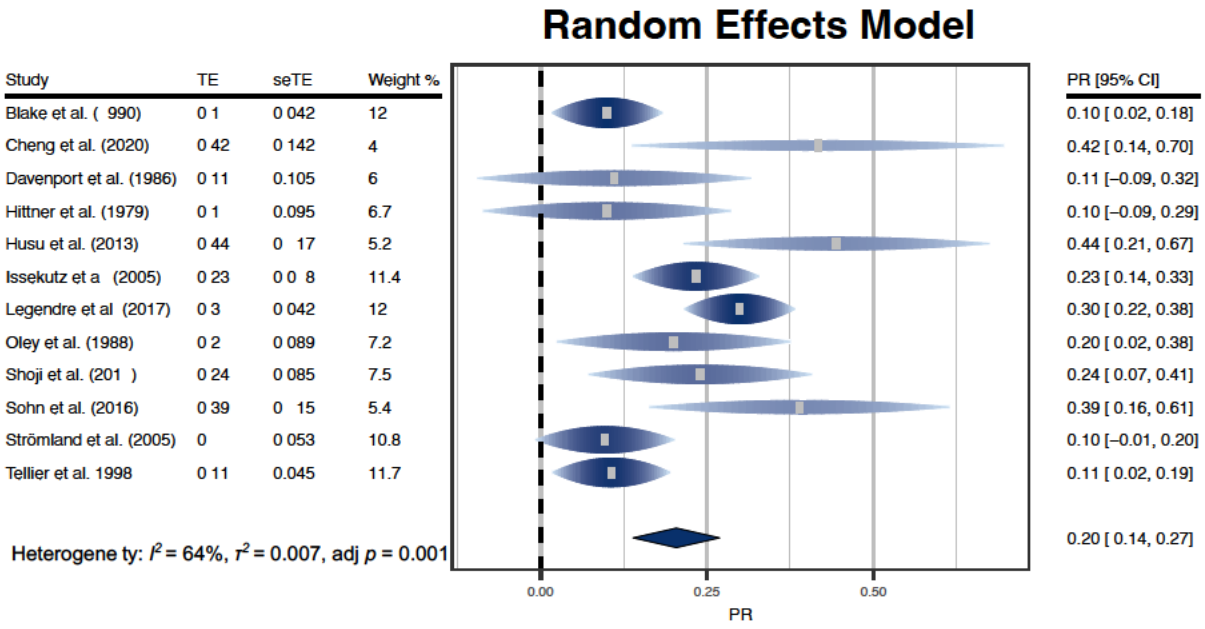
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Atrial Septal Defect



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 12 studies reporting atrial septal defect in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 22b

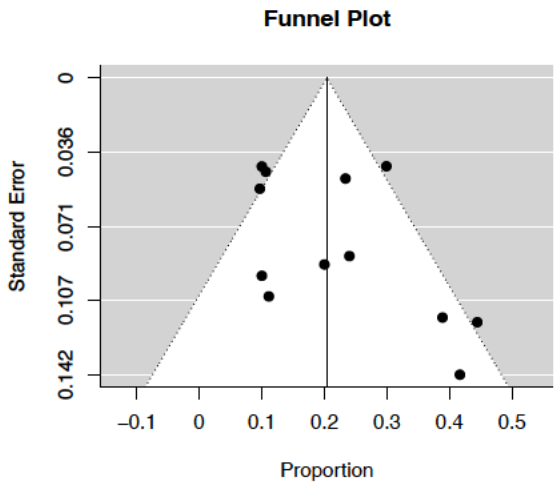
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Atrial Septal Defect in CHARGE Syndrome



Note. The pooled prevalence estimate for atrial septal defect in CHARGE syndrome is 20% (95% CI, 14-27%; permuted p-value = 0.007; k = 12) with moderate heterogeneity (I^2 = 64%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 460 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 22c

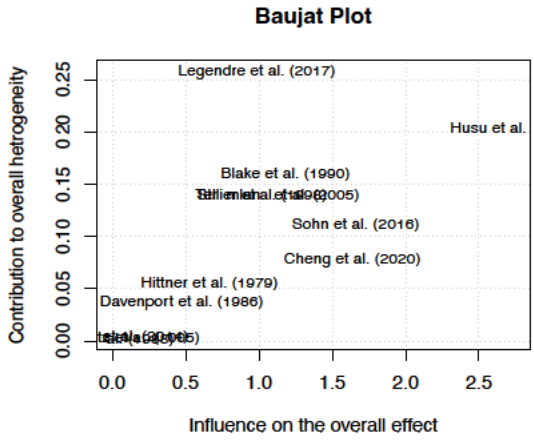
Funnel Plot of Standard Error by Prevalence of Atrial Septal Defect



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.239).

Appendix 2C. Figure 22d

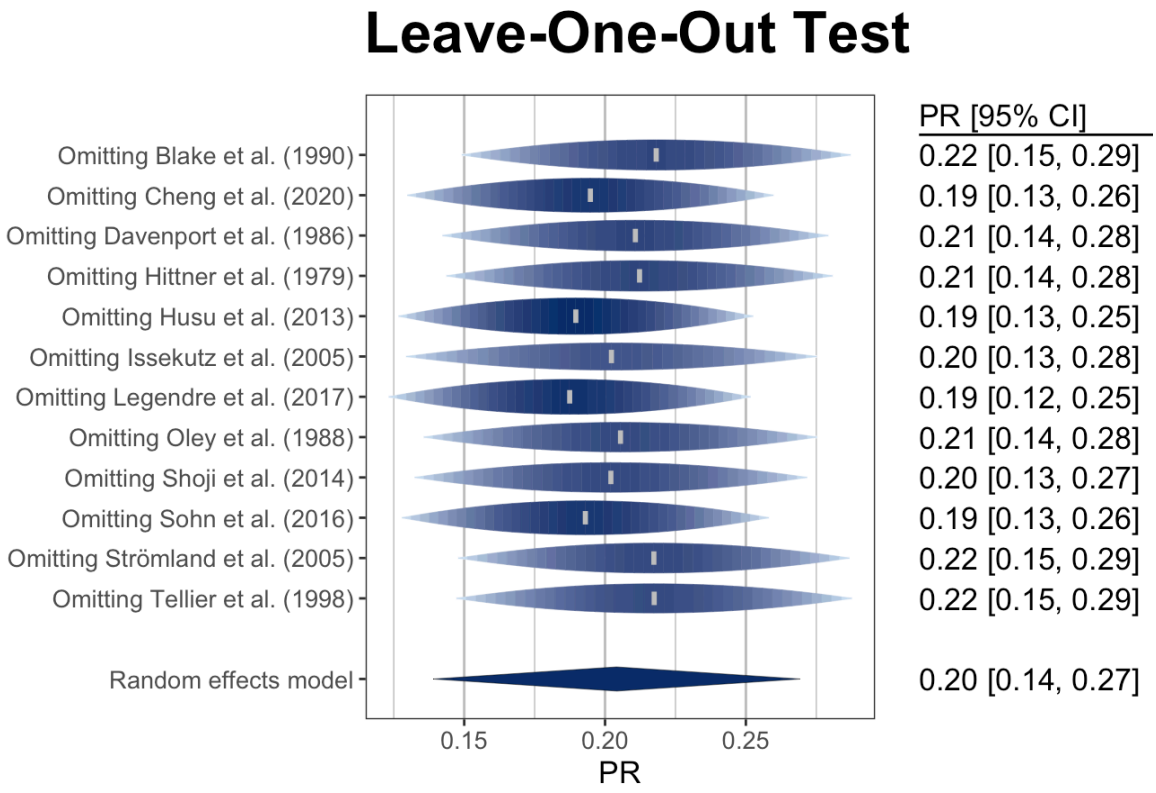
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Atrial Septal Defect



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Legendre et al. (2017) had the greatest contribution to overall heterogeneity and Husu et al. (2013) had the greatest influence on the overall effect.

Appendix 2C. Figure 22e

Leave-One-Out Random Effects Model for Studies Reporting Atrial Septal Defect

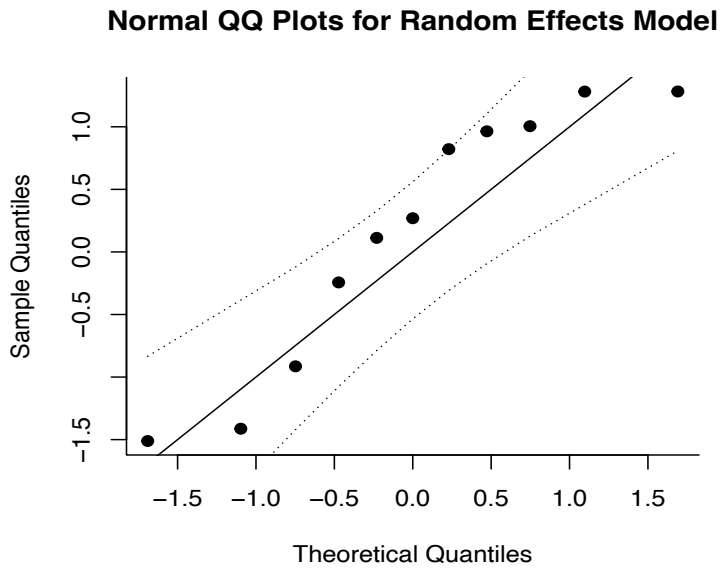


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Ventricular septal defect

Appendix 2C. Figure 23a

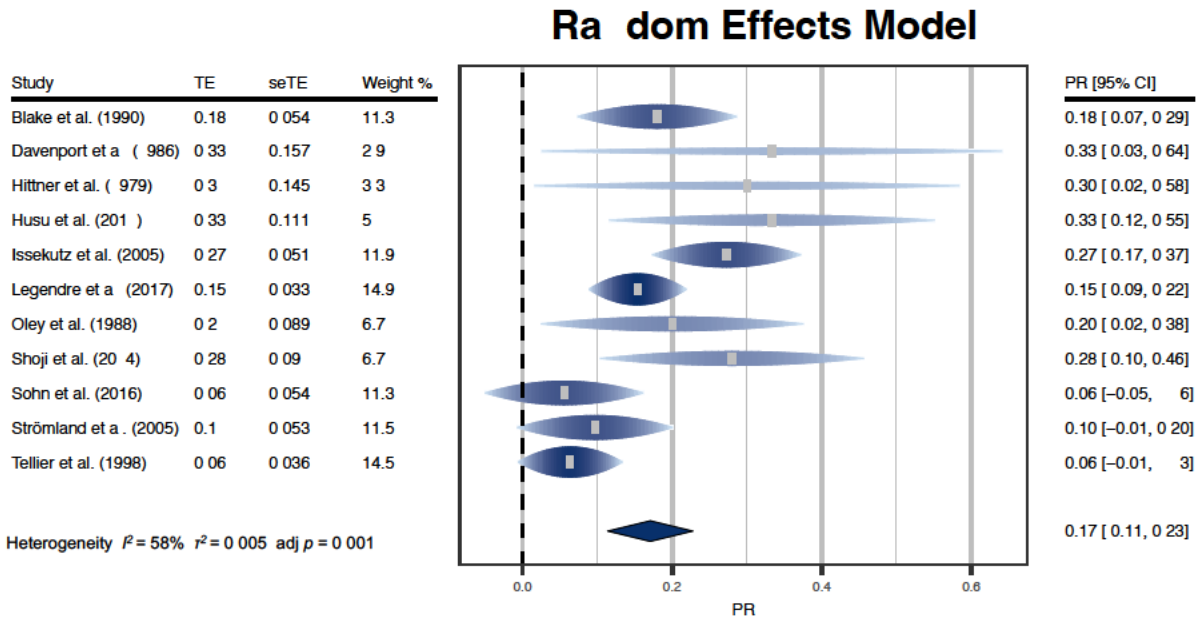
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Ventricular Septal Defect



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting ventricular septal defect in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 23b

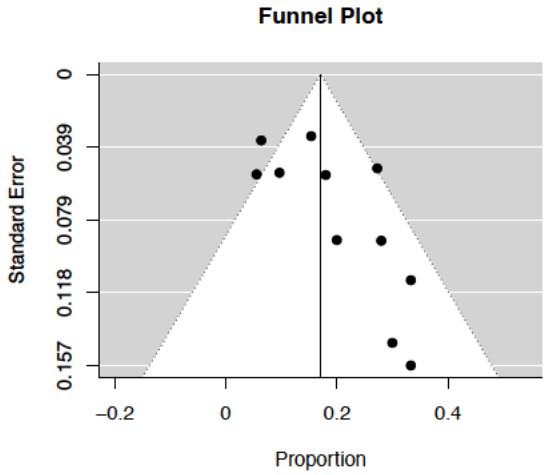
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Ventricular Septal Defect in CHARGE Syndrome



Note. The pooled prevalence estimate for ventricular septal defect in CHARGE syndrome is 17% (95% CI, 11-23%; permuted p-value = 0.001; k = 11) with moderate heterogeneity (I^2 = 58%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 333 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 23c

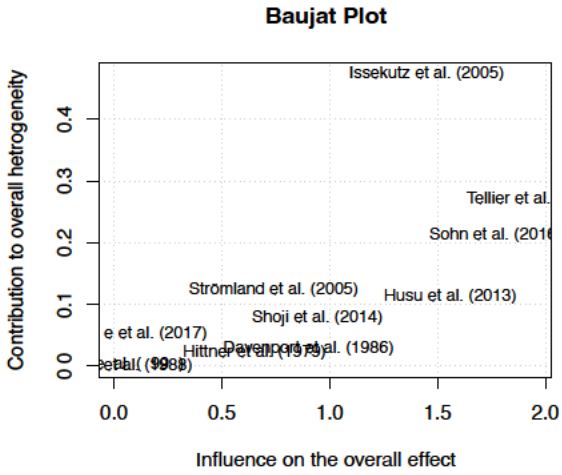
Funnel Plot of Standard Error by Prevalence of Ventricular Septal Defect



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.055).

Appendix 2C. Figure 23d

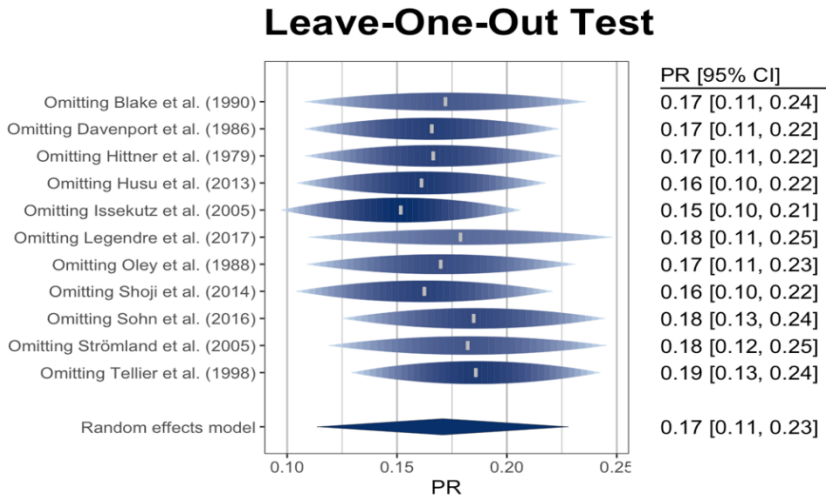
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Ventricular Septal Defect



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Issekutz et al. (2005) had the greatest contribution to overall heterogeneity and Tellier et al. (1998) had the greatest influence on the overall effect.

Appendix 2C. Figure 23e

Leave-One-Out Random Effects Model for Studies Reporting Ventricular Septal Defect

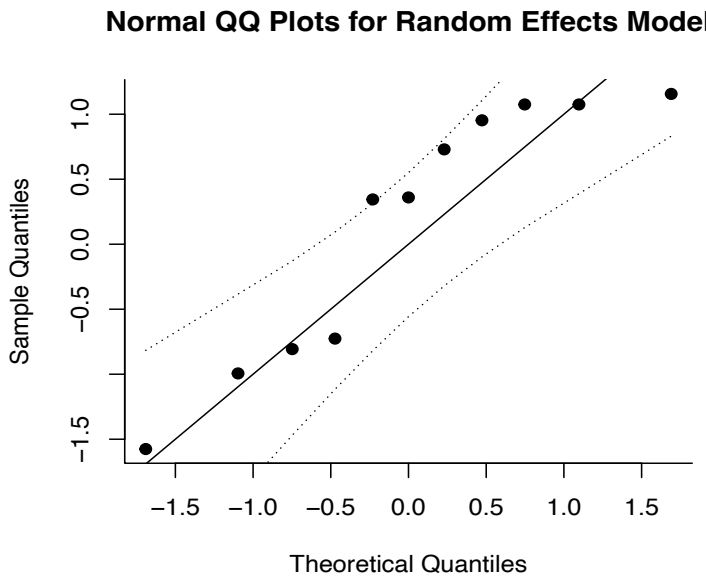


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Cerebellar Anomalies

Appendix 2C. Figure 24a

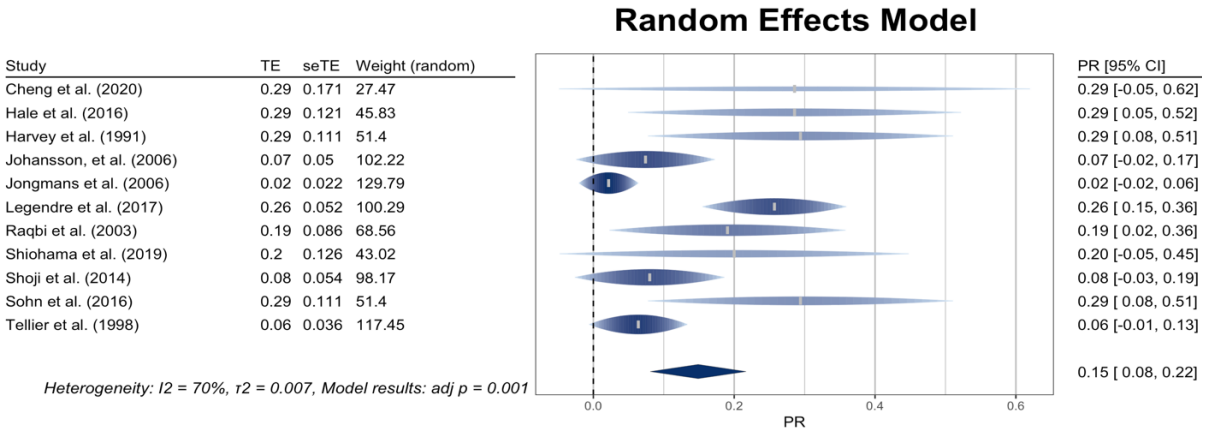
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Cerebellar Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting cerebellar anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 24b

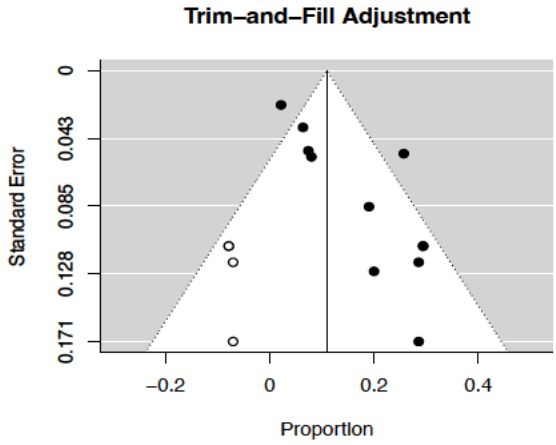
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Cerebellar Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for cerebellar anomalies in CHARGE syndrome is 15% (95% CI, 8-22%; permuted p-value = 0.001; k = 11) with moderate heterogeneity (I^2 = 70%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 199 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 24c

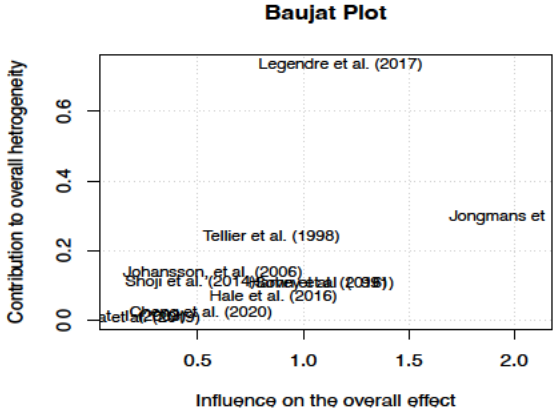
Funnel Plot of Standard Error by Prevalence of Cerebellar Anomalies Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.002). Using the trim and fill procedure it was estimated that 4 (SE = 2.15) studies were missing on the left side. Adjusted estimate = 11%, (95% *CI* = 5-17%, p = <.001; τ^2 = 0.007, I^2 = 65%).

Appendix 2C. Figure 24d

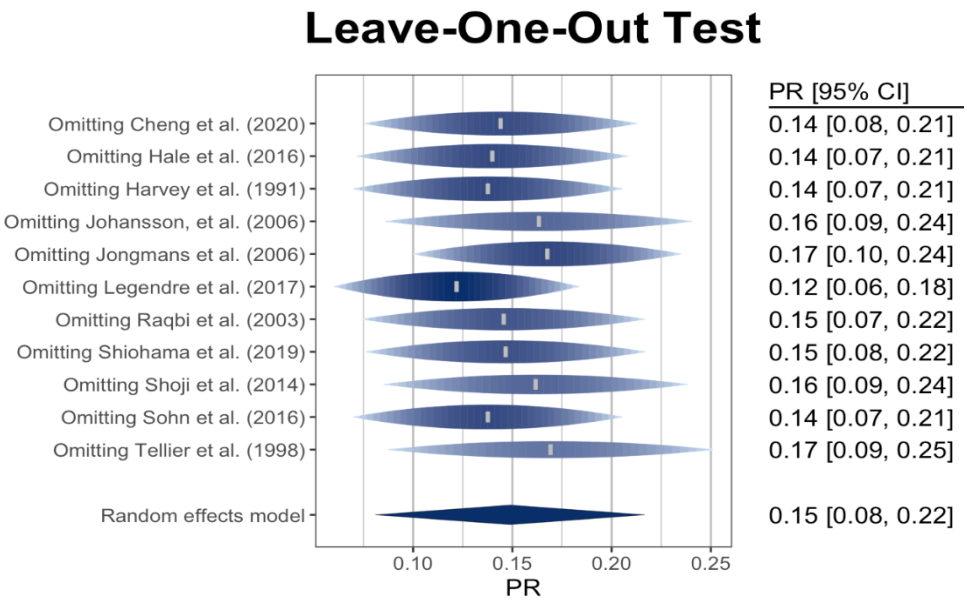
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Cerebellar Anomalies



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Legendre et al. (2017) had the greatest contribution to overall heterogeneity and Jongmans et al. (2006) had the greatest influence on the overall effect.

Appendix 2C. Figure 24e

Leave-One-Out Random Effects Model for Studies Reporting Cerebellar Anomalies

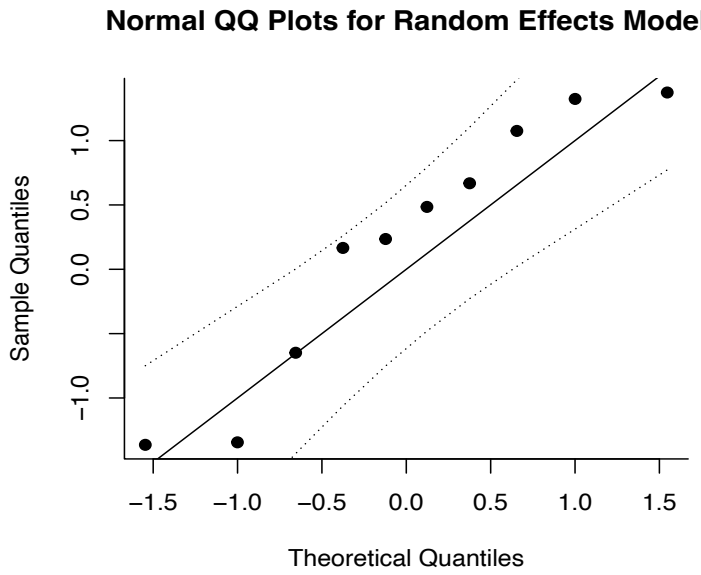


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Corpus Callosum

Appendix 2C. Figure 25a

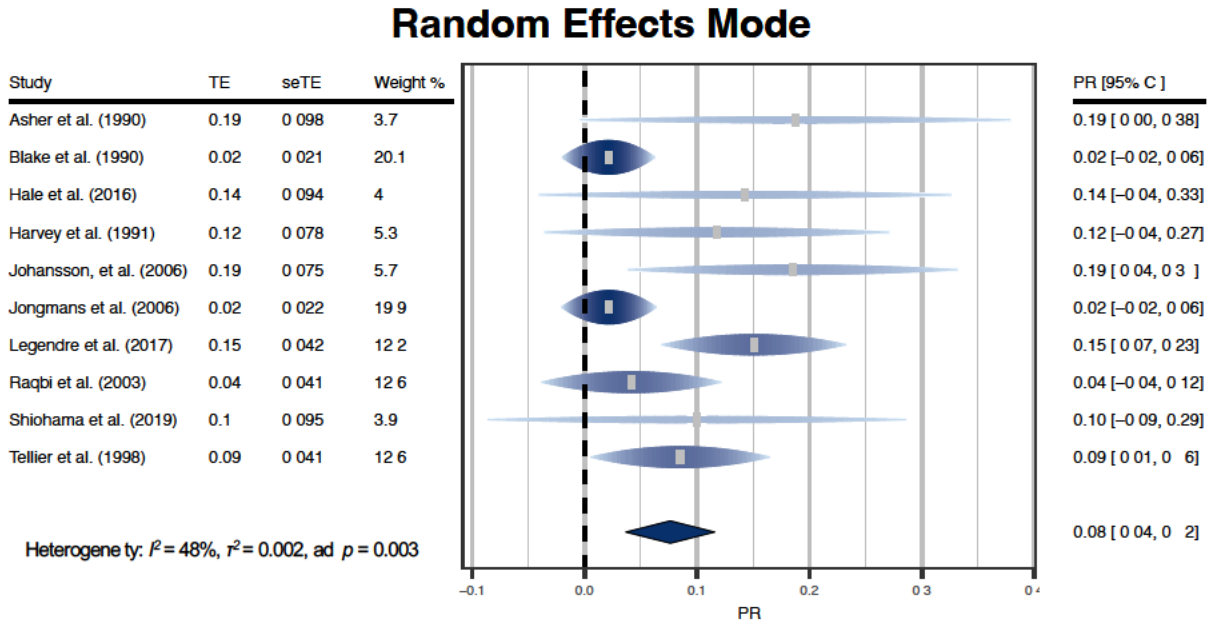
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Corpus Callosum Anomalies



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 10 studies reporting corpus callosum anomalies in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 25b

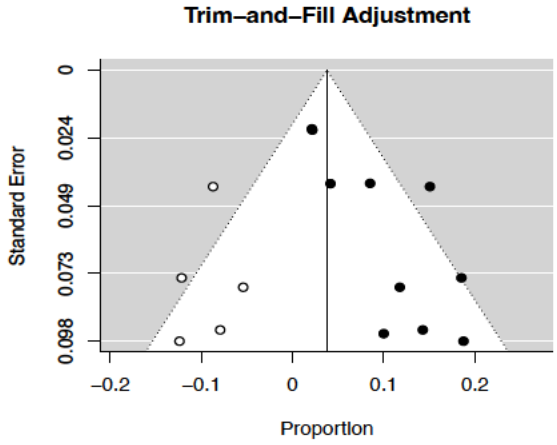
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Corpus Callosum Anomalies in CHARGE Syndrome



Note. The pooled prevalence estimate for corpus callosum anomalies in CHARGE syndrome is 8% (95% CI, 4-12%; permuted p-value = 0.003; k = 10) with low heterogeneity (I^2 = 48%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 100 suggests that the observed effect is robust to potential publication biases.

Appendix 2C. Figure 25c

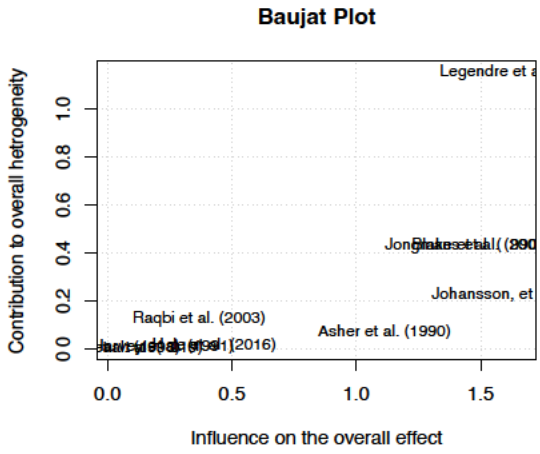
Funnel Plot of Standard Error by Prevalence of Corpus Callosum Anomalies Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.004). Using the trim and fill procedure it was estimated that 5 (SE = 1.97) studies were missing on the left side. Adjusted estimate = 4%, (95% CI = 0-8%, p = 0.001; τ2 = 0.004, I2 = 63%).

Appendix 2C. Figure 25d

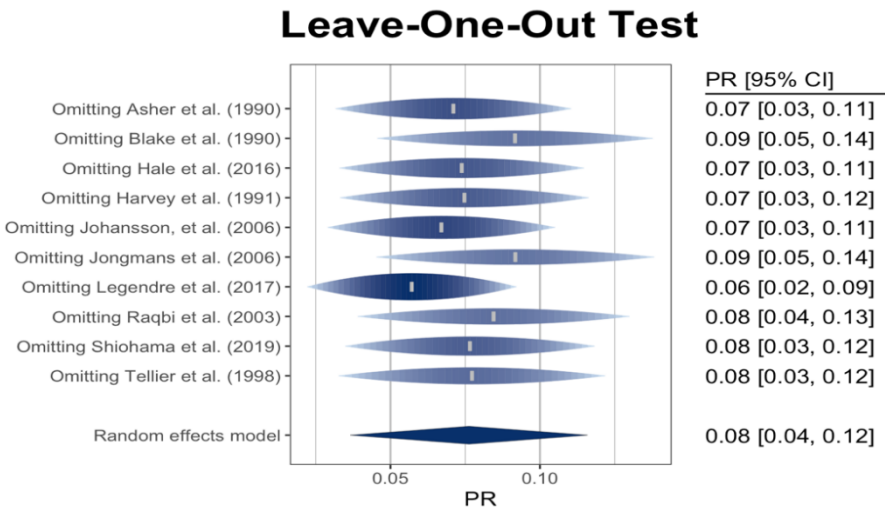
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Corpus Callosum Anomalies



Note. Legendre et al. (2017) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 25e

Leave-One-Out Random Effects Model for Studies Reporting Corpus Callosum Anomalies

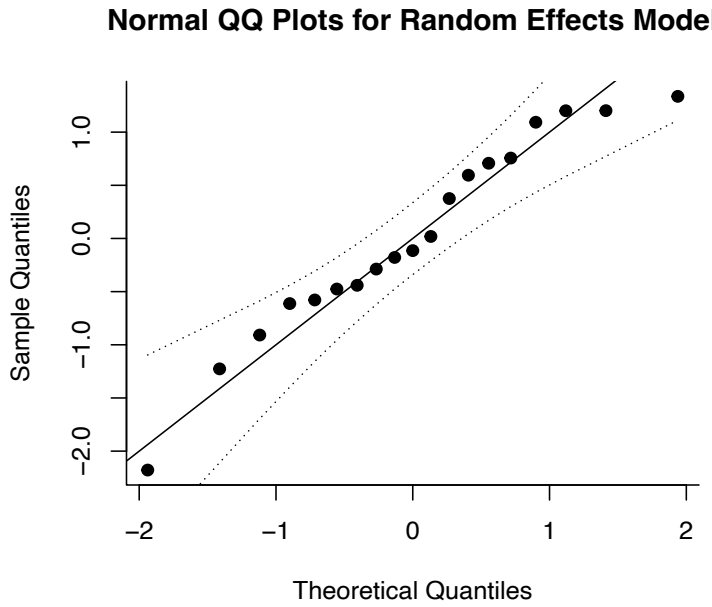


Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Severe or Profound Hearing Impairment

Appendix 2C. Figure 26a

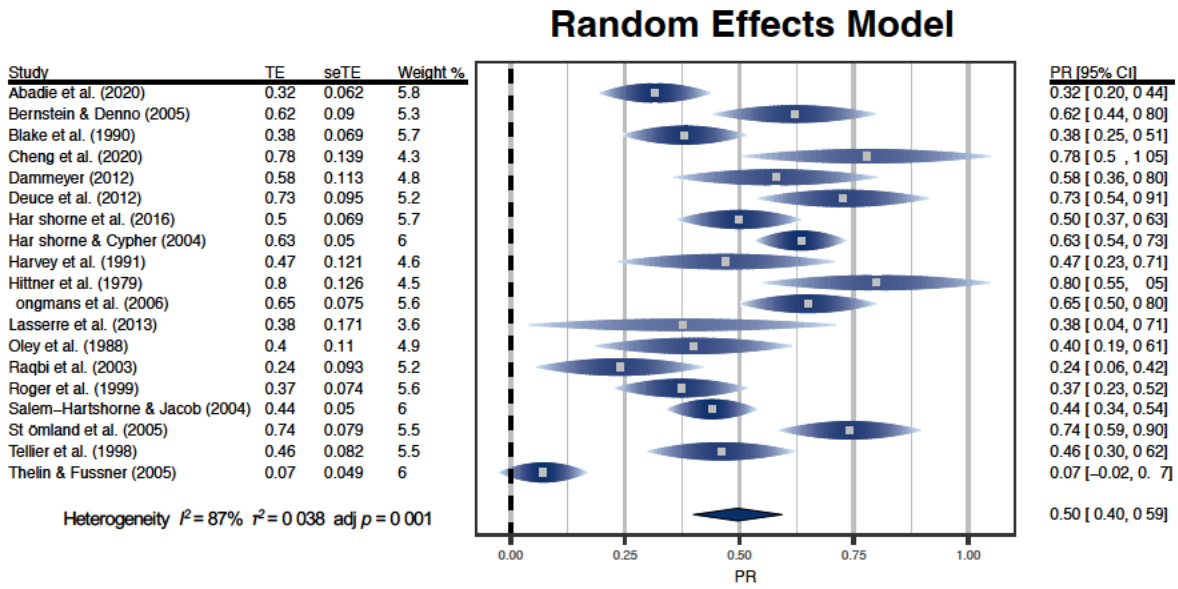
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Severe or Profound Hearing Impairment



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 19 studies reporting severe or profound hearing impairment in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2C. Figure 26b

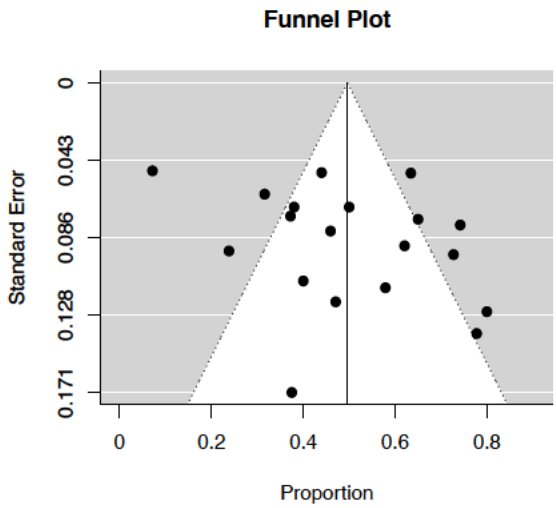
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Severe or Profound Hearing Impairment in CHARGE Syndrome



Note. The pooled prevalence estimate for severe or profound hearing impairment in CHARGE syndrome is 50% (95% CI, 40-59%; permuted p-value = 0.001; k = 19) with low heterogeneity (I^2 = 48%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 4750 suggests that the observed effect is robust to potential publication biases.

Appendix 2C, Figure 26c

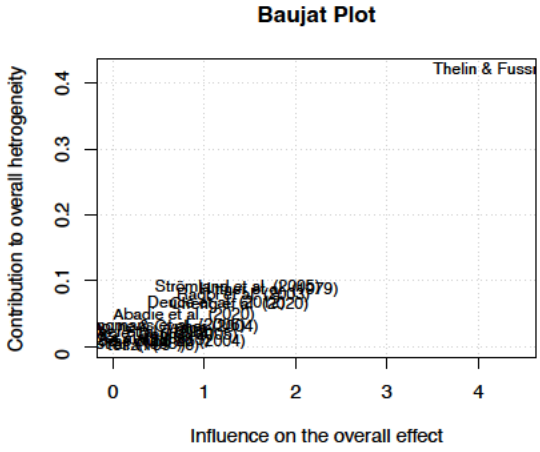
Funnel Plot of Standard Error by Prevalence of Severe or Profound Hearing Impairment



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.126).

Appendix 2C, Figure 26d

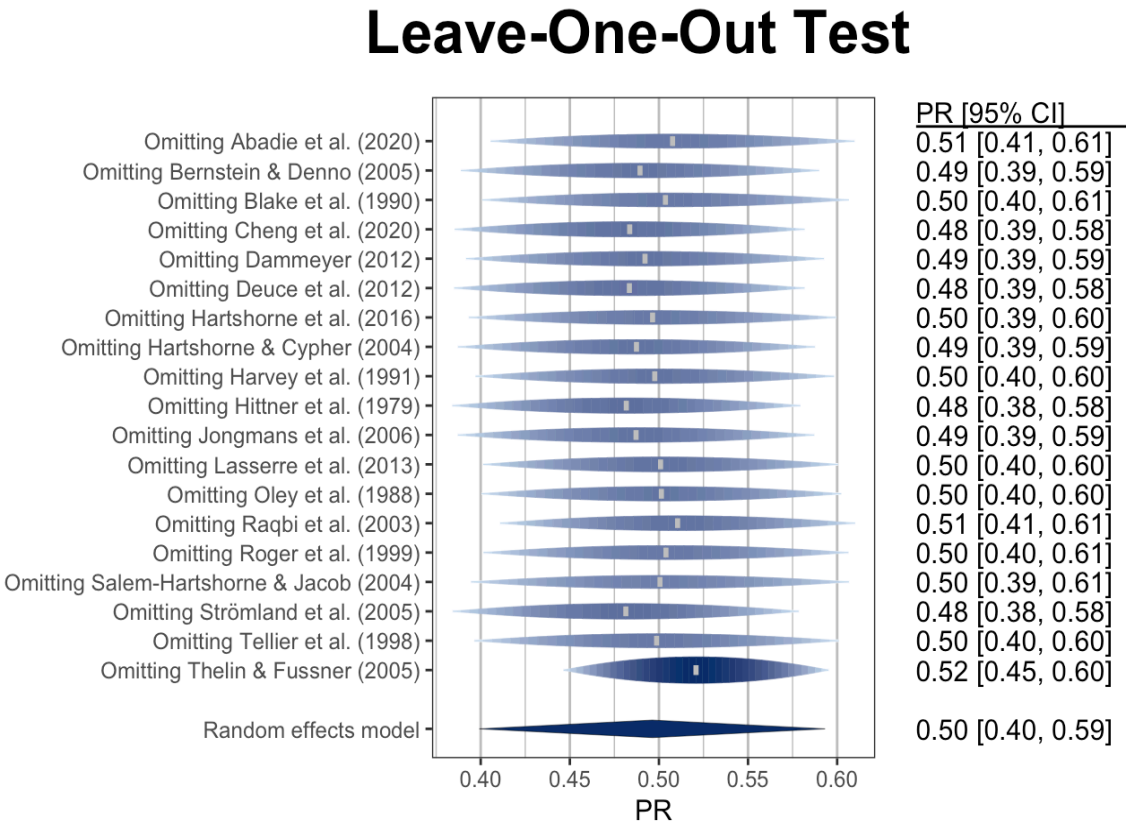
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Severe or Profound Hearing Impairment



Note. Thelin & Fussner (2005) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2C. Figure 26e

Leave-One-Out Random Effects Model for Studies Reporting Severe or Profound Hearing Impairment



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

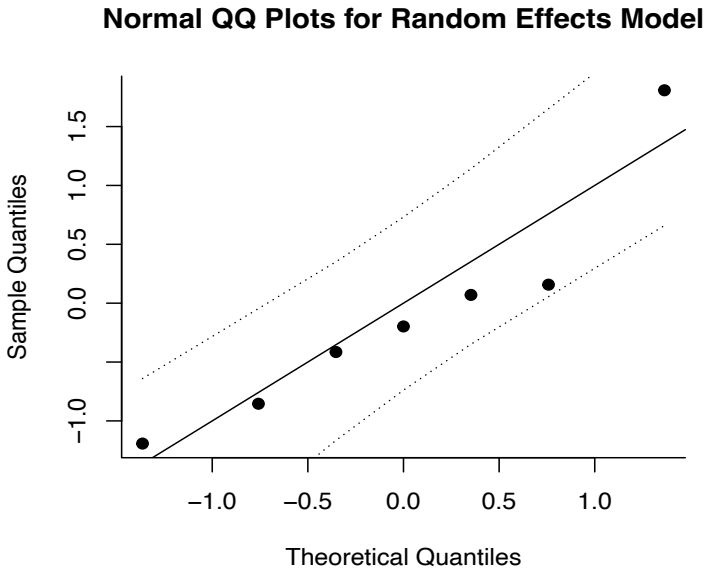
Appendix 2D: Details of Quality Weighted Pooled Prevalence Estimates and Subgroup and Sensitivity Analysis for Cognitive, Behavioural, Psychological and Sleep Characteristics

2D.1 Developmental Delay

The definition of developmental delay adopted (where stated in individual studies) was an early onset (<5 years) delay or deficit in two or more areas of functioning: cognitive skills, speech development, motor skills or social and emotional development (Pinchefsky & Shevell, 2017). Seven studies were not included in the meta-analysis because all participants presented with developmental delay (Blake et al., 2005; Hale et al., 2016; Hsu et al., 2016; Shiohama et al., 2019; Smith et al., 2005; Tellier et al., 1998; Wessels et al., 2010). Blake et al. (1990) and Harvey et al. (1991) reported an 82% and 71% prevalence of language delay in their respective samples, and speech impairment was reported in 81% and 100% in Johansson et al. (2010) and Oley et al. (1988). However, there was not enough data to synthesise these findings.

Appendix 2D. Figure 27a

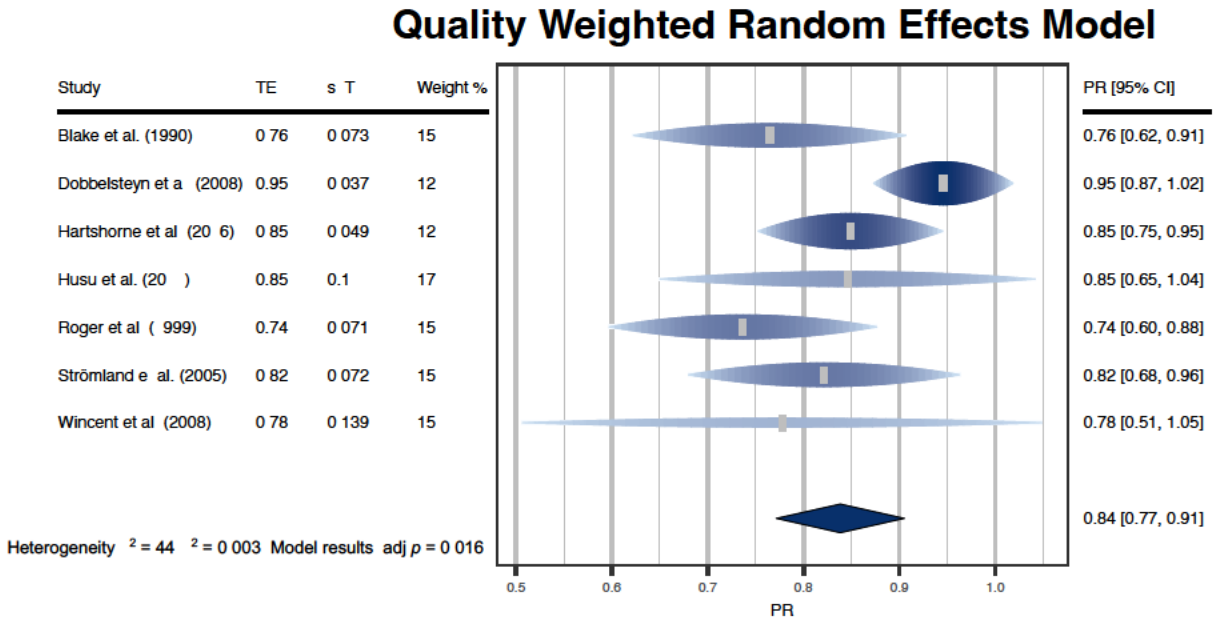
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Developmental Delay



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 7 studies reporting on developmental delay in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 27b

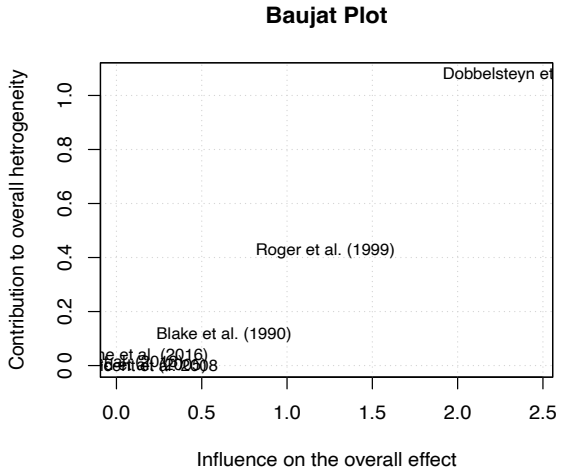
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Developmental Delay in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for developmental delay in CHARGE syndrome was 84% (95% CI, 77-91%; permuted *p*-value = 0.016; *k* = 7) with moderate heterogeneity (I^2 = 44%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 8098 suggests that the observed effect is robust to potential publication biases

Appendix 2D. Figure 27c

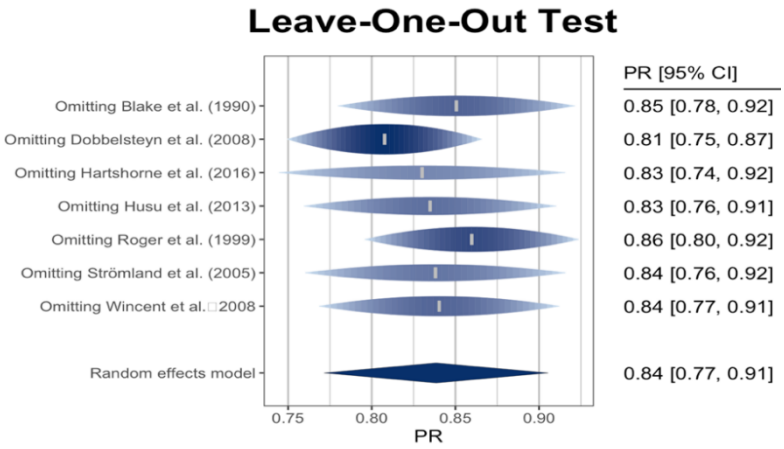
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Developmental Delay



Note. Dobbelsteyn et al. (2008) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 27d

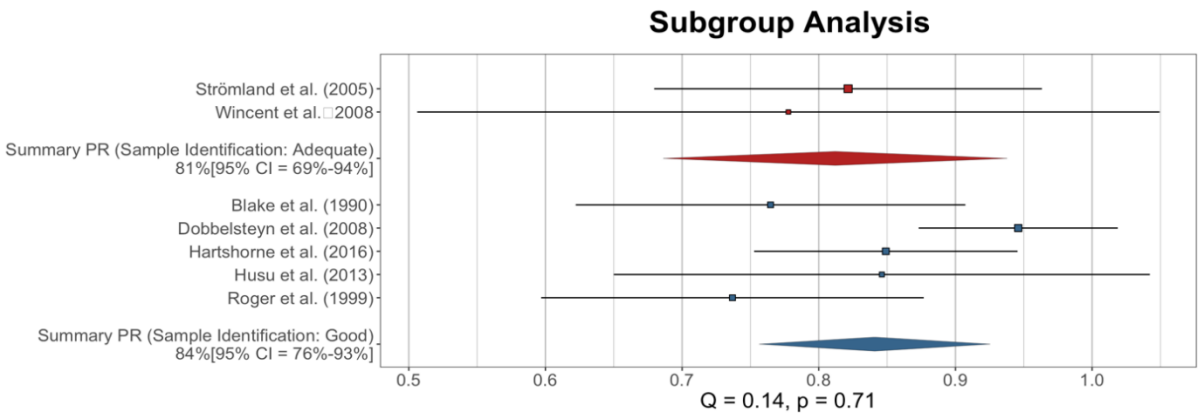
Leave-One-Out Random Effects Model for Studies Reporting Developmental Delay



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 27e

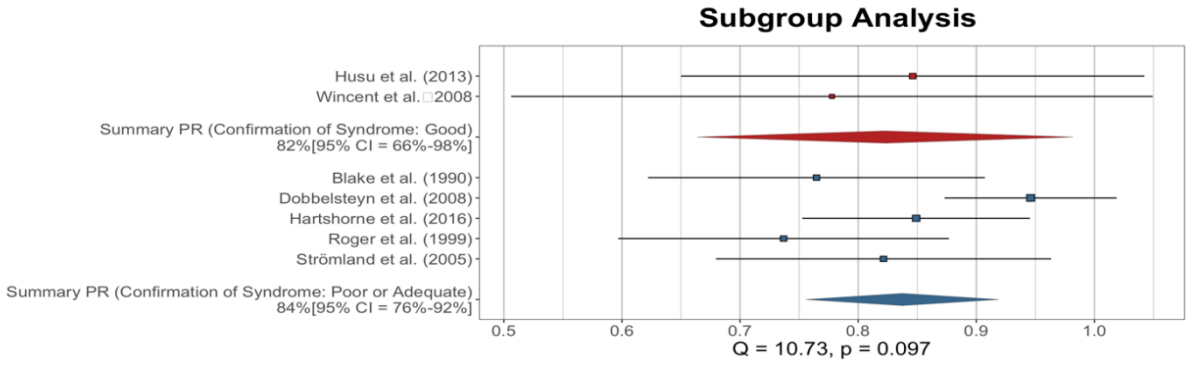
Subgroup Analysis of Studies Reporting Developmental Delay that were Rated Adequate and Studies Rated Good for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.71) between studies rated adequate or good for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 27f

Subgroup Analysis of Studies Reporting Developmental Delay that were Rated Adequate and Studies Rated Good for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.097) between studies rated adequate or good for confirmation of syndrome. Subgroup analysis was evaluated by comparison of 95% CIs.

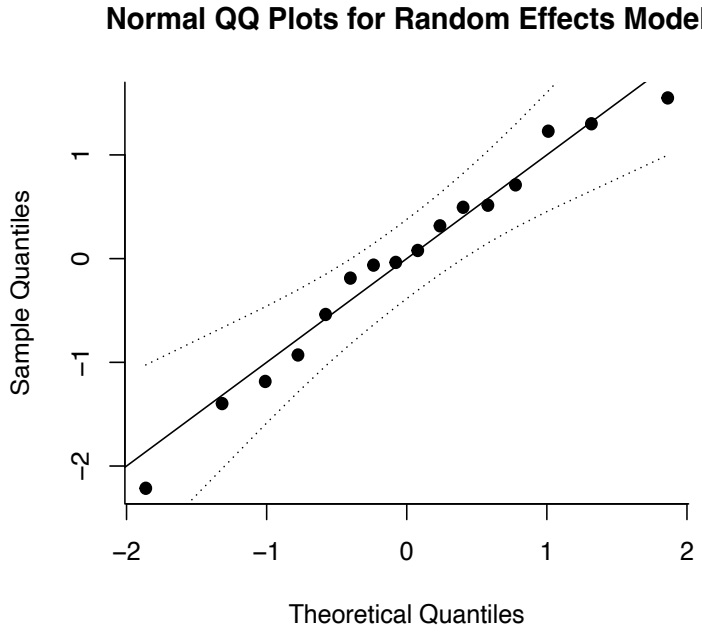
2D.2 Intellectual disability

A diagnosis of intellectual disability requires deficits in both cognitive functioning and adaptive behaviour (DSM-5; American Psychiatric Association, 2013). It was not clear that any of the studies assessed both of these constructs across all participants. Asher et al. (1990), Bernstein & Denno (2005), Jongmans et al. (2006) and Shoji et al. (2014) gave no details of assessment, Legendre et al. (2017) used estimates of ID for some participants, in Blake & Brown (1993), Deuce (2017), Oley et al. (1988)and Raqbi et al., (2003) ID was

generally based on type of school provision, with a proportion of participants in Oley et al. (1988) completing developmental tests. Hittner et al. (1979) used unspecified formal testing, Dammeyer (2012) and Davenport et al., 1986) reported results from IQ tests only, and Harvey et al. (1991), Johansson et al. (2010), Lasserre et al., (2013), and Sohn et al. (2016) assessed cognitive and adaptive functioning but not consistently across the sample. Abadie et al. (2020), Salem-Hartshorne & Jacob (2004), Smith et al. (2005) and Wulffaert et al. (2009) used adaptive functioning measures that were completed by parents or carers. Two additional studies (Blake et al., 2005; N. Hartshorne et al., 2016) reported on skills of daily living in adolescents and adults with CHARGE syndrome. As these skills are only one component of adaptive functioning, they were not included in the meta-analysis. Both studies reported little to no independence in personal care for 19-59% of participants, and little to no independence for 55-93% of individuals in higher-order tasks of daily living including independent travel, cooking, cleaning, shopping and managing personal finances. A 100% prevalence of ID was reported by Asher et al. (1990), Davenport et al. (1986), Hittner et al. (1979), Shoji et al. (2014) and Smith et al. (2005).

Appendix 2D. Figure 28a

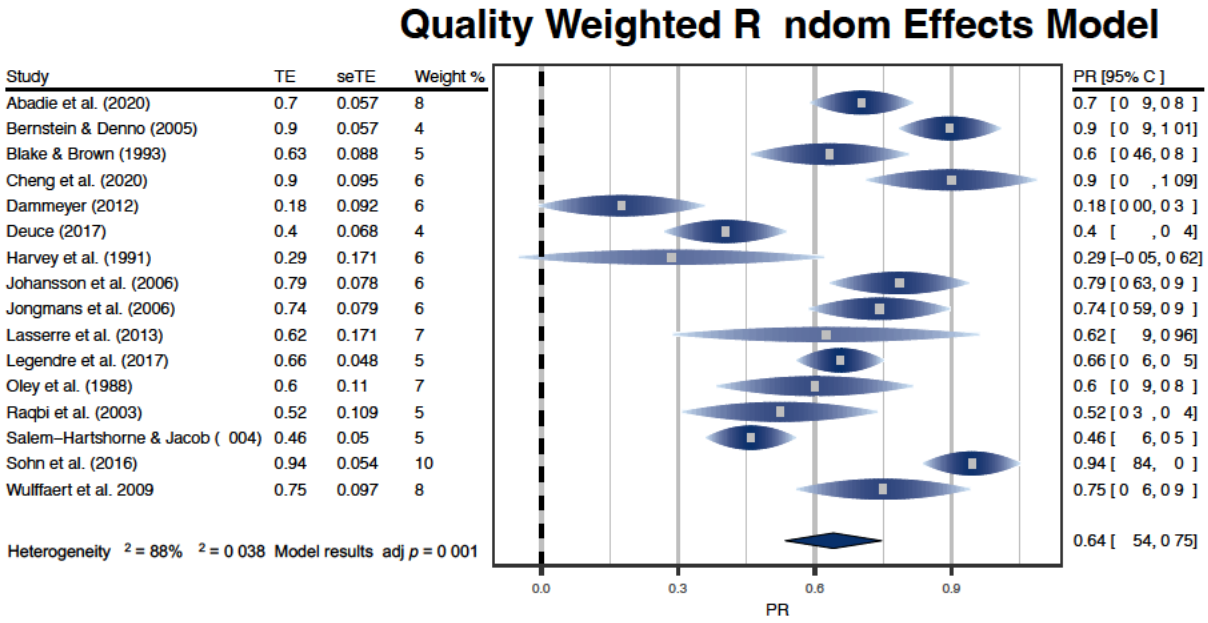
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Intellectual Disability



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 16 studies reporting on intellectual disability in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 28b

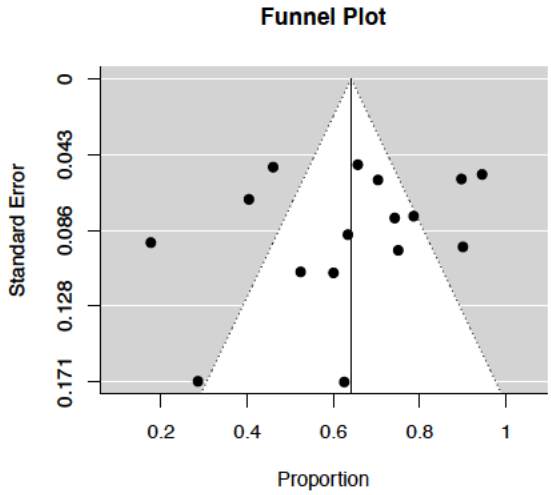
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Intellectual Disability in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for intellectual disability in CHARGE syndrome was 64% (95% CI, 54-75%; permuted *p*-value = 0.001; *k* = 16) with high heterogeneity (I^2 = 88%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 6809 suggests that the observed effect is robust to potential publication biases

Appendix 2D. Figure 28c

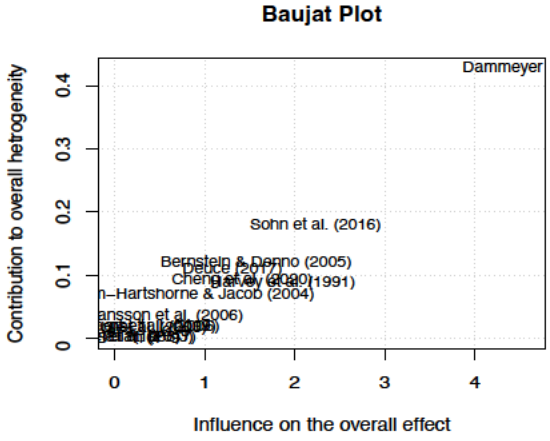
Funnel Plot of Standard Error by Prevalence of Intellectual Disability



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.429)

Appendix 2D. Figure 28d

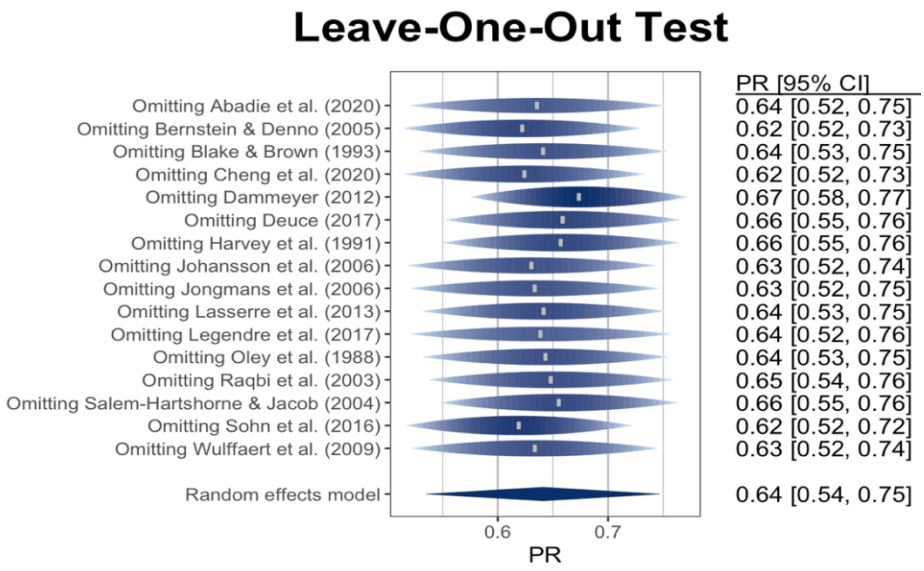
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Intellectual Disability



Note. Dammeyer (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 28e

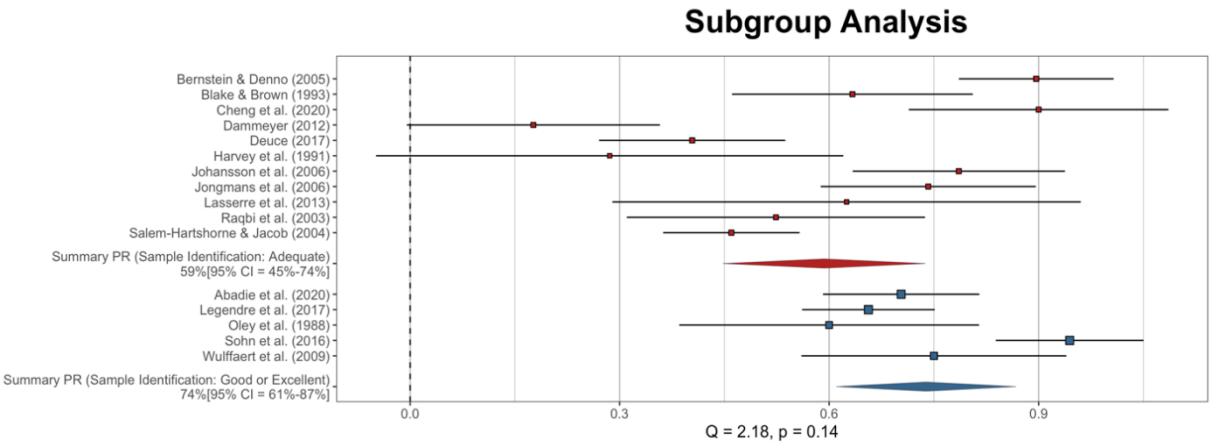
Leave-One-Out Random Effects Model for Studies Reporting Intellectual Disability



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate.

Appendix 2D. Figure 28f

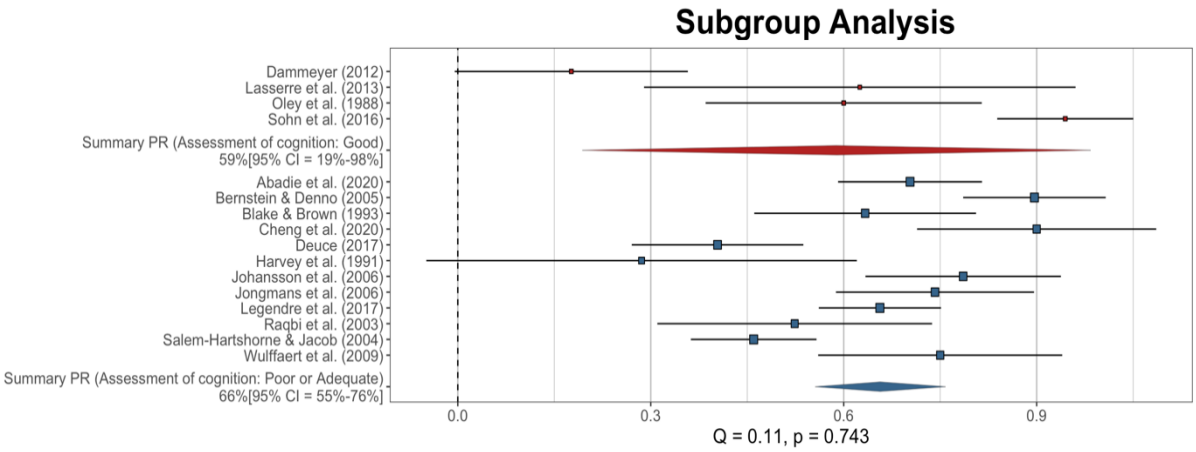
Subgroup Analysis of Studies Reporting Intellectual Disability that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.14) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 28g

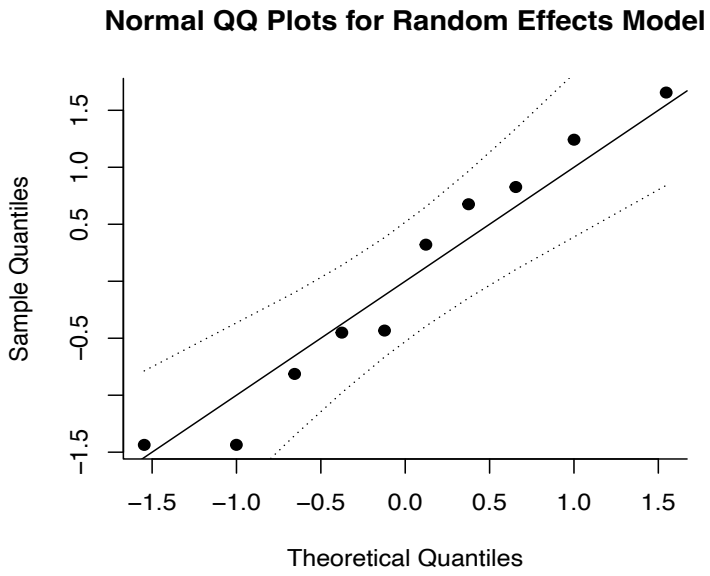
Subgroup Analysis of Studies Reporting Intellectual Disability that were Rated Poor/Adequate and Studies Rated Good for Method of Assessment



Note. Subgroup analysis found no statistical difference (p = 0.743) between studies rated poor/adequate or good for the method used to assess cognition. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 29a

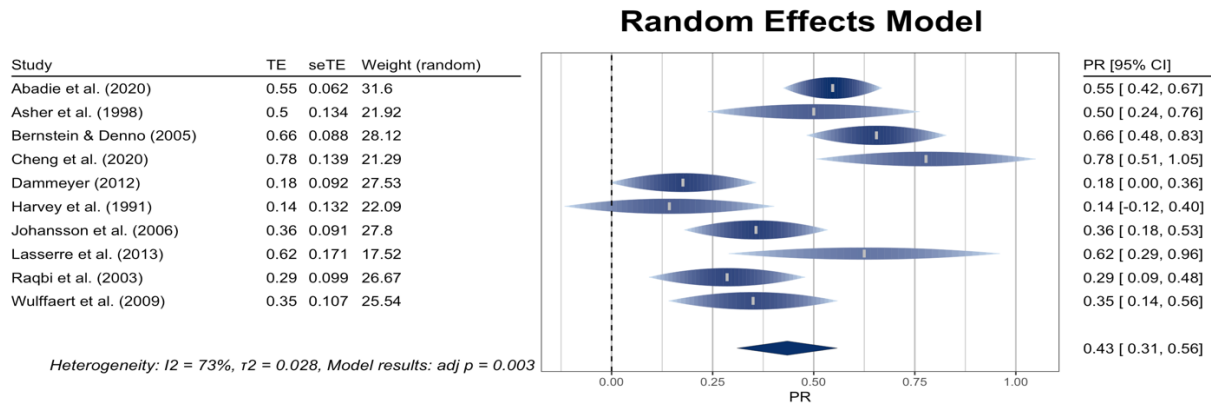
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Mild or Moderate Intellectual Disability



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 10 studies reporting on mild or moderate intellectual disability in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 29b

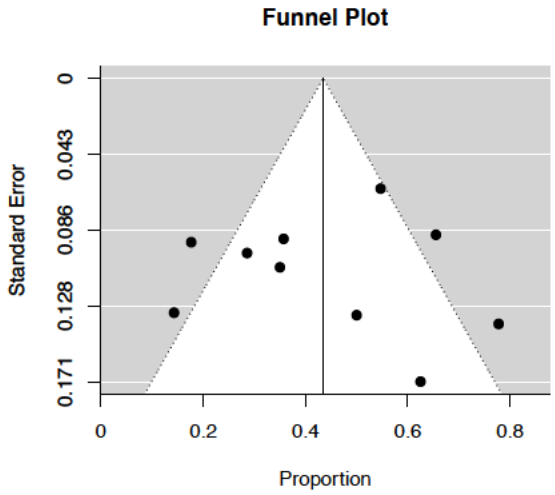
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Mild or Moderate Intellectual Disability in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for mild or moderate intellectual disability in CHARGE syndrome was 43% (95% CI, 31-56%; permuted *p*-value = 0.003; *k* = 10) with moderate heterogeneity (I^2 = 73%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 653 suggests that the observed effect is robust to potential publication biases

Appendix 2D. Figure 29c

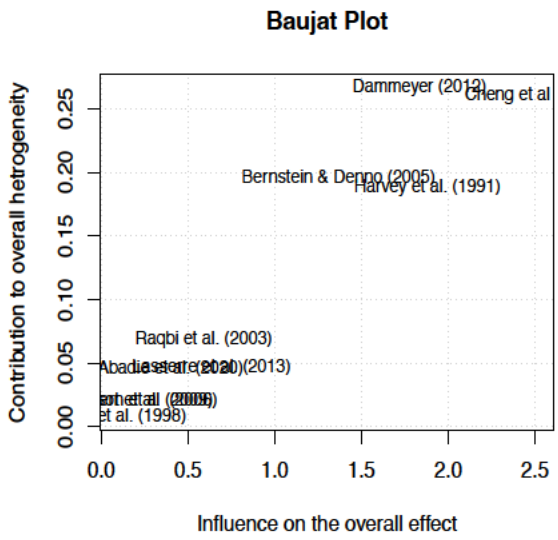
Funnel Plot of Standard Error by Prevalence of Mild or Moderate Intellectual Disability



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.839)

Appendix 2D. Figure 29d

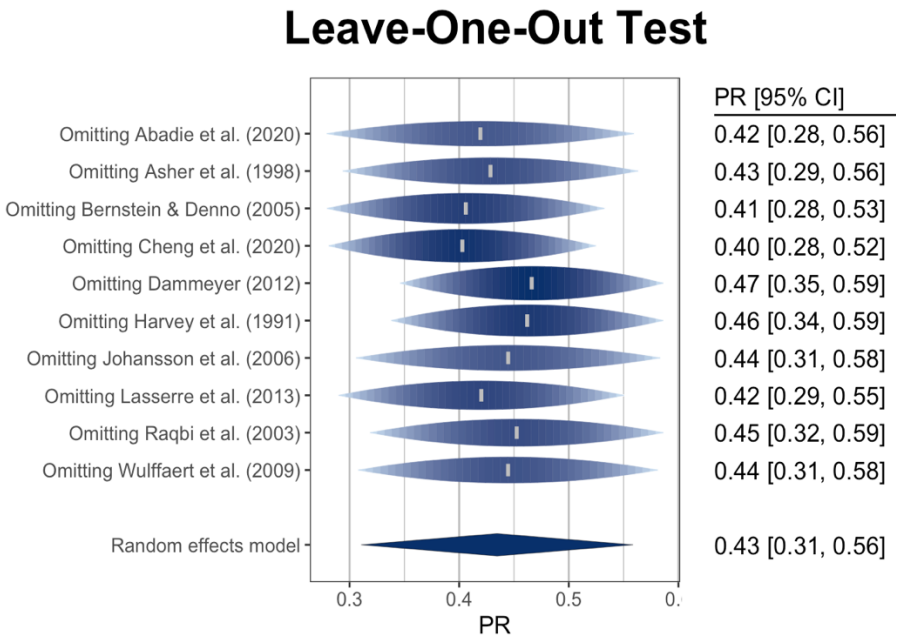
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Mild or Moderate Intellectual Disability



Note. Studies in the top right quartile have the greatest contribution to overall heterogeneity and the greatest influence on the overall effect. Dammeyer (2012) had the greatest contribution to overall heterogeneity and Cheng et al. (2020) had the greatest influence on the overall effect

Appendix 2D. Figure 29e

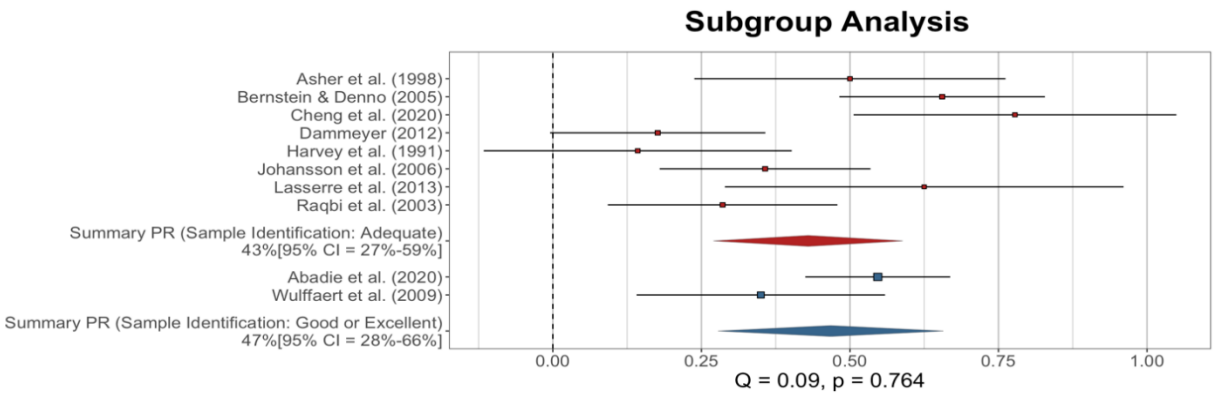
Leave-One-Out Random Effects Model for Studies Reporting Mild or Moderate Intellectual Disability



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 29f

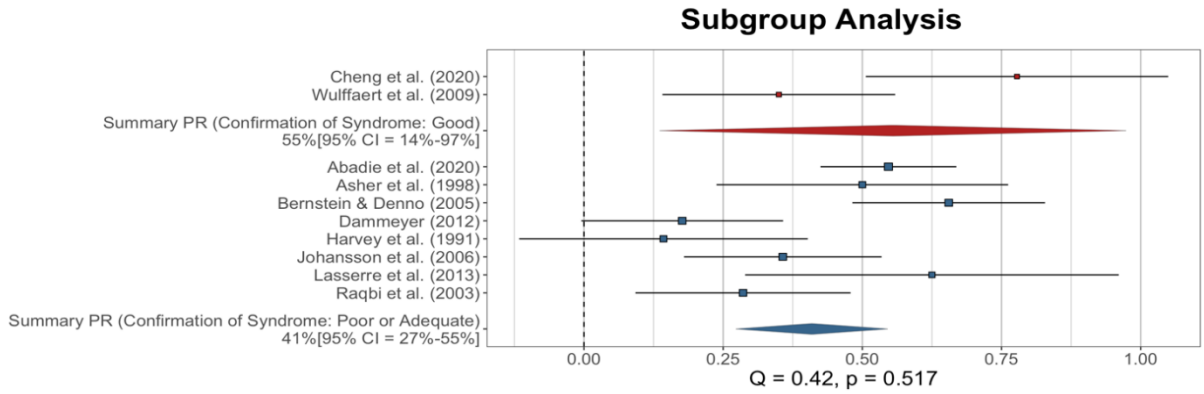
Subgroup Analysis of Studies Reporting Mild or Moderate Intellectual Disability that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.764) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 29g

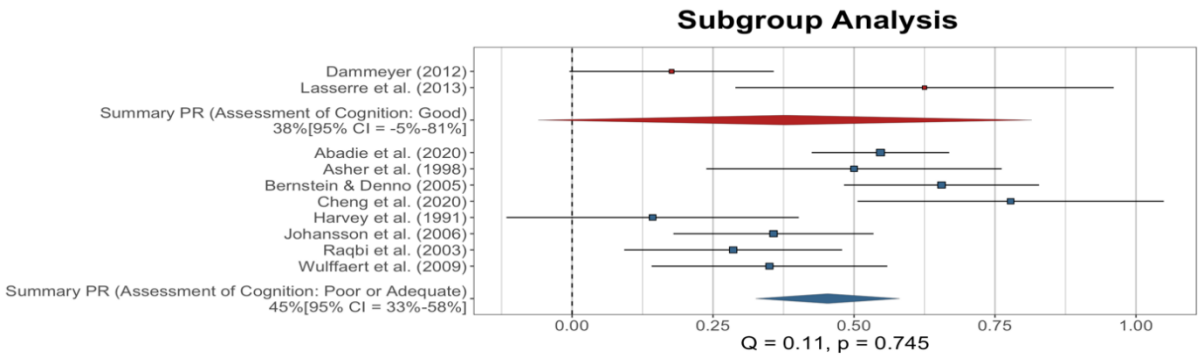
Subgroup Analysis of Studies Reporting Mild or Moderate Intellectual Disability that were Rated Poor/Adequate and Studies Rated Good for Confirmation of Syndrome



Note. Subgroup analysis found no statistical difference (p = 0.764) between studies rated poor/adequate or good quality for confirmation of syndrome. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 29h

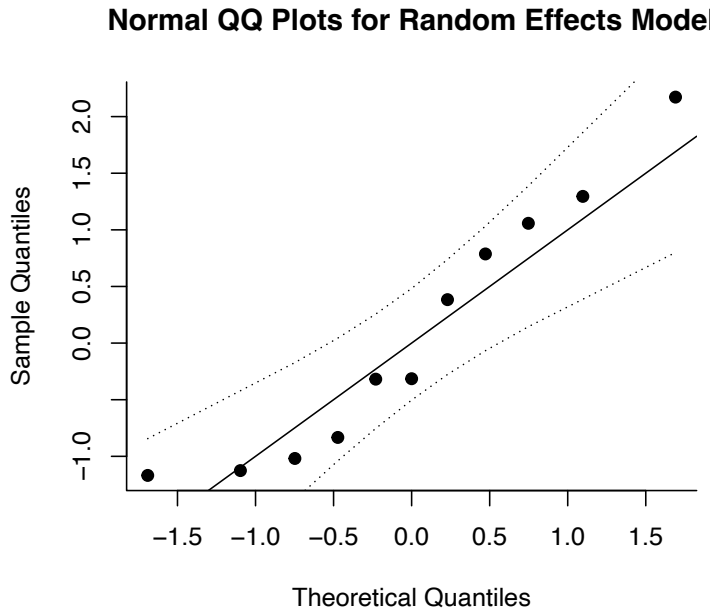
Subgroup Analysis of Studies Reporting Mild or Moderate Intellectual Disability that were Rated Poor/Adequate and Studies Rated Good for Method of Assessment



Note. Subgroup analysis found no statistical difference (p = 0.745) between studies rated poor/adequate or good for the method used to assess cognition. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 30a

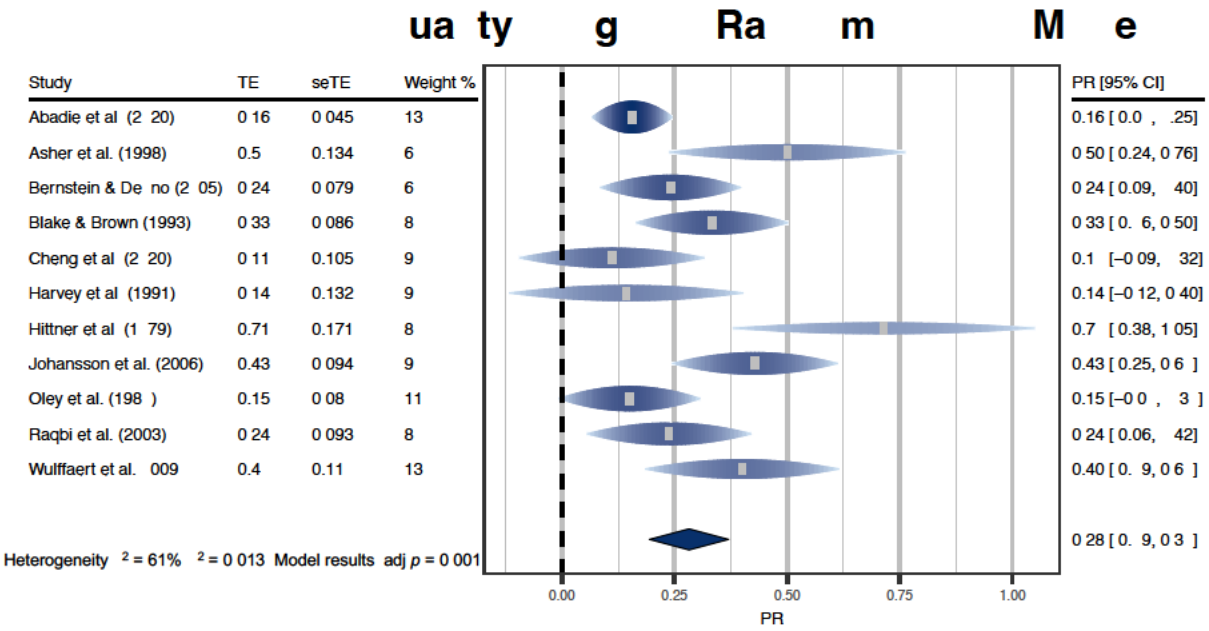
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Severe or Profound Intellectual Disability



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting on severe or profound intellectual disability in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 30b

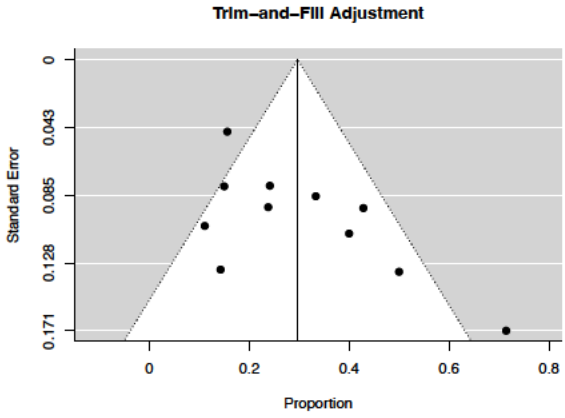
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Severe or Profound Intellectual Disability in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for severe or profound intellectual disability in CHARGE syndrome was 28% (95% CI, 19-37%; permuted *p*-value = 0.001; *k* = 11) with moderate heterogeneity (I^2 = 61%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 394 suggests that the observed effect is robust to potential publication biases

Appendix 2D. Figure 30c

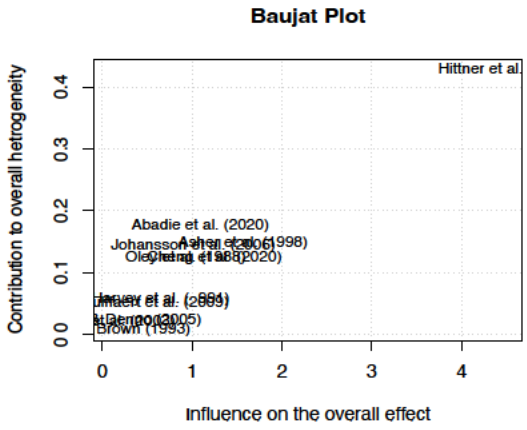
Funnel Plot of Standard Error by Prevalence of Severe or Profound Intellectual Disability Following the Trim and Fill Procedure



Note. Publication bias [small study effect] was identified (Egger's test p = 0.029). The trim and fill procedure did not impute any missing studies.

Appendix 2D. Figure 30d

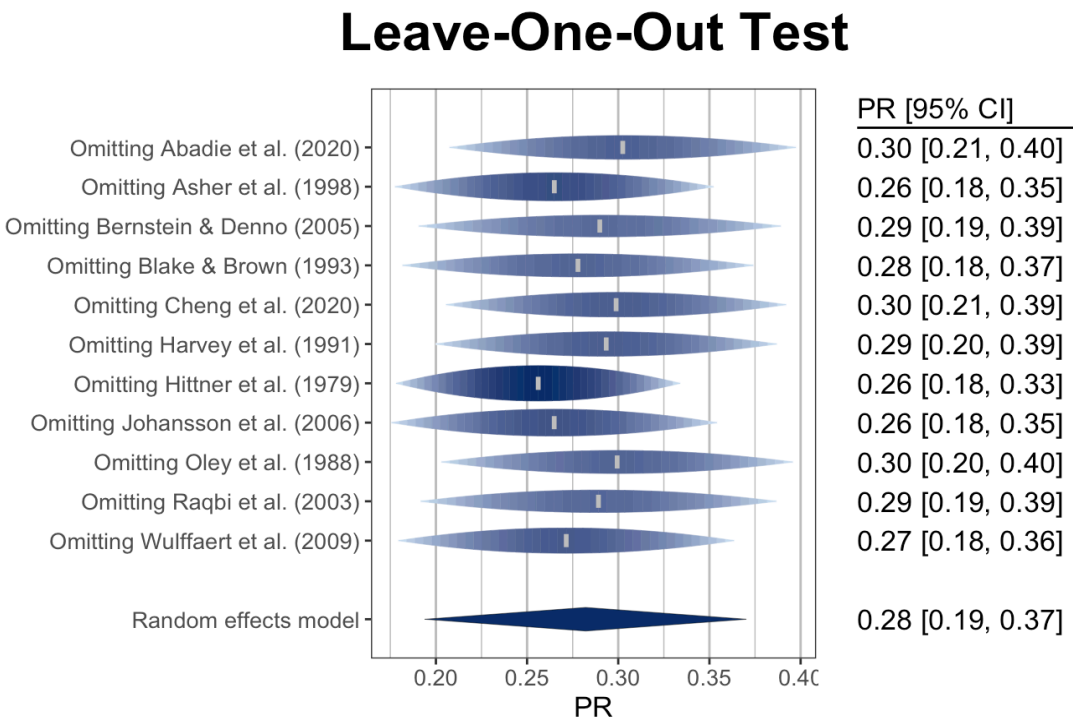
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Severe or Profound Intellectual Disability



Note. Hittner et al. (1979) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect.

Appendix 2D. Figure 30e

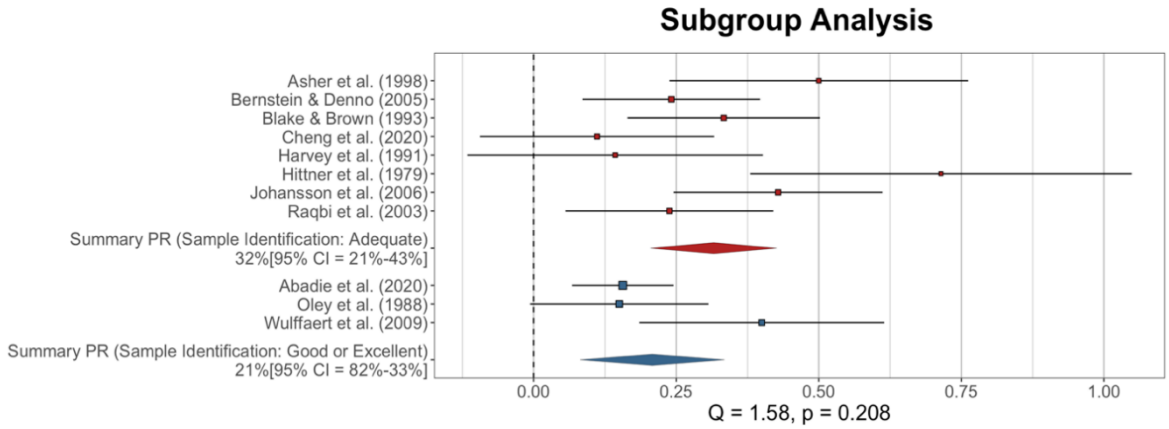
Leave-One-Out Random Effects Model for Studies Reporting Severe or Profound Intellectual Disability



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 30f

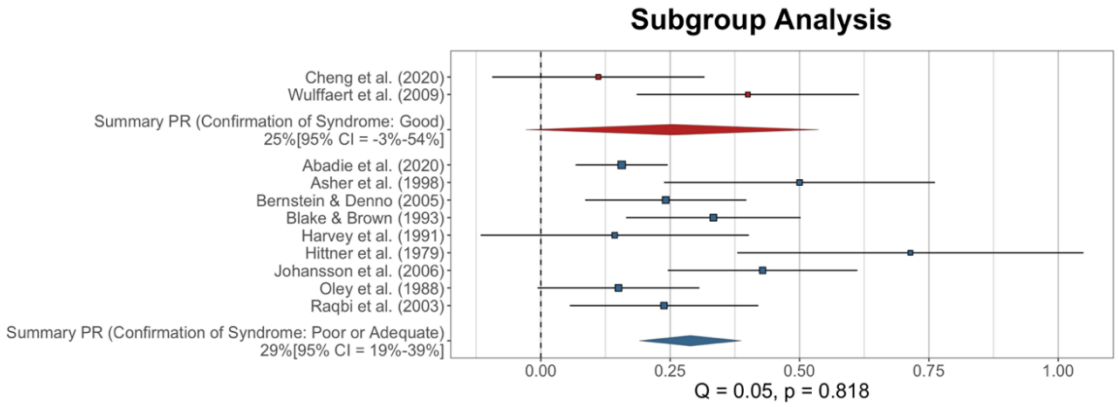
Subgroup Analysis of Studies Reporting Severe or Profound Intellectual Disability that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.208) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 30g

Subgroup Analysis of Studies Reporting Severe or Profound Intellectual Disability that were Rated Poor/Adequate and Studies Rated Good for Confirmation of Syndrome



Note. Subgroup analysis found no statistical difference (p = 0.818) between studies rated poor/adequate or good quality for confirmation of syndrome. Subgroup analysis was evaluated by comparison of 95% CIs.

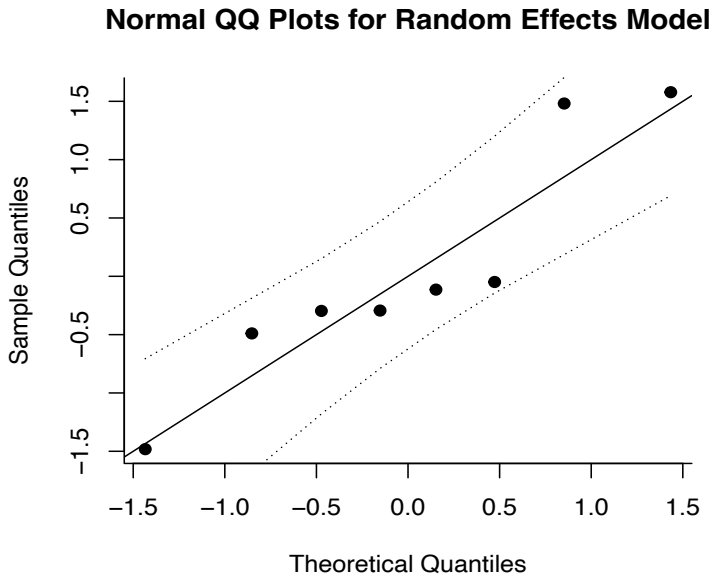
2D.2 Autism diagnosis

A number of studies also reported autistic behaviours that could not be included in the meta-analysis because they lacked continuity. Deuce et al. (2012), Hartshorne and Cypher, (2004) and Harvey et al. (1991) reported a 5%, 6% and 33% prevalence of 'autistic traits' respectively. Blake et al. (2005) suggested a 53% prevalence of socialising problems, Deuce et al. (2012) reported 48% of their sample had greater ease and more success in forming relationships with adults than with peers, and in Souriau et al. (2005), 42% of individuals with CHARGE syndrome had difficulty with social rules. Further, Hartshorne and Cypher (2004) accrued 100 survey responses regarding 25 behaviours indicative of

autism spectrum disorder presented by individuals with CHARGE syndrome and reported a prevalence rate from 16% to 66% for these behaviours

Appendix 2D. Figure 31a

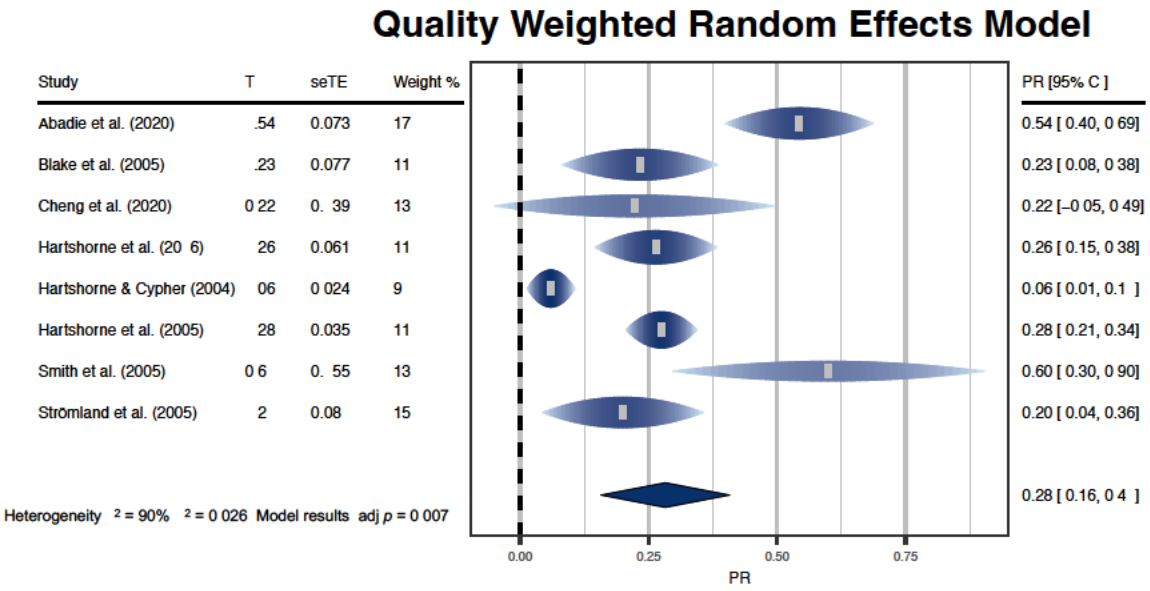
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Autism



Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 8 studies reporting on Autism diagnosis in CHARGE Syndrome. On this basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 31b

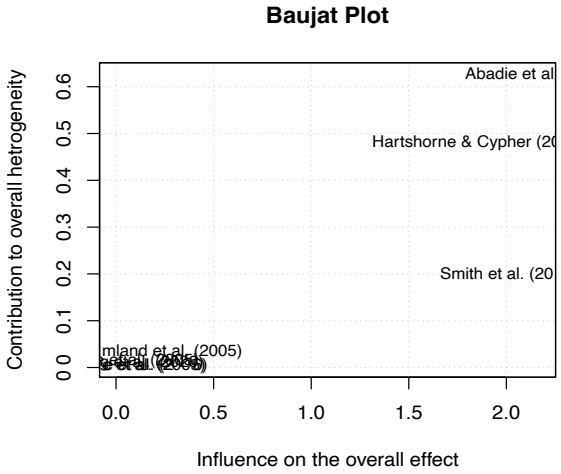
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Autism in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for an autism diagnosis in CHARGE syndrome was 28% (95% CI, 16-41%; permuted *p*-value = 0.007; *k* = 8) with high heterogeneity (I^2 = 90%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2

Appendix 2D. Figure 31c

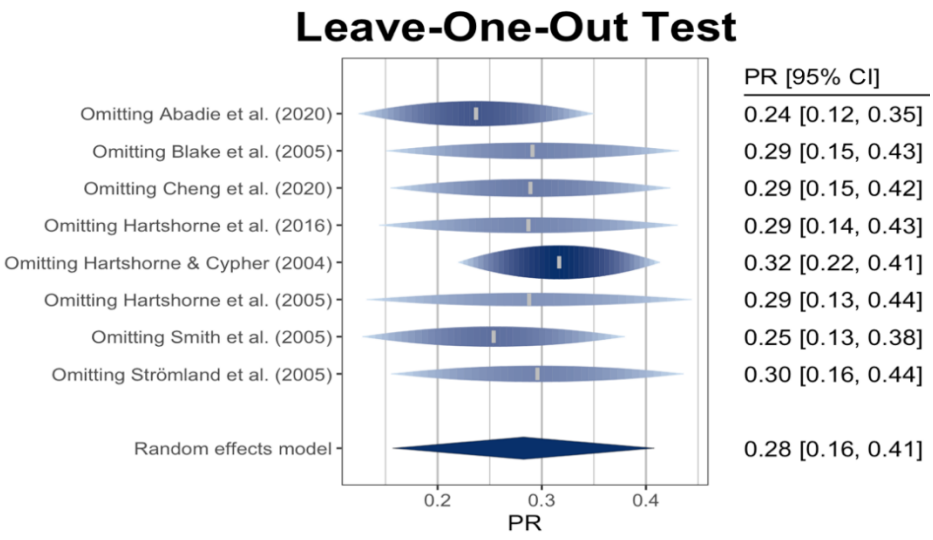
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Autism



Note. Abadie at al. (2020) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 31d

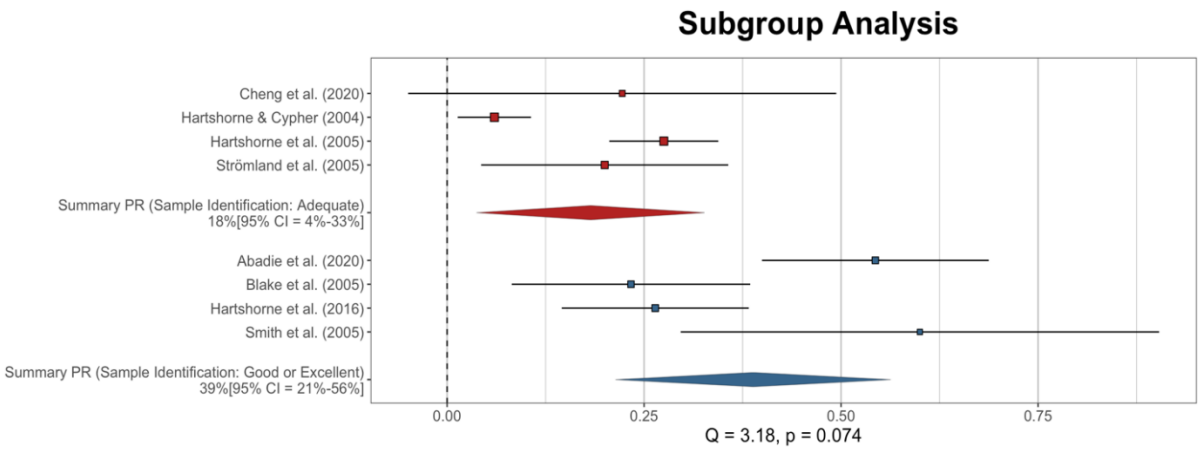
Leave-One-Out Random Effects Model for Studies Reporting Autism



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 31e

Subgroup Analysis of Studies Reporting Autism that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



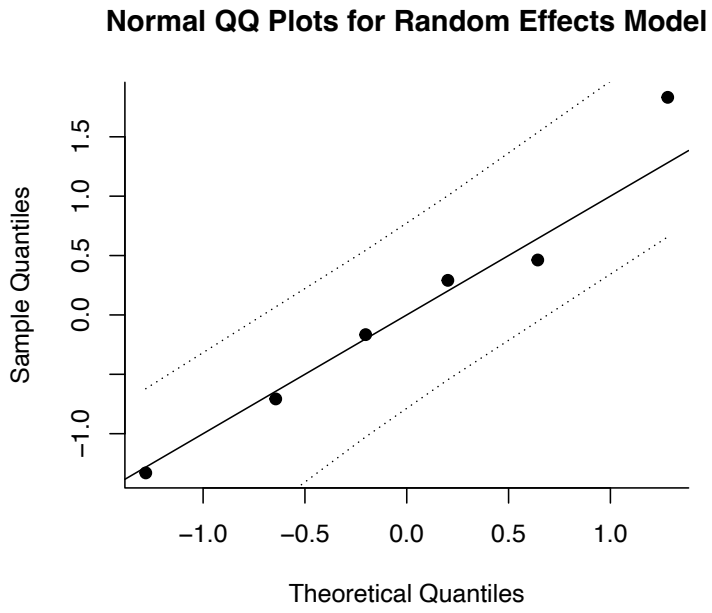
Note. Subgroup analysis found no statistical difference (p = 0.074) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

2D.3 Aggressive Behaviours

To maintain consistency, estimates excluded from the analysis included Blake et al. (2005) who reported a 13% prevalence of conduct disorder in a sample of 30 adolescents and adults with CHARGE syndrome and Hartshorne et al. (2009) reported disruptive behaviour which commonly includes aggression.

Appendix 2D. Figure 32a

QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Aggressive Behaviour

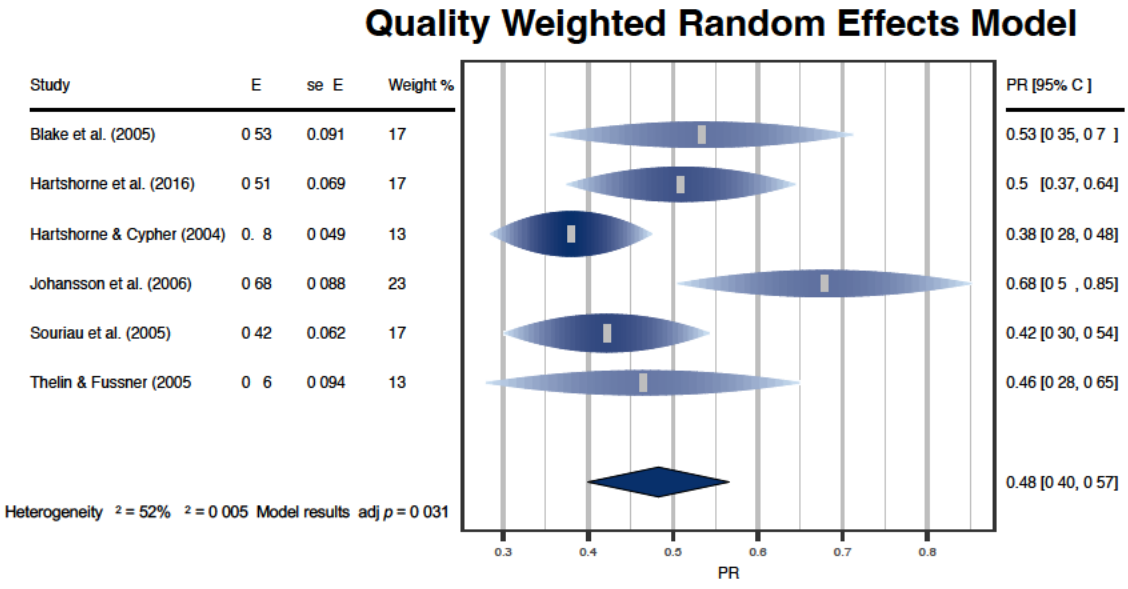


Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 6 studies reporting on aggressive behaviour in CHARGE Syndrome. On this

basis the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model

Appendix 2D. Figure 32b

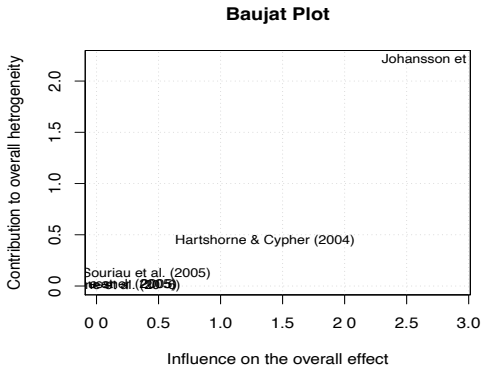
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Aggressive Behaviour in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for aggressive behaviour in CHARGE syndrome was 48% (95% CI, 40-57%; permuted *p*-value = 0.031; *k* = 6) with moderate heterogeneity (I^2 = 52%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2

Appendix 2D. Figure 32c

Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Aggressive Behaviour



Note. Johansson et al. (2006) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 32d

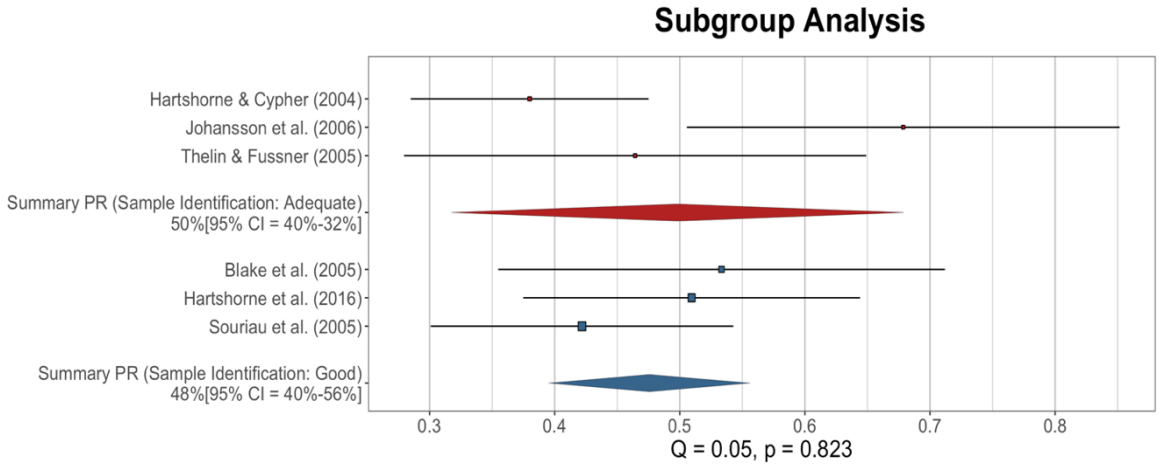
Leave-One-Out Random Effects Model for Studies Reporting Aggressive Behaviour



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 32e

Subgroup Analysis of Studies Reporting Aggressive Behaviour that were Rated Adequate and Studies Rated Good for Sample Identification



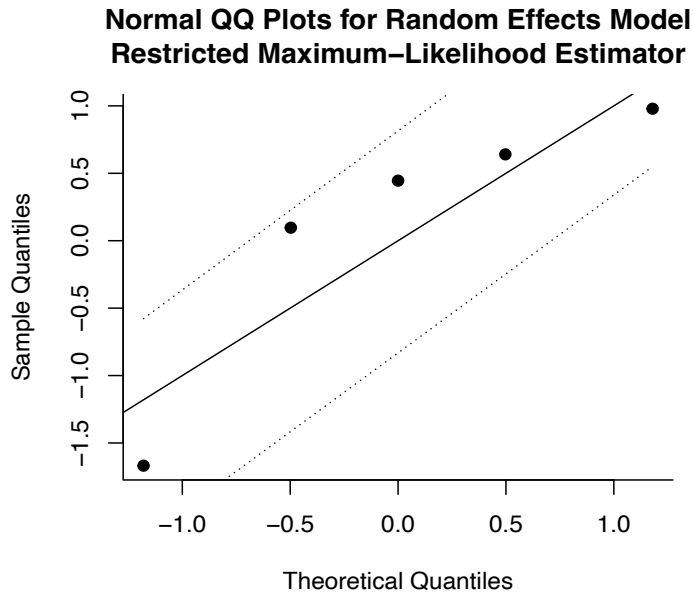
Note. Subgroup analysis found no statistical difference (p = 0.823) between studies rated adequate or good for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Self-Injurious Behaviour

Given the small number of studies included in this meta-analysis and the use of a fixed effects model, caution should be taken in generalising results beyond the five included studies.

Appendix 2D. Figure 33a

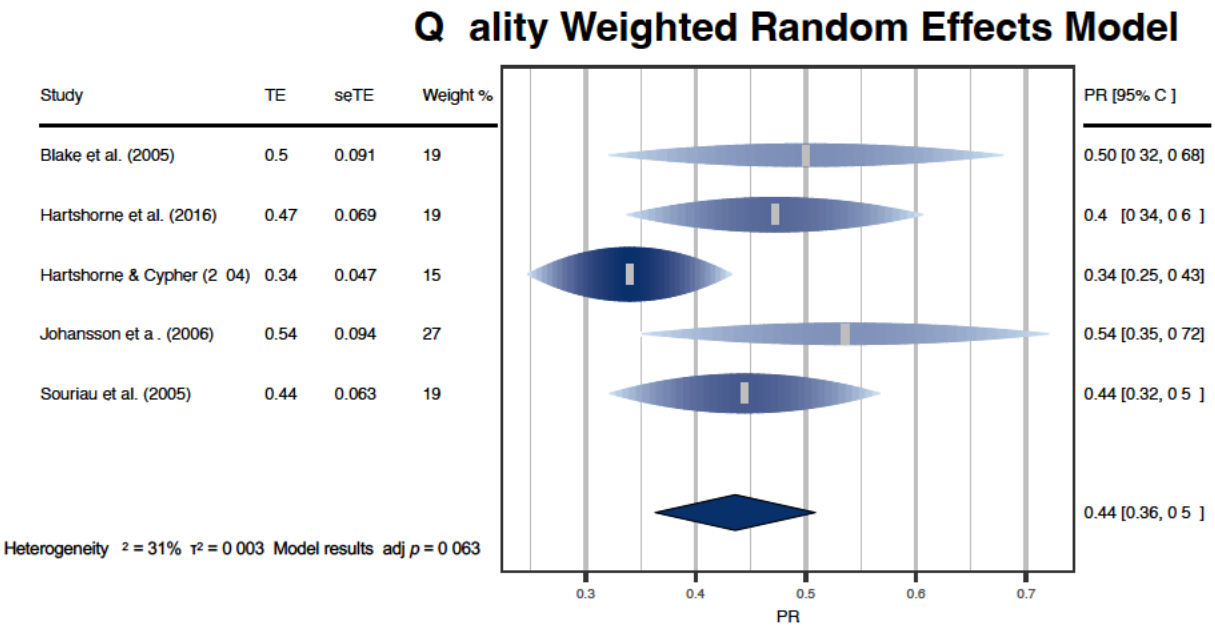
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Self-Injurious Behaviour



Note. Visual inspection of the *QQ* plot suggests a non-Gaussian distribution of study effects for the 5 studies reporting on self-injurious behaviour in CHARGE Syndrome. On this basis the restricted maximum likelihood estimator was used to calculate between studies variance in the random-effects model

Appendix 2D. Figure 33b

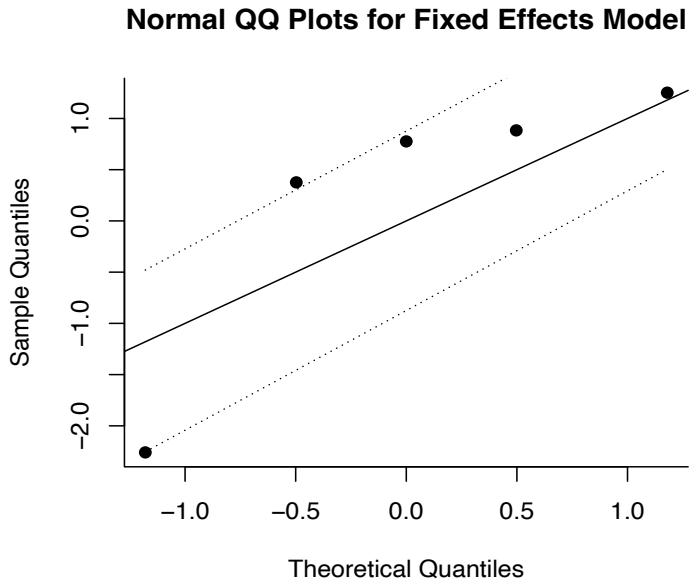
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Self-Injurious Behaviour in CHARGE Syndrome



Note. The quality weighted random effects model for self-injurious behaviour in CHARGE syndrome suggest a non-significant pooled prevalence estimate of 44% (95% CI, 36-51%; permuted *p*-value = 0.063; $k = 5$) with low heterogeneity ($I^2 = 31\%$). Random-effects model calculated using the inverse variance method and the restricted maximum likelihood estimator for τ^2

Appendix 2D. Figure 33c

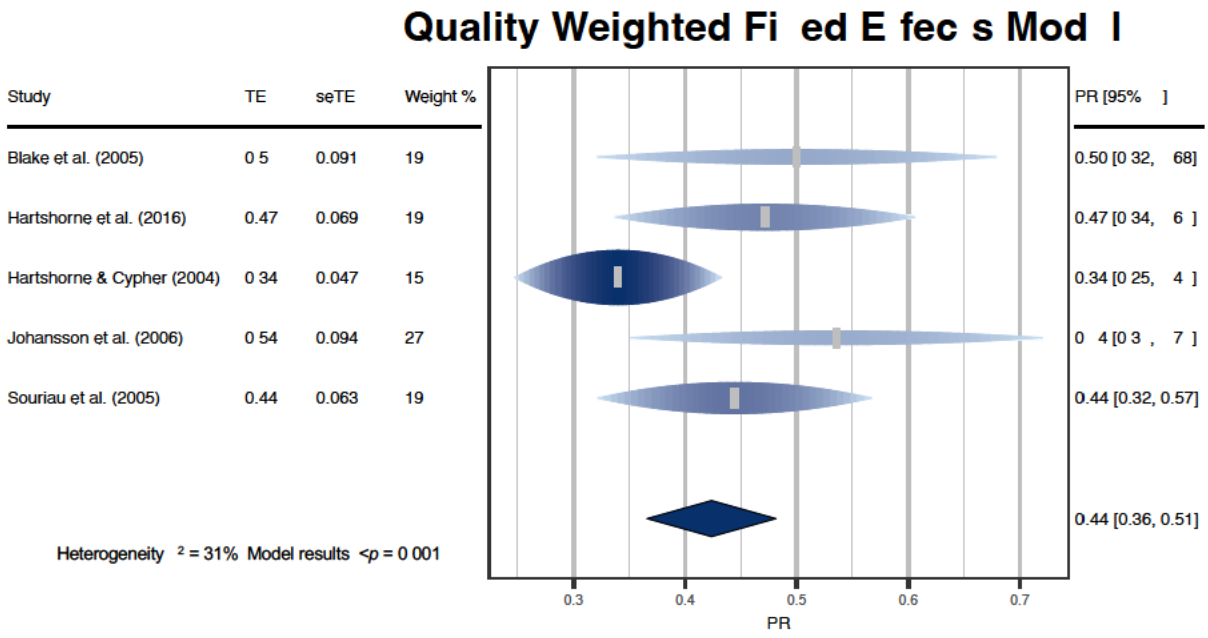
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Fixed Effects Model for Studies Reporting Self-Injurious Behaviour



Note. Revised QQ plot based on a fixed effects model: QQ plot of study effects for the 5 studies reporting on self-injurious behaviour in CHARGE Syndrome

Appendix 2D. Figure 33d

Fixed Effects Models of The Pooled Prevalence Estimate for Studies Reporting Self-Injurious Behaviour in CHARGE Syndrome

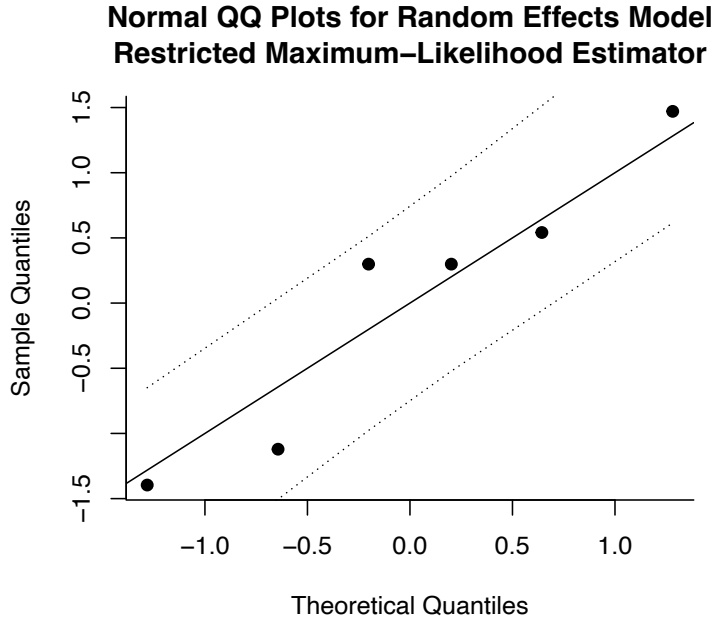


Note. The pooled prevalence estimate for self-injurious behaviour in CHARGE syndrome was 44% (95% CI, 36-51%; p = <0.001; *k* = 5). Fixed-effects model calculated using the inverse variance method.

2D.5 Obsessive or Compulsive Behaviour

Appendix 2D. Figure 34a

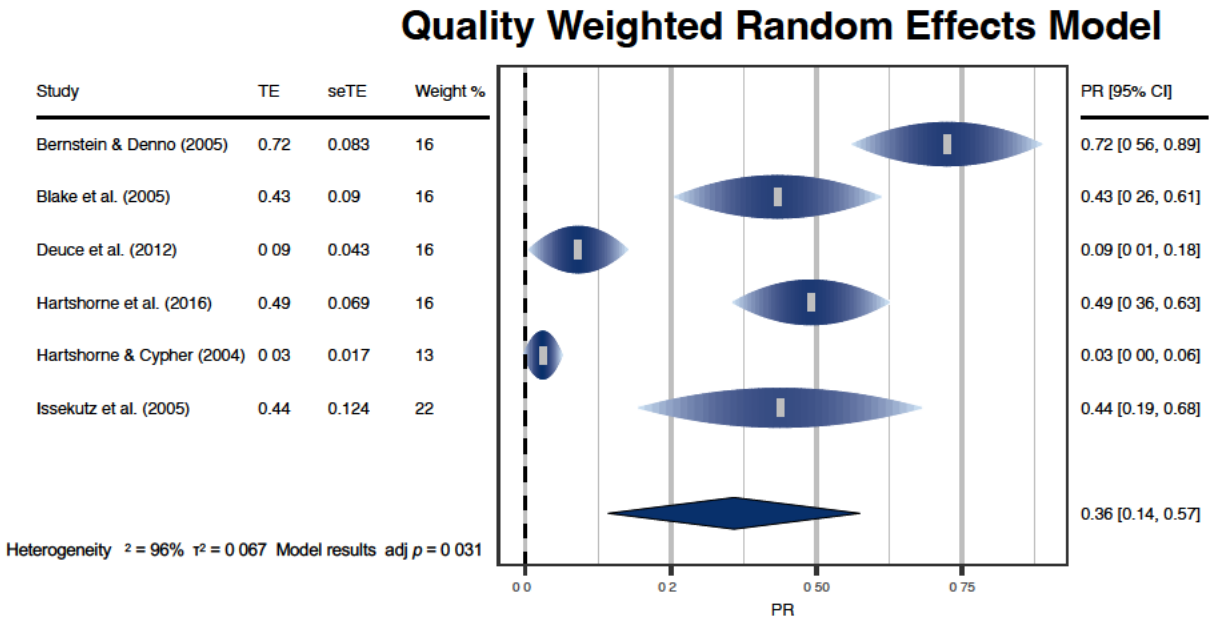
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Obsessive or Compulsive Behaviour



Note. Visual inspection of the *QQ* plot suggests a non-Gaussian distribution of study effects for the 6 studies reporting obsessive or compulsive behaviour in CHARGE Syndrome. On this basis the restricted maximum likelihood estimator was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 34b

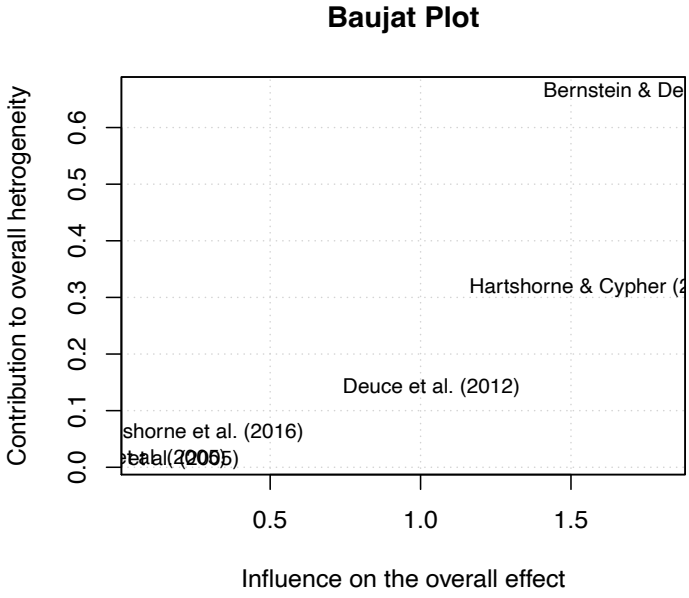
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Obsessive or Compulsive Behaviour in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for obsessive or compulsive behaviour in CHARGE syndrome was 36% (95% CI, 14-57%; permuted *p*-value = 0.031; *k* = 6) with high heterogeneity (I^2 = 96%). Random-effects model calculated using the inverse variance method and the restricted maximum likelihood estimator for τ^2

Appendix 2D. Figure 34c

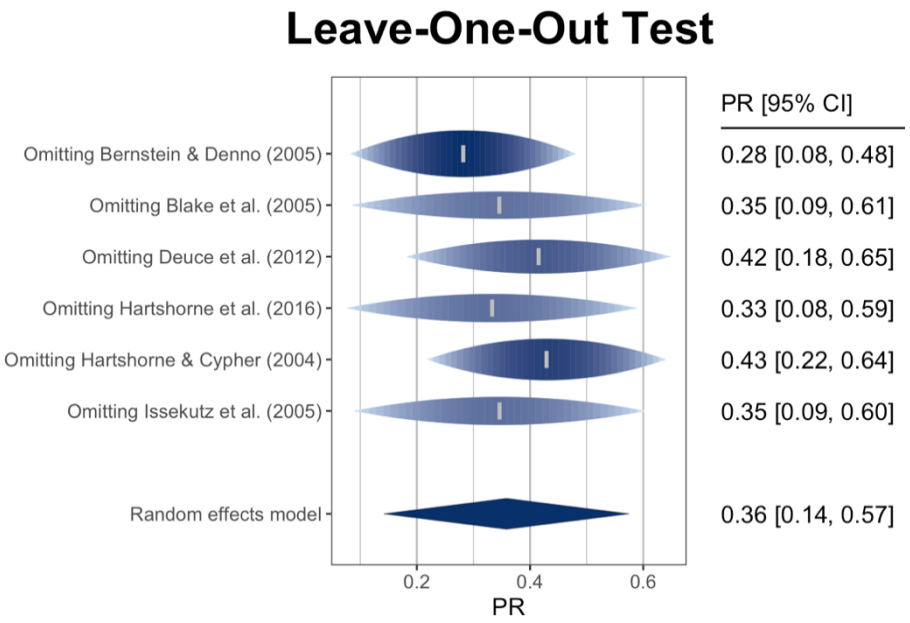
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Obsessive or Compulsive Behaviour



Note. Bernstein and Denno (2005) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 34d

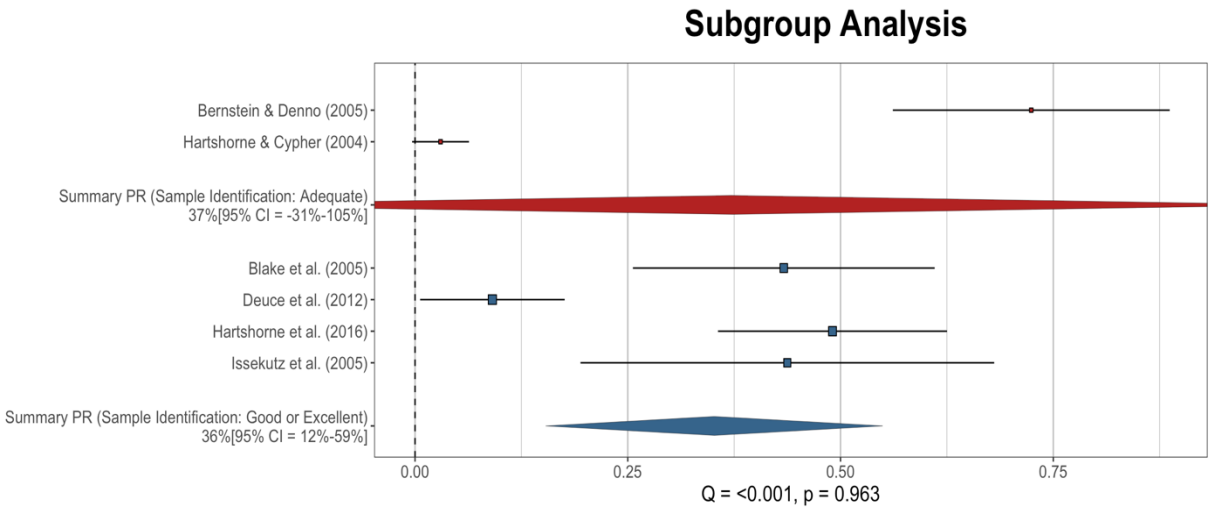
Leave-One-Out Random Effects Model for Studies Reporting Obsessive or Compulsive Behaviour



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 34e

Subgroup Analysis of Studies Reporting Obsessive or Compulsive Behaviour that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



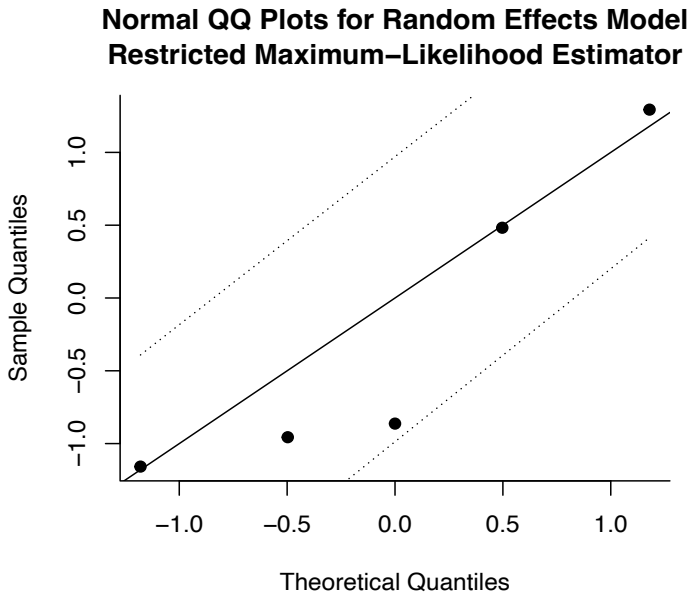
Note. Subgroup analysis found no statistical difference (p = 0.963) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

2D.6 Tactile Defensiveness

Given the small number of studies included in this meta-analysis it is unclear how representative the generated prevalence estimate is for the CHARGE population. Four additional studies reported different typologies of sensory behaviour including Deuce, (2017) who reported difficulty with sensory overload or under-stimulation (75%), Hartshorne and Cypher (2004) and Johansson et al. (2006) who reported unusual interest in auditory, visual or tactile stimuli (14-52%), Hartshorne et al. (2016) and Johansson et al. (2006) who reported movement stimulation including stereotyped body movements (50-54%), Hartshorne and Cypher (2004) reported spinning in circles (27%) and rocking behaviours (33%) and Johansson et al. (2006) and Souriau et al. (2005) reported an oversensitivity to noises or the feeling of certain substances (18-59%). However, given the idiosyncratic nature of these descriptions they could not be reliably synthesised.

Appendix 2D. Figure 35a

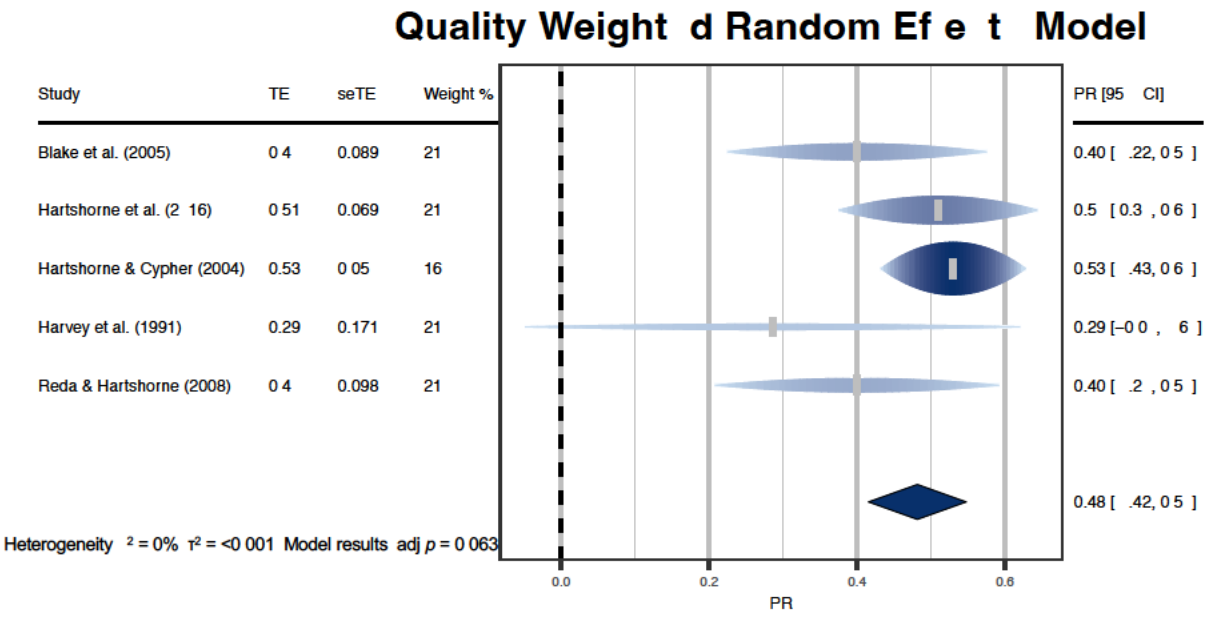
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Tactile Defensiveness



Note. Visual inspection of the *QQ* plot suggests a non-Gaussian distribution of study effects for the 5 studies reporting on tactile defensiveness in CHARGE Syndrome. On this basis the restricted maximum likelihood estimator was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 35b

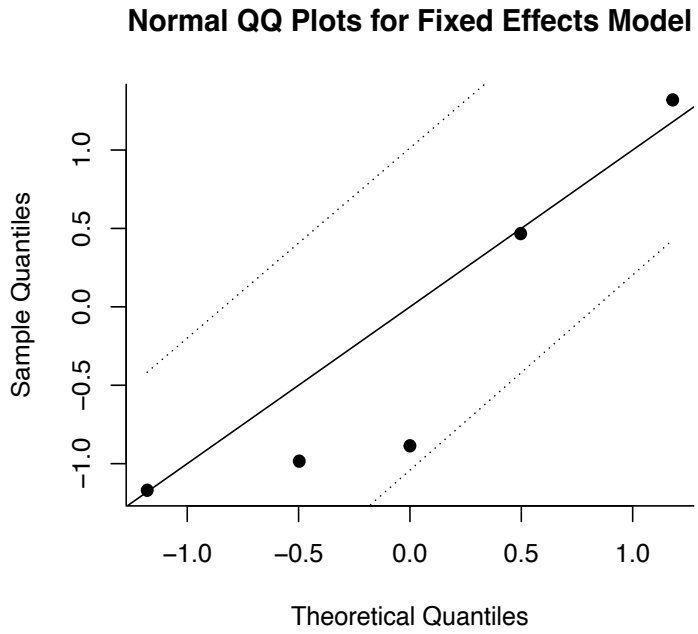
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Tactile Defensiveness in CHARGE Syndrome



Note. The quality weighted random effects model for tactile defensiveness in CHARGE syndrome suggest a non-significant pooled prevalence estimate of 48% (95% CI, 42-55%; permuted *p*-value = 0.063; *k* = 5). Heterogeneity could not be detected. Random-effects model calculated using the inverse variance method and the restricted maximum likelihood estimator for τ^2

Appendix 2D. Figure 35c

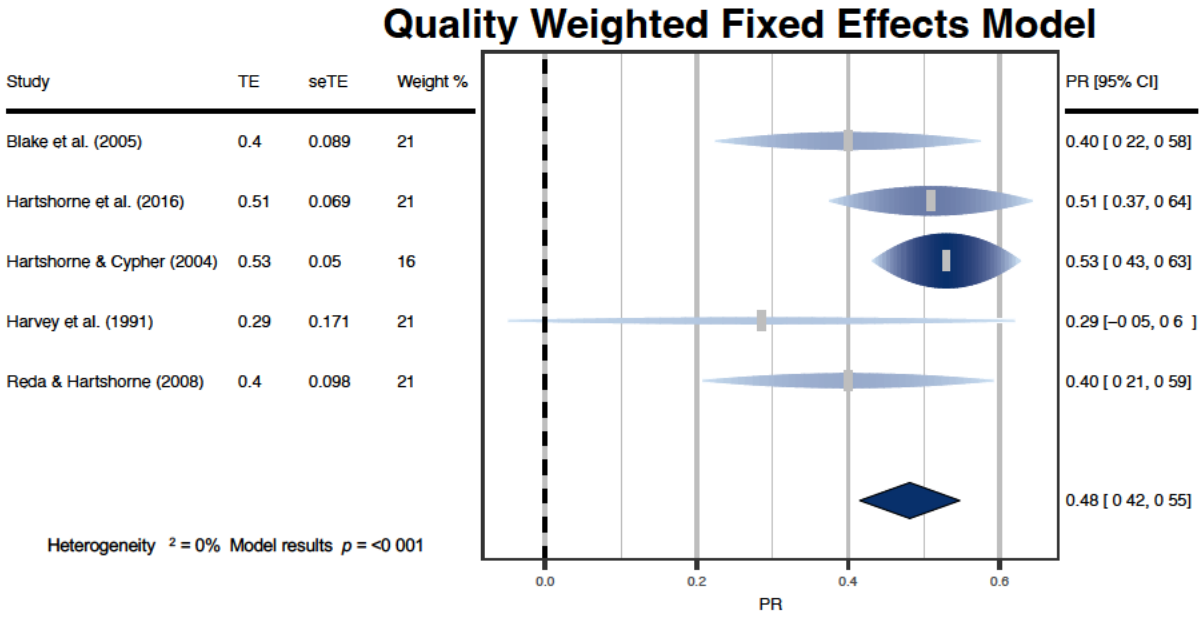
QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Fixed Effects Model for Studies Reporting Tactile Defensiveness



Note. Revised QQ plot based on a fixed effects model: QQ plot of study effects for the 5 studies reporting on tactile defensiveness in CHARGE Syndrome

Appendix 2D. Figure 35d

Fixed Effects Models of The Pooled Prevalence Estimate for Studies Reporting Tactile Defensiveness in CHARGE Syndrome



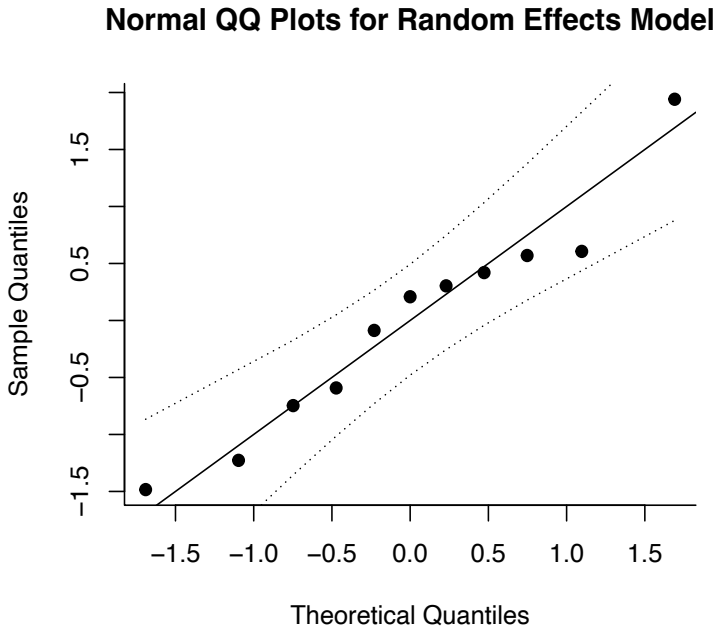
Note. The pooled prevalence estimate for tactile defensiveness in CHARGE syndrome was 48% (95% CI, 42-55%; p = <0.001; k = 5). Fixed-effects model calculated using the inverse variance method.

Sleep Difficulties

Prevalence rates for sleep difficulties in CHARGE syndrome were collated from 11 eligible studies. Sleep difficulties consist of any combination of insomnia, hypersomnolence or parasomnia disorders, sleep-related breathing disorders, circadian rhythm sleep-wake disorders or sleep-related movement disorders (World Health Organization, 2021).

Appendix 2D. Figure 36a

QQ Plot of The Distribution of Study Effects and Theoretical Quantities Based on A Normal Distribution Under the Random Effects Model for Studies Reporting Sleep Difficulties

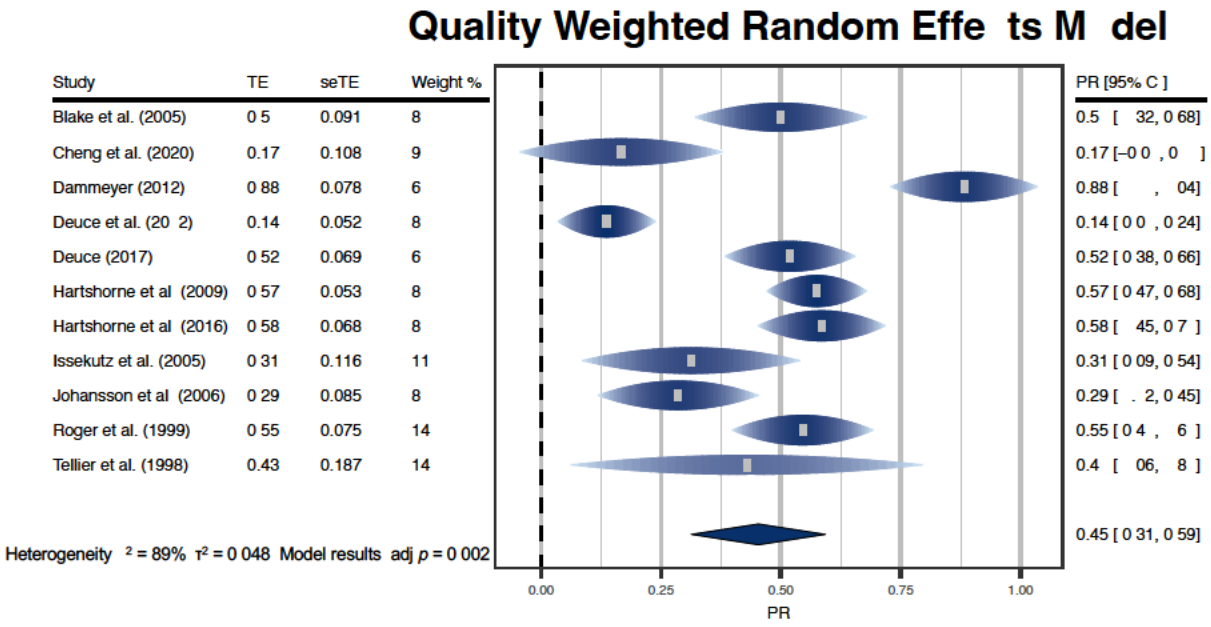


Note. Visual inspection of the *QQ* plot suggests an approximate normal distribution of study effects for the 11 studies reporting on sleep problems in CHARGE Syndrome. On this basis

the DerSimonian-Laird estimate was used to calculate between studies variance in the random-effects model.

Appendix 2D. Figure 36b

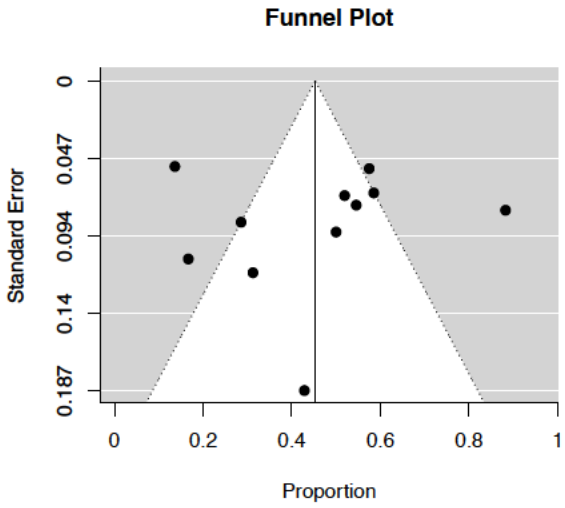
Random Effects Models of The Pooled Prevalence Estimate for Studies Reporting Sleep Difficulties in CHARGE Syndrome



Note. The quality weighted pooled prevalence estimate for sleep problems in CHARGE syndrome was 45% (95% CI, 31-59%; permuted *p*-value = 0.002; *k* = 11) with high heterogeneity (I^2 = 89%). Random-effects model calculated using the inverse variance method and the DerSimonian-Laird estimator for τ^2. Rosenthal Fail-safe N = 1481 suggests that the observed effect is robust to potential publication biased

Appendix 2D. Figure 36c

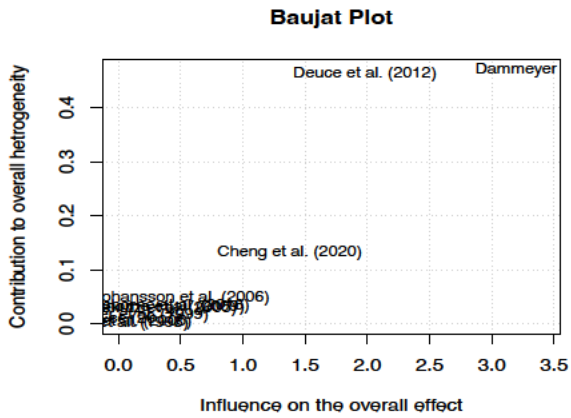
Funnel Plot of Standard Error by Prevalence of Sleep Difficulties Following the Trim and Fill Procedure



Note. Visual inspection of the funnel plot conforms to normal expectations and there is weak evidence of substantial publication bias (Egger's test p = 0.933)

Appendix 2D. Figure 36d

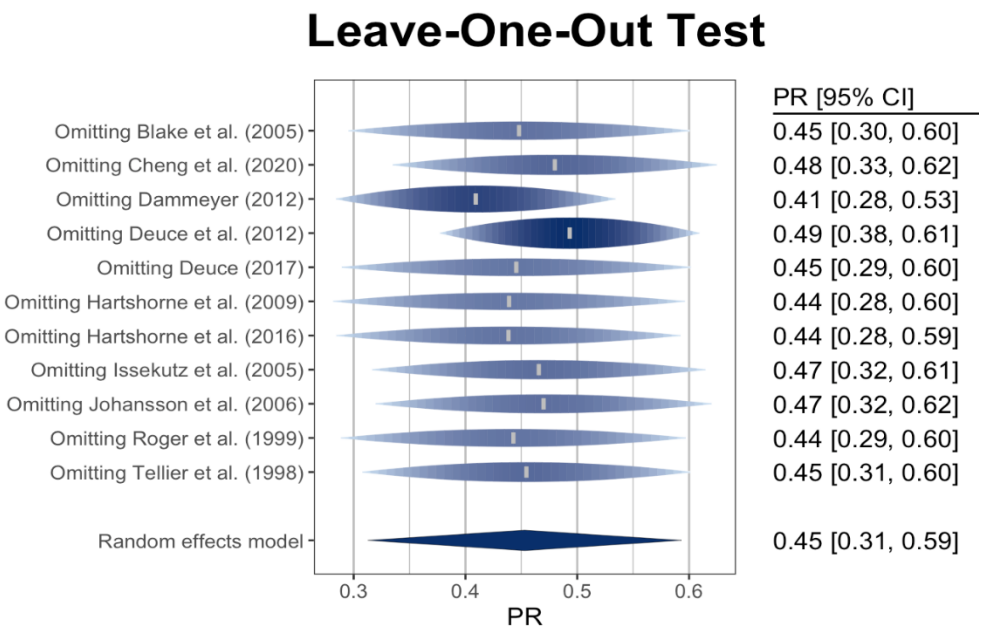
Baujat Plot of Contribution to Heterogeneity by Influence on Overall Effect for Studies Reporting Sleep Difficulties



Note. Dammeyer (2012) had the greatest contribution to overall heterogeneity and the greatest influence on the overall effect

Appendix 2D. Figure 36e

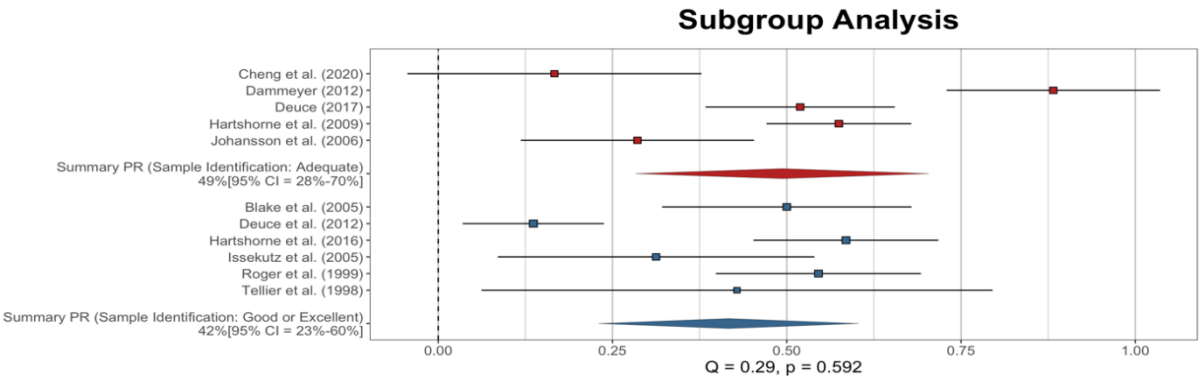
Leave-One-Out Random Effects Model for Studies Reporting Sleep Difficulties



Note. Leave one out analysis indicating that no single study is exerting a disproportional influence on the pooled prevalence estimate

Appendix 2D. Figure 36f

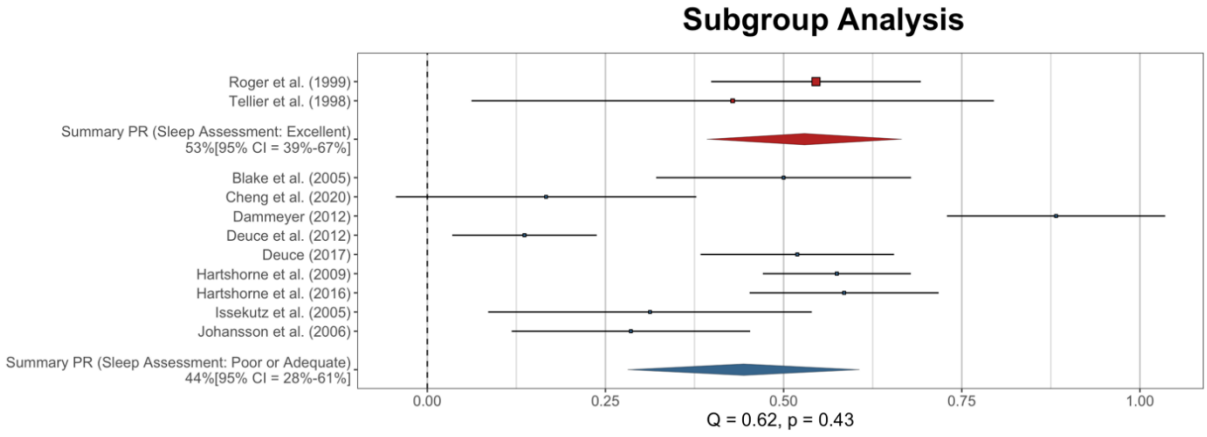
Subgroup Analysis of Studies Reporting Sleep Difficulties that were Rated Adequate and Studies Rated Good/Excellent for Sample Identification



Note. Subgroup analysis found no statistical difference (p = 0.592) between studies rated adequate or good/excellent for method of sample identification. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2D. Figure 36g

Subgroup Analysis of Studies Reporting Sleep Difficulties that were Rated Poor/Adequate and Studies Rated Excellent for Method of Sleep Assessment



Note. Subgroup analysis found no statistical difference ($p = 0.43$) between studies rated poor/adequate or excellent for method of sleep assessment. Subgroup analysis was evaluated by comparison of 95% CIs.

Appendix 2E. Operational Definitions for Behavioural, Psychological, Cognitive and Sleep Characteristics in CHARGE Syndrome

Appendix 2E. Table 1

Operational Definitions Used to Identify Behavioural, Psychological, Cognitive and Sleep Characteristics Reported in the Literature

Characteristic	Definition
Developmental delay	Early onset (<5 years) delay or deficit in two or more areas of functioning: cognitive skills, speech development, motor skills or social and emotional development (Pinchefsky & Shevell, 2017)
Intellectual disability	IQ: <69; Daily skills: Daily skills: Require at least minimum support for independent living (DSM-IV; DSM-5)
Mild or moderate intellectual disability	IQ: 36-69; Daily skills: Independent living with minimum or moderate level of support
Severe or profound intellectual disability	IQ: <35; Daily living: Requires daily assistance with self-care activities and safety supervision or requires 25-hour care
Autism	A clinical diagnosis of autism, inclusive of all previous terms

Characteristic	Definition
Aggression	Outward physical or verbal aggression
Self-injurious behaviour	Self-directed behaviors that could cause physical injury

Appendix 2F: Meta-Regression Estimates of The Effects of Co-Occurring Characteristics on Behavioural, Psychological, Cognitive and Sleep Characteristics in CHARGE Syndrome. Statistical Significance Evaluated Using Benjamini-Hochberg Adjustment for Multiple Comparisons

Appendix 2F. Table 2

Meta-Regression Estimates for of the Effects of Co-Occurring Characteristics on Behavioural, Psychological, Cognitive and Sleep Characteristics in the Eligible CHARGE Syndrome Literature

Moderator variable		N	k	β	Z	SE	p	R^2	Adj sig
Developmental Delay									
	Year	**212**	**7**	**.005**	**1.24**	**.004**	**.213**	**18%**	**0.509**
Intellectual Disability									
	Year	**515**	**16**	**.005**	**.926**	**.006**	**.354**	**0%**	**0.721**
	Mean Age	**300**	**10**	**.002**	**.045**	**.034**	**.964**	**0%**	**0.964**
	Male	**401**	**12**	**.199**	**.484**	**.411**	**.628**	**0%**	**0.886**
	Coloboma	**295**	**10**	**-.761**	**-1.18**	**.645**	**.238**	**9%**	**0.545**
p = 0.005	**Choanal Atresia**	**299**	**8**	**-.96**	**-4.61**	**.208**	**<.001**	**91%**	**0.014**
	CN-VII	**184**	**11**	**-.393**	**-1.26**	**.312**	**.208**	**0%**	**0.509**

Moderator variable		N	k	β	Z	SE	p	R^2	Adj sig
	CN-IX / X	86	6	-.117	-.2	.593	.843	0%	0.963
p = 0.0167	Inner Ear	194	5	-1.15	-4.48	.257	<.001	100%	0.014
	Heart Defect	360	13	-.073	-.113	.642	.91	0%	0.963
	Growth Deficiency	351	12	-.958	-2.51	.381	.012	53%	0.073
p = 0.059	Genital Hypoplasia	269	7	1.282	2.79	.46	.005	70%	0.034
	Cleft Lip / Palate	273	7	-.755	-1.54	.489	.123	8%	0.397
p = 0.825	Urinary Tract Anomaly	171	6	-1.76	-2.87	.612	.004	80%	0.031
	Skeletal Anomalies	134	7	.272	.712	.382	.477	0%	0.846
	Hearing Loss (HL)	372	11	1.804	2.05	.88	.04	38%	0.169
	Severe or Profound HL	194	7	.226	.53	.428	.597	21%	0.884
Mild or Moderate ID									
	Year	217	10	.012	1.666	.007	.096	11%	0.374
	Male	154	7	.596	1.486	.401	.137	7%	0.397
	Hearing Loss	74	5	3.024	1.63	1.847	.102	30%	0.374
Severe/Profound ID									
	Year	249	11	-.005	-1.43	.004	.152	8%	0.418

Moderator variable		N	k	β	Z	SE	p	R^2	Adj sig
	Male	156	7	-0.841	-2.04[illegible]	.41	.040	0%	0.169
	Hearing Loss	93	6	1.08	.817	1.322	.414	0%	0.808
Autism Spectrum Disorder									
	Year	433	8	.011	1.311	.008	.19	35%	0.498
	Age	280	6	-.014	-.621	.023	.535	0%	0.865
	Male	433	8	.103	.185	.554	.853	0%	0.963
	Coloboma	387	7	.134	.165	.812	.869	0%	0.963
	Choanal Atresia	387	7	.2	.669	.299	.504	0%	0.865
	CN-VII	302	5	.11	.152	.699	.875	0%	0.963
	Heart Defect	387	7	.238	.449	.53	.654	0%	0.899
	Growth Deficiency	384	7	-.398	-.557	.715	.578	0%	0.884
	Genital Hypoplasia	333	6	.264	.796	.331	.426	22%	0.808
	Cleft Lip / Palate	387	7	-.054	-.122	.44	.903	0%	0.963
	Tracheoesophageal fistula	377	6	.718	.745	.964	.457	3%	0.838
	Skeletal Anomalies	377	6	.114	.362	.315	.717	10%	0.939
	Gross Motor Difficulties	300	5	.104	.398	.263	.691	12%	0.927

Moderator variable		N	k	β	Z	SE	p	R^2	Adj sig
Aggression									
	Year	**303**	**6**	**.005**	**.511**	**.011**	**.609**	**0%**	**0.884**
	Male	**239**	**5**	**.446**	**.646**	**.69**	**.519**	**0%**	**0.865**
	Choanal Atresia	**239**	**5**	**-.408**	**-1.01**	**.402**	**.31**	**0%**	**0.656**
	Heart Defect	**239**	**5**	**-.904**	**-2.21**	**.409**	**.027**	**85%**	**0.149**
	Growth Deficiency	**239**	**5**	**-.238**	**-.51**	**.469**	**.611**	**0%**	**0.884**
	Cleft Lip / Palate	**239**	**5**	**-.03**	**-.06**	**.5**	**.953**	**0%**	**0.964**
Obsessive or Compulsive Behaviour									
	Year	**272**	**6**	**-.002**	**-.049**	**.03**	**.961**	**0%**	**0.964**
	Growth Deficiency	**243**	**5**	**.581**	**1.12**	**.581**	**.263**	**0%**	**0.579**
	Hearing Loss	**242**	**5**	**.263**	**.224**	**1.173**	**.823**	**0%**	**0.963**
Sleep Problems									
	Year	**390**	**11**	**-.002**	**-.201**	**.011**	**.841**	**0%**	**0.963**
	Male	**215**	**6**	**-1.243**	**-3.04**	**.41**	**.002**	**66%**	**0.018**
	Coloboma	**198**	**5**	**1.363**	**1.496**	**.911**	**.135**	**19%**	**0.397**
	Choanal Atresia	**198**	**5**	**.616**	**3.05**	**.202**	**.002**	**89%**	**0.018**
	Heart Defect	**262**	**5**	**.588**	**1.502**	**.391**	**.133**	**52%**	**0.397**

Moderator variable	N	k	β	Z	SE	p	R^2	Adj sig
Growth Deficiency	**238**	**6**	**.678**	**6.67**	**.102**	**<.001**	**100%**	**0.014**
Cleft Lip / Palate	**224**	**5**	**.85**	**2.16**	**.394**	**.031**	**61%**	**0.155**
Urinary Tract Anomaly	**186**	**5**	**-.137**	**-.136**	**1.01**	**.892**	**0%**	**0.963**
Gross Motor Difficulties	**184**	**5**	**.663**	**3.41**	**.195**	**.0007**	**76%**	**0.014**
Hearing Impairment	**264**	**6**	**-.137**	**-.136**	**1.01**	**.892**	**0%**	**0.963**

Note. Each meta-regression was calculated separately using one moderator variable

Appendix 2G. Table 3

Meta-Regression Estimates of Genotype-Phenotype Correlations in the Eligible CHARGE Syndrome Literature

Moderator variable	N	k	β	Z	SE	p	R^2	Adj sig
CHD7								
Year	**357**	**10**	**0.013**	**1.00**	**0.013**	**0.317**	**0%**	**1.000**
Male	**179**	**7**	**-0.128**	**-0.287**	**0.447**	**0.774**	**0%**	**1.000**
Coloboma	**92**	**5**	**0.355**	**0.737**	**0.483**	**0.461**	**0%**	**1.000**
Choanal Atresia	**93**	**5**	**0.173**	**0.384**	**0.451**	**0.701**	**0%**	**1.000**
Inner Ear Anomaly	**128**	**5**	**-0.007**	**-0.02**	**0.335**	**0.984**	**0%**	**1.000**
Truncating CHD7								
Year	**305**	**10**	**-0.001**	**-0.001**	**-0.111**	**0.994**	**0%**	**1.000**
Male	**260**	**10**	**-0.444**	**-1.707**	**0.26**	**0.088**	**18%**	**1.000**
Coloboma	**216**	**9**	**-0.005**	**-0.013**	**0.46**	**0.99**	**0%**	**1.000**
Choanal Atresia	**244**	**9**	**-0.07**	**-0.233**	**0.299**	**0.816**	**0%**	**1.000**

Moderator variable	N	k	β	Z	SE	p	R^2	Adj sig
CNVII – Facial Palsy	134	6	0.222	0.506	0.438	0.613	0%	1.000
External Ear	107	6	-0.002	-0.005	0.351	0.996	0%	1.000
Inner Ear	97	7	-0.148	-0.567	0.28	0.598	0%	1.000
Heart Defect	239	9	-0.993	-2	0.496	0.045	30%	0.945
Growth Deficiency	174	8	-1.353	-2.831	0.478	0.005	75%	0.115
Genital	222	9	-0.153	-0.627	0.243	0.531	0%	1.000
Cleft	217	8	0.215	0.493	0.436	0.622	0%	1.000
Tracheoesophageal Fistula	171	5	-0.29	-0.117	2.48	0.907	0%	1.000
Urinary Tract Anomaly	139	7	-0.808	-2.784	0.29	0.005	72%	0.115
Brain Anomaly	119	6	-0.318	-1.426	0.223	0.154	0%	1.000
Skeletal Anomaly	133	7	-0.311	-1.817	0.171	0.069	48%	1.000
Hearing Impairment	210	8	1.01	1.977	0.509	0.048	0%	0.960

Moderator variable	N	k	β	Z	SE	p	R^2	Adj sig
Intellectual Disability	**141**	**5**	**-0.076**	**-0.427**	**0.178**	**0.669**	**0%**	**1.000**
Developmental Delay	**74**	**5**	**0.521**	**0.378**	**1.378**	**0.706**	**0%**	**1.000**

Note. Each meta-regression was calculated separately using one moderator variable.

Appendix 3A: Ethics Approval Confirmation from NHS UK

From: no-reply-iras@hra.nhs.uk <no-reply-iras@hra.nhs.uk>

Sent: 19 December 2020 11:11

To: Andrea Thomas (PhD Psychology Lab FT) [redacted]

Subject: IRAS 20638. Amendment

IRAS Project ID: 20638

Sponsor amendment reference: NSA 01

Thank you for submitting your study amendment. In accordance with the outcome of your completed amendment tool, this amendment requires no further regulatory review. Please now share this amendment with your UK research sites, in accordance with the instructions in your completed amendment tool.

For studies with more than one UK research site, your amendment will now be automatically shared with the R&D offices of any NHS/HSC research sites in Scotland and Northern Ireland, but you should share the amendment by email directly with those Research team/s.

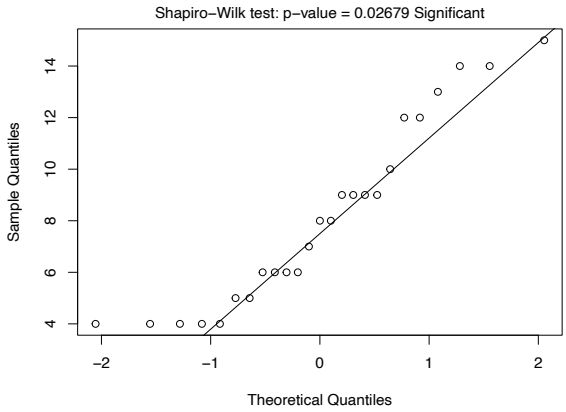
For all NHS research sites in England and Wales, please now share this amendment by email directly with those sites, including both the R&D offices and research teams.

Do not reply to this email as this is an unmonitored address and replies to this email cannot be responded to or read.

Appendix 3B: QQ Plots and Shapiro-Wilk Tests to Explore the Distribution of Continuous Variables

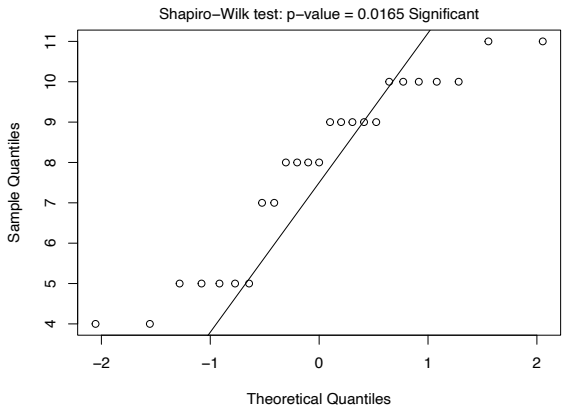
Appendix 3B. Figure 37

QQ plot: Age



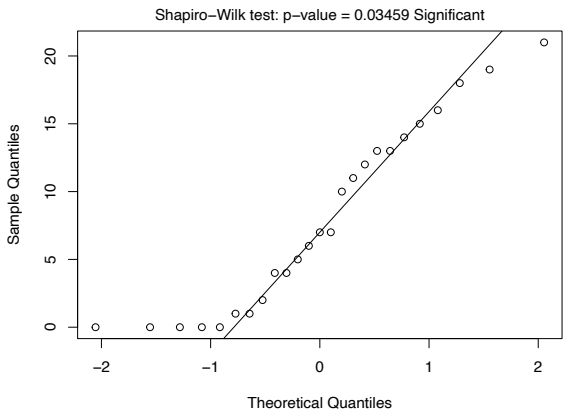
Appendix 3B. Figure 38

QQ plot: WSX Self-Help



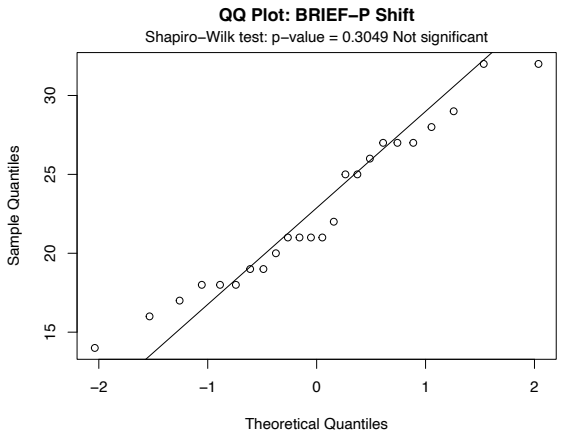
Appendix 3B. Figure 39

QQ plot: WADL Total Score



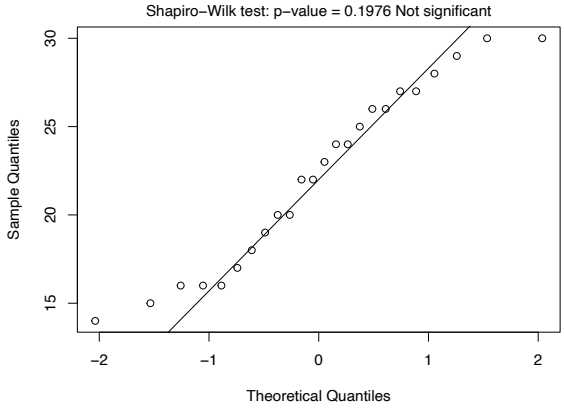
Appendix 3B. Figure 40

QQ plot: Brief-P Shift



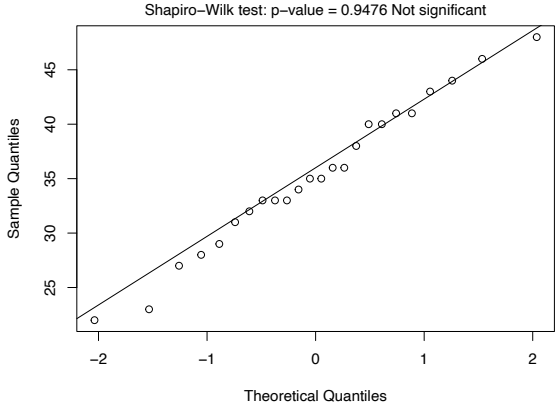
Appendix 3B. Figure 41

QQ plot: Brief-P Emotional Control



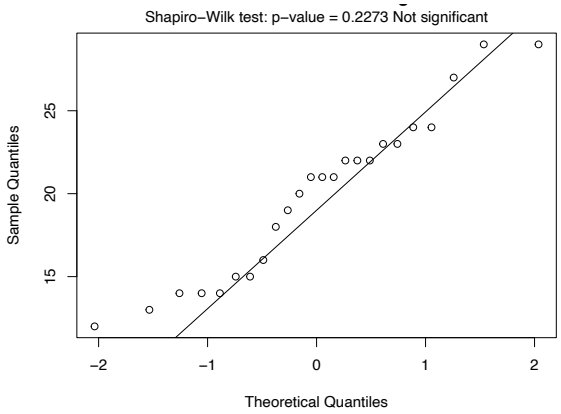
Appendix 3B. Figure 42

QQ plot: Brief-P Working Memory



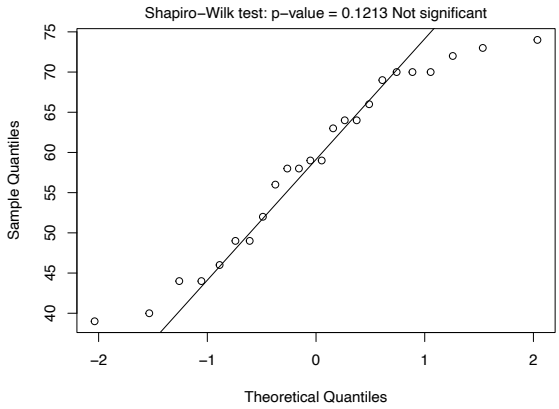
Appendix 3B. Figure 43

QQ plot: Brief-P Plan Organise



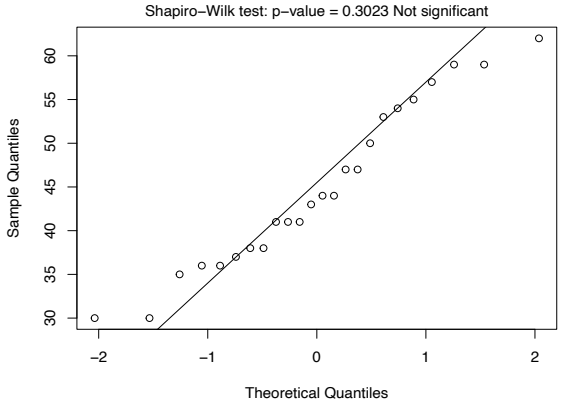
Appendix 3B. Figure 44

QQ plot: Brief-P Inhibit



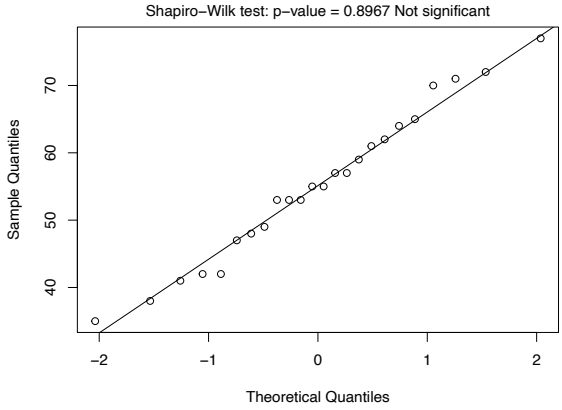
Appendix 3B. Figure 45

QQ plot: Brief-P Flexibility



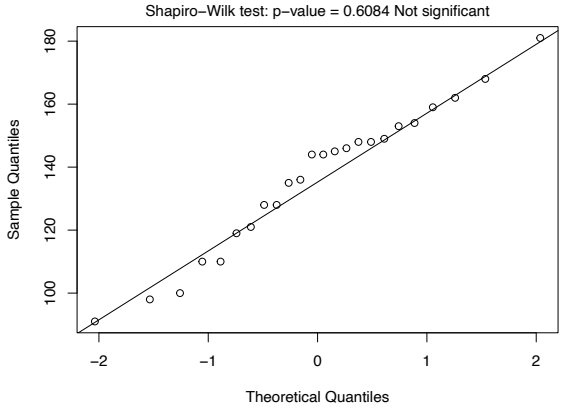
Appendix 3B. Figure 46

QQ plot: Brief-P Emergent Metacognition



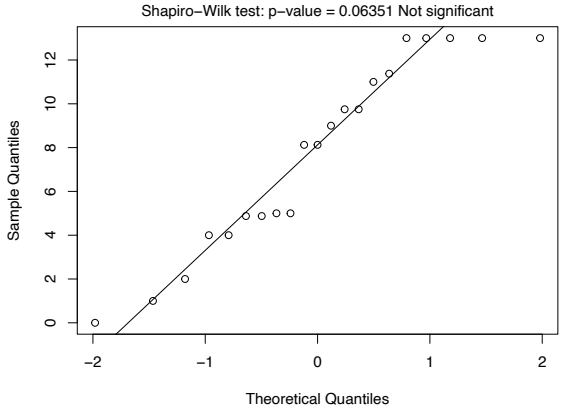
Appendix 3B. Figure 47

QQ plot: Brief-P Global Executive Composite



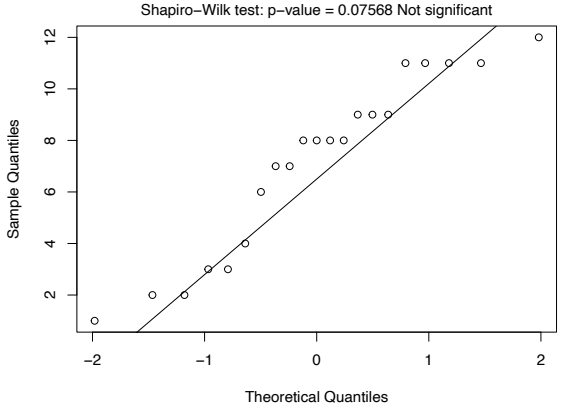
Appendix 3B. Figure 48

QQ plot: SCQ Communication



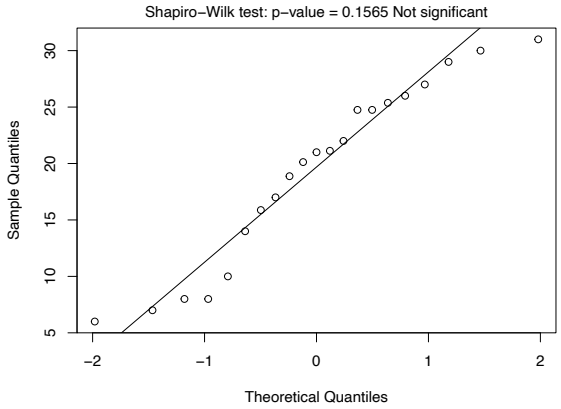
Appendix 3B. Figure 49

QQ plot: SCQ Reciprocal Social Behaviour



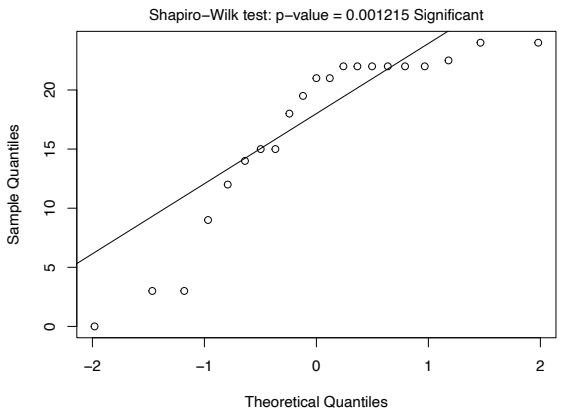
Appendix 3B. Figure 50

QQ plot: SCQ Total Score



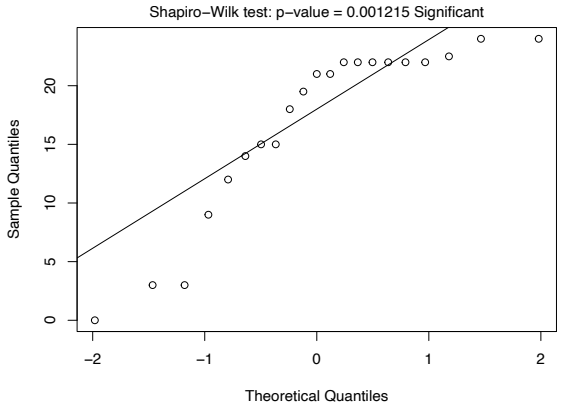
Appendix 3B. Figure 51

QQ plot: TAQ Impulsivity



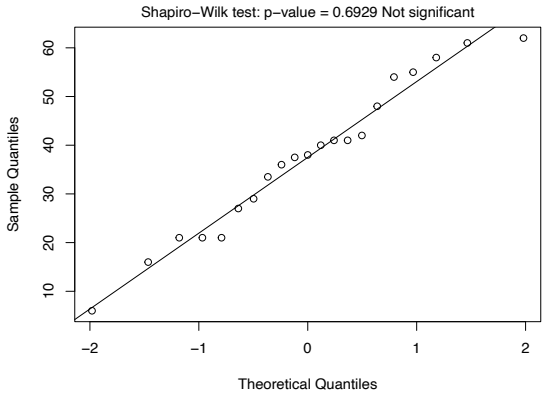
Appendix 3B Figure 52

QQ plot: TAQ Overactivity



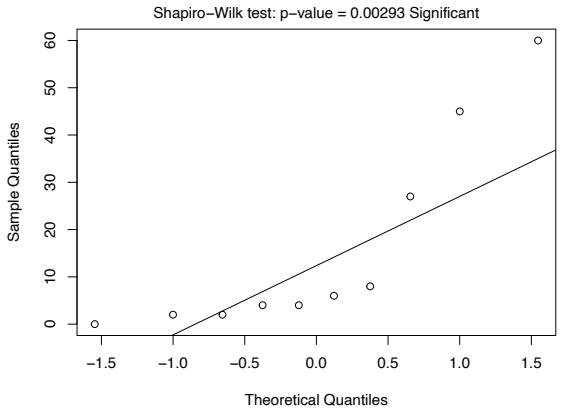
Appendix 3B. Figure 53

QQ plot: TAQ Total Score



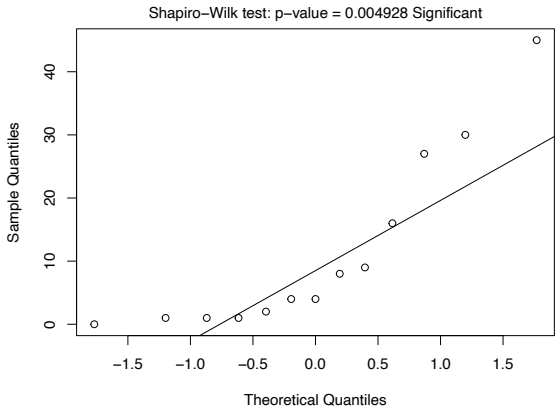
Appendix 3B. Figure 54

QQ plot: CBQ Self-Injury Severity



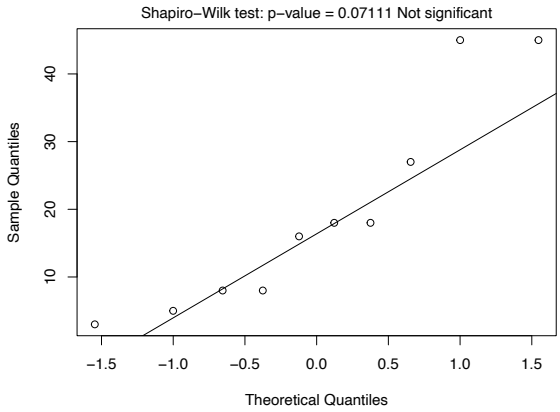
Appendix 3B. Figure 55

QQ Plot: CBQ Aggression Severity



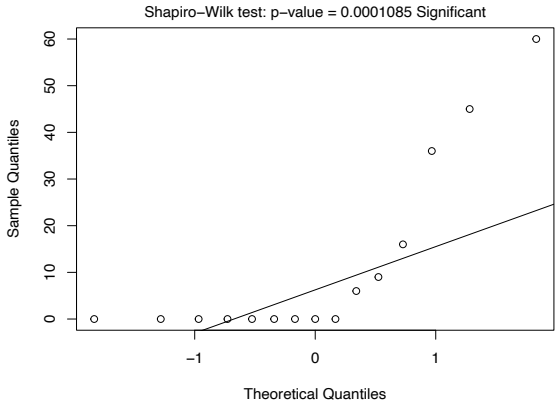
Appendix 3B. Figure 56

QQ Plot: CBQ Destruction Severity



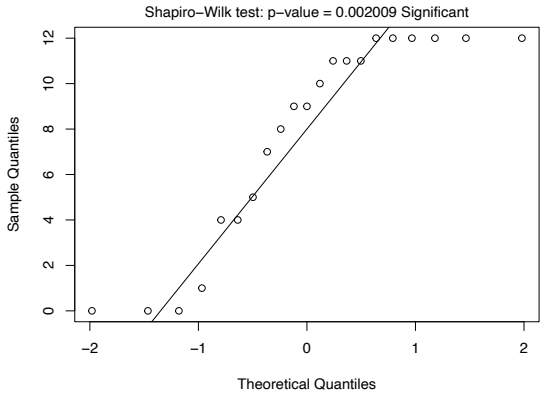
Appendix 3B. Figure 57

QQ Plot: CBQ Stereotyped Behaviour Severity



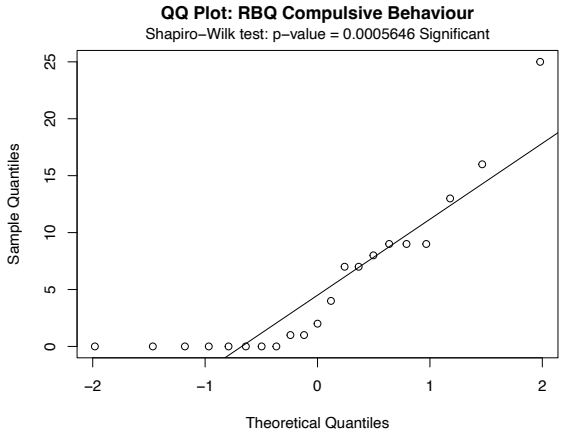
Appendix 3B. Figure 58

QQ Plot: RBQ Stereotyped Behaviour



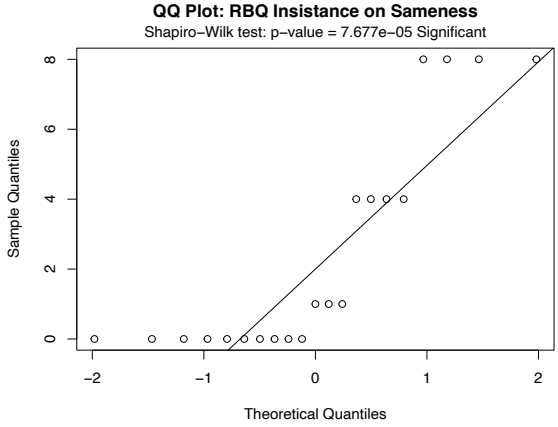
Appendix 3B. Figure 59

QQ Plot: RBQ Compulsive Behaviour



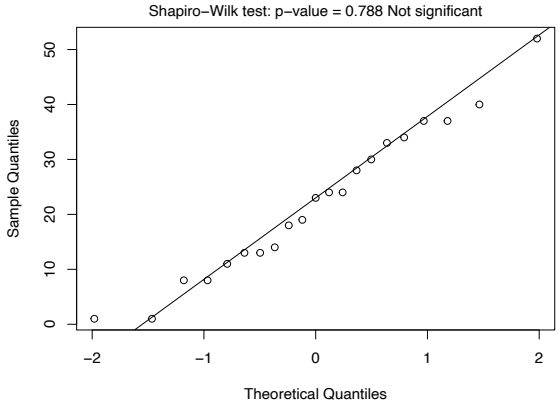
Appendix 3B. Figure 60

QQ Plot: RBQ Insistance on Sameness



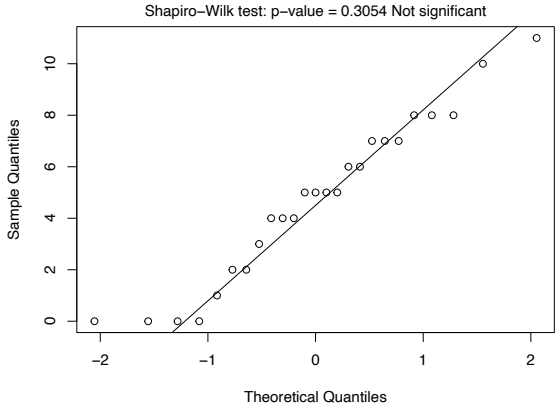
Appendix 3B. Figure 61

QQ Plot: RBQ Total Score



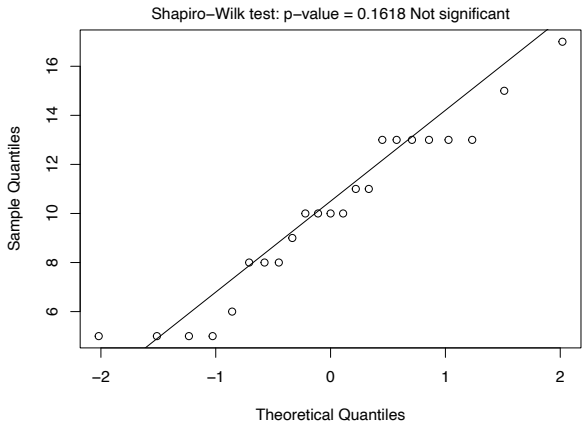
Appendix 3B. Figure 62

QQ Plot: GRQ Total Score



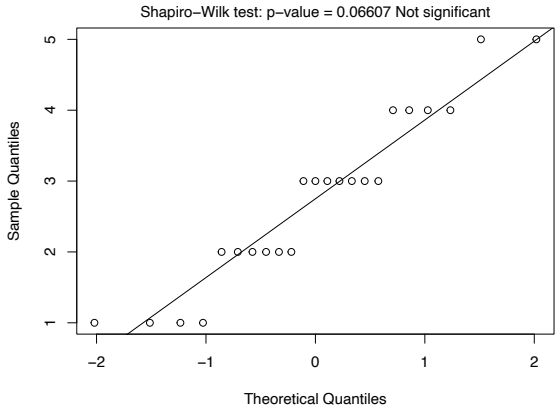
Appendix 3B. Figure 63

QQ Plot: MSPSQ Bedtime Resistance



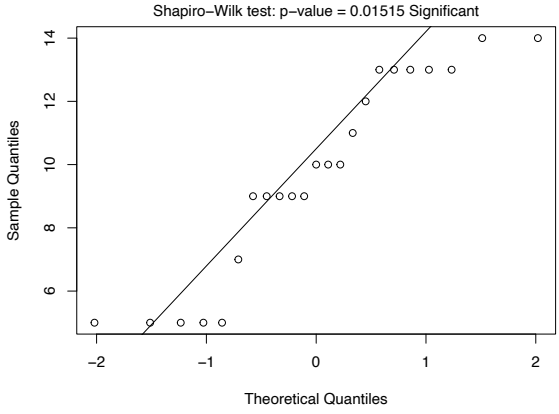
Appendix 3B. Figure 64

QQ Plot: MSPSQ Sleep Onset Delay



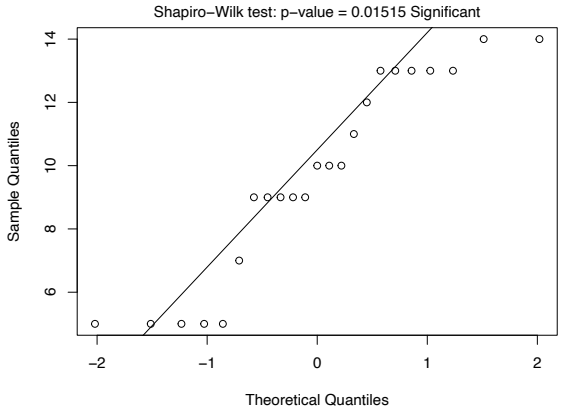
Appendix 3B. Figure 65

QQ Plot: MSPSQ Sleep Anxiety



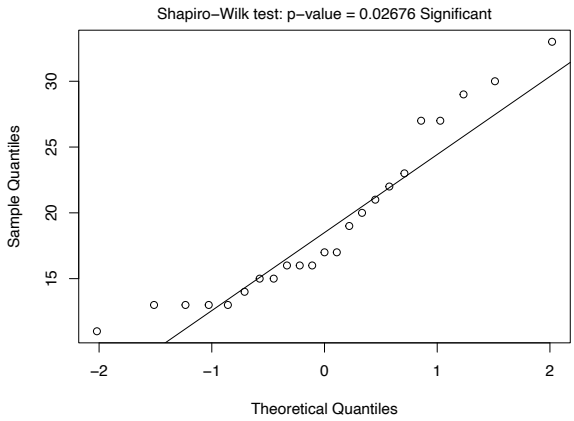
Appendix 3B. Figure 66

QQ Plot: MSPSQ Night Waking



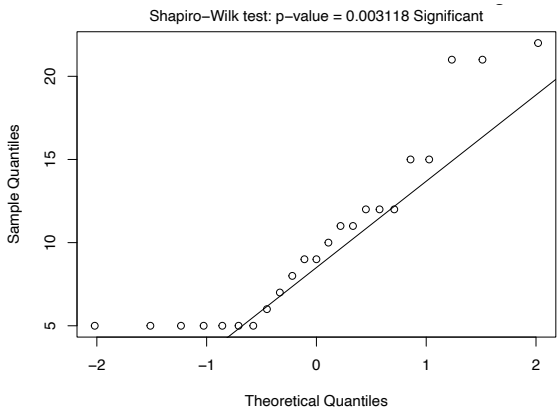
Appendix 3B. Figure 67

QQ Plot: MSPSQ Parasomnia



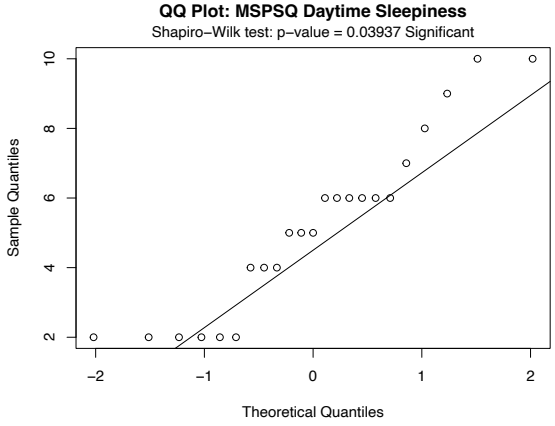
Appendix 3B. Figure 68

QQ Plot: MSPSQ Sleep Disordered Breathing



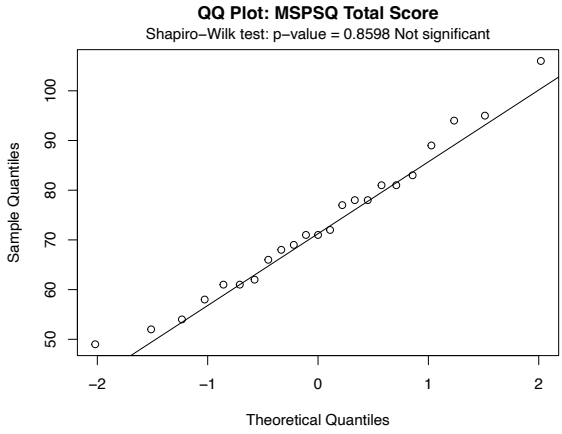
Appendix 3B. Figure 69

QQ Plot: MSPSQ Daytime Sleepiness



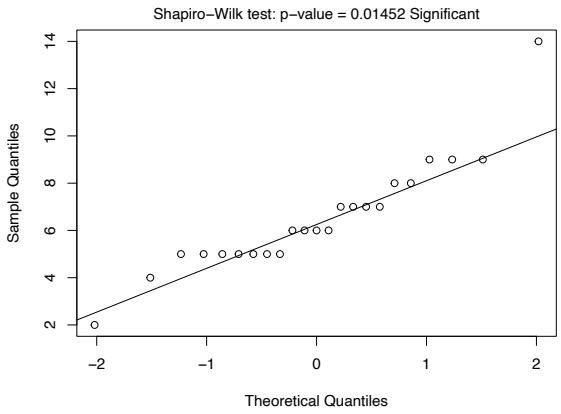
Appendix 3B. Figure 70

QQ Plot: MSPSQ Total Score



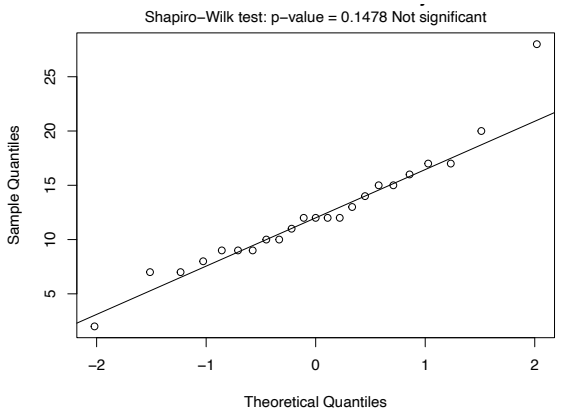
Appendix 3B. Figure 71

QQ Plot: HQ Total Number of Health Problems



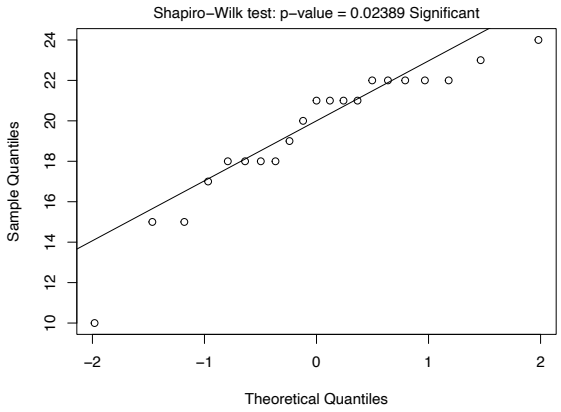
Appendix 3B. Figure 72

QQ Plot: HQ Total Health Severity Score



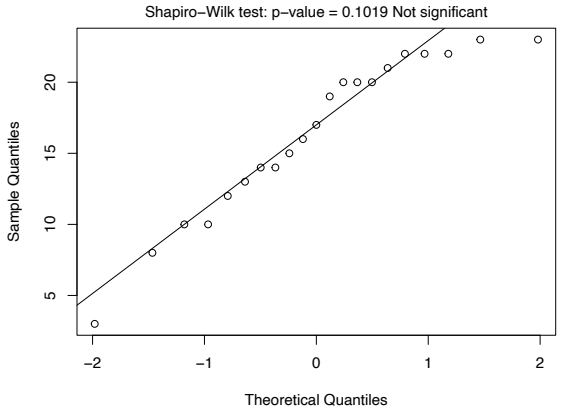
Appendix 3B. Figure 73

QQ Plot: MIPQ Mood



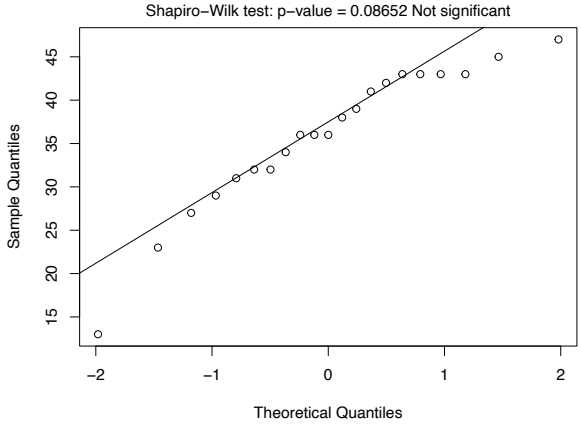
Appendix 3B. Figure 74

QQ Plot: MIPQ Interest and Pleasure



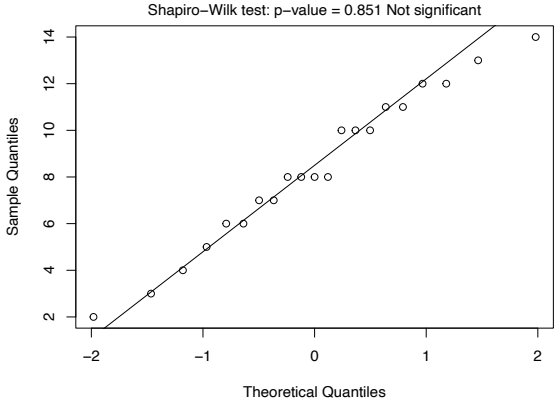
Appendix 3B. Figure 75

QQ Plot: MIPQ Total Score



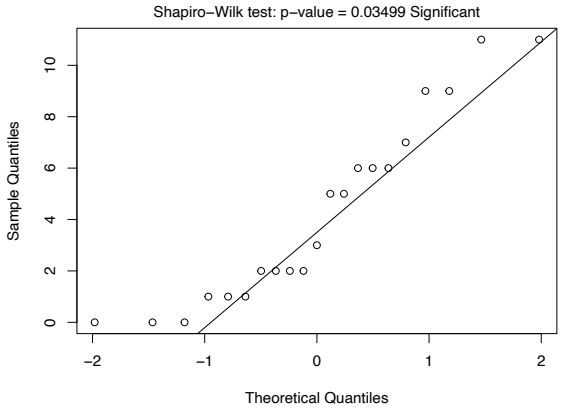
Appendix 3B. Figure 76

QQ Plot: ADAMS Manic Hyperactive Behaviour



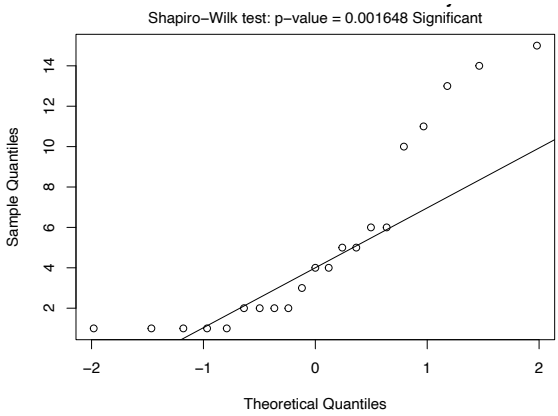
Appendix 3B. Figure 77

QQ Plot: ADAMS social avoidance



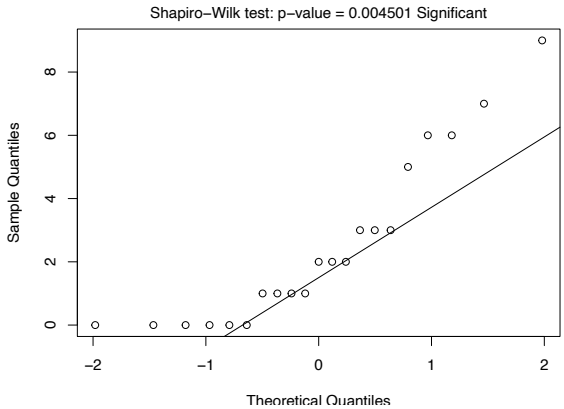
Appendix 3B. Figure 78

QQ Plot: ADAMS General Anxiety



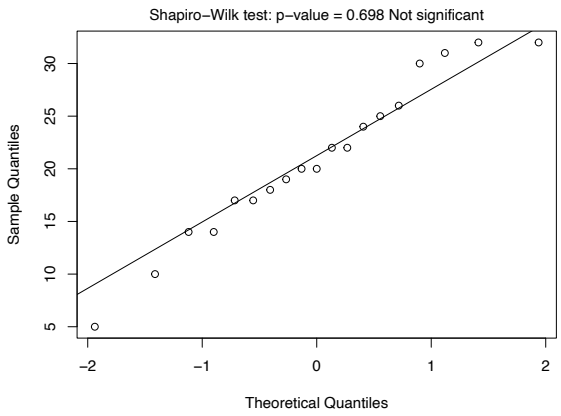
Appendix 3B. Figure 79

QQ Plot: ADAMS Compulsive Behaivour



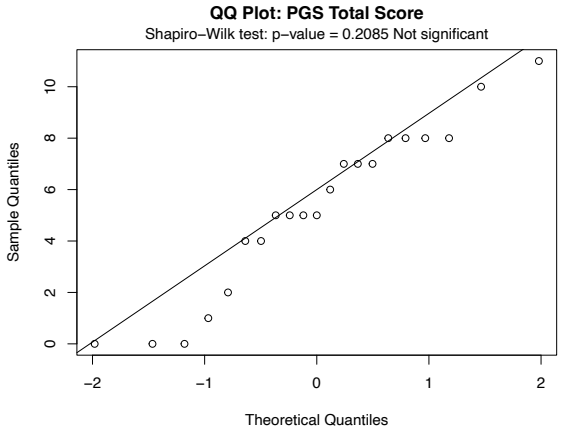
Appendix 3B. Figure 80

QQ Plot: HADS Total Score



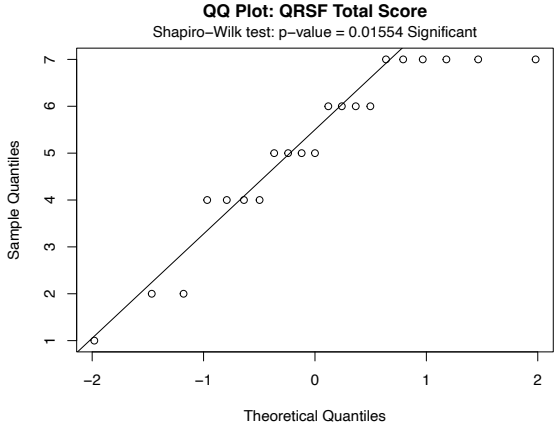
Appendix 3B. Figure 81

QQ Plot: PGS Total Score



Appendix 3B. Figure 82

QQ Plot: QRSF Total Score



Appendix 3C: Questionnaire Pack Distributed to Families

Background Questionnaire

Today's date: _____

Please answer the following about the person you care for:

1. Gender [assigned at birth]

Male o Female o

2. Date of Birth: ___/___/____

3. Age: _____

4. Please indicate which features of CHARGE syndrome the person you care for shows? (Please include any features your child was born with that have since have been treated)

- o CHD7
- o Coloboma
- o Choanal atresia
- o Missing or reduced sense of smell
- o Facial palsy
- o Feeding and swallowing difficulty
- o External ear anomalies
- o Middle ear anomalies
- o Inner ear anomalies
- o Hearing impairment
- o Heart defects
- o Growth deficiency
- o Genital abnormalities
- o Cleft lip or palate
- o Tracheoesophageal fistula
- o Urinary tract problems
- o Differences in the structure of the brain
- o Skeletal or limb anomalies
- o Developmental delay
- o Intellectual disability
- o Other features not listed here

Please specify the other features of CHARGE syndrome your child shows

_____

_____

5. When was the person you care for diagnosed? _____

6. What is the genetic mechanism causing CHARGE syndrome in the person you care for?

o Frame-shift variant o Missense variant

o Nonsense variant o Other

o Deletion o Unknown

7. Does the person you care for have any additional diagnosis other than CHARGE syndrome?

Yes o No o

If yes, please provide details of the additional diagnosis

_____

8. Who diagnosed the person you care for?

o Paediatrician o Clinical Geneticist

o GP o Other

If you selected other, please specify who diagnosed the person you care for

_____

9. Has the person you care for had any medical/health difficulties in the last six months?

Yes o No o

If yes, please provide details of the medical/health difficulties experienced

_____

_____

10. Is the person you care for verbal? (i.e. more than 30 signs/words in their vocabulary)

Yes o No o

If no, are there any alternative ways the person you care for communicates with you?

Yes o No o

Please describe the way the person you care for communicates with you

_____

_____

11. Is the person you care for able to walk unaided?

Yes o No o

12. Is the person you care for able to walk unaided when outdoors?

Yes o No o

If no, is the person you care for able to walk unaided when in a familiar indoor setting?

Yes o No o

If no, Does the person you care for have an alternative way of exploring their environment independently (for example using a walker, five-point-crawling or pushing themselves along the floor on their back)

Yes o No o

Please describe how the person you care for explores their environment

_____

_____

The following questions ask for background information about you and your family:

1. What was your age in years on your last birthday? _____

2. Please select the highest level of your educational qualifications

   - o No formal educational qualifications
   - o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma
   - o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent
   - o 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent
   - o Polytechnic/University degree, NVQ 4, or equivalent

o Masters/Doctoral degree, NVQ 5, or equivalent

3. What is your relationship to your child with CHARGE syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)? _____

4. In total how many people currently live in your home?

Children o Adults o

5. Does the person you care for normally live with you?

Yes o No o

If no, where do they live?

_____

6. What is your current marital status?

o Married, and living with spouse

o Living with partner

o Divorced/Separated/Widowed/Single and NOT living with a partner

If you are married / living with spouse / partner:

7. What was your partner/spouse's age in years on their last birthday? _____

8. Please select the highest level of your partner/spouse's educational qualifications

o No formal educational qualifications

o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma

o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent

o 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent

o Polytechnic/University degree, NVQ 4, or equivalent

o Masters/Doctoral degree, NVQ 5, or equivalent

9. What is your partner/spouse's relationship to your child with CHARGE syndrome (e.g., mother, father, stepmother, adoptive parent)? _____

Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences. However, we would like to reassure you that the question below is optional.

10. What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions. Please tick one box:

o Less than £15,000

o £15,001 to £25,000

o £25,001 to £35,000

o £35,001 to £45,000

o £45,001 to £55,000

o £55,001 to £65,000

o £65,001 or more

Please check your answers and go on to the next questionnair

WESSEX Questionnaire

These items refer to the person you care for. For each question (A, B, C, D etc …), please enter the appropriate code in each box.

A)	Wetting (nights)	**1** = frequently	**2** = occasionally	**3** = never	
B)	Soiling (nights)	**1** = frequently	**2** = occasionally	**3** = never	
C)	Wetting (days)	**1** = frequently	**2** = occasionally	**3** = never	
D)	Soiling (days)	**1** = frequently	**2** = occasionally	**3** = never	
E)	Walk with help*	**1** = not at all	**2** = not upstairs	**3** = upstairs and elsewhere	

*(note: if this person walks by himself/herself upstairs and elsewhere, please also code '3' for 'walk with help')

F)	Walk by himself	**1** = not at all	**2** = not upstairs	**3** = upstairs and elsewhere	
G)	Feed himself	**1** = not at all	**2** = with help	**3** = without help	
H)	Wash himself	**1** = not at all	**2** = with help	**3** = without help	
I)	Dress himself	**1** = not at all	**2** = with help	**3** = without help	
J)	Vision	**1** = blind or almost	**2** = poor	**3** = normal	
K)	Hearing	**1** = deaf or almost	**2** = poor	**3** = normal	
L)	Speech	**1** = never a word	**2** = odd words only		
		3 = sentences and normal	**4** = can talk but doesn't		

If this person talks in sentences, is his/her speech:

1 = Difficult to understand even by acquaintances, impossible for strangers?

2 = Easily understood for acquaintances, difficult for strangers?

3 = Clear enough to be understood by anyone?

M)	Reads	**1** = nothing	**2** = a little	**3** = newspapers and/or books	
N)	Writes	**1** = nothing	**2** = a little	**3** = own correspondence	
O)	Counts	**1** = nothing	**2** = a little	**3** = understands money values	

Please check your answers and go on to the next questionnaire.

WAISMAN ACTIVITIES OF DAILY LIVING SCALE (W-ADL)

Instructions: "We would like to know about your son or daughter's current level of independence in performing activities of daily living. For each activity please tell me the number which best describes your son/daughter's ability to do the task. For example, Independent would mean your son/daughter is able to do the

PLEASE RATE (name of child)'S LEVEL OF INDEPENDENCE IN...		**Ability to perform task**		
		does not do at all	**does with help**	**Independent or does on own**
1.	Making his/her own bed	**0**	**1**	**2**
2.	Doing household tasks, including picking up around the house, putting things away, light housecleaning, etc.	**0**	**1**	**2**
3.	Doing errands, including shopping in stores	**0**	**1**	**2**
4.	Doing home repairs, including simple repairs around the house, non-technical in nature; for example, changing light bulbs or repairing a loose screw	**0**	**1**	**2**
5.	Doing laundry, washing and drying	**0**	**1**	**2**
6.	Washing/bathing	**0**	**1**	**2**
7.	Grooming, brushing teeth, combing and/or brushing hair	**0**	**1**	**2**
8.	Dressing and undressing	**0**	**1**	**2**
9.	Toileting	**0**	**1**	**2**
10.	Preparing simple foods requiring no mixing or cooking, including sandwiches, cold cereal, etc.	**0**	**1**	**2**
11.	Mixing and cooking simple foods, fry eggs, make pancakes, heat food in microwave, etc.	**0**	**1**	**2**

12.	Preparing complete meal	**0**	**1**	**2**
13.	Setting and clearing table	**0**	**1**	**2**
14.	Drinking from a cup	**0**	**1**	**2**
15.	Eating from a plate	**0**	**1**	**2**
16.	Washing dishes (including using a dishwasher)	**0**	**1**	**2**
17.	Banking and managing daily finances, including keeping track of cash, checking account, paying bills, etc. (Note: if he/she can do a portion but not all circle '1' with help.)	**0**	**1**	**2**

Please check your answers and go on to the next questionnaire

Below is a list of statements. We would like to know if the person has had *problems* with these behaviours DURING THE PAST 6 MONTHS. Please answer *all the items* the best you can. Please do not skip any items. Think about the person as you read these statements and circle:

	During the past 6 months, how often has each of the following behaviours been a *problem*?	**Never**	**Sometimes**	**Often**
1.	Over-reacts to small problems	**N**	**S**	**O**
2.	When given two things to do, remembers only the first or last	**N**	**S**	**O**
3.	Is unaware of how his/her behaviour affects or bothers others	**N**	**S**	**O**
4.	When instructed to clean up, puts things away in a disorganised, random way	**N**	**S**	**O**
5.	Becomes upset with new situations	**N**	**S**	**O**
6.	Has explosive, angry outbursts	**N**	**S**	**O**
7.	Has trouble carrying out the actions needed to complete tasks (such as, trying one puzzle piece at a time, cleaning up to earn a reward)	**N**	**S**	**O**
8.	Does not stop laughing at funny things or events when others stop	**N**	**S**	**O**
9.	Needs to be told to begin a task even when willing to do it	**N**	**S**	**O**
10.	Has trouble adjusting to new people (such as babysitter, teacher, friend or day care worker)	**N**	**S**	**O**
11.	Becomes upset too easily	**N**	**S**	**O**
12.	Has trouble concentrating on games, puzzles or activities	**N**	**S**	**O**
13.	Has to be more closely supervised than similar peers	**N**	**S**	**O**
14.	When sent to get something, forgets what he/she is supposed to get	**N**	**S**	**O**
15.	Is upset by a change in plans or routine (for example, order of daily activities, adding last minute errands to schedule, change in driving route to shop)	**N**	**S**	**O**
16.	Has outbursts for little reason	**N**	**S**	**O**
17.	Repeats the same mistakes over and over even after help is given	**N**	**S**	**O**
18.	Acts wilder or sillier than others in groups (such as, birthday parties, class at school/college, family gatherings)	**N**	**S**	**O**
19.	Cannot find clothes, shoes, toys or books even when he/she has been given specific instructions	**N**	**S**	**O**

20.	Takes a long time to feel comfortable in new places or situations (such as visiting distant relatives or new friends)	**N**	**S**	**O**
21.	Mood changes frequently	**N**	**S**	**O**
22.	Makes silly mistakes on things he/she can do	**N**	**S**	**O**
23.	Is fidgety, restless or squirmy	**N**	**S**	**O**
24.	Has trouble following established routines for sleeping, eating or activities	**N**	**S**	**O**
25.	Is bothered by loud noises, bright lights or certain smells	**N**	**S**	**O**
26.	Small events trigger big reactions	**N**	**S**	**O**
27.	Has trouble with activities or tasks that have more than one step	**N**	**S**	**O**
28.	Is impulsive	**N**	**S**	**O**
29.	Has trouble thinking of a different way to solve a problem or complete an activity when stuck	**N**	**S**	**O**
30.	Is disturbed by changes in the environment (such as, new furniture, things in room moved around or new clothes)	**N**	**S**	**O**
31.	Angry or tearful outbursts are intensive but end suddenly	**N**	**S**	**O**
32.	Needs help from adult to stay on task	**N**	**S**	**O**
33.	Does not notice when his/her behaviour causes negative reactions	**N**	**S**	**O**
34.	Leaves messes that others have to clean up even after instruction	**N**	**S**	**O**
35.	Has trouble changing activities	**N**	**S**	**O**
36.	Reacts more strongly to situations than other peers	**N**	**S**	**O**
37.	Forgets what he/she is doing in the middle of an activity	**N**	**S**	**O**
38.	Does not realise that certain actions bother others	**N**	**S**	**O**
39.	Gets caught up in the small details of a task or situation and misses the main idea	**N**	**S**	**O**
40.	Has trouble “joining in” at unfamiliar social events (such as, birthday parties, picnics, holiday gatherings)	**N**	**S**	**O**
41.	Is easily overwhelmed or over stimulated by typical daily activities	**N**	**S**	**O**
42.	Has trouble finishing tasks (such as, games, puzzles or other activities)	**N**	**S**	**O**
43.	Gets out of control more than peers	**N**	**S**	**O**
44.	Cannot find things in room even when given specific instructions	**N**	**S**	**O**
45.	Resists change of routine, foods, places etc.	**N**	**S**	**O**
46.	After having a problem, will stay disappointed for a long time	**N**	**S**	**O**
47.	Cannot stay on the same topic when talking	**N**	**S**	**O**
48.	Talks or plays too loudly	**N**	**S**	**O**
49.	Does not complete tasks even after given directions	**N**	**S**	**O**

50.	Acts overwhelmed or over stimulated in crowded, busy situations (such as, lots of noise, activity or people)	**N**	**S**	**O**
51.	Has trouble getting started on activities or tasks even after instructed	**N**	**S**	**O**
52.	Acts too wild or out of control	**N**	**S**	**O**
53.	Does not try as hard as his/her ability on activities	**N**	**S**	**O**
54.	Has trouble putting the brakes on his/her actions even after being asked	**N**	**S**	**O**
55.	Unable to finish describing an event, person or story	**N**	**S**	**O**
56.	Completes tasks or activities too quickly	**N**	**S**	**O**
57.	Is unaware when he/she does well and not well	**N**	**S**	**O**
58.	Gets easily side-tracked during activities	**N**	**S**	**O**
59.	Has trouble remembering something, even after a brief period of time	**N**	**S**	**O**
60.	Becomes too silly	**N**	**S**	**O**
61.	Has a short attention span	**N**	**S**	**O**
62.	Behaves carelessly or recklessly in situations where he/she could be hurt (such as, playground, swimming pool)	**N**	**S**	**O**
63.	Is unaware when he/she performs a task right or wrong	**N**	**S**	**O**

Please check your answers and go on to the next questionnaire.

SOCIAL COMMUNICATION QUESTIONNAIRE

1. Is she/he now able to talk using short phrases or sentences? If no, skip to question 8.	**Yes** **No**
2. Do you have a to and fro "conversation" with her/him that involves taking turns or building on what you have said?	**Yes** **No**
3. Does she/he ever use odd phrases or say the same thing over and over in almost exactly the same way (either phrases she/he has heard other people use or ones that she/he makes up)?	**Yes** **No**
4. Does she/he ever use socially inappropriate questions or statements? For example, does she/he ever regularly ask personal questions or make personal comments at awkward times?	**Yes** **No**
5. Does she/he ever get her/his pronouns mixed up (e.g. saying *you* or *she/he* instead of *I*)	**Yes** **No**
6. Does she/he ever use words that she/he seems to have invented or made up her/himself; put things in odd, indirect ways; or use metaphorical ways of saying things (e.g. saying *hot rain* for *steam*)?	**Yes** **No**
7. Does she/he ever say the same thing over and over in exactly the same way, or insist that you say the same thing over and over again?	**Yes** **No**
8. Does she/he ever have things that she/he seems to have to do in a very particular way or order, or rituals that she/he insists that you go through?	**Yes** **No**
9. Does her/his facial expression usually seem appropriate to the particular situation, so far as you can tell?	**Yes** **No**
10. Does she/he ever use your hand like a tool, or as if it were part of her/his own body (e.g. pointing with your finger, putting your hand on a doorknob to get you to open the door)?	**Yes** **No**
11. Does she/he ever have any interests that preoccupy her/him and might seem odd to other people (e.g. traffic lights, drainpipes or timetables)?	**Yes** **No**
12. Does she/he ever seem to be more interested in parts of a toy or an object (e.g. spinning the wheels of a car), rather than using the object as it was intended?	**Yes** **No**
13. Does she/he ever have any special interests that are *unusual* in their intensity but otherwise appropriate for her/his age and peer group (e.g. trains, or dinosaurs)?	**Yes** **No**

14. Does she/he ever seem to be *unusually* interested in the sight, feel, sound, taste or smell of things or people?	**Yes** **No**
15. Does she/he ever have any mannerisms or odd ways of moving her/his hands or fingers, such as flapping or moving her/his fingers in front of her/his eyes?	**Yes** **No**
16. Does she/he ever have any complicated movements of her/his whole body, such as spinning or repeatedly bouncing up and down?	**Yes** **No**
17. Does she/he ever injure her/himself deliberately, such as by biting her/his arm or banging her/his head?	**Yes** **No**
18. Does she/he ever have any objects (*other* than a soft toy or comfort blanket) that she/he *has* to carry around?	**Yes** **No**
19. Does she/he have any particular friends or a best friend?	**Yes** **No**
20. Does she/he ever talk with you just to be friendly (rather than to get something)?	**Yes** **No**
21. Does she/he ever spontaneously copy you (or other people) or what you are doing (such as vacuuming, gardening or mending things)?	**Yes** **No**
22. Does she/he ever spontaneously point at things around her/him just to show you things (not because she/he wants them)?	**Yes** **No**
23. Does she/he ever use gestures, other than pointing or pulling your hand, to let you know what she/he wants?	**Yes** **No**
24. Does she/he nod her/his head to indicate *yes*?	**Yes** **No**
25. Does she/he shake her/his head to indicate *no*?	**Yes** **No**
26. Does she/he usually look at you directly in the face when doing things with you or talking with you?	**Yes** **No**
27. Does she/he smile back if someone smiles at her/him?	**Yes** **No**
28. Does she/he ever show you things that interest her/him to engage your attention?	**Yes** **No**

29. Does she/he ever offer to share things other than food with you?	**Yes** **No**
30. Does she/he ever seem to want you to join in her/his enjoyment of something?	**Yes** **No**
31. Does she/he ever try to comfort you if you are sad or hurt?	**Yes** **No**
32. If she/he wants something or wants help, does she/he look at you and use gestures with sounds or words to get your attention?	**Yes** **No**
33. Does she/he show a normal range of facial expressions?	**Yes** **No**
34. Does she/he ever spontaneously join in and try to copy the actions in social games, such as The Mulberry Bush or London Bridge is Falling Down?	**Yes** **No**
35. Does she/he play any pretend or make-believe games?	**Yes** **No**
36. Does she/he seem interested in other children whom she/he does not know?	**Yes** **No**
37. Does she/he respond positively when another child approaches her/him?	**Yes** **No**
38. If you come into a room and start talking to her/him without calling her/his name, does she/he usually look up and pay attention to you?	**Yes** **No**
39. Does she/he ever play imaginative games with another child in such a way that you can tell that each child understands what the other is pretending?	**Yes** **No**
40. Does she/he play cooperatively in games that need some form of joining in with a group of other children, such as hide-and-seek or ball games?	**Yes** **No**

Please check your answers and go on to the next questionnaire.

ACTIVITY QUESTIONNAIRE © C Burbidge and C Oliver (2003)

Instructions:

- **Please read each item carefully and circle the appropriate number on the scale, for the person you care for.**
- **Please ensure that you indicate a response for every item. If the particular behaviour does not apply, for example, if the person is not verbal or not mobile, please circle 0 on the scale.**

	Never/ almost never	Some of the time	Half of the time	A lot of the time	Always/ almost all the time
1. Does the person wriggle or squirm about when seated or lying down?	**0**	**1**	**2**	**3**	**4**
2. Does the person fidget or play with their hands and/or feet when seated or lying down?	**0**	**1**	**2**	**3**	**4**
3. Does the person find it difficult holding still?	**0**	**1**	**2**	**3**	**4**
4. Does the person find it difficult to remain in their seat even when in situations where it would be expected?	**0**	**1**	**2**	**3**	**4**
5. Does the person prefer to be moving around or become frustrated if left in one position for too long?	**0**	**1**	**2**	**3**	**4**
6. When the person is involved in a leisure activity (e.g. watching TV, playing a game etc.) do they make a lot	**0**	**1**	**2**	**3**	**4**
7. When the person is involved in an activity, are they boisterous and/or rough?	**0**	**1**	**2**	**3**	**4**
8. Does the person act as if they are "driven by a motor" (i.e. often very active)?	**0**	**1**	**2**	**3**	**4**
9. Does the person seem like they need very little rest to recharge their battery?	**0**	**1**	**2**	**3**	**4**
10. Does the person often talk excessively?	**0**	**1**	**2**	**3**	**4**

11. Does the person's behaviour seem difficult to manage/contain whilst out and about (e.g. in town, in supermarkets	**0**	**1**	**2**	**3**	**4**
12. Do you feel that you need to "keep an eye" on the person at all times?	**0**	**1**	**2**	**3**	**4**
13. Does the person you care for seem to act/do things without stopping to	**0**	**1**	**2**	**3**	**4**
14. Does the person blurt out answers before questions have been completed?	**0**	**1**	**2**	**3**	**4**
15. Does the person start to respond to instructions before they have been fully given or without seeming to understand them?	**0**	**1**	**2**	**3**	**4**
16. Does the person want things immediately?	**0**	**1**	**2**	**3**	**4**
17. Does the person find it difficult to	**0**	**1**	**2**	**3**	**4**
18. Does the person disturb others because they have difficulty waiting for things or waiting their turn?	**0**	**1**	**2**	**3**	**4**

Please check your answers and go on to the next questionnaire.

THE CHALLENGING BEHAVIOUR QUESTIONNAIRE (CBQ)

A) Has the person ever shown self-injurious behaviour (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing)?

Yes ☐ No ☐

1) Has the person shown self-injurious behaviour in the last month (e.g. head banging, head-punching or slapping, removing hair, self-scratching, body hitting, eye poking or pressing)?

Yes ☐ No ☐

If the behaviour has not occurred, please go to question 6.

If the behaviour occurred in the past month, please answer questions 2 to 5:

1a) Place a tick next to the item for any of the following list of behaviours which the person displays in a repetitive manner (repeats the same movement/ behaviour twice or more in succession):

Hits self with body part (e.g. slaps head or face) ……. ☐
☐

Hits self against surface or object (e.g. bangs head on floor or table)

Hits self with object…… ☐

Bites self (e.g. bites hand on wrist or arm) ……... ☐

Pulls (e.g. pulls hair or skin) ……... ☐

Rubs or scratches self (e.g. rub marks on arm or leg) ……..…. ☐

Inserts finger or objects (e.g. eye poking) …… ☐

Other form of self-injury, (please specify) _____

1b) In the last month, for how long did the **longest** episode or burst of this behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

1c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

1d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

B) Has the person ever shown aggression (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing)?

Yes ☐ No ☐

2) Has the person shown aggression in the last month (e.g. punching, pushing, kicking, pulling hair, grabbing other's clothing)?

Yes ☐ No ☐

2a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Hits other with body part (e.g. slapping, punching, kicking, head-butting) o

Hits other with an object (e.g. throwing object or using a weapon) ……... o

Bites other…… o

Pulls or grabs other (e.g. hair-pulling, grabbing clothing) ……... o

Rubs, pinches or scratches other ……..…….. o

Spits at other …… o

Verbal aggression (e.g. threatening, swearing) …… o

Other form of self-injury, (please specify) _____

2b) In the last month, for how long did the **longest** episode or burst of this behaviour last?

(Please circle one number)

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

2c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**
Never	At least once a month	At least once a week	At least once a day	At least once an hour

2d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

C) Has the person ever shown disruption and destruction of property or the environment (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal)?

Yes ☐ No ☐

3) Has the person shown disruption and destruction of property or the environment in the last month? (e.g. tearing or chewing own clothing, tearing newspapers, breaking windows or furniture, slamming doors, spoiling a meal)?

Yes ☐ No ☐

3a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Biting or chewing small objects (e.g. books, clothing) …… o

Tearing or ripping small items (e.g. books, clothing) ……..…….. o

Throwing, kicking or smashing small items (e.g. cups, mobile phones) .. o

Slamming, hitting, or kicking doors, walls or windows …… o

Tipping, smashing or throwing large items (e.g. furniture, televisions) … o

Pulling items from walls or shelves …… o

Verbal aggression (e.g. threatening, swearing) ……... o

Other form of disruption, (please specify) _____

3b) In the last month, for how long did the **longest** episode or burst of his behaviour last?

(Please circle one number)

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

3c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**

Never	At least once a month	At least once a week	At least once a day	At least once an hour

3d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

D) Has the person ever shown stereotyped behaviours? (e.g. rocking, twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing)?

Yes ☐ No ☐

4) Has the person shown stereotyped behaviours in the last month? (e.g. rocking, twiddling objects, patting or tapping part of the body, constant hand movements, eye pressing)?

Yes ☐ No ☐

4a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Full body movements (e.g. rocking, bouncing) …… o

Movement of an object (e.g. twiddling or spinning object) ……..... o

Movement of isolated body part (e.g. hand flapping, head shaking) …… o

Eye-pressing or visual regard of movement (e.g. strobing, spinning) ….. o

Mouthing or sucking on body part or object …….. o

Other form of disruption, (please specify) _____

4b) In the last month, for how long did the **longest** episode or burst of his behaviour last? *(Please circle one number)*

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

4c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	**1**	**2**	**3**	**4**

Never	At least once a month	At least once a week	At least once a day	At least once an hour

4d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	**2**	**3**	**4**	**5**
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

E) Has the person ever shown any other form of challenging behaviour?

Yes ☐ No ☐

5) Has the person shown any other form of challenging behaviour in the last month?

Yes ☐ No ☐

5a) Place a tick next to the item for any of the following list of behaviours which the person displays:

Pica (e.g. eating paper, leaves, discarded food) ……...o

Inappropriate vocalisations (e.g. screaming, shouting) ……..…….o

Removal of clothing (not for purpose of washing changing or toileting) ……o

Sexual behaviour (e.g. public masturbation, inappropriate sexual contact) ..o

Anal poking…….…….…….o

Smearing of bodily substance (non-accidental) …….o

Stealing ……..……..o

Self-induced vomiting …….o

Other form of disruption, (please specify) _____

5b) In the last month, for how long did the **longest** episode or burst of his behaviour last?

(Please circle one number)

1	**2**	**3**	**4**	**5**
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour

5c) In the last month as a result of this behaviour, has physical contact or prevention or restraint by others been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm? *(Please circle one number)*

0	1	2	3	4
Never	At least once a month	At least once a week	At least once a day	At least once an hour

5d) Think about how often this behaviour occurred in the last month. If there was no change and you watched the person now, then would you definitely see the behaviour:

1	2	3	4	5
By this time next month	By this time next week	By this time tomorrow	In the next hour	In the next 15 minutes

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THE RBQ

INSTRUCTIONS:

1. **The questionnaire asks about 19 different behaviours.**
2. **Each behaviour is accompanied by a brief definition and examples. The examples given for each behaviour are not necessarily a complete list but may help you to understand the definitions more fully.**
3. **Please read the definitions and examples carefully and circle the appropriate number on the scale to indicate how frequently the person you care for has engaged in each of the behaviours <u>WITHIN THE LAST MONTH.</u>**
4. **If a particular behaviour does not apply to the person you care for because they are not mobile or verbal please circle the number 0 on the scale**

	Never	Once a month	Once a week	Once a day	More than once a day
1. Object stereotypy: Repetitive, seemingly purposeless movement of objects in an unusual way *E.g. twirling or twiddling objects, twisting or shaking objects, banging or slapping objects.*	**0**	**1**	**2**	**3**	**4**
2. Body stereotypy: Repetitive, seemingly purposeless movement of whole body or part of body (other than hands) in an unusual way. *E.g. body rocking, or swaying or spinning, bouncing, head shaking, body posturing.* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
3. Hand stereotypy: Repetitive, seemingly purposeless movement of hands in an unusual way. *E.g. finger twiddling, hand flapping, wiggling or flicking fingers, hand posturing.* Does not include self-injurious behaviour.	**0**	**1**	**2**	**3**	**4**
4. Cleaning: Excessive cleaning, washing or polishing of objects or parts of the body *E.g. polishes windows and surfaces excessively, washes hands and face excessively.*	**0**	**1**	**2**	**3**	**4**

5. Tidying up: Tidying away any objects that have been left out. This may occur in situations when it is inappropriate to put the objects away. Objects may be put away into inappropriate places. *E.g. putting cutlery left out for dinner in the bin, removes all objects from surfaces.*	**0**	**1**	**2**	**3**	**4**
6. Hoarding: Collecting, storing or hiding objects to excess, including rubbish, bits of paper, and pieces of string or any other unusual items.	**0**	**1**	**2**	**3**	**4**
7. Organising objects: Organising objects into categories according to various characteristics such as colour, size, or function. *E.g. ordering magazines according to size, ordering toy cars according to colour, ordering books according to topic.*	**0**	**1**	**2**	**3**	**4**
8. Attachment to particular people: Continually asking to see, speak or contact a particular 'favourite' person. *E.g. continually asks to see or speak to particular friend, carer, babysitter or schoolteacher.*	**0**	**1**	**2**	**3**	**4**
9. Repetitive questions: Asking specific questions over and over. *E.g. always asking people what their favourite colour is, asking who is taking them to school the next day over and over.*	**0**	**1**	**2**	**3**	**4**
10. Attachment to objects: Strong preference for a particular object to be present at all times. *E.g. carrying a particular piece of string everywhere, taking a particular red toy car everywhere, attachment to soft toy or particular blanket.*	**0**	**1**	**2**	**3**	**4**
11. Repetitive phrases/signing: Repeating particular sounds, phrases or signs that are unrelated to the situation over and over. *E.g. repeatedly signing the word 'telephone'.*	**0**	**1**	**2**	**3**	**4**
12. Rituals: carrying out a sequence of unusual or bizarre actions before, during or after a task. The sequence will always be carried out when performing this task and will always occur in the same way. *E.g. turning round three times before sitting down, turning lights on and off twice before leaving a room, tapping door frame twice when passing through it.*	**0**	**1**	**2**	**3**	**4**

13. Restricted conversation: Repeatedly talks about specific, unusual topics in great detail. *E.g. conversation restricted to: trains, buses, dinosaurs, particular film, country or sport.*	**0**	**1**	**2**	**3**	**4**
14. Echolalia: Repetition of speech that has either just been heard or has been heard more than a minute earlier. *E.g. Mum: ' Jack don't do that' Jack: 'Jack don't do that'.*	**0**	**1**	**2**	**3**	**4**
15. Preference for routine: Insists on having the same household, school or work schedule everyday. *E.g. likes to have the same activities on the same day at the same time each week, prefers to eat lunch at exactly the same time every day, wearing the same jumper everyday.*	**0**	**1**	**2**	**3**	**4**
16. Lining up or arranging objects: Arrangement of objects into lines or patterns. *E.g. placing toy cars in a symmetrical pattern, precisely lining up story books.*	**0**	**1**	**2**	**3**	**4**
17. Just right behaviour: Strong insistence that objects, furniture and toys always remain in the same place. *E.g. all chairs, pictures and toys have a very specific place that cannot be changed.*	**0**	**1**	**2**	**3**	**4**
18. Completing behaviour: Insists on having objects or activities 'complete' or 'whole'. *E.g. Must have doors open or closed not in between, story must be read from beginning to end, not left halfway through.*	**0**	**1**	**2**	**3**	**4**
19. Spotless behaviour: Removing small, almost unnoticeable pieces of lint, fluff, crumbs or dirt from surfaces, clothes and objects. *E.g. picking fluff off a jumper, removing crumbs from the kitchen table.*	**0**	**1**	**2**	**3**	**4**

Please check your answers and go on to the next questionnaire.

MOOD, INTEREST AND PLEASURE QUESTIONNAIRE

This questionnaire contains 12 questions – <u>you should complete all 12 questions</u>. Each question will ask for your opinion about particular behaviours, which you have observed in the <u>LAST 2 WEEKS</u>. For every question you should circle <u>the most appropriate</u> response e.g.

6) In the LAST TWO WEEKS, how interested did the person appear to be in his/her surroundings?

interested all of the time	***interested most of the time***	***interested about half of the time***	***interested some of the time***	***never interested***

1) In the last two weeks, did the person seem…

sad all of the time	sad most of the time	sad about half of the time	sad some of the time	never sad

Please comment if anything has happened in the last two weeks which you feel might explain sadness if it has been observed (e.g. a bereavement):

_____

_____

2) In the last two weeks, how often did you hear positive vocalizations* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

<u>*positive vocalizations</u>: e.g. laughing, giggling, "excited sounds" etc.
*<u>engaged in activities</u>: i.e. when someone is actively involved in any activity such as a mealtime, a social interaction, a self-care task or social outing etc.

3) In the last two weeks, do you think the facial expression of the person looked "flat"*…

all of the time	most of the the time	about half of the time	some of the time	never

*flat expression: expression seems lifeless; lacks emotional expression; seems unresponsive.

4) In the last two weeks, would you say the person…

cried every day	cried nearly every day	cried 3-4 times each week	cried once or twice each week	cried less than once each week

5) In the last two weeks, how interested did the person appear to be in his/her surroundings?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

6) In the last two weeks, did the person seem to have been enjoying life…

all of the time	most of the the time	about half of the time	some of the time	never

Please comment if there are any reasons why this person might not have been enjoying him/herself e.g. illness, being in pain, experiencing a loss etc.:

_____

---

7) In the last two weeks, would you say the person smiled…

at least once every day	at least once nearly every day	3-4 times each week	once or twice each week	less than once each week

8) In the last two weeks, how disinterested did the person seem to be in his/her surroundings?

disinterested all of the time	disinterested most of the time	disinterested about half of the time	disinterested some of the time	never disinterested

9) In the last two weeks, when the person was engaged in activities*, to what extent did his/her facial expressions* suggest that s/he was interested in the activity?

interested all of the time	interested most of the time	interested about half of the time	interested some of the time	never interested

*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.
*facial expressions: interest might be indicated by the degree to which the person's gaze is being directed at the person/things involved in an activity.

10) In the last two weeks, would you say that the person…

laughed every day	laughed nearly every day	laughed 3-4 times each week	laughed once or twice each week	laughed less than once each week

11) In the last two weeks, how often did you see gestures which appeared to demonstrate enjoyment* when the person was engaged in activities*?

all of the time	most of the the time	about half of the time	some of the time	never

*gestures which appear to demonstrate enjoyment: e.g. clapping, waving hands in excitement etc.
*engaged in activities: i.e. when someone is actively involved in any activity such as a mealtime, social interaction, self-care task or social outing etc.

12) In the last two weeks, did the person's vocalizations* sound distressed…

all of the time	most of the the time	about half of the time	some of the time	never

*vocalizations: any words, noises or utterances.

Please feel free to make any additional comments about the behaviour of the person over the last two weeks (continue overleaf if necessary):

Please check your answers and go on to the next questionnaire.

THE ANXIETY DEPRESSION AND MOOD SCALE (ADAMS)

Instructions The Anxiety Depression and Mood Scale (ADAMS) contains a list of behaviors that can be found among individuals with intellectual disability. Please describe the individual's behavior over the last 6 months.

0	behavior has not occurred, or is not a problem
1	behavior occurs occasionally, or is a mild problem
2	behavior occurs quite often, or is a moderate problem
3	behavior occurs a lot, or is a severe problem

		Not a problem	Mild problem	Moderate problem	Severe problem
1.	Nervous	**0**	**1**	**2**	**3**
2.	Problems initiating communication	**0**	**1**	**2**	**3**
3.	Does not relax or settle down . .	**0**	**1**	**2**	**3**
4.	Has periods of over-activity	**0**	**1**	**2**	**3**
5.	Sleeps more than normal	**0**	**1**	**2**	**3**
6.	Withdraws from other people . . .	**0**	**1**	**2**	**3**
7.	Tense	**0**	**1**	**2**	**3**
8.	Engages in ritualistic behaviors .	**0**	**1**	**2**	**3**
9.	Depressed mood	**0**	**1**	**2**	**3**
10.	Sad	**0**	**1**	**2**	**3**
11.	Worried	**0**	**1**	**2**	**3**
12.	Has developed difficulty staying on task or completing work …….	**0**	**1**	**2**	**3**
13.	Shy	**0**	**1**	**2**	**3**
14.	Easily fatigued (not due to being overweight). . . . . …….	**0**	**1**	**2**	**3**
15.	Anxious	**0**	**1**	**2**	**3**
16.	Repeatedly checks items	**0**	**1**	**2**	**3**

17.	Easily distracted	**0**	**1**	**2**	**3**
18.	Lacks energy	**0**	**1**	**2**	**3**
19.	Avoids others, spends much of time alone	**0**	**1**	**2**	**3**
20.	Easily upset if ritualistic behaviors are interrupted	**0**	**1**	**2**	**3**
21.	Lacks emotional facial expressions	**0**	**1**	**2**	**3**
22.	Has shown difficulty in starting routine tasks	**0**	**1**	**2**	**3**
23.	Listless	**0**	**1**	**2**	**3**
24.	Experiences panic attacks	**0**	**1**	**2**	**3**
25.	Avoids eye contact	**0**	**1**	**2**	**3**
26.	Trembles when frightening situations are not present	**0**	**1**	**2**	**3**
27.	Avoids peers	**0**	**1**	**2**	**3**
28.	Tearful	**0**	**1**	**2**	**3**

Please check your answers and go on to the next questionnaire

The GDQ

Instructions:

- This questionnaire asks about behaviours sometimes shown by people with learning disabilities.
- Please read the questions and examples carefully and indicate how often each behaviour has occurred in the **last two weeks** by circling the appropriate answer.

Does the person you care for:	**More than once an hour**	**Once an hour**	**Once a day**	**Once a week**	**Not occurred**
1. Arch his/her back, lie over arms of chairs or people on his/her back?.....	**4**	**3**	**2**	**1**	**0**
2. Lie over an object on his/her stomach? e.g. a side of an armchair. …….	**4**	**3**	**2**	**1**	**0**
3. Salivate excessively?	**4**	**3**	**2**	**1**	**0**
4. Fidget, wriggle or move their body a great deal?	**4**	**3**	**2**	**1**	**0**
5. Place their hands or fingers in back of their mouth?	**4**	**3**	**2**	**1**	**0**
6. Chew on his/her clothes, fingers, hands or other parts of the body, objects or material?	**4**	**3**	**2**	**1**	**0**
7. Grind their teeth?	**4**	**3**	**2**	**1**	**0**
8. Scratch, hit, press or rub around the upper chest or throat?	**4**	**3**	**2**	**1**	**0**
9. Drink, request or seek out an excessive amount of fluids?	**4**	**3**	**2**	**1**	**0**
10. Cough, gag or regurgitate?	**4**	**3**	**2**	**1**	**0**
11. Appear in pain or discomfort (cry, groan or moan)?	**4**	**3**	**2**	**1**	**0**
12. Refuse food even though they are probably hungry?	**4**	**3**	**2**	**1**	**0**

13. Does the person you care for appear indecisive about food (edging towards table or food then moving away repeatedly, taking food and putting it back)? **Yes** ☐ **No** ☐

14. Does the person you care for wake during the night?	**Never**	**Once a week**	**Most nights**	**Every night**
15. Does the person you care for sleep sitting or propped up?	**Never**	**Once a week**	**Most nights**	**Every night**

16. Does the person you care for seem to have bad breath?

Never	**Once a week**	**At the same time everyday**	**All day every day**

17. Has the person you care for prone to respiratory tract infections? **Yes** ☐ **No** ☐

If 'yes' please indicate how often they occur:	**Monthly**	**Quarterly**	**Every six months**	**Annually**

Other (please specify) _____

Please check your answers and go on to the next questionnaire

MODIFIED SIMONDS & PARRAGA SLEEP QUESTIONNAIRE (MSPSQ)

PART 1

Instructions: Please tick either **YES** or **NO**, tick one of the boxes or, where appropriate, write your answer.

We would be grateful for the following information about your child:

Hight of your child: _____

Weight of your child: _____

Has your child had any excessive weight gain in the last six months **Yes** o **No** o

Has your child had any excessive weight loss in the last six months **Yes** o **No** o

1. Does your child have a room of their own? **Yes** o **No** o

2. How many other children sleep in the same room as your child? _____

3. Would you normally be likely to know if your child was awake either in the evening when going to sleep, or in the night or in the morning? **Yes** o **No** o

4. Does your child have a bedtime routine that is followed every night? e.g. supper, bath, drink, story, kiss, goodnight, light out etc. **Yes** o **No** o

4a. If yes, please describe _____

---

5. How often does your child resist or struggle with you around bedtime?

o Never

o About once a month

o A few times a month

o One or two times a week

o Many times a week

o Daily

6. How long does it take for your child to fall asleep at night?

o Few minutes

o Up to half an hour

o Up to one hour

o One to two hours

o More than two hours

7. If your child will not go to bed or settle to sleep what do you do about it?

---

8. Once asleep does he/she sleep soundly? **Yes** o **No** o

9. Where does your child usually fall asleep?

o His/her bedroom

o Parent's bedroom

o Sibling's bedroom

o Family/living room

o More than two hours

10. How often does your child wake up during the night?

o Never

o About once a month

o A few times a month

o One or two times a week

o Many times a week

o Daily

11. If your child usually wakes at night, how many times does your child usually wake each night? ____

12. How long does it take your child to fall back asleep?
o Few minutes

o Up to half an hour

o Up to one hour

o One to two hours

o More than two hours

13. What does your child do before getting back to sleep again?
o Nothing

o Crying

o Calling out

o Wandering about

o Playing with toys

o Looking at books and magazines

o Other (please specify) _____

14. Do you take any special steps to ensure that your child is safe if he/she wakes up during the night **Yes** o **No** o
14a. If yes, please describe _____

15. Is your child a light sleeper (i.e. any noise will wake him/her)? **Yes** o **No** o

16. Does your child report any dreams? **Yes** o **No** o

17. If he/she reports and dreams, are they generally pleasant? **Yes** o **No** o

18. If he/she reports and dreams, are they generally unpleasant? **Yes** o **No** o

19. Does your child ever sleep in unusual positions? **Yes** o **No** o
19a. If yes, please describe _____

20. If your child was not woken or did not have to get up in the morning, until what time would he/she sleep? ____

PART 2

Some children sleep differently during the week than on weekends or school holidays. Please answer the following questions about how your child has been

	Weekdays	**Weekends and Holidays**
1. What time do you start getting your child ready for bed?		
2. What time does your child usually go to bed?		
3. What time does your child usually go to sleep?		
4. What time does your child usually wake up?		
5. What time does your child usually get up?		

	Weekdays		**Weekends and Holidays**	
6. Does your child have to be woken in the morning?	**Yes** o	**No** o	**Yes** o	**No** o
7. Does your child usually wake up in the morning well rested?	**Yes** o	**No** o	**Yes** o	**No** o
8. Does your child usually wake up in the morning feeling quite tired?	**Yes** o	**No** o	**Yes** o	**No** o
9. Does he/she usually wake up in a bad mood?	**Yes** o	**No** o	**Yes** o	**No** o

10. Does he/she usually wake up in a good mood?	**Yes**	o	**No**	o	**Yes**	o	**No**	o
11. Does your child take naps during the day?	**Yes**	o	**No**	o	**Yes**	o	**No**	o

PART 3

During the **LAST ONE MONTH** has your child show any of the following

	Never	**About once a month**	**A few times a month**	**Once or twice a week**	**Many times a week**	**Daily**
21. Talks in sleep	**m**	**m**	**m**	**m**	**m**	**m**
22. Walks in sleep	**m**	**m**	**m**	**m**	**m**	**m**
23. Grinds teeth in sleep	**m**	**m**	**m**	**m**	**m**	**m**
24. Bangs head at night	**m**	**m**	**m**	**m**	**m**	**m**
25. Has quick movements of arms or legs during sleep (e.g. kicking, jumping, arm flapping)	**m**	**m**	**m**	**m**	**m**	**m**
27. Bites tongue in sleep	**m**	**m**	**m**	**m**	**m**	**m**
28. Snores loudly during sleep	**m**	**m**	**m**	**m**	**m**	**m**
29. Seems to repeatedly stop breathing for periods of time lasting up to 30 seconds during sleep	**m**	**m**	**m**	**m**	**m**	**m**
30. Wets bed during sleep	**m**	**m**	**m**	**m**	**m**	**m**
31. Wakes in night complaining of nightmares or frightening dreams and seems quite anxious. This	**m**	**m**	**m**	**m**	**m**	**m**

	Never	About once a month	A few times a month	Once or twice a week	Many times a week	Daily
usually happens in the last half of the night						
32. Wakes during the night screaming in terror. Anxiety may be so bad that sweating, gasping or trembling may happen. This usually happens in the first half of the night. He/she is not aware of their surroundings and will not remember it the next day	**m**	**m**	**m**	**m**	**m**	**m**
33. Doesn't want to go to bed because he/she is afraid	**m**	**m**	**m**	**m**	**m**	**m**
34. Expresses fear that if he/she goes to sleep they might die	**m**	**m**	**m**	**m**	**m**	**m**
35. Insists on seeping somewhere else instead of his/he bed	**m**	**m**	**m**	**m**	**m**	**m**
36. Afraid of the dark	**m**	**m**	**m**	**m**	**m**	**m**
37. Needs security blanket (e.g. teddy bear) before he/she goes to sleep	**m**	**m**	**m**	**m**	**m**	**m**
38. Insists on bedtime rituals (e.g. bedtime story) before sleep	**m**	**m**	**m**	**m**	**m**	**m**
39. Needs sleep medication	**m**	**m**	**m**	**m**	**m**	**m**
40. During the day, muscles become so weak the he/she falls to the ground or has to lie down before falling (usually after laughing, crying or being frightened)	**m**	**m**	**m**	**m**	**m**	**m**

	Never	About once a month	A few times a month	Once or twice a week	Many times a week	Daily
41. Upon waking or going to sleep, feels paralysed even though he/she is aware of their surroundings	**m**	**m**	**m**	**m**	**m**	**m**
43. Seems drowsy during the day, but can stop himself/herself sleeping	**m**	**m**	**m**	**m**	**m**	**m**
44. During the day, seems more active than other children	**m**	**m**	**m**	**m**	**m**	**m**
45. Rolls from side to side rhythmically in sleep or while going off to sleep	**m**	**m**	**m**	**m**	**m**	**m**
46. Sleeps with head tipped right back	**m**	**m**	**m**	**m**	**m**	**m**
47. Breaths through mouth rather than nose when asleep	**m**	**m**	**m**	**m**	**m**	**m**
48. Complains of headaches on waking up	**m**	**m**	**m**	**m**	**m**	**m**
49. Sweats a lot during sleep	**m**	**m**	**m**	**m**	**m**	**m**
50. Reluctant to go to bed	**m**	**m**	**m**	**m**	**m**	**m**
51. Wakes in the morning before 5am and stays awake	**m**	**m**	**m**	**m**	**m**	**m**
52. Insists on sleeping with someone else at sleep onset/in night	**m**	**m**	**m**	**m**	**m**	**m**

PART 4

This section asks some questions about treatments for sleep problems you might have tried and also the family's sleep.

1. In your opinion does your child have a sleep problem? **Yes** o **No** o

If yes, please go to question 5

If no, in your opinion has your child had a sleep problem in the past? **Yes** o **No** o

If no, please go to question 8

2. What would you say this problem was (multiple answers possible)

o Difficulty falling asleep

o Night waking

o Early waking

o Feeling sleepy during the day

o Doesn't want to sleep alone

Other (please specify) _____

3. Until when did these problems last?

o Up to 1 month ago

o 1 to 3 months ago

o 3 to 6 months ago

o 6 months to 1 year ago

o More than 1 year ago

If more than 1 year ago, please specify Year(s) ☐ Month(s) ☐ Ago

4. How long did the problems last? From (month /year) ☐ Until (month/year) ☐

5. What would you say this problem is (multiple answers possible)?

o Difficulty falling asleep

o Night waking

o Early waking

o Feeling sleepy during the day

o Doesn't want to sleep alone

Other (please specify) _____

6. At the moment, how long have these problems lasted?

o Up to 1 month ago

o 1 to 3 months ago

o 3 to 6 months ago

o 6 months to 1 year ago

o More than 1 year ago

7. In your opinion, what causes your child's sleep problems _____

_____

8. Have you ever had any advice or treatment for your child's sleep? **Yes** o **No** o

If no, please go to question 9

If YES, please select type of advice or treatment and its effectiveness.
Treatment is considered effective when it results in a substantial reduction or elimination of the sleep problems.

Education/general advice **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - operation **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - medication **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - other **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Psychological (e.g. behavioural treatment) **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

9. Are you affected by your child's sleep pattern? **Yes** o **No** o

If no, please go to question 10

If yes, how does this affect you (multiple answers possible)?

o Disrupted in sleep by child

o Fatigue due to child's sleep problem

o Memory problems

o Decline in concentration

o Feelings of irritation

o Feelings of aggression

o Feeling depressed

o Arguments with partner

o Feeling powerless

o Other (please specify) _____

10. Are other members of the family affected by your child's sleep pattern? **Yes** o **No** o

If no, please go to question 11

If yes, who and how are they affected (multiple answers possible)?

	Father/ Mother	Brother/ Sister 1	Brother/ Sister 2	Brother/ Sister 3	Other
Disturbed sleep					
Fatigue					
Memory problems					
Decline in concentration					
Feelings of irritation					
Feelings of aggression					
Feeling depressed					
Feeling powerless					
Other _____					
Other _____					

11. Has anyone on either side of the family had any sleep problems (e.g. nightmares, sleepwalking, night terrors, unusual jerks or movements, or other attacks)? **Yes** o **No** o

If yes, please specify _____

12. Does anyone on either side of the family experience restless legs when falling asleep (crawling or aching feelings in legs, unable to keep legs still, having to get out of bed to ease aching legs)? **Yes** o **No** o

If yes, please specify _____

13. Does anyone on either side of the family startle or jerk their arms or legs in a rhythmic way, whilst asleep? **Yes** o **No** o

If yes, please specify _____

14. Is there anything else about your child's sleep, or anything else, that you think is important and we have not mentioned? Please give details below

_____

_____

_____

_____

_____

_____

_____

Please check your answers and go on to the next questionnaire

HEALTH QUESTIONNAIRE

PART A: Instructions:

- Have these problems **EVER** affected your child or person you care for?
- Please rate as **0** – if the problem has never affected the person you care for, **1** – if it has been a mild problem, **2** - if the problem has been moderately serious, or **3** – if the problem has been severe.
- If the person you care for has had these problems, please state whether any treatment has been implemented by circling **yes** or **no**.

	Never	Mild	Moderate	Severe
1a. Eye Problems (e.g. glaucoma / blocked tear duct/s)	**0**	**1**	**2**	**3**
1b. Corrective surgery / medication / treatment:	**yes / no**			
2a. Ear Problems (e.g. infections, glue ear)	**0**	**1**	**2**	**3**
2b. Corrective surgery / medication / treatment (e.g. grommets):	**yes / no**			
3a. Dental Problems (e.g. toothache / gum problems / mouth ulcers / delayed eruption of teeth)	**0**	**1**	**2**	**3**
3b. Dental surgery / treatment (e.g. teeth removal):	**yes / no**			
4a. Cleft Palate	**0**	**1**	**2**	**3**
4b. Repaired:	**yes / no**			
5a. Gastrointestinal Difficulties (e.g. reflux / stomach problems)	**0**	**1**	**2**	**3**
5b. Corrective surgery / medication / treatment (e.g. Nissen fundoplication):	**yes / no**			
6a. Bowel Problems (e.g. obstruction)	**0**	**1**	**2**	**3**
6b. Corrective surgery / treatment:	**yes / no**			
7a. Heart Abnormalities or Circulatory Problems (e.g. congenital heart lesions or murmur)	**0**	**1**	**2**	**3**

7b. Corrective surgery / medication / treatment:	**yes / no**			
8a. Problems with Genitalia (e.g. prostate/ testicular problems i.e. undescended testes)	**0**	**1**	**2**	**3**
8b. Corrective surgery / treatment:	**yes / no**			
9a. Hernia (e.g. inguinal or hiatal)	**0**	**1**	**2**	**3**
9b. Repair / treatment:	**yes / no**			
10. Limb Abnormalities (e.g. malformed arm)	**0**	**1**	**2**	**3**
11a. Epilepsy / Seizures / Neurological Referrals	**0**	**1**	**2**	**3**
11b. Medication:	**yes / no**			
12a. Lung or Respiratory Problems (asthma/bronchitis)	**0**	**1**	**2**	**3**
12b. Corrective surgery / medication / treatment:	**yes / no**			
13a. Liver or Kidney Problems	**0**	**1**	**2**	**3**
13b. Corrective surgery / medication / treatment:	**yes / no**			
14a. Diabetes or Thyroid Function Problems	**0**	**1**	**2**	**3**
14b. Corrective surgery / medication / treatment:	**yes / no**			
15a. Skin Problems (e.g. tinea, eczema, psoriasis, dry skin)	**0**	**1**	**2**	**3**
15b. Medication / treatment:	**yes / no**			
16a. Other (please specify problem, severity from 0-3)	**0**	**1**	**2**	**3**
16b. Corrective surgery / medication / treatment:	**yes / no**			

PART B: Instructions:

- Have these medical problems affected the person you care for in the **PAST MONTH?**
- Please rate as **0** – if your child has not been affected by this problem in the past month, **1 -** if they have been mildly affected, **2** – if the problem has moderately affected your child and **3** - if your child has been severely affected by the problem.

	No	Mild	Moderate	Severe
1. Eye problems (e.g. glaucoma/blocked tear duct/s)	**0**	**1**	**2**	**3**
2. Ear problems (e.g. infections, glue ear)	**0**	**1**	**2**	**3**
3. Dental problems (e.g. toothache/gum problems/mouth ulcers/delayed eruption of teeth)	**0**	**1**	**2**	**3**
4. Cleft palate	**0**	**1**	**2**	**3**
5. Gastrointestinal difficulties (e.g. reflux/stomach problems)	**0**	**1**	**2**	**3**
6. Bowel problems (e.g. obstruction)	**0**	**1**	**2**	**3**
7. Heart abnormalities or circulatory problems (e.g. congenital heart lesions or murmur)	**0**	**1**	**2**	**3**
8. Problems with genitalia (e.g. prostate/testicular problems i.e. undescended testes)	**0**	**1**	**2**	**3**
9. Hernia (e.g. inguinal or hiatal)	**0**	**1**	**2**	**3**
10. Limb abnormalities (e.g. malformed arm)	**0**	**1**	**2**	**3**
11. Epilepsy/seizures/neurological referrals	**0**	**1**	**2**	**3**
12. Lung or respiratory problems (asthma/bronchitis)	**0**	**1**	**2**	**3**
13. Liver or kidney problems	**0**	**1**	**2**	**3**
14. Diabetes or thyroid function problems	**0**	**1**	**2**	**3**
15. Skin problems (e.g. tinea/eczema/psoriasis/dry skin)	**0**	**1**	**2**	**3**
16. Other (please specify problem and severity from 0-3)	**0**	**1**	**2**	**3**

Please check your answers and go on to the next questionnaire

YOUR FEELINGS AND EMOTIONS

The following questions focus on how *you* feel about things. Please read each item and circle the reply underneath the item which comes closest to how you have been feeling in the past week. Do not take too long over your replies; your immediate reaction to each item will probably be more accurate than a long thought-out response.

1. I feel tense or 'wound up'

Most of the time | A lot of the time | From time to time | Not at all

2. I still enjoy the things I used to enjoy

Definitely as much | Not quite so much | Only a little | Hardly at all

3. I get a sort of frightened feeling as if something awful is going to happen

Very definitely and quite badly | Yes, but not too bad | A little, but it doesn't worry me | Not at all

4. I can laugh and see the funny side of things

As much as I always could | Not quite so much now | Definitely not so much now | Not at all

5. Worrying thoughts go through my mind

A great deal of the time | A lot of the time | From time to time but not too often | Only occasionally

6 I feel cheerful

Not at all | Not often | Sometimes | Most of the time

7. I can sit at ease and feel relaxed

Definitely | Usually | Not often | Not at all

8. I feel as if I am slowed down

Nearly all the time | Very often | Sometimes | Not at all

9. I get a sort of frightened feeling like 'butterflies' in the stomach

Not at all | Occasionally | Quite often | Very often

10. I have lost interest in my appearance

Definitely	I don't take as much care as I used to	I may not take quite as much care	I take just as much care as ever

11. I feel restless as if I have to be on the move

Very much indeed	Quite a lot	Not very much	Not at all

12. I look forward with enjoyment to things

As much as I ever did	Rather less than I used to	Definitely less than I used to	Hardly at all

13. I get sudden feelings of panic

Very often indeed	Quite often	Not very often	Not at all

14. I can enjoy a good book, radio or TV programme

Often	Sometimes	Not often	Very seldom

Appendix 3D: Variables for Bootstrap Correlation Matrix Analysis

Appendix 3D, Table 5

Variables Included and Excluded for Bootstrap Correlation Matrix Analysis

Measure	Variable	Included	Reason for not including
Wessex	Continence	No	Not applicable
	Mobility	Yes	
	Self-help	Yes	
	Speech	Yes	
	Literacy	No	Not applicable
W-ADL	Total Score	Yes	
BRIEF-P	Inhibition	Yes	
	Shift	Yes	
	Emotional Control	Yes	

	Working Memory	Yes	
	Plan Organise	Yes	
	Inhibition Self-Control	No	Subscales available
	Flexibility	No	Subscales available
	Emergent Metacognition	No	Subscales available
	Global Executive Composite	No	Subscales available
SCQ	Communication	Yes	
	Restricted, Repetitive and Stereotyped Behaviours	Yes	
	Reciprocal Social Interaction	Yes	
	Total Score	No	Subscales available
TAQ	Impulsivity	Yes	

	Overactivity	Yes	
	Total Score	No	Subscales available
CBQ	Severity of Self-Injurious Behaviour	Yes	
	Severity of Aggressive Behaviour	Yes	
	Severity of Destruction of Property	Yes	
	Severity of stereotyped Behaviour	No	Conceptual Overlap[a]
RBQ	Stereotyped Behaviour	Yes	
	Compulsive Behaviour	Yes	
	Insistence on sameness	Yes	
	Restricted preferences	No	Unsuitable for non-verbal participants
	Repetitive language	No	Unsuitable for non-verbal participants

	Total Score	No	Subscales available
MIPQ	Mood	Yes	
	Interest and Pleasure	Yes	
	Total Score	No	Subscales available
ADAMS	Manic/Hyperactive Behaviour	No	Conceptual Overlap[b]
	Depressed Mood	No	Conceptual Overlap[c]
	Social Avoidance	Yes	
	General Anxiety	Yes	Conceptual Overlap[d]
	Compulsive Behaviour	No	Conceptual Overlap[e]
GDQ	Total Score	Yes	
MSPSQ	Bedtime-Resistance	Yes	
	Sleep onset Delay	Yes	

	Sleep Anxiety	Yes	
	Night Waking	Yes	
	Parasomnia	Yes	
	Sleep Disordered Breathing	Yes	
	Daytime Sleepiness	Yes	
	Total Score	No	Subscales available
HQ	Health Problems in the Last Month	No	Conceptual Overlap[f]
	Severity of Problems in the Last Month	No	Conceptual Overlap[g]
	Health Problems Ever	No	Conceptual Overlap[h]
	Severity of Health Problems Ever	Yes	
HADS	Total Score	Yes	

Note. WESX = Wessex Behaviour Scales (Kushlicket al., 1973). W-ADL = Waisman Activities of Daily Living Scale (Maenner et al., 2013). BRIEF-P = Behaviour Rating

Inventory of Executive Function (Gioia et al., 2000). SCQ = The Social Communication Questionnaire – Lifetime Version (Berument et al., 1999). TAQ = The Activity Questionnaire (Burbidge et al., 2010). Challenging Behaviour Questionnaire (Hyman et al., 2002). RBQ = The Repetitive Behaviour Questionnaire (Moss et al., 2009). MIPQ = Mood, Interest, and Pleasure Questionnaire – Short Form (Ross & Oliver, 2003). ADAMS = Anxiety Depression and Mood Scale (Esbensen et al., 2003). GDQ = Gastro-oesophageal Distress Questionnaire (Oliver & Wilkie, 2005). MSPSQ = Modified Simonds and Parraga Sleep (Simonds & Parraga, 1982). HQ = The Health Questionnaire (Hall et al., 2008). HADS = Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983)

[a] CBQ severity of stereotyped behaviour and RBQ stereotyped behaviour report on the same underlying construct.

[b] ADAMS manic/hyperactive behaviour and TAQ overactivity likely measure the same underlying construct.

[c] ADAMS depressed mood and MIPQ mood report on the same underlying construct.

[d] ADAMS general anxiety was excluded from correlations with MIPQ sleep anxiety as they measure a similar underlying construct.

[e] ADAMS compulsive behaviour and RBQ compulsive behaviour measure the same underlying construct.

[f,g,h] These measures all assess health. Severity of health problems ever and HQ total score were chosen as the most informative.

Appendix 3E: Power analysis for Bootstrap Correlation Matrix Analysis

Snippet of R code for an N of 30, an r of 0.30 (medium effect size) and a significance level of 0.05

```
library(pwr)

# Power for correlation, N = 30, r = 0.30

pwr.r.test (n = 30, r = 0.30, sig.level = 0.05)
```

Interpretation:

Only relatively strong correlations are likely to reach statistical significance

Appendix 3F: Bootstrap Correlation Results

Table 11 displays the significant correlations between different CBQ severity subscale variables and MSPSQ subscales. Each row represents a correlation between two variables. The "Variable 1" and "Variable 2" columns indicate the names of the variables being correlated. The "Mean Corr" column represents the mean bootstrap correlation coefficient, the correlation coefficient. The "P" column represents the p-value associated with the correlation.

Appendix 3I. Table 11

Bootstrap Correlation Final Output

Variable1	Variable2	Mean Corr	P_Value
CBQ Destruction of Property	HQ Health Severity: Ever	0.54	0.044
CBQ Self-Injurious Behaviour	ADAMS General Anxiety	0.64	0.034
CBQ Self-Injurious Behaviour	MIPQ Mood	-0.59	0.016
CBQ Self-Injurious Behaviour	RBQ Insistence on Sameness	0.54	0.016
CBQ Destruction of Property	ADAMS General Anxiety	0.52	0.014
MSPSQ Parasomnia	HQ Health Severity: Ever	0.59	0.012
CBQ Aggression	RBQ Insistence on Sameness	0.56	0.01
BRIEF-P Emotional Control	CBQ Self-Injurious Behaviour	0.55	0.01
Wessex Mobility	CBQ Self-Injurious Behaviour	-0.54	0.006
RBQ Stereotyped Behaviour	MSPSQ Parasomnia	0.50	0.006
CBQ Aggression	GDQ Total Score	0.51	0.004
SCQ Restrictive, Repetitive Behaviour	MSPSQ Bedtime Resistance	0.62	0.002
BRIEF-P Shift	CBQ Destruction of Property	0.60	0.002
BRIEF-P Emotional Control	CBQ Destruction of Property	0.68	<0.001
BRIEF-P Emotional Control	CBQ Aggression	0.64	<0.001
BRIEF-P Shift	CBQ Aggression	0.61	<0.001
CBQ Aggression	ADAMS General Anxiety	0.61	<0.001
CBQ Self-Injurious Behaviour	MIPQ Insistence on Sameness	-0.60	<0.001
SCQ Restrictive, Repetitive Behaviour	MSPSQ Sleep Anxiety	0.58	<0.001
SCQ Restrictive, Repetitive Behaviour	MSPSQ Night Waking	0.58	<0.001

Appendix 4A. Ethical Approval for the Third Empirical Study of the Thesis

Dear Dr Richards,

Re: "The Behavioural Phenotype of CHARGE Syndrome"

Application for Ethical Review ERN_18-1805

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards,

Ms Sam Waldron (she/her)

Research Ethics Officer

Appendix 4B. Subjective Measures

Background Questionnaire

Today's date: _____

Please answer the following about the person you care for:

13. Gender [assigned at birth]

    Male o Female o

14. Date of Birth: ___/___/____

15. Age: _____

16. Please indicate which features of CHARGE syndrome the person you care for shows? (Please include any features your child was born with that have since have been treated)

o CHD7	o Growth deficiency
o Coloboma	o Genital abnormalities
o Choanal atresia	o Cleft lip or palate
o Missing or reduced sense of smell	o Tracheoesophageal fistula
o Facial palsy	o Urinary tract problems
o Feeding and swallowing difficulties	o Differences in the structure of the brain
o External ear anomalies	o Skeletal or limb anomalies
o Middle ear anomalies	o Developmental delay
o Inner ear anomalies	o Intellectual disability
o Hearing impairment	o Other features not listed here

o Heart defects

Please specify the other features of CHARGE syndrome your child shows

_____

_____

17. When was the person you care for diagnosed? _____

18. What is the genetic mechanism causing CHARGE syndrome in the person you care for?

o Frame-shift variant	o Missense variant
o Nonsense variant	o Other
o Deletion	o Unknown

19. Does the person you care for have any additional diagnosis other than CHARGE syndrome?

Yes o No o

If yes, please provide details of the additional diagnosis

_____

20. Who diagnosed the person you care for?

o Paediatrician	o Clinical Geneticist
o GP	o Other

If you selected other, please specify who diagnosed the person you care for

_____

21. Has the person you care for had any medical/health difficulties in the last six months?

Yes o No o

If yes, please provide details of the medical/health difficulties experienced

_____

_____

22. Is the person you care for verbal? (i.e. more than 30 signs/words in their vocabulary)

Yes o No o

If no, are there any alternative ways the person you care for communicates with you?

Yes o No o

Please describe the way the person you care for communicates with you

_____

_____

23. Is the person you care for able to walk unaided?

Yes o No o

24. Is the person you care for able to walk unaided when outdoors?

Yes o No o

If no, is the person you care for able to walk unaided when in a familiar indoor setting?

Yes o No o

If no, Does the person you care for have an alternative way of exploring their environment independently (for example using a walker, five-point-crawling or pushing themselves along the floor on their back)

Yes o No o

Please describe how the person you care for explores their environment

_____

_____

The following questions ask for background information about you and your family:

11. What was your age in years on your last birthday? _____

12. Please select the highest level of your educational qualifications

    o No formal educational qualifications

    o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma

    o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent

    o 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent

    o Polytechnic/University degree, NVQ 4, or equivalent

    o Masters/Doctoral degree, NVQ 5, or equivalent

13. What is your relationship to your child with CHARGE syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)? _____

14. In total how many people currently live in your home?

    Children o Adults o

15. Does the person you care for normally live with you?

    Yes o No o

    If no, where do they live?

    _____

16. What is your current marital status?

    o Married, and living with spouse

    o Living with partner

    o Divorced/Separated/Widowed/Single and NOT living with a partner

If you are married / living with spouse / partner:

17. What was your partner/spouse's age in years on their last birthday? _____

18. Please select the highest level of your partner/spouse's educational qualifications.

    - o No formal educational qualifications
    - o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma
    - o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent
    - o 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent
    - o Polytechnic/University degree, NVQ 4, or equivalent
    - o Masters/Doctoral degree, NVQ 5, or equivalent

19. What is your partner/spouse's relationship to your child with CHARGE syndrome (e.g., mother, father, stepmother, adoptive parent)? _____

Recent data from research with families of children with special needs has shown that a family's financial resources are important in understanding family member's views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences. However, we would like to reassure you that the question below is optional.

20. What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions.

    Please tick one box:

    - o Less than £15,000

o £15,001 to £25,000

o £25,001 to £35,000

o £35,001 to £45,000

o £45,001 to £55,000

o £55,001 to £65,000

o £65,001 or more

Vineland Adaptive Behaivour Scales – Third Edition

Vineland-3

Vineland Adaptive Behavior Scales™–Third Edition

Comprehensive Interview Form

(aminee's Name: _____ Today's Date: _____ Examinee's Birth Date: _____
(first, middle, last) (month, day, year) (month, day, year)

(aminee's Age: _____ Examinee's Sex: ☐ Female ☐ Male Respondent's Name: _____

espondent's Relationship to the Examinee: ☐ Mother ☐ Father ☐ Other _____ Interviewer's Name: _____

IRECTIONS

omplete instructions for administering this form are provided in Chapter of the Vineland–3 Manual. The Manual also includes a list of suggested terview questions and scoring criteria for the items in Appendix G, hich you may wish to have available when conducting the interview.

eep in mind that the Coping Skills subdomain does not begin ge 2; the Written, Domestic, and Community subdomains do not begin ntil age 3; and the optional Maladaptive Behavior domain does not begin ntil age 3.

CORING THE ITEMS

ore each item 2, 1, or 0 as follows:

ircle 2 if, when the behavior is needed or appropriate, the individual *ually* performs it without help or prompting (or if he/she performed e behavior when younger, but has now outgrown it).

ircle 1 if, when the behavior is needed or appropriate, the individual *metimes* performs it without help or prompting.

rcle 0 if the individual *never* performs the behavior, or never performs without help or prompting. Whether he/she hasn't learned the behavior, not physically able to perform it, is not expected or allowed to perform or chooses not to perform it, circle 0.

Some items use a different scoring system: 2 = Yes, 0 = No. This is indicated in the booklet.

If the respondent has not had the opportunity to observe a behavior, ask him/her to estimate a score for that item. In addition to marking the item score, also check the box to the right of the item score, in the column labeled **Check if Est**.

If the individual performed a behavior when he/she was younger, but has now outgrown it, circle 2. Do not check the Estimated box.

Some items include a Scoring Tip, indicated with the symbol ☑. Use the tips to help you score those items.

BASAL AND CEILING RULES

A basal is established when there are *four consecutive items* with scores of 2. A ceiling is established when there are *four consecutive items* with scores of 0. Continue administering Interview Topics until you have established a basal and a ceiling, and all items between the basal and ceiling have been scored. If there is no basal, you must score all items from the first item in the subdomain up to the ceiling. If there is no ceiling, you must score all items from the last item in the subdomain back to the basal.

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PsychCorp

Product Number 31321

RECEPTIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Responding
B Understanding Words
C Understanding Nonverbal Communication
D Identifying Things
E Following Basic Instructions
F Understanding Questions
G Understanding Implied Messages
H Attending to Entertaining Material
I Following Complex Instructions
J Attending to Informational Material

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

0	A	1. Looks toward parent or caregiver when hearing parent's or caregiver's voice. ? How can you tell that he/she hears your voice or the voice of someone else he/she knows?	2 1 0	☐
	A	2. Looks toward parent or caregiver who is gesturing to get his/her attention. ? What about when you gesture to get his/her attention?	2 1 0	☐
	A	3. Responds upon hearing his/her name called (for example, turns toward speaker, smiles). ? How does he/she react when you call his/her name?	2 1 0	☐
	C	4. When parent or caregiver looks or points at something, looks in that direction. ? What does he/she do when you point or look toward something?	2 1 0	☐
	B	5. Understands at least 10 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she understand?	2 0	☐
	C	6. Responds appropriately to at least three basic gestures (for example, head nod for *yes*, head shake for *no*, hand out for *give me*, reaching, waving, clapping). ? What about simple gestures like this one [shake your head "no"]?	2 1 0	☐
	B	7. Understands the meaning of *no*. ? What about simple words like *yes* and *no*?	2 1 0	☐
	C	8. Responds appropriately to at least three facial expressions being made by others (for example, frown, smile, surprised look, angry face). ? How does he/she respond to your facial expressions, for example, when you frown or look sad?	2 1 0	☐
	B	9. Understands the meaning of *yes*. ? What about simple words like *yes* and *no*?	2 1 0	☐
	E	10. Follows instructions requiring only one action (for example, "Sit down"; "Come here"). ? How about one-step instructions, like "Sit down" or "Come here"?	2 1 0	☐
	D	11. Identifies at least three *actual* objects when asked (for example, points to a dog, car, cup, key, etc.). ? What about real life objects?	2 1 0	☐
	B	12. Understands at least 50 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she understand?	2 0	☐
	G	13. Responds to the tone of spoken words (for example, approaches eagerly when "Come here" is spoken lovingly, but hesitantly when "Come here" is spoken sharply). ? What about when you change the tone of your voice to emphasize what you mean, like the difference between saying "Come here" in a loving way and an angry way?	2 1 0	☐
	D	14. Identifies at least three body parts on self when asked (for example, points to own nose, mouth, hands, feet, etc.). ? What about his/her own body parts?	2 1 0	☐
	E	15. Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"). ? What about instructions that include one action and one object, like "Bring me the book" or "Close the door"?	2 1 0	☐
	C	16. Responds appropriately to at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning *be quiet*, hands apart to show *this big*). ? What about more advanced gestures like this one [motion "come here"]?	2 1 0	☐
	D	17. Identifies at least three objects pictured in a book, magazine, or electronic screen when asked (for example, points to a dog, car, cup, key, etc.). ? What about objects shown in pictures, like when you are reading together?	2 1 0	☐
1	D	18. Identifies at least three body parts pictured in a book, magazine, or electronic screen when asked (for example, points to a nose, a mouth, hands, feet, etc.). ? What about body parts shown in pictures?	2 1 0	☐
	F	19. Responds to questions that use *what* (for example, when asked "What is this?" replies "A ball"). ? How about questions that use *what*?	2 1 0	☐
	F	20. Responds to questions that use *who* (for example, when asked "Who is that?" replies "Auntie Kesha"). ? How about questions that use *who*?	2 1 0	☐
	D	21. Identifies at least three basic actions pictured in a book, magazine, or electronic screen when asked (for example, points to someone eating, sitting, jumping, etc.). ? What kinds of actions does he/she identify when they are shown in pictures, like when you are reading together?	2 1 0	☐

RECEPTIVE — COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

	F	22. Responds to questions that use *where* (for example, when asked "Where did Felipe go?" points where Felipe went). ? How about questions that use *where*?	2 1 0	☐
	E	23. Follows instructions with two related actions (for example, "Pick up those toys and put them away"; "Get your coat and put it on"). ? What about instructions to do two things that go together, like "Get your coat and put it on"?	2 1 0	☐
	E	24. Follows instructions with one action and two objects (for example, "Bring me the crayons and the ball"; "Put on your shirt and your shoes"). ? What about instructions that include one action and two objects, like "Bring me the crayons and the ball" or "Put on your shirt and your shoes"?	2 1 0	☐
	E	25. Follows instructions in "if–then" form (for example, "If you're thirsty, then get a drink"; "If you are cold, then get a sweatshirt"). ? What about if–then instructions, like "If you're thirsty, then get a drink" or "If you are cold, then get a sweatshirt"?	2 1 0	☐
	H	26. Pays attention to a story for at least 15 minutes. ☑ Score 2 if the individual did this when younger, but has now outgrown listening to stories. ? For how long does he/she listen to a story?	2 1 0	☐
2	F	27. Responds to questions that use *why* (for example, when asked "Why are you crying?" replies "My toy broke"). ? How about questions that use *why*?	2 1 0	☐
	E	28. Follows instructions with two unrelated actions (for example, "Turn off the TV and get my keys"). ? What about instructions to do two things that don't go together, like "Turn off the TV and get my keys"?	2 1 0	☐
	F	29. Responds to questions that use *when* (for example, when asked "When do you eat breakfast?" replies "In the morning"). ? How about questions that use *when*?	2 1 0	☐
	H	30. Pays attention to a show for at least 30 minutes and understands what is happening. ? For how long does he/she pay attention to a TV show, movie, or live performance, and how can you tell if he/she understands what is happening?	2 1 0	☐
	I	31. Identifies left and right on own body (for example, hands, feet, arms). ? What about identifying left and right on his/her own body?	2 1 0	☐
	I	32. Follows instructions requiring three actions (for example, "Get dressed, eat breakfast, and brush your teeth"). ? What about three-step instructions, like "Get dressed, eat breakfast, and brush your teeth"?	2 1 0	☐
3+	H	33. Pays attention to a show for at least 60 minutes and understands what is happening. ? For how long does he/she pay attention to a TV show, movie, or live performance, and how can you tell if he/she understands what is happening?	2 1 0	☐
	G	34. Understands sarcasm (for example, understands when a comment such as "That's just great!" really means "That's awful!"). ? What about understanding sarcasm?	2 1 0	☐
	J	35. Pays attention to a 15-minute informational presentation and understands what is being said. ? For how long does he/she pay attention to information being presented that's serious or educational, and how can you tell if he/she understands what is being said?	2 1 0	☐
	I	36. Follows instructions involving left and right (for example, "Go to the left"; "Look to the right"). ? How does he/she respond to directions that involve left and right?	2 1 0	☐
	I	37. When instructed to do something up to an hour later, remembers to do it (for example, "When your show is over, put your dishes in the sink"). ? How often does he/she remember to do something meant to be done a little later, like something you've asked him/her to do after a show that he/she is watching is over?	2 1 0	☐
	I	38. When instructed to do something several hours later, remembers to do it (for example, "When you get home from school, let the dog out"). ? How often does he/she remember to do something that you ask to be done much later that day, for example, letting the dog out after school?	2 1 0	☐
	J	39. Pays attention to a 30-minute informational presentation and understands what is being said. ? For how long does he/she pay attention to information being presented that's serious or educational, and how can you tell if he/she understands what is being said?	2 1 0	☐

)mments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest Numbered Basal Item ____ × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**rec** Raw Score	C + D

EXPRESSIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Beginning Sounds & Gestures	D Using Gestures	G Using Intermediate Grammatical Forms	J Using Complex Grammatical Forms	M Giving Directions
B Beginning Speech	E Communicating Names & Age	H Using Pronouns	K Expressing Ideas & Experiences	
C Vocabulary	F Using Simple Grammatical Forms	I Asking Questions	L Stating Age, Birthday, & Address	

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0	A	1. Makes sounds of pleasure (for example, coos, laughs). ? What sounds does he/she make when happy?	2 1 0	☐
	A	2. Cries or fusses when uncomfortable (thirsty, hungry, wet, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about when he/she is uncomfortable, maybe hungry, thirsty, or wet?	2 1 0	☐
	A	3. Vocalizes or gestures (for example, cries or waves arms) to get parent's or caregiver's attention. ? What does he/she do to get your attention when you are not paying attention to him/her?	2 1 0	☐
	A	4. Makes at least three one-syllable speech sounds (for example, "Mah," "Bah," "Ee," "Oh"). ☑ Score 2 if the individual did this when younger, but now says words. ? What about making one-syllable sounds, like "Mah," "Bah," or "Oh"?	2 1 0	☐
	A	5. Babbles in strings of sounds (for example, "Ba-ba-ba-ba," "Ma-ma-ma-ma," "Da-da-da-da"). ☑ Score 2 if the individual did this when younger, but now says words. ? What about making strings of sounds, like "Ba-ba-ba-ba," "Ma-ma-ma-ma," or "Da-da-da-da"?	2 1 0	☐
	A	6. Vocalizes or gestures if he/she wants an activity to keep going or stop (for example, says "Again," shakes head *no*). ? What does he/she do if he/she wants an activity to stop or keep going?	2 1 0	☐
	B	7. Says "Dada," "Mama," or another name for parent or caregiver (including parent's or caregiver's first name or nickname). ? What about words to represent Mom or Dad?	2 1 0	☐
	D	8. Uses at least three basic gestures (for example, head nod for *yes*, head shake for *no*, reaching or pointing toward something desired, waving, clapping). ? How does he/she gesture when he/she wants something or wants to express himself/herself?	2 1 0	☐
	B	9. Repeats or tries to repeat common words immediately upon hearing them (for example, *ball*, *car*, *more*). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about repeating words that he/she hears?	2 1 0	☐
	B	10. Says "No"; must actually mean *no*, not just repeat the word. ? What does he/she say if he/she doesn't want something?	2 1 0	☐
	C	11. Names at least three objects (for example, ball, dog, favorite toy). ? What about common objects, such as a ball, dog, or favorite toy?	2 1 0	☐
1	B	12. Says one-word requests (for example, "Want," "More," "Open"). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she express what he/she wants, such as being picked up or having more of something?	2 1 0	☐
	C	13. Names at least 10 objects. ☑ Score 2 for Yes or 0 for No. ? About how many objects can he/she label?	2 0	☐
	B	14. Says "Yes"; must actually mean *yes*, not just repeat the word. ? What does he/she say if you say "Do you want this," and he/she does want it?	2 1 0	☐
	C	15. Names at least three actions (for example, drink/drinking, eat/eating, play/playing). ? What about labeling actions, like drinking, eating, or playing?	2 1 0	☐
	E	16. Calls brothers, sisters, or friends by their name or nickname. ? Whose names or nicknames does he/she use?	2 1 0	☐
	C	17. Says at least 50 words. ☑ Score 2 for Yes or 0 for No. ? About how many total words does he/she say?	2 0	☐

EXPRESSIVE — COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

F	18. Uses phrases with a noun and a verb (for example, "Mommy stay," "Give ball"). ? What about using both a noun and a verb, such as "Mommy stay" or "Give ball"?	2 1 0	☐
E	19. Says own first name or nickname. ? What about his/her own name or nickname?	2 1 0	☐
H	20. Uses pronouns to refer to self; grammar need not be correct (for example, "Give me," "Me want," "Mine toy"). ? What about using pronouns to refer to himself/herself, such as "I want" or "Give me"?	2 1 0	☐
F	21. Uses simple adjectives to describe things (for example, *dirty, pretty, big, loud*). ? What about using adjectives to describe things, such as "Pretty picture" or "Big doggie"?	2 1 0	☐
F	22. Says what he/she is doing using simple sentences; grammar need not be correct (for example, "Ginger and me play," "Dan read me a book"). ? Can you give me some examples of how he/she talks about what he/she is doing?	2 1 0	☐
D	23. Uses at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning *be quiet*, hands apart to show *this big*). ? What about more advanced gestures like this one [motion *come here*]?	2 1 0	☐
F	24. Uses negatives in sentences; grammar need not be correct (for example, "I won't drink it," "Me no go"). ? What about using negatives in sentences, such as "I won't drink it" or "Me no go"?	2 1 0	☐
E	25. Says correct age when asked; holding up correct number of fingers counts. ? What about when you ask how old he/she is?	2 1 0	☐
G	26. Uses possessives in phrases or sentences; grammar need not be correct (for example, "This is mine," "Your book," "This is Carol's desk"). ? What about using possessives, words like "mine," "Mommy's," or "your"?	2 1 0	☐
G	27. Uses *and* in phrases or sentences (for example, "Mom and Dad," "I want ice cream and cake"). ? How about using the word *and* in phrases or sentences, such as "Mom and Dad" or "I want ice cream and cake"?	2 1 0	☐
I	28. Asks questions beginning with *who* (for example, "Who's that?"; "Who went to the store?"); just asking "Who?" (one word) doesn't count. ? How about questions beginning with *who*, like "Who's that?" or "Who went to the store?"	2 1 0	☐
2 G	29. Uses plural nouns (for example, "Two cats," "More crackers," "Those flowers"). ? What does he/she say to mean more than one of something, like more than one cat or more than one cracker?	2 1 0	☐
H	30. Uses pronouns to refer to others; pronoun gender and grammar need not be correct (for example, "You want?"; "Her happy"; "Him ball"). ? What about using pronouns to refer to others, such as "You want" or "Give him"?	2 1 0	☐
G	31. Uses *in*, *on*, and *under* correctly in phrases or sentences (for example, "In the box," "Ball go under table"). ? How about using the words *in*, *on*, and *under*?	2 1 0	☐
I	32. Asks questions beginning with *why* (for example, "Why do I have to go?"; "Why did you put my stuff away?"); just asking "Why?" (one word) doesn't count. ? How about questions beginning with *why*, like "Why do I have to go?" or "Why did you put my stuff away?"	2 1 0	☐
E	33. Says first and last name when asked; saying first name only doesn't count. ? What about when you ask for his/her full name?	2 1 0	☐
H	34. Uses pronouns correctly; pronoun gender and grammar must be correct (for example, "I want," "Their ball," "Call her"). ? What about using pronouns correctly?	2 1 0	☐
I	35. Asks questions beginning with *when* (for example, "When is dinner?"; "When can we go home?"); just asking "When?" (one word) doesn't count. ? How about questions beginning with *when*, like "When is dinner?" or "When can we go home?"	2 1 0	☐
J	36. Uses *because* in phrases or sentences (for example, "Because I want to," "Kathy went home because she was sick"). ? How about using the word *because*?	2 1 0	☐
L	37. Says his/her age at next birthday correctly when asked; holding up correct number of fingers counts. ? What about his/her age at his/her next birthday?	2 1 0	☐

EXPRESSIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Beginning Sounds & Gestures
B Beginning Speech
C Vocabulary
D Using Gestures
E Communicating Names & Age
F Using Simple Grammatical Forms
G Using Intermediate Grammatical Forms
H Using Pronouns
I Asking Questions
J Using Complex Grammatical Forms
K Expressing Ideas & Experiences
L Stating Age, Birthday, & Address
M Giving Directions

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	J 38. Uses past tense verbs (for example, *walked*, *baked*). ? How does he/she use verbs to mean that something happened in the past?	2 1 0	☐
	K 39. Tells the basic parts of a familiar story or book or movie plot (the characters, what happens, how it ends, etc.). ? How much detail does he/she tell about a familiar story when asked?	2 1 0	☐
	J 40. Uses *behind*, *in front of*, and *between* correctly in phrases or sentences (for example, "Terrell is behind you," "I walked in front of her," "The ball went between the cars"). ? How about using the words *behind*, *in front of*, and *between*?	2 1 0	☐
	M 41. Gives simple directions involving one or two steps (for example, how to make, find, or do something). ? What about giving simple directions, like how to make something or find something?	2 1 0	☐
	J 42. Uses compound sentences joined by *and* or *but* (for example, "She asked me, and I told her no"; "Jerome wanted to go, but I didn't"). ? How about putting sentences together using *and* or *but*, for example, "She asked me, and I told her no"?	2 1 0	☐
3+	K 43. Uses own knowledge or opinions to comment on things, situations, and emotions (for example, "I think he's mad at her because she said mean things about him"). ? What about using his/her own knowledge or opinions to comment on things, for example, why a friend is mad at someone?	2 1 0	☐
	K 44. Tells about everyday (i.e., routine) experiences in detail (for example, when asked what he/she did with a friend today, tells who was involved, where the activity took place, etc.). ? How much detail does he/she give when he/she talks about everyday experiences, like what happened at a friend's house?	2 1 0	☐
	K 45. Tells about one-time (i.e., non-routine) experiences in detail (for example, when asked to describe a trip, tells who was involved, where the activity took place, etc.). ? What about when you ask about one-time experiences, like what he/she did on a recent vacation?	2 1 0	☐
	L 46. Says both the month and day of his/her birthday when asked. ? How about the month and day of his/her birthday?	2 1 0	☐
	K 47. Clarifies by restating with different words when he/she is not fully understood at first. ? If he/she is telling you something, and you aren't quite following, what does he/she do to help you understand what he/she is trying to say?	2 1 0	☐
	L 48. Says complete home address correctly when asked (that is, street or rural route, apartment number, city, and state, with or without zip code). ? What about his/her complete home address?	2 1 0	☐
	M 49. Gives complex directions involving three or more steps in logical order (for example, to a distant location, for a recipe requiring many steps). ? What about giving multiple-step directions, like how to get somewhere or prepare a recipe?	2 1 0	☐

Comments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**exp** Raw Score	C + D

WRITTEN — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Identifying Signs & Letters
B Understanding How Writing Works
C Copying
D Beginning Reading
E Beginning Writing
F Working With Written Information
G Personal Writing
H Reading Level
I Advanced Writing
J Forms & Business Letters

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0–2	B	1. Holds a book correctly for reading and turns the pages from front to back. ? How does he/she hold a book and turn the pages?	2 1 0	☐
	A	2. Recognizes one or more simple signs and icons/symbols (for example, STOP signs, bathroom door signs, arrows, smiley face). ? What about familiar signs, symbols, and icons, like STOP signs, bathroom door signs, and arrows?	2 1 0	☐
	A	3. Identifies one or more alphabet letters. ? What letters of the alphabet does he/she identify?	2 1 0	☐
	A	4. Recognizes own name in printed form. ? What about recognizing his/her own name in printed form?	2 1 0	☐
	A	5. Identifies at least 10 alphabet letters. ☑ Score 2 for Yes or 0 for No. ? What letters of the alphabet does he/she identify?	2 0	☐
3	B	6. Understands what direction his/her language is written in (for example, from left to right in English; in other languages from right to left or top to bottom). ? What does he/she understand about writing going from left to right? [Or a substitution appropriate to the individual's language]	2 1 0	☐
	B	7. Writes in the correct direction (for example, from left to right in English; in other languages from right to left or top to bottom). ? How often does he/she write words from left to right? [Or a substitution appropriate to the individual's language]	2 1 0	☐
	C	8. Copies own first name without mistakes. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy his/her first name?	2 1 0	☐
4	C	9. Copies simple words from an example without mistakes (for example, *cat, see, go*); copying name doesn't count. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy simple words like *cat, see, go*?	2 1 0	☐
	D	10. Identifies all alphabet letters, both uppercase and lowercase. ☑ Score 2 for Yes or 0 for No. ? For how many letters does he/she recognize both uppercase and lowercase?	2 0	☐
	E	11. Writes alphabet letters using the correct orientation (that is, not reversed or upside down). ? How many alphabet letters does he/she write correctly, not backwards or upside down?	2 1 0	☐
	D	12. Reads at least 10 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she read out loud?	2 0	☐
	E	13. Writes own first and last name from memory; writing first name only doesn't count. ? How often does he/she write both his/her first and last name without copying and without help?	2 1 0	☐
5	D	14. Reads simple sentences of three or more words out loud. ? How long are the sentences that he/she reads out loud?	2 1 0	☐
	C	15. Copies phrases or sentences of four or more words without mistakes. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy phrases or sentences with four words or more?	2 1 0	☐
	E	16. Writes at least 10 simple words from memory (for example, *hat, ball, the*); may make small spelling errors. ☑ Score 2 for Yes or 0 for No. ? What words does he/she write from memory, other than his/her name?	2 0	☐

WRITTEN — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Identifying Signs & Letters	D Beginning Reading	G Personal Writing	J Forms & Business Letters
B Understanding How Writing Works	E Beginning Writing	H Reading Level	
C Copying	F Working With Written Information	I Advanced Writing	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

	D 17. Reads simple stories out loud. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about reading simple stories?	2 1 0	☐
	E 18. Writes simple sentences of three or more words; may make small errors in spelling or grammar. ? How long are the sentences that he/she writes?	2 1 0	☐
	E 19. Writes at least 20 words from memory; may make small spelling errors. ☑ Score 2 for Yes or 0 for No. ? What words does he/she write from memory, other than his/her name?	2 0	☐
	H 20. Reads and understands material of a second-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
	G 21. Writes simple notes, letters, emails, or texts that include at least three sentences (for example, thank you notes, postcards, invitations); may use abbreviated words and make small errors in spelling or grammar. ☑ Score 2 for Yes or 0 for No. ? How long are the simple notes, letters, emails, or texts that he/she writes?	2 0	☐
	F 22. Finds or sorts things in alphabetical order (for example, finds a name in an alphabetized address book or list of phone numbers, finds a word in a dictionary, alphabetizes a list of words or movie titles). ? How often is he/she able to find things that are in alphabetical order—for example, words in a dictionary—or put words or actual things like books or music in alphabetical order himself/herself?	2 1 0	☐
	F 23. Accurately interprets information presented in simple tables, graphs, or charts. ? How accurately does he/she read tables, graphs, or charts?	2 1 0	☐
	I 24. Writes short reports or summaries (for example, a summary of something read) at least three sentences long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports or summaries. ? What about writing a short report or summary of three sentences or more?	2 1 0	☐
6–7	F 25. Accurately interprets visual instructions (for example, assembly instructions, directions shown on a map). ? How well does he/she understand and follow visual instructions, such as assembly instructions, diagrams, or directions on a map?	2 1 0	☐
	F 26. Uses a table of contents or index to find information within a book or electronic resource. ? What about using a table of contents or index to find information within a book or electronic file?	2 1 0	☐
	H 27. Reads and understands material of a fourth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
	G 28. Writes emails, stories, letters, journal entries, etc. at least 10 sentences long; may use abbreviated words and make small errors in spelling or grammar. ☑ Score 2 for Yes or 0 for No. ? How long are the emails, stories, letters, or other longer things that he/she writes?	2 0	☐
	F 29. Uses the Internet or a library to find information for writing a paper or completing a job assignment. ? How does he/she go about finding information that he/she needs to write a paper or complete a job assignment?	2 1 0	☐
8+	I 30. Writes reports, papers, or essays at least one page long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports, papers, or essays. ? How long are the reports, papers, or essays that he/she writes using his/her own words, not just copying something?	2 1 0	☐
	G 31. Writes or draws instructions for others (for example, how to do something, how to get somewhere). ? What about writing or drawing instructions or directions for someone, like how to do something or get somewhere?	2 1 0	☐

WRITTEN COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

I	32. Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.); use of computer spell-checker is okay. ? What does he/she do to check and correct his/her written work before handing it in?	2 1 0	☐
J	33. Accurately completes paper or electronic forms of one page or less (for example, forms for school or work). ? How long are the paper or electronic forms that he/she completes accurately on his/her own, such as forms for school or work?	2 1 0	☐
H	34. Reads and understands material of a sixth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
I	35. Writes reports or compositions at least three pages long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports or compositions. ? How long are the reports or compositions that he/she writes using his/her own words, not just copying something?	2 1 0	☐
H	36. Reads and understands material of a ninth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
J	37. Accurately completes paper or electronic forms of two pages or more (for example, a job, college, or credit application). ? How long are the paper or electronic forms that he/she completes accurately on his/her own, such as a job, college, or credit application?	2 1 0	☐
J	38. Writes business or application letters (for example, requests information, makes a complaint, applies for a job or to a school). ? What kinds of business or application letters does he/she write?	2 1 0	☐

mments or Observations: _____

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Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**wrn** Raw Score	C + D

PERSONAL — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Eat	D Using Spoon & Fork	G Cleaning Hands & Face	J Fastening Fasteners	M Using Knives When Eating	P Health Care
B Cooperating in Dressing & Washing	E Removing Clothing	H Putting on Clothes & Shoes	K Bathing	N Eating & Exercise Choices	
C Beginning to Drink	F Toilet Training	I Hygiene	L Using the Bathroom	O Preparing for Weather	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

0	A	1. Opens mouth when food is offered. ☑ Score 2 if the individual did this when younger, but has now outgrown being fed. ? What does he/she do when you put some food in front of his/her mouth?	2 1 0	☐
	C	2. Drinks from a bottle or spill-proof drinking cup (often called a "sippy cup"); must hold the bottle or cup himself/herself. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How much help does he/she need with a bottle or a "sippy cup?"	2 1 0	☐
	A	3. Sucks or chews on finger foods (for example, crackers, cookies, toast). ? What about finger foods like small crackers or cookies?	2 1 0	☐
	A	4. Eats solid foods (for example, cooked vegetables, chopped meats). ? What about solid foods like cooked vegetables or chopped meat?	2 1 0	☐
	B	5. Cooperates actively in undressing and dressing (raises arms for removing top, holds out feet for putting on pants or shoes, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about undressing and getting dressed?	2 1 0	☐
	B	6. Cooperates actively in washing of hands and face (holds out hands, turns face toward parent or caregiver, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about when someone washes his/her hands and face?	2 1 0	☐
	D	7. Feeds self with a spoon; may spill. ? How about using a spoon?	2 1 0	☐
	E	8. Removes shoes and socks. ? What about shoes and socks?	2 1 0	☐
1	C	9. Drinks from a regular cup or glass (sippy cups don't count); some spilling may occur. ? What about a regular glass or cup?	2 1 0	☐
	D	10. Feeds self with a fork; may spill. ? How about using a fork?	2 1 0	☐
	E	11. Removes clothing that opens in the front (for example, a coat or jacket); does not have to unbutton or unzip the clothing. ? What about a jacket or something else that opens in the front?	2 1 0	☐
	F	12. Lets someone know when he/she has a wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What does he/she do when he/she has a wet or dirty diaper or pants?	2 1 0	☐
	H	13. Pulls up clothing with elastic waistbands (for example, underwear, sweatpants). ? What about clothes that have elastic waistbands?	2 1 0	☐
	C	14. Drinks from a regular cup or glass without spilling (sippy cups don't count). ? What about a regular glass or cup?	2 1 0	☐
	F	15. Urinates in a toilet or potty chair; parent or caregiver may initiate. ? How is he/she using the toilet or a potty chair?	2 1 0	☐
	G	16. Washes hands using soap and water and dries them; does not need to turn the water on and off or adjust the temperature. ? What about washing his/her hands?	2 1 0	☐
	D	17. Feeds self with a spoon without spilling. ? How about using a spoon?	2 1 0	☐
	E	18. Removes pullover garments (for example, T-shirt, sweatshirt, dress). ? What about a T-shirt or something else that he/she has to pull off over his/her head?	2 1 0	☐

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* | Check if Est

H	19. Puts on shoes; may be on the wrong feet and does not need to tie or fasten. ? Who puts on his/her shoes?	2 1 0	☐
H	20. Puts on clothing that opens in the front (for example, a coat or jacket); does not need to zip or button. ? What about a jacket or something else that opens in the front?	2 1 0	☐
F	21. Defecates in a toilet or potty chair; parent or caregiver may initiate. ? How is he/she using the toilet or a potty chair?	2 1 0	☐
F	22. Is toilet-trained during the day; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet.* ? What happens during the day?	2 1 0	☐
H	23. Puts on pullover garments (for example, T-shirt, sweatshirt, dress). ? What about a T-shirt or something else that he/she has to put on over his/her head?	2 1 0	☐
I	24. Wipes or blows nose using tissue, napkin, toilet paper, or other appropriate material. ? What about wiping and blowing his/her nose?	2 1 0	☐
2 G	25. Washes and dries face; does not need to turn the water on and off or adjust the temperature. ? What about washing his/her face?	2 1 0	☐
G	26. Wipes or cleans face and hands as needed during or after meals. ? What about wiping or cleaning his/her face and hands while eating and afterwards?	2 1 0	☐
H	27. Puts clothing on with the right side forward and correct side out. ? What about putting his/her clothes on with the right side forward and the correct side out?	2 1 0	☐
F	28. Is toilet-trained during the night; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet.* ? What about accidents during the night?	2 1 0	☐
I	29. Covers mouth and nose when coughing or sneezing. ? What does he/she do when he/she coughs or sneezes?	2 1 0	☐
F	30. Uses the toilet during the day and at night without help; must wipe, flush, and wash hands by himself/herself. ? How much help does he/she need?	2 1 0	☐
J	31. Fastens snaps. ? What about snaps?	2 1 0	☐
I	32. Brushes teeth; must put toothpaste on toothbrush, brush adequately, and rinse. ? What about brushing his/her teeth?	2 1 0	☐
3 J	33. Buttons large buttons, in the correct buttonholes (for example, coat buttons). ? How about big buttons, like on a coat?	2 1 0	☐
I	34. Changes clothing that has become dirty, wet, muddy, or smelly. ? What about changing clothes if they've gotten dirty, wet, muddy, or smelly?	2 1 0	☐
J	35. Connects and zips zippers that are not already fastened at the bottom (for example, on a coat or jacket). ? What about zippers that are not already fastened at the bottom, like on a coat or jacket?	2 1 0	☐
K	36. Bathes or showers and dries self; does not need to turn the water on and off or adjust the temperature. ? What about taking a bath or a shower?	2 1 0	☐
H	37. Puts shoes on the correct feet and securely ties or fastens them. ? What about tying or fastening his/her shoes?	2 1 0	☐
M	38. Spreads food with a table knife (for example, butter, jam, mustard). ? How does he/she use a table knife?	2 1 0	☐
J	39. Buttons small buttons, in the correct buttonholes (for example, shirt buttons). ? How about small buttons, like on a shirt?	2 1 0	☐
N	40. Shows awareness that some foods are healthier than others (for example, states that fruits and vegetables are healthier than foods high in sugar or fat). ? What does he/she know about healthy and unhealthy foods?	2 1 0	☐

PERSONAL — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Eat	D Using Spoon & Fork	G Cleaning Hands & Face	J Fastening Fasteners	M Using Knives When Eating	P Health Care
B Cooperating in Dressing & Washing	E Removing Clothing	H Putting on Clothes & Shoes	K Bathing	N Eating & Exercise Choices	
C Beginning to Drink	F Toilet Training	I Hygiene	L Using the Bathroom	O Preparing for Weather	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

L	41. Finds and uses an appropriate restroom when away from home. ? What happens if he/she needs to use the bathroom away from home?	2 1 0	☐
K	42. Turns faucets on and adjusts the water temperature. ? What about turning faucets on and adjusting the water temperature?	2 1 0	☐
O	43. Selects appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater). ? What kind of clothes does he/she choose if it's rainy or cold?	2 1 0	☐
M	44. Cuts easy-to-cut food with a table knife (for example, fish, pancakes, butter). ? How does he/she use a table knife?	2 1 0	☐
4+ N	45. Shows awareness that physical exercise is good for people (for example, states that exercise is healthy, that people should exercise, etc.). ? What does he/she know about the health benefits of exercise?	2 1 0	☐
K	46. Washes and rinses hair; does not need to turn the water on and off or adjust the temperature. ? Who washes his/her hair?	2 1 0	☐
N	47. Chooses to exercise for health and/or enjoyment. ? How often does he/she choose to exercise on his/her own?	2 1 0	☐
L	48. Uses the toilet before going out if uncertain about the availability of a restroom. ? What about using the toilet before going out if there might not be a bathroom at his/her destination?	2 1 0	☐
N	49. Makes healthy eating choices (eats a balanced diet, eats unhealthy foods in moderation, etc.). ? How often does he/she choose to eat healthy foods?	2 1 0	☐
M	50. Cuts harder-to-cut food with a sharp knife (for example, meat, raw vegetables). ? How does he/she use a sharp knife?	2 1 0	☐
O	51. Plans for changes in weather by taking along an umbrella, a sweater, etc. ? What does he/she do to prepare for a change in the weather while he/she is out?	2 1 0	☐
P	52. Takes own temperature when needed. ? What about taking his/her own temperature?	2 1 0	☐
P	53. Takes medicine as directed on his/her own. ? What about taking medicine?	2 1 0	☐
P	54. Goes to the doctor when needed (that is, when illness or injury requires professional care). ? What happens when he/she is sick or hurt enough that he/she needs to see a doctor or nurse?	2 1 0	☐
P	55. Monitors supply of medications (nonprescription and prescription) and replaces them as needed. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What about keeping track of and refilling any medicines that he/she takes?	2 1 0	☐

Comments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item	× 2 = C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**per** Raw Score	C + D

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DOMESTIC — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning Home Safety
B Cleaning Up After Self
C Putting Clothes, etc. Where They Belong
D Food Preparation Basics
E Advanced Home Safety
F Basic Household Chores
G Cleaning Up After Meals
H More Complex Food Preparation
I Advanced Household Chores

		Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0–2	A 1. Is careful around hot objects (for example, the stove or oven, an open fire). ? What about safety concepts like being careful around hot objects?	2 1 0	☐
	A 2. Is careful when using sharp objects (for example, scissors, knives). ? What about sharp things like knives or scissors?	2 1 0	☐
	B 3. Wipes up own spills; must get wiping material and clean the spill adequately. ? What does he/she do if he/she spills something?	2 1 0	☐
	C 4. Puts dirty clothes in the proper place to be washed (for example, a laundry basket or chute). ? What about his/her dirty clothes?	2 1 0	☐
3–4	B 5. Removes dirty shoes or wipes them on a doormat before entering a residence. ? What does he/she do if his/her shoes are dirty when he/she is going into someone's house?	2 1 0	☐
	B 6. Puts away his/her books, toys, etc. when done using them. ? What about after he/she is done using things like toys, books, or magazines?	2 1 0	☐
	D 7. Washes hands before preparing food. ? What about washing his/her hands before preparing food?	2 1 0	☐
	B 8. Fully clears own dishes, utensils, napkins, cups, etc. after eating. ? What about clearing his/her own dishes and things after eating?	2 1 0	☐
	F 9. Does at least two simple household chores (for example, dusts, empties trash cans, feeds pet). ? What simple chores does he/she do?	2 1 0	☐
5–6	D 10. Prepares a simple snack or meal (for example, a sandwich, cheese and crackers, microwave foods). ? What about preparing a simple snack or meal like a sandwich, cheese and crackers, or microwave food?	2 1 0	☐
	E 11. Understands what to do in dangerous situations (for example, when to get help, when to call 911, how to distance self from danger). ? What does he/she understand about what to do in dangerous situations, for example, when to get help or call 911?	2 1 0	☐
	C 12. Hangs wet towel on a towel rack or hook, or puts in the proper place to be washed. ? What about his/her wet towels?	2 1 0	☐
	C 13. Puts clean clothes away where they belong (for example, in drawers or closet, on hooks). ? What about his/her clean clothes after they've been washed?	2 1 0	☐
	D 14. Uses at least two simple kitchen appliances (for example, toaster, microwave, electric can opener). ? What kitchen appliances does he/she use, things like a toaster, microwave, or electric can opener?	2 1 0	☐
	D 15. Washes fruits and vegetables before eating or cooking them. ? What about washing fruits and vegetables before eating or cooking them?	2 1 0	☐
	E 16. Secures home against intruders when home (keeps doors locked, finds out who is at the door before opening it, etc.). ? What does he/she do to keep intruders out when he/she is home, things like locking the doors and asking who's at the door before opening it?	2 1 0	☐
	D 17. Uses at least three kitchen utensils to prepare food (for example, knives, tongs, spatula, vegetable peeler). ? What kitchen utensils does he/she use, things like knives, spatulas, and vegetable peelers?	2 1 0	☐
7–8	E 18. Is careful when operating household appliances or equipment (for example, vacuum cleaner, lawnmower, iron, power tools). ? How careful is he/she when using household appliances or equipment like a vacuum cleaner, lawnmower, iron, or power tools?	2 1 0	☐
	D 19. Prepares and eats leftovers. ? What about preparing leftovers?	2 1 0	☐

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* | Check if Est

F	20. Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner). ? What about using household products like cleaners correctly?	2 1 0	☐
G	21. Puts dishes away when clean and dry. ? What about putting away clean dishes when he/she is supposed to?	2 1 0	☐
E	22. Secures home against intruders when leaving home (locks doors, closes windows, turns on alarm, etc.). ? What does he/she do to keep intruders out when he/she leaves home?	2 1 0	☐
G	23. Washes dishes (either by hand, or by loading and running the dishwasher when needed). ? What about washing dishes when he/she is supposed to?	2 1 0	☐
F	24. Cleans floors thoroughly (sweeps, vacuums, mops, etc.). ? What about cleaning floors when he/she is supposed to?	2 1 0	☐
9+ G	25. Puts leftover food away (for example, in plastic bags or wrap, in containers). ? What about putting away leftover food when he/she is supposed to?	2 1 0	☐
H	26. Uses the stove or oven for cooking or baking (turns burners on and off, sets oven temperature, etc.). ? What about using the stove or oven?	2 1 0	☐
I	27. Recognizes when simple maintenance tasks need to be done and does them (for example, replaces light bulbs, batteries, filters, or vacuum cleaner bag). ? What about noticing when things like light bulbs or batteries need changing and doing it on his/her own?	2 1 0	☐
I	28. Cleans bathroom (toilet, sink, tub or shower, etc.). ? What about cleaning a bathroom when he/she is supposed to?	2 1 0	☐
I	29. Does laundry; must wash, dry, and fold/hang. ? What about doing laundry when he/she is supposed to?	2 1 0	☐
H	30. Prepares a full meal consisting of three or more food items. ? What's an example of a big meal that he/she prepares by himself/herself?	2 1 0	☐

mments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**dom** Raw Score	C + D

COMMUNITY — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Basic Money Skills	D Basic Rights & Responsibilities	G Using Money	J Advanced Safety Outside the Home	M Achieving Goals	P Earning Money
B Basic Safety Outside the Home	E Calendar Basics	H Using Technology	K Being On Time	N Understanding Rights	Q Managing Money
C Telling Time	F Telephone Use	I Eating Out	L Shopping Skills	O Traveling	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	F	1. Talks to a familiar person using a phone, computer, or other electronic device; does not need to place the call. ? How often does he/she talk with someone he/she knows?	2 1 0 ☐
0–2	A	2. Understands that money is used to buy things. ? How can you tell that he/she understands what money is used for?	2 1 0 ☐
	A	3. Counts at least 10 objects, one by one. ? To use money, you have to be able to count things. How many things like blocks or other objects does he/she count correctly?	2 1 0 ☐
	B	4. Remains within safe distance of caregiver when in public places; being carried, pushed in a stroller, etc. doesn't count. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about staying within a safe distance from you when you are out in public?	2 1 0 ☐
	B	5. Understands and follows safety precautions while riding in a car (for example, keeps seat belt on, refrains from unnecessarily distracting the driver). ? What about staying safe in the car, for example, keeping his/her seatbelt on and not distracting the driver?	2 1 0 ☐
	C	6. Understands that a clock is used to tell time. ? How can you tell if he/she knows what a clock is used for?	2 1 0 ☐
	H	7. Operates at least two technology devices for entertainment (for example, a television, DVD player, music player, handheld game, computer used for entertainment). ? What electronic devices does he/she use for entertainment?	2 1 0 ☐
	I	8. Uses appropriate manners when eating in public (for example, uses utensils, sits properly, doesn't disrupt others). ? How are his/her manners when eating out?	2 1 0 ☐
	E	9. Says all seven days of the week in order when asked. ? If you ask him/her to say the days of the week in order, how often does he/she get it right?	2 1 0 ☐
3–4	B	10. Looks both ways when crossing streets or roads. ? What does he/she do in terms of safety when crossing streets or roads?	2 1 0 ☐
	D	11. Respects the right to personal privacy for self and others (for example, while using the restroom or changing clothes; not opening others' mail). ? What about people's right to privacy?	2 1 0 ☐
	A	12. Names a penny, nickel, dime, and quarter when asked; does not need to know the value of the coins. ? What coins does he/she identify?	2 1 0 ☐
5	E	13. Says the current day of the week when asked. ? What if you ask him/her "What day of the week is it today?"	2 1 0 ☐
	A	14. Understands that some items cost more than others (for example, might say "I have enough money to buy stickers but not a book" or "Which pens cost less?"). ? What does he/she understand about some things costing more than others?	2 1 0 ☐
	F	15. Knows what phone number to call in an emergency and how to make the call (for example, knows how to call 911 or an emergency contact). ? What does he/she know about making a call in an emergency?	2 1 0 ☐
	B	16. Obeys traffic lights and *Walk/Don't Walk* signs when crossing streets or roads. ? What about crossing when there's a light or a *Walk/Don't Walk* sign?	2 1 0 ☐
	C	17. Tells time using a digital clock or watch. ? What kinds of clocks or watches can he/she tell time on?	2 1 0 ☐
	D	18. Understands and follows community rules and laws (for example, rules and laws regarding littering, pet control, respecting others' property, etc.). ? What about community rules and laws, like those regarding littering, pet control, and respecting others' property?	2 1 0 ☐
	F	19. Makes calls to others using a phone, computer, or other electronic device. ? How often does he/she call someone on his/her own?	2 1 0 ☐
	G	20. Knows the difference between bills of different values ($1, $5, $10 bills, etc.). ? What does he/she know about the values of different bills, for example, the difference between a one-dollar bill and a ten-dollar bill?	2 1 0 ☐

		Response Options: 2 = Usually, 1 = Sometimes, 0 = Never	Check if Est
B	21. Understands signs or symbols used to indicate danger (for example, skull and crossbones for poison, circle with slash for "don't do"). ? What does he/she know about signs or symbols that are used to indicate danger, like the warning sign that's a circle with a slash through it?	2 1 0	☐
E	22. Identifies a specific date (either the current date or another) on a calendar when asked. ? What if you ask him/her to find a specific date on a calendar, like today's date or his/her birthday?	2 1 0	☐
G	23. Says the value of a penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents) when asked. ? What does he/she know about how much different coins are worth?	2 1 0	☐
J	24. Chooses to avoid dangerous or risky activities or situations (for example, walking in an unsafe area, jumping off high places, picking up a hitchhiker). ? How often does he/she do something risky, like walking in an unsafe area, jumping off high places, or picking up a hitchhiker?	2 1 0	☐
G	25. Makes small purchases at a store (for example, candy, stickers). ? How often does he/she make purchases by himself/herself?	2 1 0	☐
G	26. Combines coins to equal a specific amount (for example, 87 cents). ? What if he/she needs to combine coins to equal a specific amount, 87 cents for example?	2 1 0	☐
J	27. Follows safety precautions in work and/or leisure activities (for example, wears safety equipment, uses caution when operating tools and machinery). ? What does he/she do to stay safe when working or having fun?	2 1 0	☐
H	28. Watches or listens to TV or radio or uses the Internet to obtain current information (for example, news, weather report, traffic conditions). ? How often does he/she use a technology device to get current information like news, weather, or traffic conditions?	2 1 0	☐
K	29. Uses a clock to keep track of when to do something (for example, watch a TV show, meet a friend). ? How well does he/she use a clock to keep track of when to do something?	2 1 0	☐
M	30. Sets a short-term goal and achieves it (for example, completes all homework by Thursday night in order to have the weekend free). ? What are some short-term goals that he/she has achieved recently?	2 1 0	☐
F	31. Finds a needed phone number (for example, uses a contact list, the Internet, a phone book, 411). ? What does he/she do if he/she needs to find a phone number?	2 1 0	☐
J	32. Keeps personal belongings secure (wallet, purse, phone, etc.) when away from home (for example, when shopping, eating out, or traveling). ? What does he/she do to keep his/her money, phone, and other belongings from being lost or stolen when he/she is away from home?	2 1 0	☐
K	33. Gets up on time when needed (for example, sets alarm, arranges to be awakened). ? What does he/she do when he/she needs to get up at a certain time?	2 1 0	☐
L	34. Carries or stores money/debit card/credit cards safely, without losing (for example, in a wallet, purse, or money belt). ? What does he/she do to keep his/her money, debit card, and credit cards safe when out in public?	2 1 0	☐
H	35. Operates technology to accomplish at least two kinds of tasks (for example, writing documents, school-related email, organizing information, finding information on the Internet). ? How does he/she use technology to get tasks done, such as schoolwork?	2 1 0	☐
N	36. Understands the right to vote. ? What about the right to vote?	2 1 0	☐
H	37. Uses at least two social interaction technologies (for example, personal email, texting, social media, Skype™; telephone calls don't count). ? How does he/she use technology for social purposes?	2 1 0	☐
L	38. Checks change to make sure it is correct after buying something. ? How often does he/she check his/her change after buying something to make sure it's correct?	2 1 0	☐
L	39. Evaluates quality and price when deciding what to buy. ? What factors does he/she consider in deciding what to buy?	2 1 0	☐
N	40. Understands the right to begin or discontinue services (for example, telephone or Internet service). ? What about the right to start or stop a service, for example, phone service?	2 1 0	☐
N	41. Understands the right to report legitimate problems with products, services, living situation, etc. ? What about the right to report a problem with a product, a service, or his/her living situation?	2 1 0	☐

INTERVIEW TOPICS

A Basic Money Skills
B Basic Safety Outside the Home
C Telling Time
D Basic Rights & Responsibilities
E Calendar Basics
F Telephone Use
G Using Money
H Using Technology
I Eating Out
J Advanced Safety Outside the Home
K Being On Time
L Shopping Skills
M Achieving Goals
N Understanding Rights
O Traveling
P Earning Money
Q Managing Money

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
K	42. Notifies an appropriate person when he/she will be late or absent for school, work, an appointment, etc. ? What about calling in on his/her own if he/she will be late or absent for school, work, or an appointment?	2 1 0	☐
M	43. Sets a goal that can be done in six months or more and achieves it (for example, works and saves money to buy something expensive, gets in better physical shape). ? How about any goals that need six months or more to achieve?	2 1 0	☐
12+ O	44. Travels at least one mile to a familiar destination when needed (using public transportation, walking, biking, driving, etc.). ? What about traveling to places where he/she has gone many times?	2 1 0	☐
P	45. Has worked to earn money outside the home (for example, babysitting or yard work for a neighbor, having a job). ☑ Score 2 for Yes or 0 for No. ? What has he/she done to earn money outside the home, like babysitting or yard work for a neighbor, or having a job?	2 0	☐
I	46. At a restaurant, gets seating, chooses what to order, places order, and pays for meal. ? What parts of eating in a restaurant does he/she do completely on his/her own, like getting a place to sit, ordering, and paying?	2 1 0	☐
N	47. Understands the right to access records and information (for example, school or medical records, credit history). ? What about the right to see records or other information about him/her, like school or doctor's records?	2 1 0	☐
O	48. Travels at least one mile to an unfamiliar destination when needed (using public transportation, walking, biking, driving, etc.). ? What about traveling to new places?	2 1 0	☐
M	49. Sets a long-range goal requiring two years or more and achieves it (for example, makes a sports or academic team, gets into college). ? How about any goals that need two years or more to achieve?	2 1 0	☐
O	50. Uses a city, highway, bus, or electronic map (or GPS) to figure out how to reach a destination when needed. ? What does he/she do to figure out how to get somewhere?	2 1 0	☐
L	51. Buys groceries and household supplies when needed. ? How often does he/she get groceries and household supplies?	2 1 0	☐
Q	52. Manages daily expenses responsibly (for example, meals, bus fare). ? What about planning for daily expenses like meals and bus fare and sticking to that plan?	2 1 0	☐
Q	53. Uses a bank account responsibly (keeps money in the account, keeps tracks of the balance, doesn't overdraw, etc.). ? What about using a bank account responsibly?	2 1 0	☐
P	54. Has held a job (10 hours or more a week) for at least one month. ☑ Score 2 for Yes or 0 for No. ? What's the longest he/she has held a job?	2 0	☐
Q	55. Uses a credit or debit card in his/her name responsibly (for example, does not exceed credit limit, pays on time). ? What about using a credit or debit card responsibly?	2 1 0	☐
Q	56. Manages monthly expenses responsibly (for example, rent, utilities). ? What about planning for monthly expenses like rent and utilities and sticking to that plan?	2 1 0	☐
Q	57. Pays bills on time. ? How often does he/she pay his/her bills on time?	2 1 0	☐
P	58. Has held the same job (10 hours or more a week) for at least one year. ☑ Score 2 for Yes or 0 for No. ? What's the longest he/she has held a job?	2 0	☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item	× 2 = C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**cmm** Raw Score	C + D

INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning Social Behavior	D Identifying Self & Others	G Friendships	J Taking Others' Perspective
B Responding to Familiar People	E Imitating Others	H Demonstrating Caring	K Interpersonal Flexibility
C Expressing & Recognizing Emotions	F Interpersonal Appropriateness	I Conversational Skills	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
0	A	1. Looks at the face of parent or caregiver. (?) When does he/she look at your face?	2 1 0 ☐
	A	2. Smiles in response to a smile or a friendly voice. (?) What does he/she do when you smile at him/her or speak pleasantly to him/her?	2 1 0 ☐
	B	3. Recognizes family members or other significant people. (?) How can you tell when he/she recognizes family members or other people who he/she knows well?	2 1 0 ☐
	B	4. Smiles or makes sounds when approached by a familiar person. (?) What does he/she do when someone who he/she knows comes up to him/her?	2 1 0 ☐
	C	5. Shows at least three different emotions (for example, happiness, sadness, surprise, fear). (?) What kinds of emotions does he/she show?	2 1 0 ☐
	A	6. Tries to interact with others (for examples, smiles or makes noises at someone, reaches for someone). (?) How do you know if he/she wants to interact with you?	2 1 0 ☐
	B	7. Reaches for familiar person when that person holds out arms to him/her. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What does he/she do when you hold out your arms to pick him/her up?	2 1 0 ☐
	B	8. Shows affection to familiar people (for example, touches, hugs, kisses, cuddles). (?) How does he/she show affection to familiar people?	2 1 0 ☐
	A	9. Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them). (?) What does he/she do around other children his/her age, apart from his/her brothers or sisters?	2 1 0 ☐
	B	10. Looks around from time to time to check that parent, caregiver, or other familiar person is nearby. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) How typical is it of him/her to look around from time to time to be sure that someone familiar is nearby?	2 1 0 ☐
	D	11. Identifies self while looking at own image in mirror or photo. (?) What does he/she do when he/she sees himself/herself in a mirror or photo?	2 1 0 ☐
	C	12. Smiles in response to praise or compliments (for example, "Good job," "That's a nice shirt"). (?) How does he/she respond when someone praises him/her or gives him/her a compliment?	2 1 0 ☐
	E	13. Imitates or tries to imitate parent's or caregiver's facial expressions (for example, when parent or caregiver makes a happy, sad, or surprised face). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What about copying your facial expressions, for example, when you make a happy, sad, or surprised face?	2 1 0 ☐
1	C	14. Recognizes emotions in others (for example, might say "You look sad" or "Rachel is happy"). (?) How can you tell that he/she knows what other people are feeling?	2 1 0 ☐
	E	15. Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, vacuuming, hammering nails). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What about copying an activity while you or someone else is doing it, like pretending to shave, put on makeup, or vacuum?	2 1 0 ☐
	H	16. Uses actions or words to show happiness, sympathy, or concern for others on own initiative (for example, hugs, holds hands, asks "Are you okay?"). (?) How does he/she show other people that he/she feels happy for them, sad for them, or concerned about them?	2 1 0 ☐
	G	17. Tries to make friends with others his/her age (that is, shows particular interest in interacting with certain other children). (?) How does he/she try to make friends with others his/her age?	2 1 0 ☐

INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning Social Behavior
B Responding to Familiar People
C Expressing & Recognizing Emotions
D Identifying Self & Others
E Imitating Others
F Interpersonal Appropriateness
G Friendships
H Demonstrating Caring
I Conversational Skills
J Taking Others' Perspective
K Interpersonal Flexibility

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
D	18. Says the relationship of family members to self (for example, "That's my mom," "He's my brother"); simply calling parents Mom, Dad, or equivalent doesn't count. ? How does he/she describe how family members are related to him/her, things like "that's my mom" or "he's my brother"?	2 1 0	☐
C	19. Uses words to express own emotions (for example, "I'm happy," "I'm scared," "I don't like him"). ? What words does he/she use to show his/her emotions?	2 1 0	☐
F	20. Maintains culturally appropriate eye contact during social interactions. ? What about making proper eye contact when he/she interacts with people?	2 1 0	☐
F	21. Answers politely when familiar adults make small talk (for example, if asked "How are you?" says "I'm fine"; if told "You look nice," says "Thank you"). ? How does he/she respond when adults who he/she knows make "chit chat" or small talk, like asking "How are you?" or saying "You look nice"?	2 1 0	☐
E	22. Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, vacuuming, hammering nails). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about copying an activity several hours after seeing you or someone else do it, like pretending to shave, put on makeup, or vacuum?	2 1 0	☐
2 F	23. Speaks using a loudness, speed, and level of excitement that is appropriate for the conversation. ? What about adjusting his/her voice to the proper loudness, talking speed, and level of excitement for the conversation?	2 1 0	☐
H	24. Does things to try to please others on own initiative (for example, makes someone a card or gift, helps without being asked). ? How often does he/she do things to try to please others, like making them a card or gift or helping with something without being asked?	2 1 0	☐
G	25. Has a best friend or a few good friends. ☑ Score 2 for Yes or 0 for No. ? What about a best friend or a few really good friends?	2 0	☐
F	26. Maintains an acceptable distance between self and others in social situations (for example, does not get too close to another person when talking). ? What about not standing too close or too far away from other people in social situations?	2 1 0	☐
G	27. Is a good friend: Treats his/her friends fairly and with respect, is supportive, etc. ? How does he/she usually treat his/her friends?	2 1 0	☐
I	28. Talks with others about shared interests (for example, sports, TV shows, summer plans). ? What about talking with someone about things that they're both interested in?	2 1 0	☐
G	29. Maintains friendships over time (for example, has had the same good friend for over a year). ? How long have his/her best friendships lasted?	2 1 0	☐
J	30. Recognizes that the likes and dislikes of others can differ from his/her own (for example, might say "Kelly likes pizza, but I don't"; "I liked that movie, but Gretchen hated it"). ? How well does he/she realize that other people might not like and dislike the same things that he/she does, for example, movies or kinds of food?	2 1 0	☐
3 I	31. Starts small talk when he/she meets people he/she knows (for example, says "How are you?"; "What's up?"). ? How often does he/she start "chit chat" or small talk when seeing people who he/she knows, like asking "How are you?"	2 1 0	☐
G	32. Chooses friends with good qualities: Friends who treat him/her with respect, are supportive, stay out of trouble, etc. ? What kinds of friends does he/she usually choose in terms of how they treat him/her, if they're troublemakers, and so on?	2 1 0	☐
I	33. Moves easily from one topic to another in conversation when needed; does not "get stuck" on one topic. ? How flexible is he/she at moving from one topic to another in conversations?	2 1 0	☐

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INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	I	34. Talks with others without interrupting or being rude. ? What about talking with others without interrupting or being rude?	2 1 0 ☐
	J	35. Tells others what he/she is thinking and feeling instead of assuming that they know. ? How often does he/she tell people what he/she is thinking and feeling, instead of assuming that they know?	2 1 0 ☐
4	I	36. Stays on topic in conversations when needed; does not digress. ? What about staying on topic in conversations, rather than getting off track?	2 1 0 ☐
	H	37. Responds positively to the good fortune of others on own initiative (for example, congratulates a friend who receives an award). ? What does he/she do when something good has happened to someone, like when a friend gets an award?	2 1 0 ☐
	H	38. Gives cards and/or gifts to immediate family members on "special days" on own initiative. ? What about giving cards or gifts to family members on special days like birthdays or holidays without being reminded or told?	2 1 0 ☐
	K	39. Will engage in activities suggested by friends, even if not preferred. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? How often does he/she do something suggested by friends when he/she would rather do something else?	2 1 0 ☐
5+	J	40. Starts conversations with others by talking about things that interest them (for example, "Tyrone tells me you like cars"). ? How often does he/she start a conversation with someone by bringing up something that he/she knows that the other person is interested in?	2 1 0 ☐
	K	41. Participates in conversations on a topic not of interest to him/her. ? What about talking with others about things that they're interested in, even though he/she really isn't?	2 1 0 ☐
	J	42. Responds to hints or indirect cues in conversation (for example, knows that a yawn may mean "I'm bored," an abrupt change of subject may mean "I don't want to talk about that," looking at the time may mean "I need to end this conversation"). ? When someone he/she is talking with drops a hint like yawning because they're bored, looking at the time, or changing the subject, how often does he/she get the hint and react appropriately to it?	2 1 0 ☐
	J	43. Provides additional explanation when needed in order for someone to follow what he/she is saying (for example, "In case you missed what I said…," "What we were talking about was…"). ? What about recognizing when someone he/she is talking with needs some background information or something explained in order to follow what's being said?	2 1 0 ☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**ipr** Raw Score	C + D

PLAY AND LEISURE — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning to Play
B Playing With Others
C Make-Believe
D Sharing
E Responding to Social Cues
F Following Rules in Games & Sports
G Playing Games
H Doing Things With Peers
I Planning Activities

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0	A	1. Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands). ? How does he/she respond when you act playful with him/her?	2 1 0	☐
	A	2. Shows interest in surroundings (for example, looks or moves around, touches objects or people). ? What does he/she do that shows that he/she is interested in the things around him/her?	2 1 0	☐
	A	3. Plays simple interaction games with others (for example, peek-a-boo, patty-cake). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about playing baby games like peek-a-boo and patty-cake?	2 1 0	☐
	A	4. Plays near another child, each doing different things. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about playing near another child who is playing, even if they're not playing together?	2 1 0	☐
	A	5. Copies the play of a child playing nearby with little or no interaction between the two. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about copying what a child playing nearby is doing, even though they're not really playing together?	2 1 0	☐
	B	6. Plays interactively with one or more children for at least 5 minutes with someone older supervising. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How long does he/she play interactively with one or more other children when someone older is supervising?	2 1 0	☐
1	B	7. Chooses to join other children who are playing rather than watching them or playing alone. ? When you let him/her decide, how often does he/she choose to join other children who are playing, versus just watching them or playing by himself/herself?	2 1 0	☐
	C	8. Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car or a box is a house). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about using things around the house for make-believe, like pretending a big box is a house?	2 1 0	☐
	D	9. Shares toys or possessions when told to do so. ? How often does he/she share when he/she is told to?	2 1 0	☐
	E	10. Joins in with a group when verbal cues indicate that he/she is welcome. ? What does he/she do when asked to join a group activity?	2 1 0	☐
	B	11. Plays interactively with one or more children for at least 30 minutes with someone older supervising. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How long does he/she play interactively with one or more other children when someone older is supervising?	2 1 0	☐
	B	12. Protects self by moving away from those who try to hurt others or destroy things (those who bite, hit, throw things, smash things, etc.). ? What does he/she do when a child nearby is acting aggressive by trying to hurt other children or destroy things?	2 1 0	☐
	C	13. Plays simple make-believe activities with other children (for example, plays "dress-up," pretends to be superheroes). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of make-believe games does he/she play with other children?	2 1 0	☐
	G	14. Plays with others at simple outdoor group games with no score (for example, tag, jump rope, catch). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about outdoor group games where you don't keep score, like tag, jump rope, or catch?	2 1 0	☐
	B	15. Seeks out others for play or companionship (for example, asks others to play or spend time together). ? How often does he/she take the initiative to ask other children to play?	2 1 0	☐
	B	16. Plays with other children with minimal supervision. ? How about playing interactively with one or more other children without someone older supervising?	2 1 0	☐
	F	17. Takes turns when asked while playing games or sports. ? How often does he/she take turns when he/she is asked to?	2 1 0	☐
	C	18. Engages with other children in elaborate make-believe activities involving more than one role (for example, plays "school" or "restaurant," enacts a TV show or movie). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of make-believe games does he/she play with other children?	2 1 0	☐
2	D	19. Shares toys or possessions without having to be told to do so. ? How often does he/she share without having to be told to?	2 1 0	☐

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Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	E	20. Joins in with a group when nonverbal cues indicate that he/she is welcome. ? What does he/she do when a group lets him/her know without words that they want him/her to join in, like motioning "come join us" or pointing to an empty chair?	2 1 0 ☐
	F	21. Takes turns without having to be asked while playing games or sports. ? How often does he/she take turns without having to be asked?	2 1 0 ☐
3	G	22. Plays with others at simple indoor or outdoor games where the players keep score (for example, tic-tac-toe, kickball, card games). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about simple indoor or outdoor games where the players keep score?	2 1 0 ☐
	F	23. Follows rules in games or sports without being told to do so. ? How often does he/she follow rules in games or sports without being told to?	2 1 0 ☐
	G	24. Plays with others at simple card or board games based only on chance (for example, Candyland®, the card game "war"). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of card or board games does he/she play without anyone helping him/her?	2 1 0 ☐
	E	25. Refrains from entering a group when verbal cues indicate that he/she is not welcome. ? What does he/she do when told that he/she is not welcome to join a group activity?	2 1 0 ☐
	D	26. Asks permission before using things that belong to or are being used by another. ? How often does he/she ask permission before using something that belongs to someone else or that someone else is using?	2 1 0 ☐
	F	27. Shows good sportsmanship in games or sports: Plays fair, is not overly aggressive, congratulates winning players, does not act mean when he/she loses, etc. ? What about showing good sportsmanship, like playing fair, congratulating other players when they win, and not getting mad when he/she loses?	2 1 0 ☐
4+	H	28. Gets together with two or more peers at someone's home. ? How often does he/she get together with a group at someone's home?	2 1 0 ☐
	E	29. Refrains from entering a group when nonverbal cues indicate that he/she is not welcome. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What does he/she do when a group lets him/her know without words that they *don't* want him/her to join in, like ignoring his/her presence?	2 1 0 ☐
	H	30. Goes places with peers during the day or evening with someone supervising (for example, shopping, a movie, a sports event). ☑ Score 2 if the individual did this when younger, but has now outgrown the need to be supervised. ? What places does he/she go with others his/her age with someone supervising, either during the day or at night?	2 1 0 ☐
	G	31. Plays with others at two or more board, card, or electronic games requiring skill and decision making (for example, Monopoly™, poker, Scrabble®, interactive video games). ? What board or card or electronic games requiring skill does he/she play without anyone helping him/her?	2 1 0 ☐
	I	32. Plans ahead to do things with peers on his/her own. ? What kinds of activities does he/she plan ahead with others his/her age?	2 1 0 ☐
	I	33. Obtains schedule information for movies, sports events, concerts, etc. (for example, looks at a newspaper or on the Internet, phones a movie theater). ? What about looking up schedule information for movies, sports events, concerts, and so on?	2 1 0 ☐
	H	34. Goes places with peers during the day without someone supervising (for example, a shopping mall, park, community center). ? What places does he/she go during the day with others his/her age without someone supervising?	2 1 0 ☐
	I	35. Plans fun activities with more than two things to be arranged (for example, birthday party, group outing). ? What about activities that require a lot of things to be planned, like a birthday party or group outing?	2 1 0 ☐
	H	36. Goes places with peers in the evening without someone supervising (for example, a concert, lecture, sports event, movie). ? What places does he/she go at night with others his/her age without someone supervising?	2 1 0 ☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation		
	No. of Est	A	Highest-Numbered Basal Item	× 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling		D
	(A ÷ B) × 100 =	% Est	**pla** Raw Score		C + D

COPING SKILLS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Handling Transitions
B Beginning Emotional Control
C Good Manners
D Asking For & Accepting Help
E Adapting Behavior to the Situation
F Respecting Others
G Controlling Anger
H Obeying Time Limits
I Managing Social Risks
J Making Decisions

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

				Check if Est
0	B	1. Seeks comfort from parent, caregiver, or other when hurt or upset. (?) What does he/she do to try to feel better when he/she gets hurt or upset?	2 1 0	☐
	A	2. Looks or moves toward parent or caregiver when approached by an unfamiliar person. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) How often does he/she look or move toward you when someone he/she doesn't know approaches?	2 1 0	☐
	A	3. Separates easily from parent or caregiver when left with another person (that is, does not have a temper tantrum, sulk, etc. when parent or caregiver leaves or attempts to leave). (?) How often are you able to leave him/her with another person without him/her getting upset?	2 1 0	☐
	A	4. Transitions easily from one activity to another. (?) How often is he/she able to change from one activity to another, like playtime to bath time, without getting upset?	2 1 0	☐
	C	5. Responds politely when given something (that is, expresses thanks either verbally or nonverbally). (?) How often does he/she remember to say *thank you* when given something?	2 1 0	☐
1	C	6. Is polite when asking for something (that is, uses *please* or an appropriate nonverbal gesture). (?) How often does he/she remember to say *please* when asking for something?	2 1 0	☐
	A	7. Handles changes in routine without becoming overly distressed. (?) How does he/she usually react to changes in his/her everyday routine?	2 1 0	☐
	B	8. Recovers quickly from a minor setback or disappointment (for example, doesn't pout for long after losing a game or not getting something that he/she wants). (?) How long does it usually take him/her to get over a small disappointment, like losing a game or not getting something that he/she wants?	2 1 0	☐
	B	9. Uses words or gestures to express distress rather than screaming, hitting, throwing something, etc. (?) What about using words or gestures when he/she is upset rather than screaming, hitting, throwing something, and so on?	2 1 0	☐
	F	10. Apologizes for small, unintentional mistakes (for example, burping, bumping into someone). (?) What does he/she do if he/she makes a small, accidental mistake like burping or bumping into someone?	2 1 0	☐
	C	11. Acts appropriately when introduced to new people (for example, smiles, shakes hands, says "Happy to meet you"). (?) What does he/she do when introduced to someone new?	2 1 0	☐
	D	12. Requests help when encountering a problem beyond own capability to solve (for example, a computer problem, fixing something). (?) How often does he/she ask for help when he/she can't figure out how to do something?	2 1 0	☐
	E	13. Changes behavior intentionally depending on how well he/she knows another person (for example, acts more formally with someone new than with a friend or family member). (?) What about understanding that people are usually expected to act differently with someone they've just met than with a friend or family member?	2 1 0	☐
2	D	14. Accepts helpful suggestions or solutions from others. (?) How is he/she about accepting helpful suggestions from others?	2 1 0	☐
	F	15. Apologizes with sincerity after hurting another's feelings. (?) What does he/she do if he/she hurts someone's feelings?	2 1 0	☐
	E	16. Copies appropriate behavior of others when in a new situation and unsure how to act. (?) What does he/she do when he/she is in a new situation where he/she is not sure how to act?	2 1 0	☐
3	F	17. Is willing to compromise in order to get along with peers. (?) How often is he/she willing to compromise in order to get along with others his/her age?	2 1 0	☐
	G	18. Controls anger or hurt feelings when plans change for reasons that can't be helped (for example, an event cancelled due to bad weather, a trip postponed due to car trouble). (?) How does he/she usually respond when plans change for reasons that can't be helped, like when something he/she is looking forward to has to be called off because of bad weather?	2 1 0	☐
	H	19. Follows time limits imposed by parent or caregiver (for example, amount of time allowed to watch TV, play a game, use the Internet, or play outside). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) When you tell him/her that he/she is only allowed to do something for a limited amount of time, how often does he/she obey that time limit without having to be reminded; for example, "You can watch TV until this show is over, then you have to turn it off"?	2 1 0	☐

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COPING SKILLS — SOCIALIZATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

	G	20. Understands that when someone does or says something that hurts, it may be accidental rather than intentional. ? What about understanding that when someone does or says something that hurts, it might have been an accident or mistake, and that the person may not have been trying to hurt him/her?	2 1 0	☐
	E	21. Adjusts behavior to keep from disrupting others nearby (for example, is quiet near others who are working, listening to a show, etc.). ? What about realizing when he/she needs to adjust his/her behavior so that he/she doesn't disturb others nearby, like someone who is working or listening to a show?	2 1 0	☐
4–5	G	22. Controls anger or hurt feelings when he/she does not get his/her way (for example, when not allowed to watch television or attend a party, when a suggestion is rejected by a friend or supervisor). ? How does he/she usually respond when he/she doesn't get his/her way, like not being allowed to do something that he/she wants to?	2 1 0	☐
	F	23. Keeps promises. ? How often does he/she keep his/her promises, like paying back money or returning things that he/she borrows, without having to be reminded?	2 1 0	☐
	G	24. Controls anger or hurt feelings when given constructive criticism (for example, correction of misbehavior, discussion of a test score or grade, a performance review). ? How does he/she usually respond when someone criticizes him/her in a way that's intended to be helpful, like suggesting how to do something better next time?	2 1 0	☐
	I	25. Understands that a friendly appearing person may actually intend harm. ? What does he/she understand about how a friendly acting person may actually want to take advantage of him/her?	2 1 0	☐
	F	26. Respects others' time (for example, doesn't keep others waiting or interrupt others who are busy). ? What about respecting other people's time, like not keeping them waiting or interrupting them when they're busy?	2 1 0	☐
	I	27. When possible, avoids or leaves harmful relationships or situations (for example, being bullied, coerced into breaking the law, taken advantage of sexually or financially). ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What about staying away from or leaving a relationship or situation where he/she or someone else might get hurt?	2 1 0	☐
6+	I	28. Avoids being manipulated, dominated, or taken advantage of by others. ? What does he/she do to keep others from controlling or taking advantage of him/her?	2 1 0	☐
	J	29. Thinks through the consequences of his/her actions before acting (for example, refrains from acting impulsively, considers relevant information). ? How often does he/she think through the consequences before doing something?	2 1 0	☐
	H	30. Obeys curfews (that is, comes home when he/she is told to, during the day or at night). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? When you tell him/her that he/she needs to be home at a certain time, how often is he/she home at that time?	2 1 0	☐
	I	31. Is aware of and uses caution when encountering risky social situations (for example, Internet solicitations, a stranger's offer of a ride or money, "binge" drinking parties, social media, personal ads). ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? How is he/she at being cautious when people he/she doesn't know well try to get him/her to do something risky, either in person or through the Internet?	2 1 0	☐
	H	32. Informs parent or caregiver about his/her plans when he/she goes out (for example, what time he/she is leaving and returning, where he/she is going). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about telling you about his/her plans when he/she goes out, like where he/she is going and when he/she will be home?	2 1 0	☐
	J	33. Recognizes that advertising messages may not be accurate. ? What about understanding that the purpose of advertising is to influence our decisions, and that everything in ads isn't always totally true?	2 1 0	☐

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**cop** Raw Score	C + D

GROSS MOTOR — MOTOR SKILLS DOMAIN

INTERVIEW TOPICS

A Sitting
B Pre-Walking Mobility
C Standing
D Walking
E Ball Activities
F Climbing
G Running
H Using Stairs
I Jumping & Hopping
J Catching a Ball
K Riding a Tricycle or Bicycle

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
0	A	1. Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute. ? How long does he/she sit with his/her back supported, like in a chair with a back or propped up by pillows?	2 1 0 ☐
	B	2. Rolls over from back onto stomach. ? How about rolling over from his/her back onto his/her stomach?	2 1 0 ☐
	A	3. Sits unsupported for at least 1 minute. ? How long does he/she sit without anything supporting his/her back?	2 1 0 ☐
	B	4. Moves, scoots, or crawls across the floor. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about moving, scooting, or crawling across the floor?	2 1 0 ☐
	A	5. Sits unsupported for at least 10 minutes. ? How long does he/she sit without anything supporting his/her back?	2 1 0 ☐
	C	6. Stands holding on to a stable object for at least 5 seconds. ☑ Score 2 if the individual did this when younger, but now stands without holding on to anything. ? How long does he/she stand while holding on to something?	2 1 0 ☐
	C	7. Pulls self up to standing position. ? What about pulling himself/herself up to standing?	2 1 0 ☐
	C	8. Stands supported with one hand and reaches for an object with the other hand without falling. ☑ Score 2 if the individual did this when younger, but now stands without holding on to anything. ? What happens if he/she is standing holding on to something with one hand and reaches for something with his/her other hand?	2 1 0 ☐
	D	9. Takes steps while supporting self using furniture or another stable object. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about taking steps while holding on to furniture or something else?	2 1 0 ☐
	B	10. Crawls up stairs. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go up stairs?	2 1 0 ☐
	C	11. Stands unsupported for at least 1 minute. ? How long does he/she stand without holding on to anything?	2 1 0 ☐
	D	12. Takes at least two steps without support. ? How many steps does he/she take without holding on to anything?	2 1 0 ☐
	C	13. Stands unsupported and reaches for an object without falling. ? What happens if he/she is standing without holding on to anything and reaches for something?	2 1 0 ☐
	D	14. Walks to get around; does not need to hold on to anything. ? How often does he/she walk to get around rather than crawling?	2 1 0 ☐
	F	15. Safely climbs on and off low objects (for example, child's chair, step stool, low bench). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about low objects like a child's chair?	2 1 0 ☐
	B	16. Goes down stairs by crawling backwards or scooting on bottom. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go down stairs?	2 1 0 ☐
	C	17. Squats or bends down to pick up objects without falling. ? What happens when he/she needs to pick up something off the ground?	2 1 0 ☐
	E	18. Throws a ball with one hand; accuracy not important. ? How about throwing a ball with one hand?	2 1 0 ☐
	F	19. Safely gets on and off an adult-sized chair. ? How about an adult-sized chair?	2 1 0 ☐
1	G	20. Runs without falling; may be awkward and uncoordinated. ? How smoothly does he/she run, and how often does he/she fall?	2 1 0 ☐
	H	21. Walks up stairs, putting both feet on each step; may use railing. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go up stairs?	2 1 0 ☐
	E	22. Kicks a ball while standing; accuracy not important. ? How about kicking a ball while standing?	2 1 0 ☐

31321-2/6/9/

GROSS MOTOR — MOTOR SKILLS DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

D	23. Walks two or more blocks without having to rest or needing physical support. ? What about walking two or more blocks without needing to rest or be helped?	2 1 0	☐
H	24. Walks down stairs, facing forward, putting both feet on each step; may use railing. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go down stairs?	2 1 0	☐
I	25. Jumps off the ground with both feet without falling. ? How about jumping off the ground with both feet without falling?	2 1 0	☐
G	26. Runs smoothly without falling. ? How smoothly does he/she run, and how often does he/she fall?	2 1 0	☐
F	27. Safely climbs up and down high objects (for example, jungle gym, ladder, tree). ? What about high objects like a jungle gym, a ladder, or a tree?	2 1 0	☐
D	28. Walks carefully on a sidewalk or road that is slippery or uneven. ? What does he/she do if he/she is walking outside and the sidewalk or road is slippery or uneven?	2 1 0	☐
I	29. Jumps forward at least three times with both feet without falling. ? How many times can he/she jump forward with both feet without falling?	2 1 0	☐
G	30. Runs smoothly, changing speed and direction (for example, when playing tag or sports, or chasing a pet). ? How about changing his/her speed and direction while running, like when playing tag or sports?	2 1 0	☐
J	31. Catches a beach ball-sized ball from a distance of 2 or 3 feet. ? What about a beach ball-sized ball thrown from 2 or 3 feet away?	2 1 0	☐
H	32. Walks up stairs, alternating feet; may use railing. ? How does he/she go up stairs?	2 1 0	☐
2 H	33. Walks down stairs, alternating feet; may use railing. ? How does he/she go down stairs?	2 1 0	☐
H	34. Climbs a flight of eight or more stairs at a normal pace; may use railing. ? How fast does he/she go up a flight of eight or more stairs?	2 1 0	☐
K	35. Pedals a tricycle or other three-wheeled vehicle for at least 6 feet. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How far does he/she pedal a tricycle or other three-wheeled vehicle?	2 1 0	☐
I	36. Hops on one foot at least once without falling; may hold on to something for balance. ? How about hopping on one foot while holding on to something?	2 1 0	☐
K	37. Pedals a tricycle or other three-wheeled vehicle around corners. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about pedaling a tricycle or other three-wheeled vehicle around corners?	2 1 0	☐
3+ J	38. Catches a beach ball-sized ball from at least 6 feet away. ? What about a beach ball-sized ball thrown from 6 feet away or more?	2 1 0	☐
I	39. Hops forward on one foot with ease without holding on (for example, during hopscotch). ? How about hopping forward on one foot multiple times without holding on?	2 1 0	☐
J	40. Catches a tennis- or baseball-sized ball from a distance of 2 or 3 feet, using one or both hands extended away from body. ? What about a tennis- or baseball-sized ball thrown from 2 or 3 feet away?	2 1 0	☐
K	41. Rides a balance bike or bicycle with training wheels for at least 10 feet. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How far does he/she ride a balance bike or a bicycle with training wheels?	2 1 0	☐
J	42. Catches a tennis- or baseball-sized ball from a distance of at least 10 feet, moving to catch it if necessary. ? What about a tennis- or baseball-sized ball thrown from 10 feet away or more when he/she needs to move to catch it?	2 1 0	☐
K	43. Rides a regular bicycle without training wheels without falling. ? What about riding a regular bicycle without falling?	2 1 0	☐

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**gmo** Raw Score	C + D

FINE MOTOR — MOTOR SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Handle Objects
B Manipulating Things
C Opening Doors
D Beginning Crayon/Pen Use
E Hand Coordination
F Drawing
G Coloring
H Using Scissors
I Tying
J Precise Movements

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

				Check if Est
0	A	1. Reaches for a toy or object. ? How often does he/she reach to try to grab a toy or other object?	2 1 0	☐
	A	2. Picks up objects; may use both hands. ? How does he/she pick up things like a toy or a ball?	2 1 0	☐
	A	3. Moves an object from one hand to the other. ? What about moving an object from one hand to the other?	2 1 0	☐
	B	4. Removes an object (for example, a block or small toy) from a box or other container with no lid. ? How about taking something out of a box or other container?	2 1 0	☐
	A	5. Picks up small objects (no larger than 2 inches on any side) with thumb and fingers (for example, raisins, beads, small blocks). ? How does he/she pick up small objects?	2 1 0	☐
	A	6. Picks up a small toy or object with one hand and hands it to someone without dropping it. ? How does he/she pick up something small and hand it to someone?	2 1 0	☐
	B	7. Puts an object (for example, a block or small toy) into a box or other container with no lid. ? How about putting something into a box or other container?	2 1 0	☐
	D	8. Marks on paper with a crayon, pen, or pencil; method of grasping the crayon, pen, or pencil is not important. ? What about making marks on paper with a crayon, pen, or pencil?	2 1 0	☐
	C	9. Opens doors that require only pushing or pulling (for example, cabinet, refrigerator, sliding, or swinging doors). ? What about opening doors that only need to be pushed or pulled, like cabinet doors or sliding doors?	2 1 0	☐
1	B	10. Stacks at least four small blocks or other small objects; alignment need not be perfect, but the stack must remain upright. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How many blocks or other small objects does he/she stack before they fall?	2 1 0	☐
	B	11. Turns book or magazine pages one by one; books with cardboard pages don't count. ? How about turning book or magazine pages one at a time?	2 1 0	☐
	E	12. Unwraps small objects (for example, gum or candy). ? How often does he/she unwrap small objects like a piece of candy or gum by himself/herself?	2 1 0	☐
	C	13. Opens doors by turning a doorknob or handle. ? What about opening doors by turning a doorknob or handle?	2 1 0	☐
2	E	14. Uses a twisting hand–wrist motion (for example, winds up a toy or music box, screws/unscrews the lid of a jar). ? What about holding something in one hand and twisting with the other, like winding up a toy or music box, or unscrewing the lid of a jar?	2 1 0	☐
	D	15. Holds a crayon, pen, or pencil in proper position (that is, using a tripod grasp, not with fist) for writing or drawing. ? How does he/she hold a crayon, pen, or pencil?	2 1 0	☐
	E	16. Presses buttons accurately on a small keyboard or touch screen (for example, on a calculator, cell phone, or other handheld device). ? What about pressing buttons on a small keyboard or touchscreen, like on a cell phone or calculator?	2 1 0	☐
	H	17. Opens and closes scissors with one hand; does not have to cut with them. ? What about opening and closing scissors with one hand?	2 1 0	☐
	F	18. Draws a circle freehand while looking at an example. ? What about copying a circle?	2 1 0	☐
	G	19. Colors simple shapes or animals; more coloring is inside the lines than outside. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0	☐
3	F	20. Draws more than one recognizable form (for example, a person, house, tree). ? What does he/she draw well enough that you can recognize what it is?	2 1 0	☐
	E	21. Pours liquid from one container to another with little or no spilling (for example, pouring milk or juice into a glass). ? What happens when he/she tries to pour liquid, like pouring milk or juice into a glass?	2 1 0	☐
	F	22. Draws a square freehand while looking at an example. ? What about copying a square?	2 1 0	☐
	H	23. Uses scissors to cut along a straight line across a standard sheet of paper. ? How far does he/she cut with scissors on a straight line across a sheet of paper?	2 1 0	☐

31321-2/5/9/

FINE MOTOR — MOTOR SKILLS DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	F	24. Draws a triangle freehand while looking at an example. ? What about copying a triangle?	2 1 0 ☐
	F	25. Uses an eraser without tearing the paper. ? How about using an eraser without tearing the paper?	2 1 0 ☐
4	H	26. Cuts out simple shapes (circles, squares, rectangles, etc.). ? What kinds of things does he/she cut out?	2 1 0 ☐
	G	27. Colors simple pictures with all coloring inside the lines. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0 ☐
	G	28. Colors a full-page drawing or scene using two or more colors; all coloring is inside the lines. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0 ☐
	F	29. Draws a straight line using a ruler or straightedge. ? What about drawing a straight line using a ruler or straightedge?	2 1 0 ☐
5+	I	30. Ties a knot. ? What about tying a knot without help?	2 1 0 ☐
	H	31. Cuts out complex shapes (for example, stars, animals, alphabet letters). ? What kinds of things does he/she cut out?	2 1 0 ☐
	I	32. Ties a secure bow (for example, shoe laces, gift wrapping). ? What about tying a secure bow without help, for example, shoe laces or a gift wrapping bow?	2 1 0 ☐
	J	33. Manipulates very small objects (for example, sets hands on a watch, threads a sewing needle, glues miniature model parts). ? What about working with very small objects, like setting the hands on a watch, threading a sewing needle, or gluing tiny model parts?	2 1 0 ☐
	J	34. Assembles, builds, or creates complex building toy structures, model sets, homemade jewelry, arts and crafts, etc. ? What kinds of complex building toy structures, model sets, homemade jewelry, arts and crafts, and things like that does he/she make?	2 1 0 ☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation		
	No. of Est	A	Highest-Numbered Basal Item	× 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling		D
	(A ÷ B) × 100 =	% Est	**fmo** Raw Score		C + D

MALADAPTIVE BEHAVIOR DOMAIN

Unlike the adaptive behavior items that you have just completed, the maladaptive behavior items are read directly to the respondent. Read (or paraphrase) each item as it is written, clarify if needed, and ask the respondent to tell you how often the behavior happens:

2 = *Often*, **1** = *Sometimes*, **0** = *Never*

SUGGESTED INTRODUCTION

Say to the respondent, "We're going to finish by talking about problem behaviors that [name] may or may not be exhibiting. This time I'm going to read you a description of each behavior and ask you to tell me if it happens often, happens sometimes, or never happens."

INTERNALIZING — MALADAPTIVE BEHAVIOR DOMAIN

	Response Options: 2 = Often, 1 = Sometimes, 0 = Never			Check if Est
1.	Is overly needy or dependent (for example, insists on help even when he/she does not need it, clings to parent or teacher).	2	1 0	☐
2.	Has eating problems (for example, overeats, refuses to eat, will only eat one or two things, hoards food).	2	1 0	☐
3.	Has sleep problems (for example, walks in his/her sleep, has a lot of nightmares, sleeps way more or less than others his/her age).	2	1 0	☐
4.	Refuses to go to school or work, or has to come home, because of worrying, sadness, nervousness, etc.	2	1 0	☐
5.	Is extremely anxious or nervous.	2	1 0	☐
6.	Cries or is sad for no clear reason.	2	1 0	☐
7.	Avoids interacting with others (withdraws, prefers to be alone, etc.).	2	1 0	☐
8.	Lacks interest in doing things that he/she enjoys or used to enjoy.	2	1 0	☐
9.	Is extremely fearful of one or more common objects or situations (for example, heights, snakes, elevators).	2	1 0	☐
10.	Worries for no clear reason.	2	1 0	☐
11.	Is very irritable or moody.	2	1 0	☐
12.	Feels helpless or hopeless (for example, says that things are bad and will never get better).	2	1 0	☐
13.	Complains of feeling sick, exhausted, or in pain, even though there is no medical reason.	2	1 0	☐

Office Use Only — **Internalizing** Raw Score ☐

EXTERNALIZING — MALADAPTIVE BEHAVIOR DOMAIN

	Response Options: 2 = Often, 1 = Sometimes, 0 = Never			Check if Est
1.	Has temper tantrums: Screams, cries, kicks, etc.	2	1 0	☐
2.	Disobeys those in authority.	2	1 0	☐
3.	Bullies others physically or with words.	2	1 0	☐
4.	Lies, cheats, or steals.	2	1 0	☐
5.	Is physically aggressive (for example, hits, kicks, bites).	2	1 0	☐
6.	Is stubborn or argues.	2	1 0	☐
7.	Is verbally abusive (that is, hurts others on purpose with insults, put-downs, etc.).	2	1 0	☐
8.	Breaks rules or laws because of peer pressure.	2	1 0	☐
9.	Is much more active or restless than others his/her age (for example, moves all the time, cannot sit still, fidgets).	2	1 0	☐
10.	Takes or uses school or work property when not allowed (for example, books, office supplies).	2	1 0	☐
11.	Destroys his/her own or someone else's possessions on purpose.	2	1 0	☐

Office Use Only — **Externalizing** Raw Score ☐

313212/4/9/

CRITICAL ITEMS — MALADAPTIVE BEHAVIOR DOMAIN

Response Options: 2 = *Often*, 1 = *Sometimes*, 0 = *Never*

		Check if Est
1. Gets fixated on objects or parts of objects (for example, stares at spinning wheels or fan blades, lines up objects, flips light switches over and over).	2 1 0	☐
2. Talks about hearing voices that others do not hear, or seeing things that others do not see.	2 1 0	☐
3. Harms himself/herself (for example, bangs his/her head, hits or bites self, cuts self, tears at skin, pulls out his/her hair).	2 1 0	☐
4. Uses strange or repetitive speech (for example, has conversations with himself/herself in public, says things that make no sense, repeats the same thing over and over).	2 1 0	☐
5. Loses awareness of what is happening around him/her (for example, seems to be "in a fog," "zones out").	2 1 0	☐
6. Repeats physical movements over and over (for example, rocks back and forth, spins, flaps hands).	2 1 0	☐
7. Has toileting accidents (that is, wets or soils self when not in diapers).	2 1 0	☐
8. Eats non-food items such as dirt, paste, or soap.	2 1 0	☐
9. Engages in compulsive behavior (for example, repeated hand washing, repeatedly checking and rechecking something, other compulsive rituals).	2 1 0	☐
10. Shows far more interest in weapons or extreme violence than others his/her age.	2 1 0	☐
11. Harms animals (for example, tortures or kills pets or wild animals).	2 1 0	☐
12. Has beliefs that are not true (for example, believes he/she has a "true" identity or "special" powers, believes that others secretly want to cause harm).	2 1 0	☐
13. Gets so fixated on a particular topic that it annoys others (for example, trains, reptiles, maps, subway systems).	2 1 0	☐
14. Talks about killing himself/herself or has tried to kill self.	2 1 0	☐
15. Has no response to pain (for example, does not cry or seek help when cut, bruised, or badly hurt).	2 1 0	☐
16. Wanders, darts away, or takes off from home, school, or someone watching him/her without regard for safety.	2 1 0	☐
17. Threatens to hurt or kill someone.	2 1 0	☐
18. Is tricked by others into doing something that could seriously harm him or her, or someone else.	2 1 0	☐
19. Gets fixated on a person in a way that is annoying or intrusive to that person.	2 1 0	☐
20. Engages in unwanted sexual behavior (for example, unwanted comments, unwanted physical contact, exposing himself/herself, masturbating in public, having sex at school or work).	2 1 0	☐

GENERAL COMMENTS

Use this space to record any general comments about the interview that you want included in the test record.

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Vineland-3

Comprehensive Interview Form
Score Report

Examinee's Name:

Examiner's Name:

Interview Respondent's Name:

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Score Summary

	Subdomains				
	Raw Score	v-Scale Score	Age Equivalent (AE)	Growth Scale Value (GSV)	% Est
Receptive (rec)					
Expressive (exp)					
Written (wrn)					
COMMUNICATION (COM) Sum of v-Scale Scores:		1			
Personal (per)					
Domestic (dom)					
Community (cmm)					
DAILY LIVING SKILLS (DLS) Sum of v-Scale Scores:		2			
Interpersonal Relationships (ipr)					
Play and Leisure (pla)					
Coping Skills (cop)					
SOCIALIZATION (SOC) Sum of v-Scale Scores:		3			
Gross Motor (gmo)					
Fine Motor (fmo)					
MOTOR SKILLS (MOT) Sum of v-Scale Scores:		4			

	Domains and Adaptive Behavior Composite			
	Sum of v-Scale Scores	Standard Score	85% 90% 95% Confidence Interval	Percentile Rank
Communication (COM)	1		—	
Daily Living Skills (DLS)	2		—	
Socialization (SOC)	3		—	
Sum of Domain Standard Scores				
See Table B.3 to convert to ABC		▼		
Adaptive Behavior Composite (ABC)			—	
Motor Skills (MOT)	4		—	

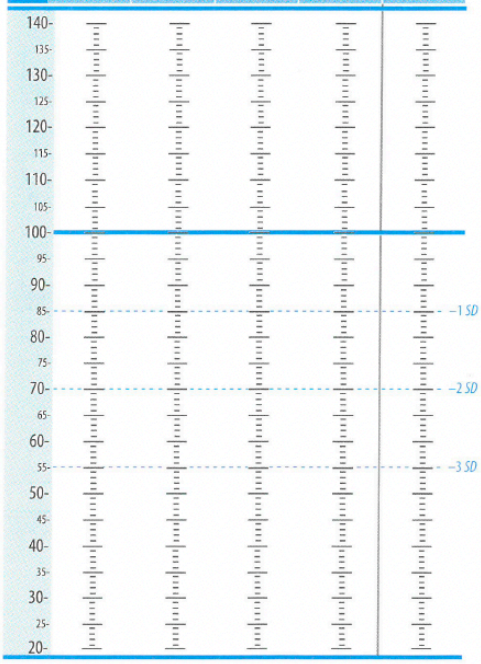
PEARSON

PsychCorp

Subdomain v-Scale Score Profile

	COMMUNICATION			DAILY LIVING SKILLS			SOCIALIZATION			MOTOR SKILLS		
	rec	exp	wrn	per	dom	cmm	ipr	pla	cop	gmo	fmo	
24	•	•	•	•	•	•	•	•	•	•	•	24
23	•	•	•	•	•	•	•	•	•	•	•	23
22	•	•	•	•	•	•	•	•	•	•	•	22
21	•	•	•	•	•	•	•	•	•	•	•	21
20	•	•	•	•	•	•	•	•	•	•	•	20
19	•	•	•	•	•	•	•	•	•	•	•	19
18	•	•	•	•	•	•	•	•	•	•	•	18
17	•	•	•	•	•	•	•	•	•	•	•	17
16	•	•	•	•	•	•	•	•	•	•	•	16
15	•	•	•	•	•	•	•	•	•	•	•	15
14	•	•	•	•	•	•	•	•	•	•	•	14
13	•	•	•	•	•	•	•	•	•	•	•	13
12	•	•	•	•	•	•	•	•	•	•	•	12
11	•	•	•	•	•	•	•	•	•	•	•	11
10	•	•	•	•	•	•	•	•	•	•	•	10
9	•	•	•	•	•	•	•	•	•	•	•	9
8	•	•	•	•	•	•	•	•	•	•	•	8
7	•	•	•	•	•	•	•	•	•	•	•	7
6	•	•	•	•	•	•	•	•	•	•	•	6
5	•	•	•	•	•	•	•	•	•	•	•	5
4	•	•	•	•	•	•	•	•	•	•	•	4
3	•	•	•	•	•	•	•	•	•	•	•	3
2	•	•	•	•	•	•	•	•	•	•	•	2
1	•	•	•	•	•	•	•	•	•	•	•	1

Domain and ABC Standard Score Profile



MALADAPTIVE BEHAVIOR

	Raw Score	v-Scale Score	Critical Items (Circle all item scores of 2 or 1)
Internalizing			1. 2 1 2. 2 1 3. 2 1 4. 2 1 5. 2 1 6. 2 1 7. 2 1 8. 2 1 9. 2 1 10. 2 1
Externalizing			11. 2 1 12. 2 1 13. 2 1 14. 2 1 15. 2 1 16. 2 1 17. 2 1 18. 2 1 19. 2 1 20. 2 1

STRENGTH/WEAKNESS ANALYSIS

Domains	Standard Score (SS)	SS Minus Mean SS	.10 or .05 Critical Value	Strength or Weakness	Base Rate
COM				S or W	
+					
DLS				S or W	
+					
SOC				S or W	
+					
MOT				S or W	
=					
	Sum of SS	÷ No. of domains (3 or 4)	= Mean SS (one decimal)	Calculation of Mean Domain Standard Score	

Subdomains	v-Scale Score (vS)	vS Minus Mean vS	.10 or .05 Critical Value	Strength or Weakness	Base Rate
rec				S or W	
+					
exp				S or W	
+					
wrn				S or W	
+					
per				S or W	
+					
dom				S or W	
+					
cmm				S or W	
+					
ipr				S or W	
+					
pla				S or W	
+					
cop				S or W	
+					
gmo				S or W	
+					
fmo				S or W	
=					
	Sum of vS	÷ No. of subdomains	= Mean vS (one decimal)	Calculation of Mean Subdomain v-Scale Score	

PAIRWISE DIFFERENCE COMPARISONS

Domain Comparisons	Standard Score	<, >, or =	Standard Score	Standard Score Difference	.10 or .05 Critical Value	Statistically Significant	Base Rate
COM		_	DLS			Y or N	
COM		_	SOC			Y or N	
DLS		_	SOC			Y or N	
COM		_	MOT			Y or N	
DLS		_	MOT			Y or N	
SOC		_	MOT			Y or N	

Subdomain Comparisons	v-Scale Score	<, >, or =	v-Scale Score	v-Scale Score Difference	.10 or .05 Critical Value	Statistically Significant	Base Rate
Communication							
rec		_	exp			Y or N	
rec		_	wrn			Y or N	
exp		_	wrn			Y or N	
Daily Living Skills							
per		_	dom			Y or N	
per		_	cmm			Y or N	
dom		_	cmm			Y or N	
Socialization							
ipr		_	pla			Y or N	
ipr		_	cop			Y or N	
pla		_	cop			Y or N	
Motor Skills							
gmo		_	fmo			Y or N	
Across-Domain Comparisons							
		_				Y or N	
		_				Y or N	
		_				Y or N	

Abbreviations

COM	Communication	DLS	Daily Living Skills	SOC	Socialization	MOT	Motor Skills
rec	Receptive	per	Personal	ipr	Interpersonal Relationships	gmo	Gross Motor
exp	Expressive	dom	Domestic	pla	Play and Leisure	fmo	Fine Motor
wrn	Written	cmm	Community	cop	Coping Skills		

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3 4 5 6 7 8 9 10 11 12 B C D E Product Number 31321

MODIFIED SIMONDS & PARRAGA SLEEP QUESTIONNAIRE (MSPSQ)

PART 1

Instructions: Please tick either **YES** or **NO**, tick one of the boxes or, where appropriate, write your answer.

We would be grateful for the following information about your child:

Hight of your child: _____

Weight of your child: _____

Has your child had any excessive weight gain in the last six months **Yes** o **No** o

Has your child had any excessive weight loss in the last six months **Yes** o **No** o

1. Does your child have a room of their own? **Yes** o **No** o

2. How many other children sleep in the same room as your child? _____

3. Would you normally be likely to know if your child was awake either in the evening when going to sleep, or in the night or in the morning? **Yes** o **No** o

4. Does your child have a bedtime routine that is followed every night? e.g. supper, bath, drink, story, kiss, goodnight, light out etc. **Yes** o **No** o

4a. If yes, please describe _____

---

5. How often does your child resist or struggle with you around bedtime?

o Never

o About once a month

o A few times a month

o One or two times a week

o Many times a week

o Daily

6. How long does it take for your child to fall asleep at night?
o Few minutes

o Up to half an hour

o Up to one hour

o One to two hours

o More than two hours

7. If your child will not go to bed or settle to sleep what do you do about it?

---

8. Once asleep does he/she sleep soundly? **Yes** o **No** o

9. Where does your child usually fall asleep?
o His/her bedroom

o Parent's bedroom

o Sibling's bedroom

o Family/living room

o More than two hours
10. How often does your child wake up during the night?
o Never

o About once a month

o A few times a month

o One or two times a week

o Many times a week

o Daily

11. If your child usually wakes at night, how many times does your child usually wake each night? ____

12. How long does it take your child to fall back asleep?
o Few minutes

o Up to half an hour

o Up to one hour

o One to two hours

o More than two hours

13. What does your child do before getting back to sleep again?
o Nothing

o Crying

o Calling out

o Wandering about

o Playing with toys

o Looking at books and magazines

o Other (please specify) _____

14. Do you take any special steps to ensure that your child is safe if he/she wakes up during the night **Yes** o **No** o
14a. If yes, please describe _____

_____

15. Is your child a light sleeper (i.e. any noise will wake him/her)? **Yes** o **No** o

16. Does your child report any dreams? **Yes** o **No** o

17. If he/she reports and dreams, are they generally pleasant? **Yes** o **No** o

18. If he/she reports and dreams, are they generally unpleasant? **Yes** o **No** o

19. Does your child ever sleep in unusual positions? **Yes** o **No** o
19a. If yes, please describe _____

_____

20. If your child was not woken or did not have to get up in the morning, until what time would he/she sleep? ____

PART 2

Some children sleep differently during the week than on weekends or school holidays. Please answer the following questions about how your child has been

	Weekdays	**Weekends and Holidays**
1. What time do you start getting your child ready for bed?		
2. What time does your child usually go to bed?		
3. What time does your child usually go to sleep?		
4. What time does your child usually wake up?		
5. What time does your child usually get up?		

	Weekdays	**Weekends and Holidays**
6. Does your child have to be woken in the morning?	**Yes** o **No** o	**Yes** o **No** o
7. Does your child usually wake up in the morning well rested?	**Yes** o **No** o	**Yes** o **No** o
8. Does your child usually wake up in the morning feeling quite tired?	**Yes** o **No** o	**Yes** o **No** o
9. Does he/she usually wake up in a bad mood?	**Yes** o **No** o	**Yes** o **No** o
10. Does he/she usually wake up in a good mood?	**Yes** o **No** o	**Yes** o **No** o

11. Does your child take naps during the day? **Yes** o **No** o **Yes** o **No** o

PART 3

During the **LAST ONE MONTH** has your child show any of the following

	Never	About once a month	A few times a month	Once or twice a week	Many times a week	Daily
21. Talks in sleep	**m**	**m**	**m**	**m**	**m**	**m**
22. Walks in sleep	**m**	**m**	**m**	**m**	**m**	**m**
23. Grinds teeth in sleep	**m**	**m**	**m**	**m**	**m**	**m**
24. Bangs head at night	**m**	**m**	**m**	**m**	**m**	**m**
25. Has quick movements of arms or legs during sleep (e.g kicking, jumping, arm flapping)	**m**	**m**	**m**	**m**	**m**	**m**
27. Bites tongue in sleep	**m**	**m**	**m**	**m**	**m**	**m**
28. Snores loudly during sleep	**m**	**m**	**m**	**m**	**m**	**m**
29. Seems to repeatedly stop breathing for periods of time lasting up to 30 seconds during sleep	**m**	**m**	**m**	**m**	**m**	**m**
30. Wets bed during sleep	**m**	**m**	**m**	**m**	**m**	**m**
31. Wakes in night complaining of nightmares or frightening dreams and seems quite anxious. This usually happens in the last half of the night	**m**	**m**	**m**	**m**	**m**	**m**

	Never	About once a month	A few times a month	Once or twice a week	Many times a week	Daily
32. Wakes during the night screaming in terror. Anxiety may be so bad that sweating, gasping or trembling may happen. This usually happens in the first half of the night. He/she is not aware of their surroundings and will not remember it the next day	m	m	m	m	m	m
33. Doesn't want to go to bed because he/she is afraid	m	m	m	m	m	m
34. Expresses fear that if he/she goes to sleep they might die	m	m	m	m	m	m
35. Insists on seeping somewhere else instead of his/he bed	m	m	m	m	m	m
36. Afraid of the dark	m	m	m	m	m	m
37. Needs security blanket (e.g. teddy bear) before he/she goes to sleep	m	m	m	m	m	m
38. Insists on bedtime rituals (e.g. bedtime story) before sleep	m	m	m	m	m	m
39. Needs sleep medication	m	m	m	m	m	m
40. During the day, muscles become so weak the he/she falls to the ground or has to lie down before falling (usually after laughing, crying or being frightened)	m	m	m	m	m	m
41. Upon waking or going to sleep, feels paralysed even though he/she is aware of their surroundings	m	m	m	m	m	m

	Never	About once a month	A few times a month	Once or twice a week	Many times a week	Daily
43. Seems drowsy during the day, but can stop himself/herself sleeping	**m**	**m**	**m**	**m**	**m**	**m**
44. During the day, seems more active than other children	**m**	**m**	**m**	**m**	**m**	**m**
45. Rolls from side to side rhythmically in sleep or while going off to sleep	**m**	**m**	**m**	**m**	**m**	**m**
46. Sleeps with head tipped right back	**m**	**m**	**m**	**m**	**m**	**m**
47. Breaths through mouth rather than nose when asleep	**m**	**m**	**m**	**m**	**m**	**m**
48. Complains of headaches on waking up	**m**	**m**	**m**	**m**	**m**	**m**
49. Sweats a lot during sleep	**m**	**m**	**m**	**m**	**m**	**m**
50. Reluctant to go to bed	**m**	**m**	**m**	**m**	**m**	**m**
51. Wakes in the morning before 5am and stays awake	**m**	**m**	**m**	**m**	**m**	**m**
52. Insists on sleeping with someone else at sleep onset/in night	**m**	**m**	**m**	**m**	**m**	**m**

PART 4

This section asks some questions about treatments for sleep problems you might have tried and also the family's sleep.

1. In your opinion does your child have a sleep problem? **Yes** o **No** o

If yes, please go to question 5

If no, in your opinion has your child had a sleep problem in the past? **Yes** o **No** o

If no, please go to question 8

2. What would you say this problem was (multiple answers possible)

o Difficulty falling asleep

o Night waking

o Early waking

o Feeling sleepy during the day

o Doesn't want to sleep alone

Other (please specify) _____

3. Until when did these problems last?

o Up to 1 month ago

o 1 to 3 months ago

o 3 to 6 months ago

o 6 months to 1 year ago

o More than 1 year ago

If more than 1 year ago, please specify Year(s) ☐ Month(s) ☐ Ago

4. How long did the problems last? From (month /year) ☐ Until (month/year) ☐

5. What would you say this problem is (multiple answers possible)?

o Difficulty falling asleep

o Night waking

o Early waking

o Feeling sleepy during the day

o Doesn't want to sleep alone

Other (please specify) _____

6. At the moment, how long have these problems lasted?

o Up to 1 month ago

o 1 to 3 months ago

o 3 to 6 months ago

o 6 months to 1 year ago

o More than 1 year ago

7. In your opinion, what causes your child's sleep problems _____

_____

8. Have you ever had any advice or treatment for your child's sleep? **Yes** o **No** o

If no, please go to question 9

If YES, please select type of advice or treatment and its effectiveness.
Treatment is considered effective when it results in a substantial reduction or elimination of the sleep problems.

Education/general advice **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - operation **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - medication **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Medical - other **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

Psychological (e.g. behavioural treatment) **Yes** o **No** o

If yes, please specify _____

Was the treatment effective? **Yes** o **No** o **Partially** o

9. Are you affected by your child's sleep pattern? **Yes** o **No** o

If no, please go to question 10

If yes, how does this affect you (multiple answers possible)?

o Disrupted in sleep by child

o Fatigue due to child's sleep problem

o Memory problems

o Decline in concentration

o Feelings of irritation

o Feelings of aggression

o Feeling depressed

o Arguments with partner

o Feeling powerless

o Other (please specify) _____

10. Are other members of the family affected by your child's sleep pattern? **Yes** o **No** o

If no, please go to question 11

If yes, who and how are they affected (multiple answers possible)?

	Father/ Mother	Brother/ Sister 1	Brother/ Sister 2	Brother/ Sister 3	Other
Disturbed sleep					
Fatigue					
Memory problems					
Decline in concentration					
Feelings of irritation					
Feelings of aggression					
Feeling depressed					
Feeling powerless					
Other _____					
Other _____					

11. Has anyone on either side of the family had any sleep problems (e.g. nightmares, sleepwalking, night terrors, unusual jerks or movements, or other attacks)? **Yes** o **No** o

If yes, please specify _____

12. Does anyone on either side of the family experience restless legs when falling asleep (crawling or aching feelings in legs, unable to keep legs still, having to get out of bed to ease aching legs)? **Yes** o **No** o

If yes, please specify _____

13. Does anyone on either side of the family startle or jerk their arms or legs in a rhythmic way, whilst asleep? **Yes** o **No** o

_____

If yes, please specify _____

14. Is there anything else about your child's sleep, or anything else, that you think is important and we have not mentioned? Please give details below

_____

_____

_____

_____

_____

_____

_____

Information booklet



UNIVERSITY OF BIRMINGHAM

Richards Lab Birmingham

The Cerebra Network for Neurodevelopmental Disorders

Introduction

Dear Parents and Guardians

Thank you for agreeing to take part in the study. This booklet includes all the information you need to help us understand more about your child's sleep, behaviour and behavioural indicators of pain.

This booklet has five sections:

Section 1: Actiwatch: FAQs

Section 2: Research Diary Information

Section 3: Behaviour Rating

Section 4: Behavioural Indicators of Pain

Section 5: Morning and Evening Sleep Dairy

If you have any questions or anything is not clear, please email Andrea Thomas at **ATT644@bham.ac.uk**

Actiwatch: FAQs

What does the Actiwatch do?
The Actiwatch measures movement and helps us to know when your child is awake or asleep.



Why are you using Actiwatches?
Directly measuring sleep this way gives us the most accurate picture of sleep/wake patterns.

How is the Actiwatch worn?
The Actiwatch can be worn on the wrist or ankle, whichever your child finds most comfortable. The watch should fit snuggly but doesn't need to be too tight.

When should the Actiwatch be removed?
The Actiwatch only needs to be removed in cases of submersion in water and for sports activities. Please use the research diary, when possible, to let us know the times the Actiwatch was removed.

When do I press the event marker?
The button on the side of the Actiwatch is called the event marker. The event marker needs to be pressed once in the evening when the lights are turned down for your child to go to sleep and again in the morning when your child wakes up. *

What if the Actiwatch is uncomfortable?
Wearing the Actiwatch over clothing may help. However, if there are any signs of reddening or inflammation you should remove the watch and contact me (att644@bham.ac.uk).

What if my child does not want to wear the Actiwatch?
That's fine. If your child does feel comfortable to start wearing the watch again, that would be great.

***The Actiwatch will not light up, vibrate, or make a noise when you press the event marker. Don't worry, if you have pressed the event marker the Actiwatch will register this information.**

2

Research Diary Information

Please complete the research diary <u>twice a day:</u> Once in the morning and again in the evening. Try to complete the diary as accurately as possible at around the same time each day.

<u>Sections of the research diary to complete in the evening</u>

Your first diary entry will be on the evening following your child's first day of wearing the Actiwatch. Each evening you should complete the following three sections:

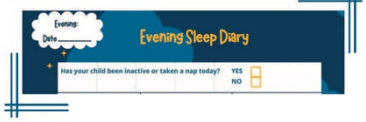
1. The Behaviour Rating Table:



2. The Behavioural Indicators of Pain Observation:

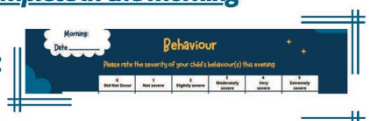


3. The Evening Sleep Diary.



<u>Sections of the research diary to complete in the morning</u>

1. The Behaviour Rating Table:



2. The Behavioural Indicators of Pain Observation:



3. The Morning Sleep Diary.



The following pages provide further information about how to fill in each section. If anything is unclear or you would like me to talk you through any of these sections, please email me **Andrea Thomas: att644@Bham.ac.uk**

Behaviour Rating

You will find a behaviour rating table for each morning and evening of the sleep study in the research diary. Here, we ask you to rate the severity of your child's self-injury, aggression, destruction or disruption of property, irritability, overactivity, impulsivity and daytime sleepiness. There is also a box for you to indicate if the behaviour did not occur. Below are definitions of behaviours. We also provide examples that may help you when rating the severity of your child's behaviour.

Definitions of Behaviour

Self-injury: examples include self-biting, headbanging, head-punching, or slapping, removing hair, self-scratching or body hitting.

Aggression: examples include punching, pinching, kicking, pulling hair, grabbing others' clothing or verbal aggression.

Destruction of Property: examples include tearing or chewing own clothing, tearing newspapers, breaking windows, or furniture, slamming doors, and spoiling a meal.

Irritability: examples include being easily annoyed by others, often and easily losing his/her temper, staying angry for a long time, getting angry frequently, and overall irritability causes him/her problems.

Overactivity: examples include finding it difficult to wait, and acting as if driven by a motor.

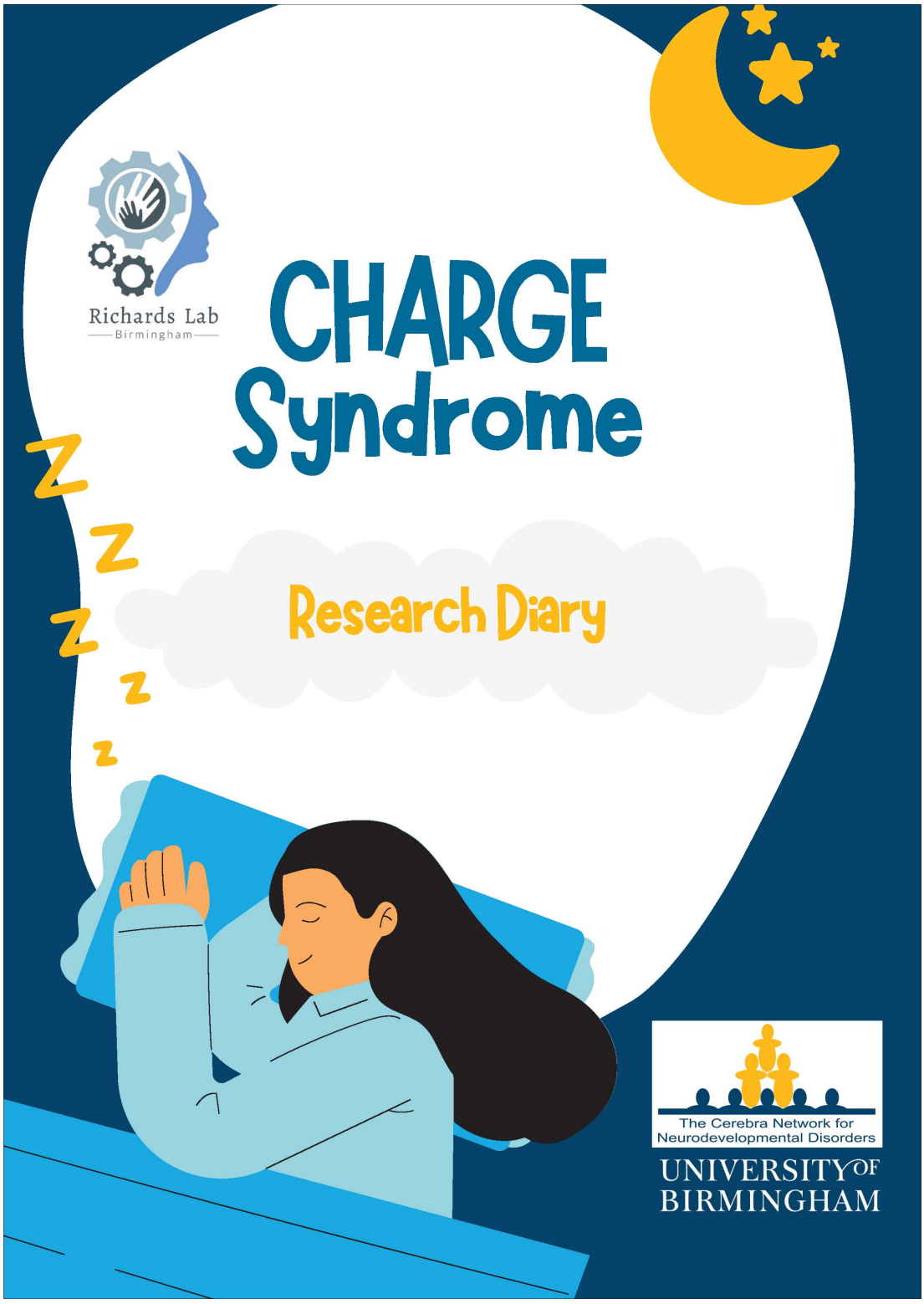
Impulsivity: examples include wanting things immediately, and finding it difficult to hold still.

Daytime sleepiness: examples may include yawning, rubbing eyes, dazed/daydreaming, and eyes closed.

Behaviour Severity Rating

1. Not severe: for example, a verbal reminder or discouragement was needed
2. Slightly severe: Some degree of physical contact, prevention or restraint was necessary e.g., blocking, taking objects from your child, temporary restraint of an arm
3. Moderately severe: Physical contact was required to my child/others safe. For example, a protective device or restraint by more than one person was required
4. Very severe: Emergency medication or assistance or advice was required

Example 24 Hour Research Diary



Evening:

Date _____

Behaviour

Please rate the severity of your child's behaviour(s) this evening

	0 Did Not Occur	1 Not severe	2 Slightly severe	3 Moderately severe	4 Very severe	5 Extremely severe
Self-injury						
Aggression						
Destruction or disruption of property						
Irritability						
Overactivity						
Impulsivity						
Daytime sleepiness						



Behavioural Indicators of Pain

Please observe your child for 10 minutes using a timer

Time observation started _____

Time observation ended _____

Please circle the behaviours you observed according to the following categories: Face, Legs, Activity, Cry and Consolability

Face	No particular expression or smile	Occasional grimace or frown, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

Evening:

Date _____

Evening Sleep Diary

Has your child been inactive or taken a nap today? YES ☐ NO ☐

Type of activity (select one)	Activity 1 Start time:	Activity 1 End time:
☐ Watching TV/iPad ☐ Quiet reading ☐ Naps ☐ Actiwatch Removal ☐ Other	HH:MM	HH:MM
Type of activity (select one)	**Activity 2 Start time:**	**Activity 2 End time:**
☐ Watching TV/iPad ☐ Quiet reading ☐ Naps ☐ Actiwatch Removal ☐ Other	HH:MM	HH:MM
Type of activity (select one)	**Activity 3 Start time:**	**Activity 3 End time:**
☐ Watching TV/iPad ☐ Quiet reading ☐ Naps ☐ Actiwatch Removal ☐ Other	HH:MM	HH:MM



Time to bed: _____ **Time lights turned off:** _____

To your knowledge was the event marker pressed at the correct time YES ☐ NO ☐

Notes:

Morning:

Date _____

Morning Sleep Diary

Did your child wake at any point during the night? YES ☐ NO ☐

Waking 1

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Waking 2

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Waking 3

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Waking 4

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Waking 5

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Waking 6

Time of waking

End of waking

Perceived reason for waking (select one)

☐ Wet/Needing toilet ☐ Hungry/Thirsty

☐ Anxious/Nightmares ☐ Pain/Discomfort

☐ Other - Please state ☐ Unknown

Estimated time to fall asleep: _____

Time woke up: _____ Time got out of bed: _____

To your knowledge was the event marker pressed at the correct time? YES ☐ NO ☐



Morning:

Date _____

Behaviour

Please rate the severity of your child's behaviour(s) this evening

	0 Did Not Occur	1 Not severe	2 Slightly severe	3 Moderately severe	4 Very severe	5 Extremely severe
Self-injury						
Aggression						
Destruction or disruption of property						
Irritability						
Overactivity						
Impulsivity						
Daytime sleepiness						



Behavioural Indicators of Pain

Please observe your child for 10 minutes using a timer

Time observation started _____

Time observation ended _____

Please circle the behaviours you observed according to the following categories: Face, Legs, Activity, Cry and Consolability

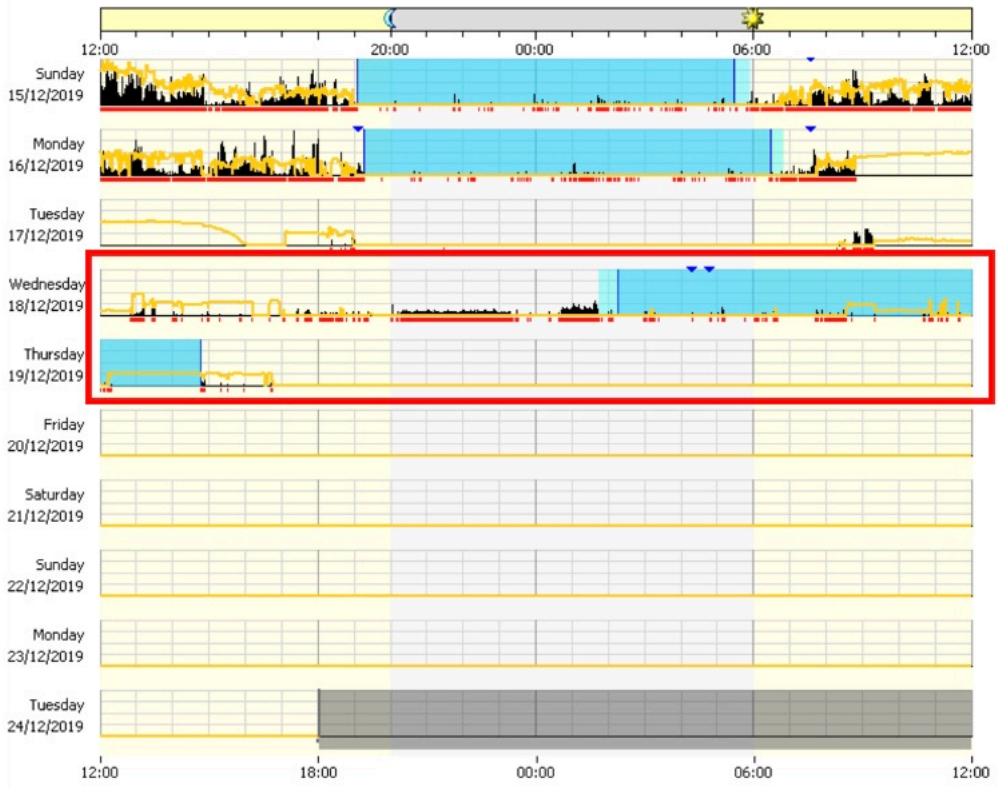
Face	No particular expression or smile	Occasional grimace or frown, disinterested	Frequent to constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No crying (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractible	Difficult to console or comfort

Appendix 4C: Actigraphy Cleaning Protocol

Step 1

Exclude any nights which appear on actogram that occur before or after data collection according to diary information (i.e. when actiwatch was in transit, if data collection was delayed).

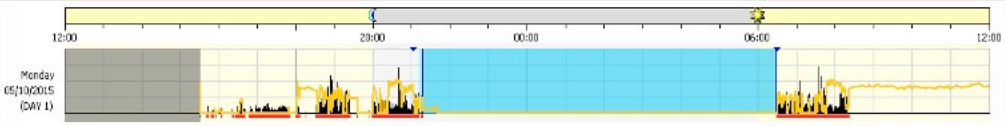
a) First click the automatically calculated sleep interval that has erroneously been created before or after the sleep assessment dates, and click 'delete' (if applicable).
b) Enter exclusion interval(s) for days before and/or after data collection, when the watch was in transit or not worn by the child (Interval → Add interval → Interval type: excluded). Exclude whole non-assessment day (from 12:00 – 12:00), even if there are black activity lines.



In the example above, a) delete automatically calculated sleep interval; b) enter exclusion interval from 12:00 (17/12/2019) to point at which watch stopped collecting data = 18:00 (24/12/2019).



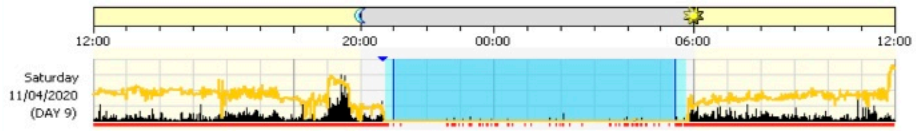
The parent did not report removal of the watch during the night of Monday 21st, but through visually inspecting the actogram, and systematically examining the activity count data, over 7 hours of inactivity (ac = 0) was confirmed (see section in red). As there is an inactive period of over 2 hours, this automatically calculated sleep interval would be deleted and replaced with an exclusion interval.



Parent reported that the actiwatch was removed during the night of Monday 5th. This occurred within the sleep period reported in the sleep diary. The actogram supports this information as there was no evidence of activity during this night. This is consistent with parent report. Therefore, data should be excluded for Monday .

Saturday 11th	To be completed in the evening			
Time and duration of any daytime naps	Nap 1	Nap 2	Nap 3	
Timings and durations of activities in the evening when child sedate and not moving (e.g. watching TV or reading)				
Time got into bed	8.45pm			
Time lights turned off	8.50pm			

Sunday 12th	To be completed throughout the day:	by (initials)
Time Actiwatch removed	Think watch was taken off last night – wasn't wearing at breakfast	
Time Actiwatch replaced		
Time Actiwatch removed		
Time Actiwatch replaced		
Time Actiwatch removed		
Time Actiwatch replaced		



Parent reported that the actiwatch was removed during the night of Saturday 11th. This occurred within the sleep period reported in the sleep diary. The actogram does not support this information as there was activity during this night. This is inconsistent with parent report. Therefore, this interval ***should not*** *be excluded within this step.*

Step 2

Check overlap between actiwatch removal times and "time lights turned off" in the child's sleep diary. Exclude any sleep intervals where the caregiver identifies that the watch has been taken off/removed for a **large proportion of the night (2 hours or more)**. Short actiwatch removals that overlap with the start time of the automatically calculated sleep interval (e.g. 20 minute watch removal during bath time) are not adjusted here (see Step 8).

a. If actiwatch removal is identified, check whether actiwatch removal occurs within the reported sleep period (i.e. between sleep diary lights out and wake up time). If actiwatch removal occurs before the automatically calculated sleep interval, adjustments are not to be made.
b. If any removal times are identified within the reported sleep period, check times against actogram for consistency by visually inspecting the specific night in question (i.e. no black lines of activity at this time).
c. In Actiware, examine the night in question systematically. Click on the automatically calculated sleep interval for that night, and use the > key to scroll through the sleep interval. Examine the 'ac =' counter. If ac = 0 occurs continuously for a period of 2 hours or more between diary lights out and wake up time (check against time epochs when scrolling), exclude this 24 hour period. First delete this sleep interval, then enter exclusion period from 12:00 – 12:00 (Interval → Add interval → Interval type: excluded).
d. If parent reports that the actiwatch has been removed, but this is not evident on the actogram (i.e. evidence of movement and activity during this time, ac = 0 does not occur continuously for a period of 2 hours or more), keep the existing sleep interval as it is and continue to Step 3.

Monday 5th	To be completed in the evening			
Time and duration of any daytime naps	Nap 1	Nap 2	Nap 3	
Timings and durations of activities in the evening when child sedate and not moving (e.g. watching TV or reading)				
Time got into bed	8.55pm			
Time lights turned off	9.00pm			

Tuesday 6th	To be completed throughout the day:	by (initials)
Time Actiwatch removed	Child would not wear watch last night – removed at 9.15pm	
Time Actiwatch replaced	Replaced around 6.30am	
Time Actiwatch removed		
Time Actiwatch replaced		
Time Actiwatch removed		
Time Actiwatch replaced		

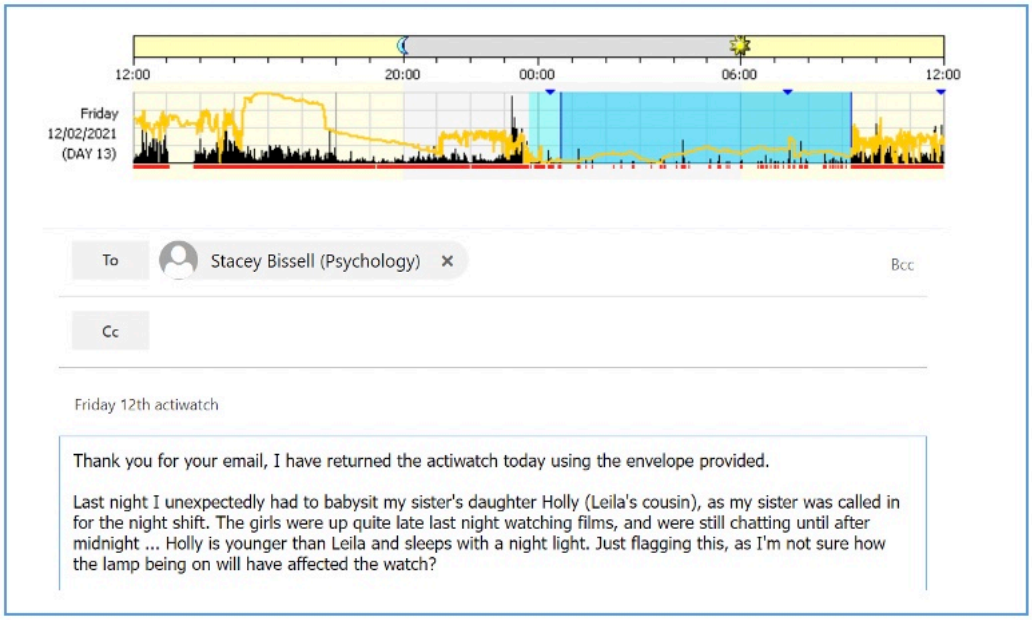
Step 3

Exclude any nights where the actiwatch appears to have been taken off but this **was not** noted in the sleep diary information.

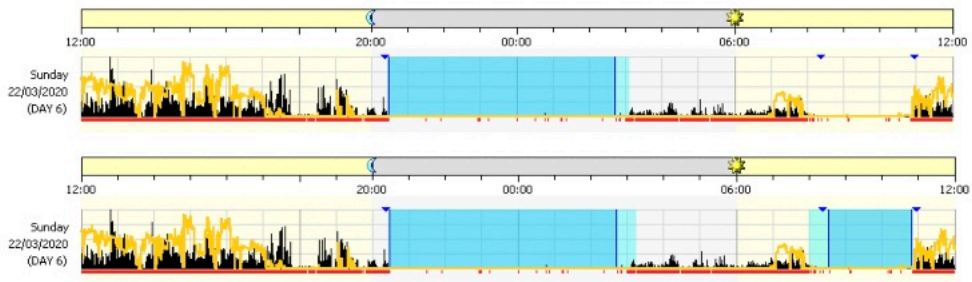
a. Initially, visually inspect the **entire actogram** at a glance and identify any overnight periods with continuous intervals where no black lines are present.
b. If any periods are identified, check whether these 'inactive' periods are within the reported sleep period (i.e. between sleep diary lights out and wake up time). If 'inactivity' occurs before the automatically calculated sleep interval, adjustments are not to be made in this step.
c. If 'inactive' periods are identified within the reported sleep period, examine the night in question systematically. Click on the automatically calculated sleep interval for that night, and use the > key to scroll through the sleep interval. Examine the 'ac =' counter. If ac = 0 occurs continuously for a period of 2 hours or more between diary lights out and wake up time (check against time epochs when scrolling), exclude this 24 hour period. First delete this sleep interval, then enter exclusion period from 12:00 – 12:00 (Interval → Add interval → Interval type: excluded).
d. If inactivity is suspected, but this is not evident on the actogram (i.e. evidence of movement and activity during this time, ac = 0 does not occur continuously for a period of 2 hours or more), keep the existing sleep interval as it is and continue to Step 4.

Step 7

Exclude nights where parents reported that the child had a sleepover with a friend/experienced sleep that is not defined as 'typical' as part of their usual routine (see mock example below). Exclude this 24 hour period from the actogram. First delete this sleep interval, then enter exclusion period from 12:00 – 12:00 (Interval → Add interval → Interval type: excluded).

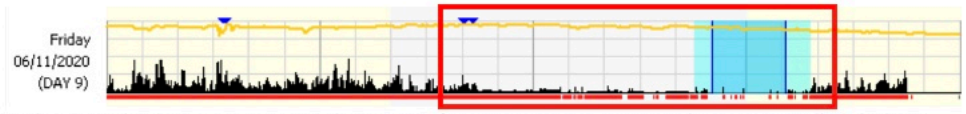


a. Please note, provisions are made within the mobile app sleep diary for overnight respite/overnight care by family members or relatives, if this is part of the child's usual routine (i.e sleeping overnight at grandparents, co-parenting arrangement). If sleep diary has been completed by parent/relative/professional according to pre-determined arrangements on these respite/alternative childcare nights, these nights do not need to be excluded.



In this example, the parent reports a morning nap of more than 2 hours after a significant period of waking of more than 2 hours. This is adjusted to indicate two separate sleep intervals using the epochs principle ***FOR THE PURPOSES OF THE FEEDBACK REPORT ONLY****. The actigraphy used for the purposes of data analysis would not adjust/extend the automatically calculated sleep interval here.*

b. In some instances (due to a technical fault with older watches) the automatically calculated sleep interval may need to be extended, but this is not possible. If there are low level constant periods of activity that make it difficult to extend the sleep interval (40 epochs coded as **0 in the sleep/wake column** before or after sleep period reported in the child's sleep diary cannot be found) THIS DAY MUST BE EXCLUDED. Exclusion interval would be inserted from 12:00 to 12:00 for the entire day.



In this example, the parent reported sleep time is from 20.45pm to 07.30am. The automatically calculated sleep interval has appeared to calculate the start of sleep time as being 'too late' and the sleep interval start time would be adjusted according to the epochs principle. However, there are constant periods of low level activity, which means 40 epochs of 0 between 20:45:00 and 04:32:30 cannot be found to adjust the sleep interval start time. Therefore, this assessment day must be excluded (12:00 to 12:00).

If this error is observed: a) do not send out this watch again for data collection with another family, b) report this faulty watch immediately to the Principal Investigator.

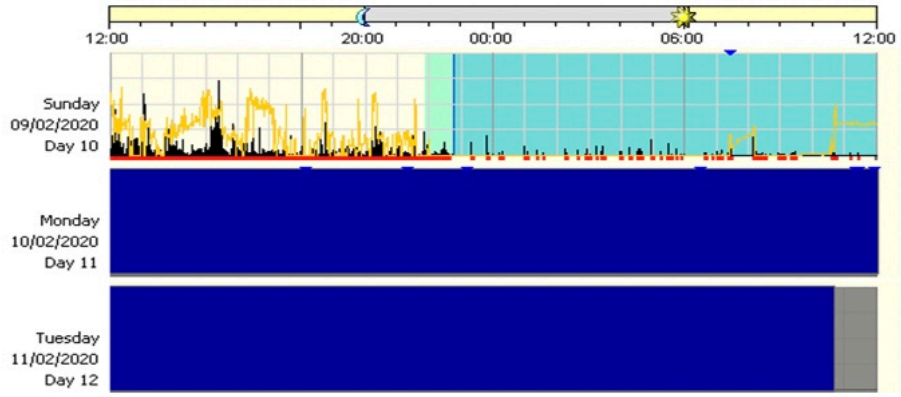
Step 8

Adjust sleep intervals where automatically calculated interval start time overlaps with sedentary activity or short actiwatch removal (e.g. watch removal that coincides with bath time before bed) reported in the sleep diary information.

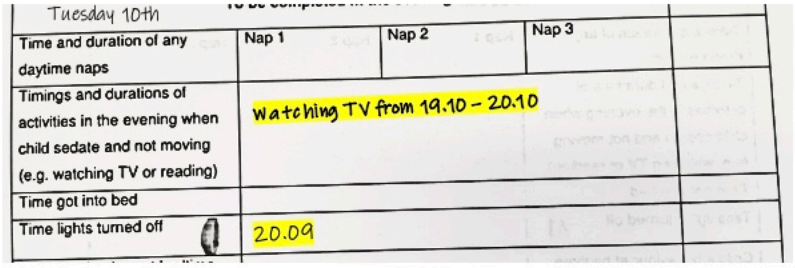
a. For each night, check if any of these activities/short removals overlap with the automatically calculated sleep interval for that night.
b. If the sedentary activity/short removal in the sleep diary ends before the automatically calculated sleep interval created in Actiware, do not change the sleep interval for this given night.
c. If the automatically calculated sleep interval starts during the period of sedentary activity/actiwatch removal, **keep the automatically coded end time**, but change the start time of the sleep interval according to the following guidance:
    - If the diary 'time lights turned off' and the event marker are congruent (+/- 15 minutes) use the time the event marker was pressed as the start of the adjusted sleep interval.
    - If the diary 'time lights turned off' and event marker are incongruent (> +/- 15 minutes) use the time the event marker was pressed as the start of the adjusted sleep interval.

The following actions apply if the event marker or sleep diary information **cannot be used** for *step c* as above. Follow **either** i ii iii or iv as outlined below.

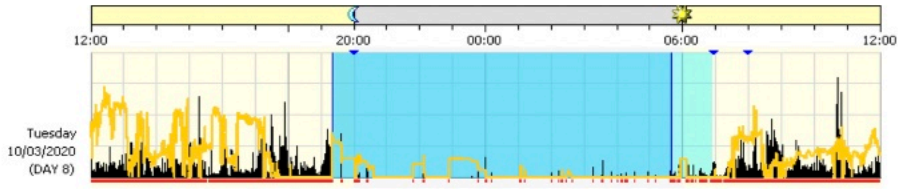
i. If the event marker was pressed before/during the sedentary activity or removal, use the diary 'time lights turned off' as the start of the adjusted sleep interval.
ii. If the event marker was not pressed, use parent reported 'time lights turned off' as the start of the adjusted sleep interval.
iii. If the 'time lights turned off' is +/- 15 minutes congruent with the **start time** of the sedentary activity (i.e 'time lights turned off' is being used to indicate when the child goes to lie in bed and watch television, not being used to indicate lights out to begin sleep), 'time lights turned off' cannot be used reliably. Use the **end time of the sedentary activity/short removal** in the sleep diary as the start of the adjusted sleep interval.
iv. If the event marker was not pressed and the sleep diary does not report 'time lights turned off' **use the end time of the sedentary activity/short removal** in the sleep diary as the start of the adjusted sleep interval.



Need to adjust automatically calculated sleep interval for Sunday 9th. Event marker has been pressed at 07:27:00. Previous wake up times reported in the mobile app vary between 07.00am and 08.30am. Using this information as a guide, the data list is inspected. Around 07.00am on the morning of Monday 10th, 40 epochs coded as 0 are identified in the data list (end of 40 epochs at 06:37:00). Looking ahead, 20 epochs coded as 1 cannot be found. Last 0 before this sequence cannot be recorded to indicate a new end time. This sleep interval needs to be deleted, and an exclusion interval entered from 12:00 – 12:00 on Sunday 9th.



Tuesday 10th			
Time and duration of any daytime naps	Nap 1	Nap 2	Nap 3
Timings and durations of activities in the evening when child sedate and not moving (e.g. watching TV or reading)	watching TV from 19.10 – 20.10		
Time got into bed			
Time lights turned off	20.09		



Overlap between automatically calculated sleep interval (19:22:30-06:53:00) and sedentary activity reported in sleep diary. Event marker pressed at 20:02:00 – pressed during sedentary activity and cannot be used. Lights out information reported in sleep diary as 20.09pm. Adjust sleep interval to 20:09:00-06:53:00.

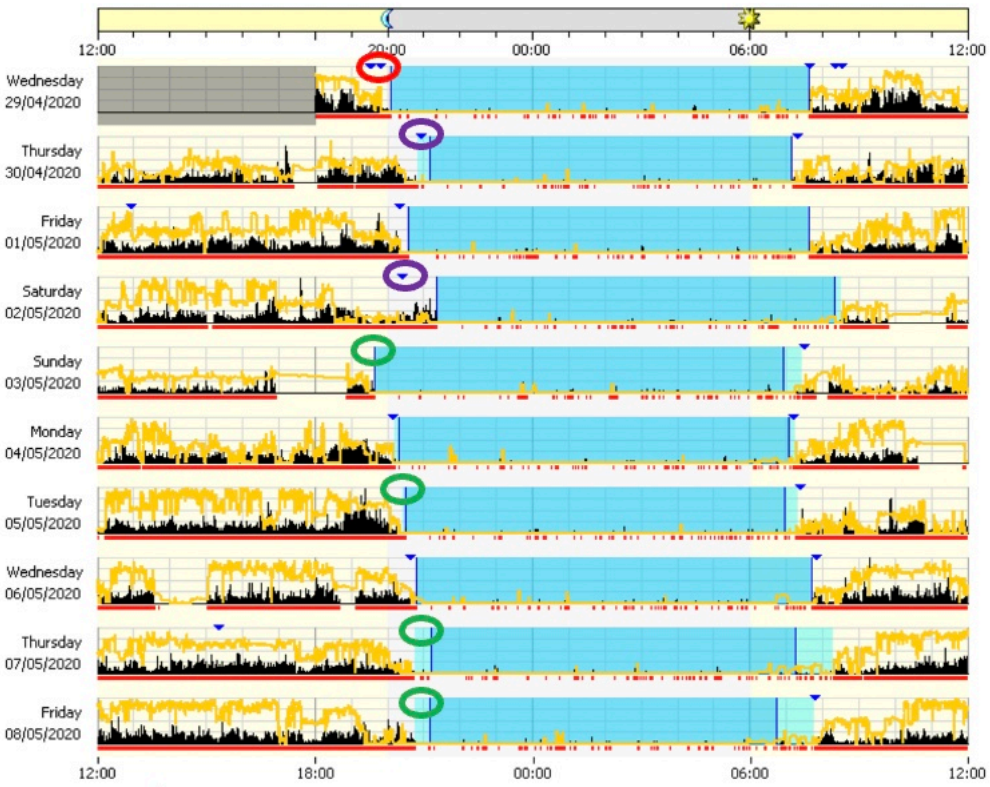
Step 9

Visually inspect the actogram and review the sleep diary information. Look over the whole data collection period and note the number of nights where:

a. The event marker is missing
b. The event marker has been pressed multiple times within two hours of the automatically calculated sleep interval start time
c. The sleep diary information indicates that the event marker was pressed at the incorrect time

THE EVENT MARKER SHOULD BE DEEMED INACCURATE

- If on half the nights or more (5/10, 4/7) any of these apply, the event marker is deemed inaccurate for the **whole sleep assessment**. Use the **alternative algorithm** to decide whether the start of the sleep interval needs to be changed FOR ALL NIGHTS OF THE SLEEP ASSESSMENT.
- If the event marker is deemed inaccurate for a minority of nights (1/10, 3/7), even if only on one night, use the **alternative algorithm** to decide whether the start of the sleep interval needs to be changed FOR EACH NIGHT SPECIFICALLY WHERE THE EVENT MARKER IS DEEMED INACCURATE.



On Wednesday 29th the event marker has been pressed multiple times within two hours of the automatically calculated sleep interval. On Thursday 30th and Saturday 2nd, the event marker has been identified as inaccurate within the mobile app diary. On Sunday 3rd, Tuesday 5th, Thursday 7th and Friday 8th the event marker is missing. This means that the event marker is inaccurate for the majority of nights (7/10), and so the event marker should be discounted FOR ALL NIGHTS OF THE SLEEP ASSESSMENT. The alternative algorithm should be used for every night in the sleep assessment (including Friday 1st, Monday 4th and Wednesday 6th).

(If the event marker has been discounted on half the nights or more, do not follow these guidelines, follow the alternative algorithm for all nights).

Use the following guidelines to decide whether to change the start of the sleep interval, for nights when the event marker **has not** been discounted.

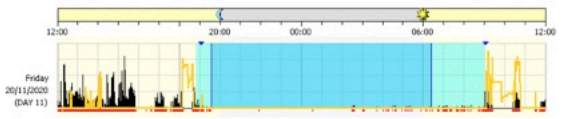
i. Look at the event marker, sleep diary and the automatically calculated sleep interval start time. If they are concordant (all three within +/-15 minutes of each other; SI – LO, SI – EM, EM – LO = +/-15 minutes) then leave the automatically calculated sleep interval.

ii. **If the event marker and sleep diary are concordant but either are discordant with the automatically calculated sleep interval start time, adjust the start time of the sleep interval to the event marker time.**

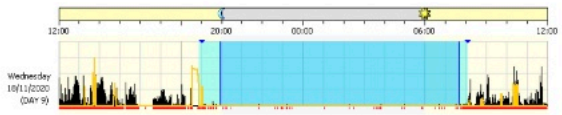
iii. If the event marker is discordant with the sleep diary but concordant with the automatically calculated sleep interval start time, leave the automatically calculated sleep interval.

iv. If the sleep diary is discordant with the event marker but concordant with the automatically calculated sleep interval start time, leave the automatically calculated sleep interval.

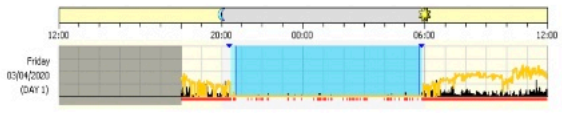
v. If the sleep diary, event marker and automatically calculated sleep interval are all discordant, leave the automatically calculated sleep interval.



Sleep interval = 18:50:30
Event marker = 19:06:00
Sleep diary = 19:20:00
Event marker and sleep diary are concordant, event marker discordant with sleep interval =
Adjust to event marker



Sleep interval = 18:55:00
Event marker = 19:03:30
Sleep diary = 19:02:00
Event marker and sleep diary and sleep interval are concordant =
Do not adjust sleep interval



Sleep interval = 20:28:00
Event marker = 20:24:30
Sleep diary = 20:45:00
Event marker and sleep diary are discordant, event marker concordant with sleep interval =
Do not adjust sleep interval

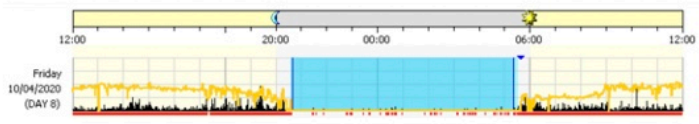
ALTERNATIVE ALGORITHM

- Use when the event marker is deemed inaccurate for the **whole sleep assessment**. Use the **alternative algorithm** to determine whether changing the sleep interval is required FOR ALL NIGHTS OF THE SLEEP ASSESSMENT.
- If the event marker is deemed inaccurate for a minority of nights (even if this is just 1/10, 3/7) use the **alternative algorithm** to determine whether changing the sleep interval is required FOR EACH NIGHT SPECIFICALLY WHERE THE EVENT MARKER IS DEEMED INACCURATE.

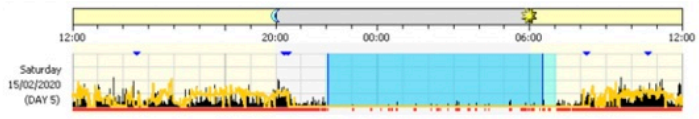
Use the following guidelines to decide whether to change the start of the sleep interval, for nights when the event marker **cannot be considered**.

i. If the event marker has been identified as inaccurate, but the sleep diary "time lights out" and sleep interval start time are +/- 15 minutes **concordant**, leave the automatically calculated sleep interval for that night.

ii. **If the event marker has been identified as inaccurate, and the sleep diary "time lights out" and sleep interval start time are +/- 15 minutes discordant, use the child's sleep diary "time lights out" to change interval start time for that night.**



EVENT MARKER IS MISSING
Sleep interval = 20:34:30
Sleep diary = 20:38:00
Sleep interval and sleep diary are concordant =
Do not adjust sleep interval



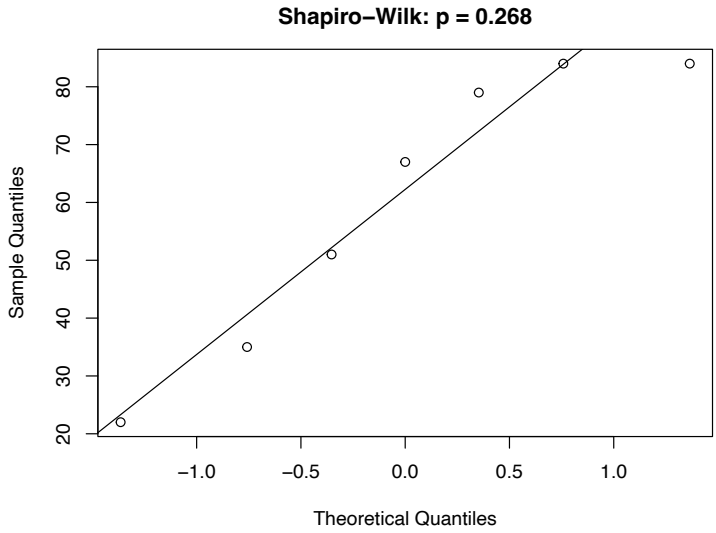
EVENT MARKER PRESSED MULTIPLE TIMES
Sleep interval = 22:00:00
Sleep diary = 20:30:00
Sleep interval and sleep diary are discordant =
Adjust to sleep diary

Appendix 4D. QQ Plots to Examine the Distribution of the variables

Correlations Between ABC Scores and Subjective Sleep Parameters

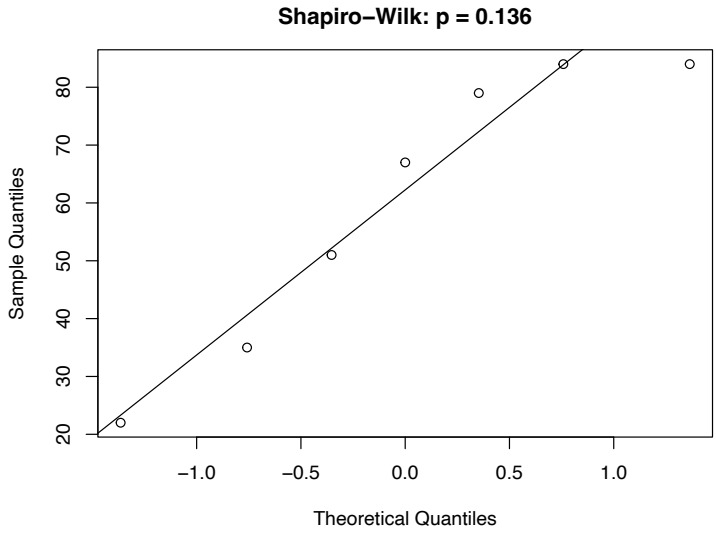
Appendix 4D. Figure 83

QQ Plot: Adaptive Behaviour Composite Scores



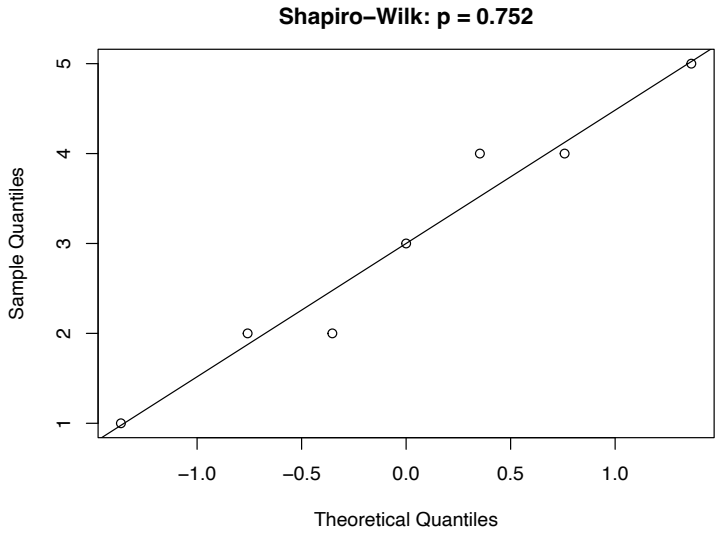
Appendix 4D. Figure 84

QQ Plot: Bedtime Resistance Scores



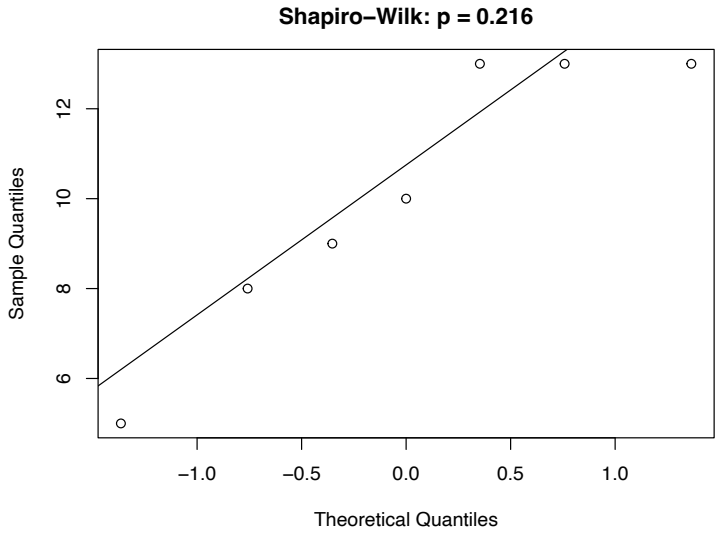
Appendix 4D. Figure 85

QQ Plot: Sleep Onset Delay Scores



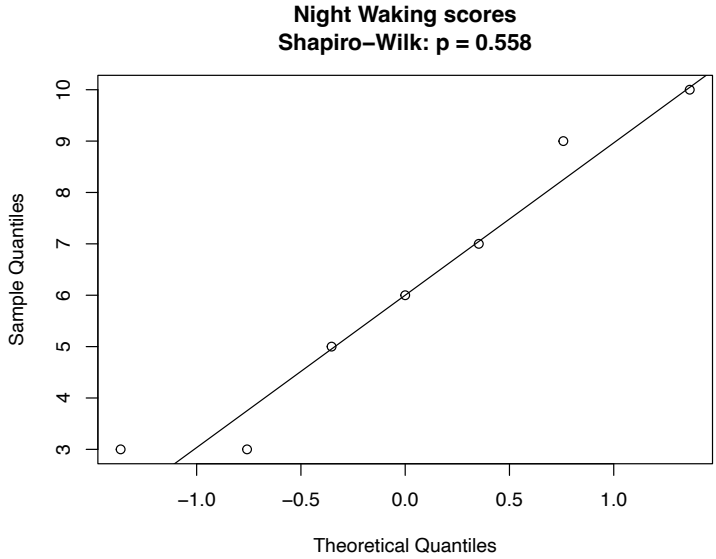
Appendix 4D. Figure 86

QQ Plot: Sleep Anxiety Scores



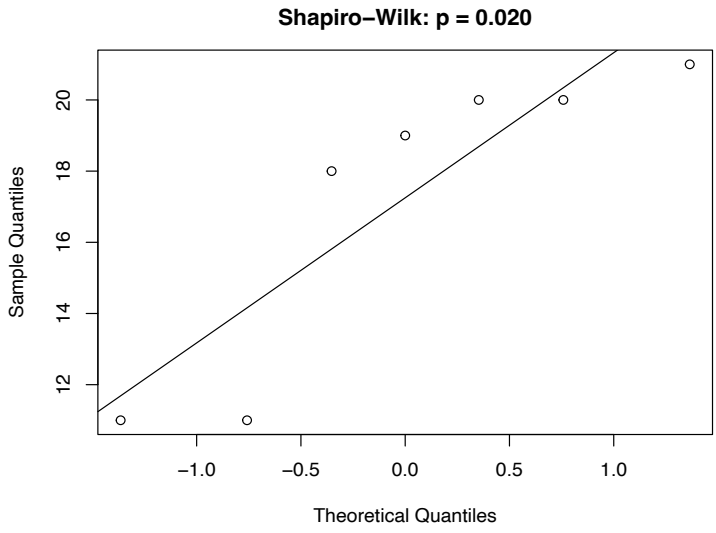
Appendix 4D. Figure 87

QQ Plot: Night Waking Scores



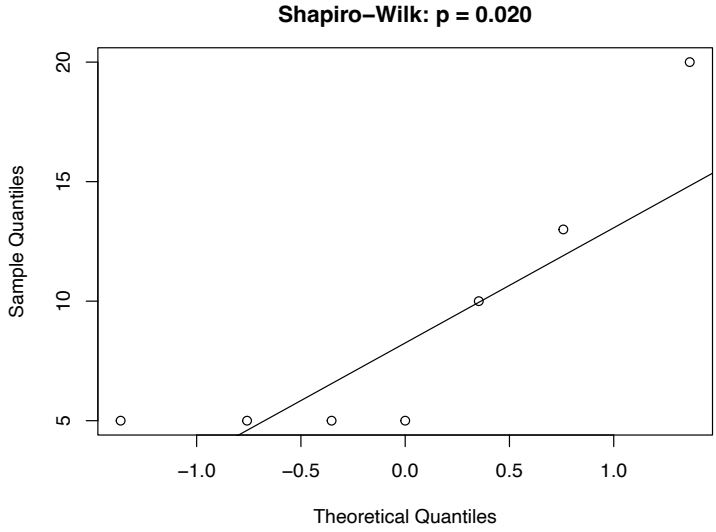
Appendix 4D. Figure 88

QQ Plot: Parasomnias Scores



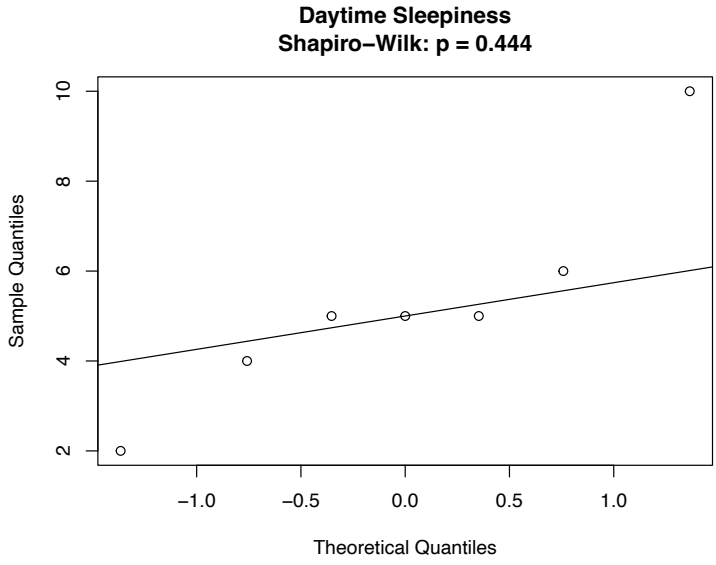
Appendix 4D. Figure 89

QQ Plot: Sleep Disordered Breathing Scores



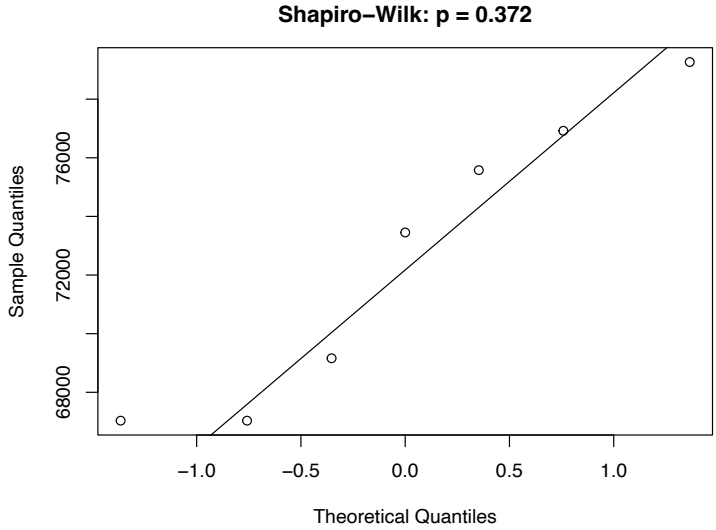
Appendix 4D. Figure 90

QQ Plot: Daytime Sleepiness Scores



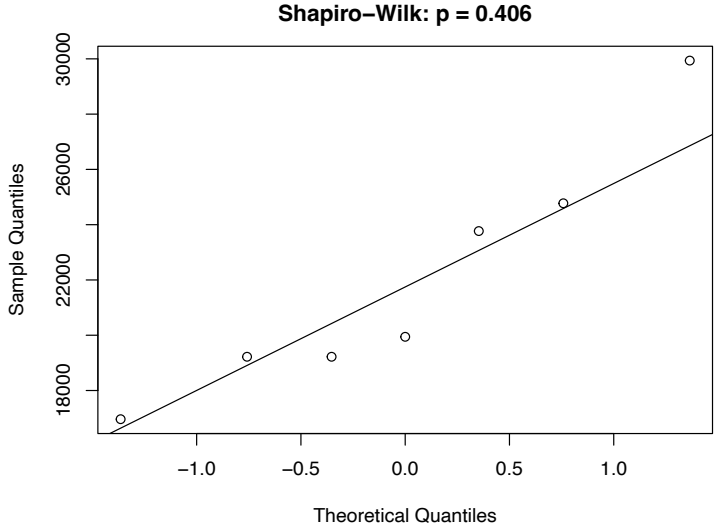
Appendix 4D. Figure 91

QQ Plot: Bedtime



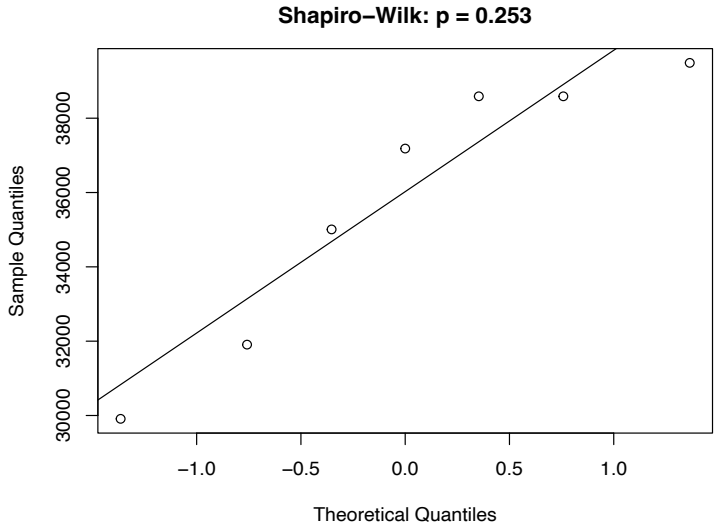
Appendix 4D. Figure 92

QQ Plot: Get Up Time



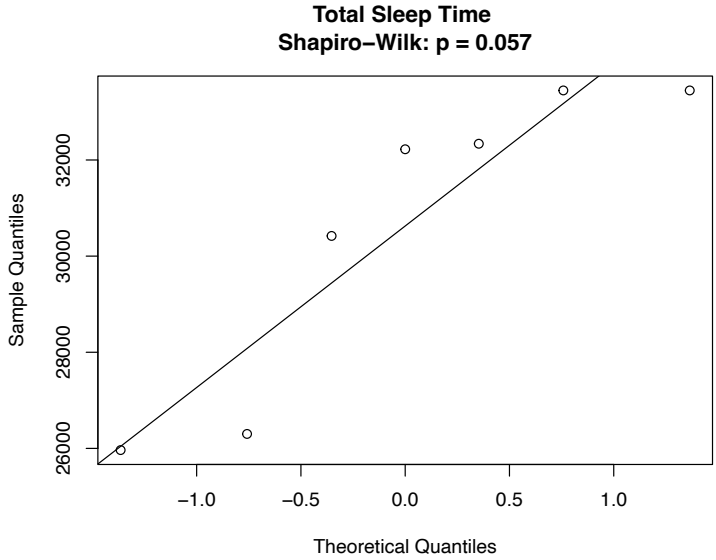
Appendix 4D. Figure 93

QQ Plot: Time in Bed



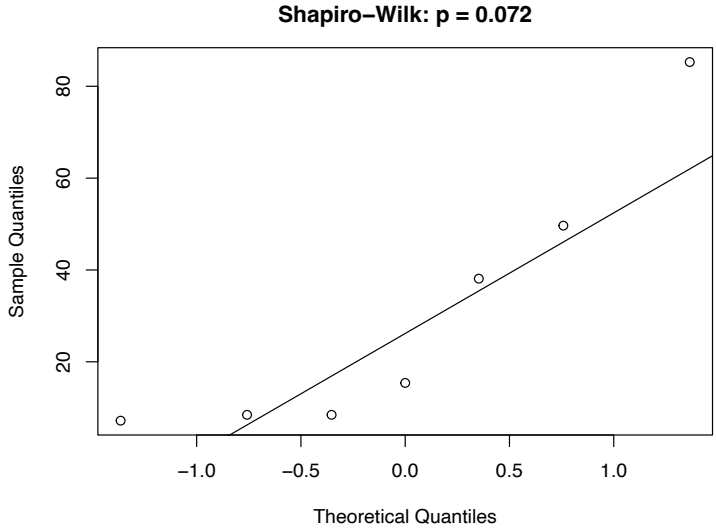
Appendix 4D. Figure 94

QQ Plot: Total Sleep Time



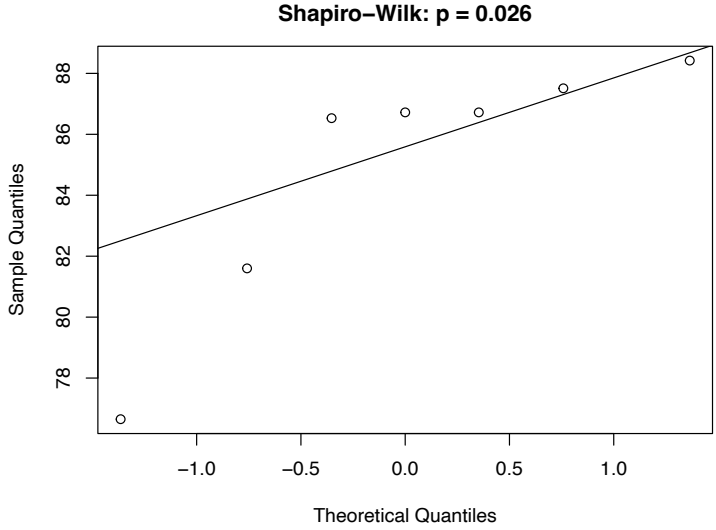
Appendix 4D. Figure 95

QQ Plot: Onset Latency



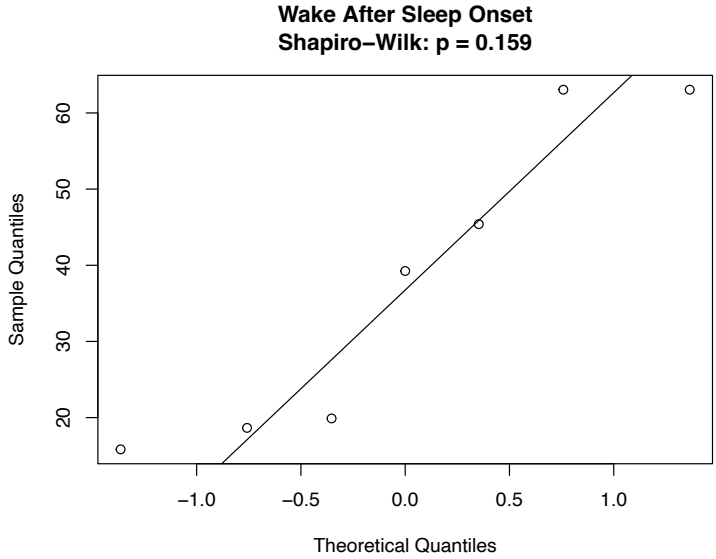
Appendix 4D. Figure 96

QQ Plot: Sleep Efficiency



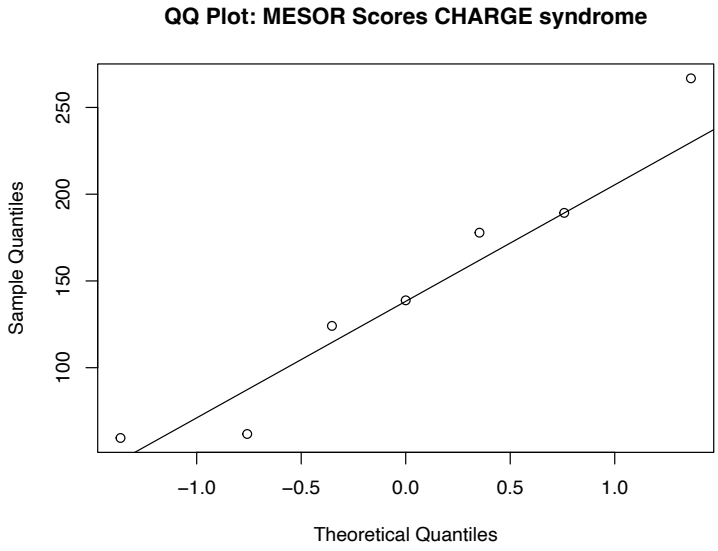
Appendix 4D. Figure 97

QQ Plot: Wake After Sleep Onset



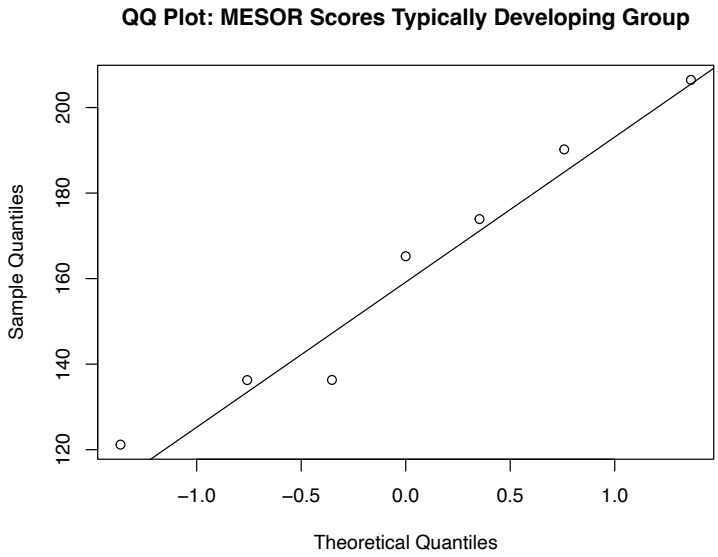
Appendix 4D. Figure 98

QQ Plot: MESOR CHARGE Syndrome Group: Data Comes from a Normally Distributed Population (p = 0.676)



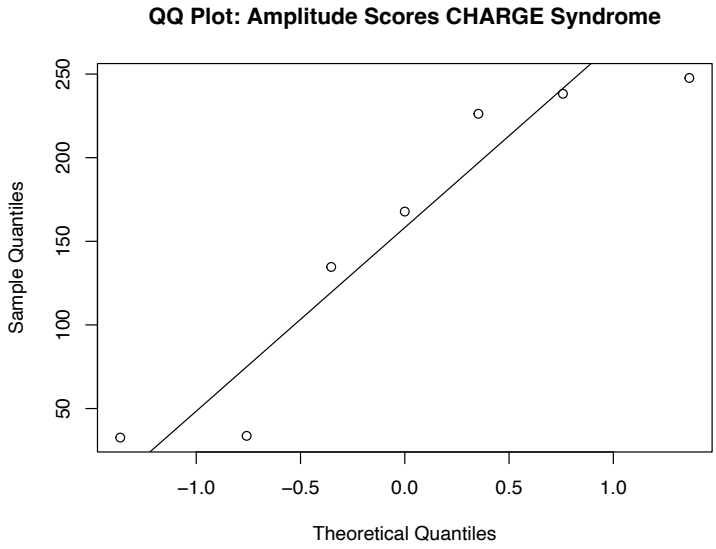
Appendix 4D. Figure 99

QQ Plot: MESOR Typically Developing Group: Data Comes from a Normally Distributed Population (p = 0.697)



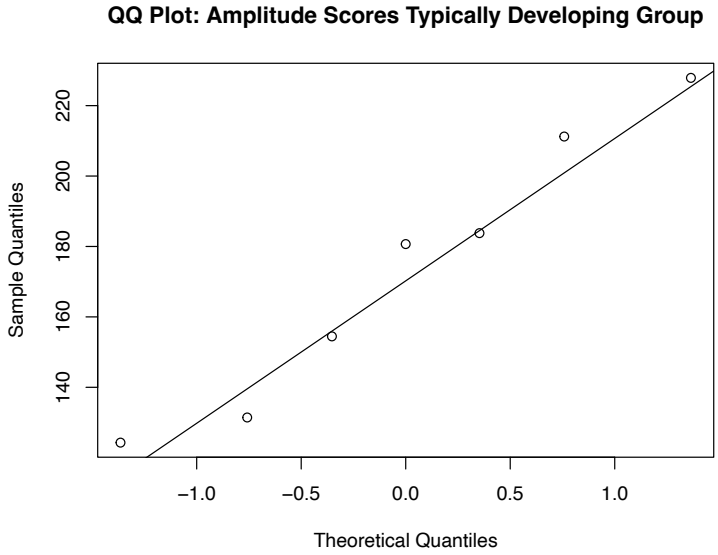
Appendix 4D. Figure 100

QQ Plot: Amplitude CHARGE Syndrome: Data Comes from a Normally Distributed Population (p = 0.145)



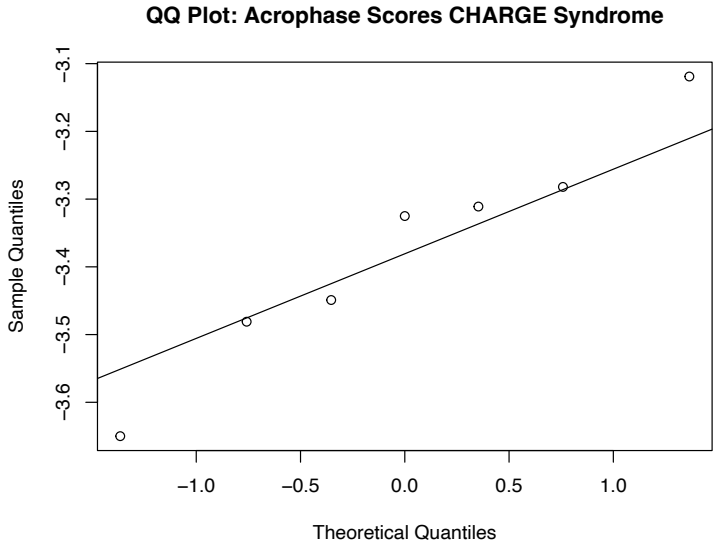
Appendix 4D. Figure 101

QQ Plot: Amplitude Typically Developing Group: Data Comes from a Normally Distributed Population (p = 0.717)



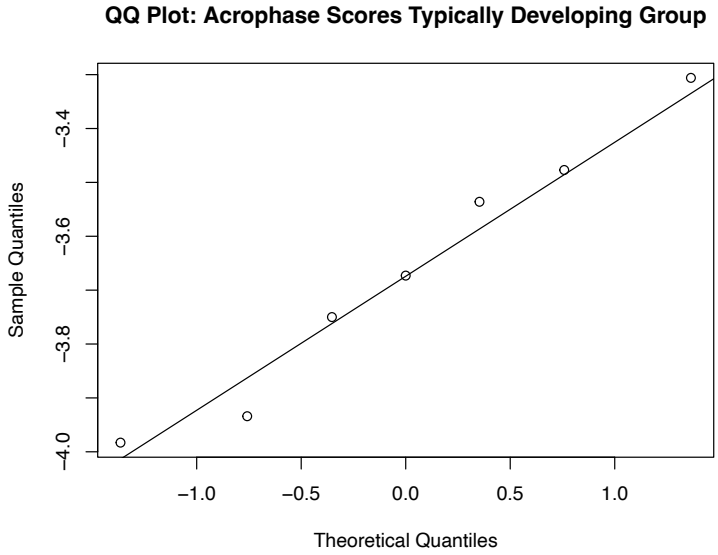
Appendix 4D. Figure 102

QQ Plot: Acrophase CHARGE Syndrome: Data Comes from a Normally Distributed Population (p = 0.9265)



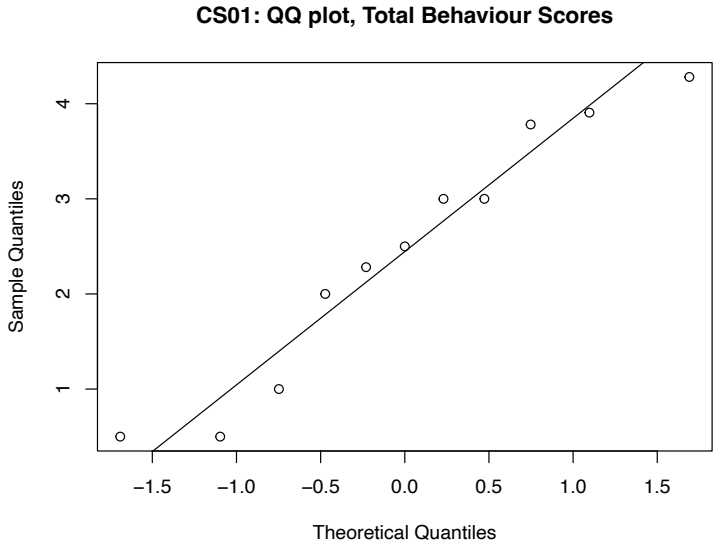
Appendix 4D. Figure 103

QQ Plot: Acrophase Typically Developing Group: Data Comes from a Normally Distributed Population (p = 0.855)



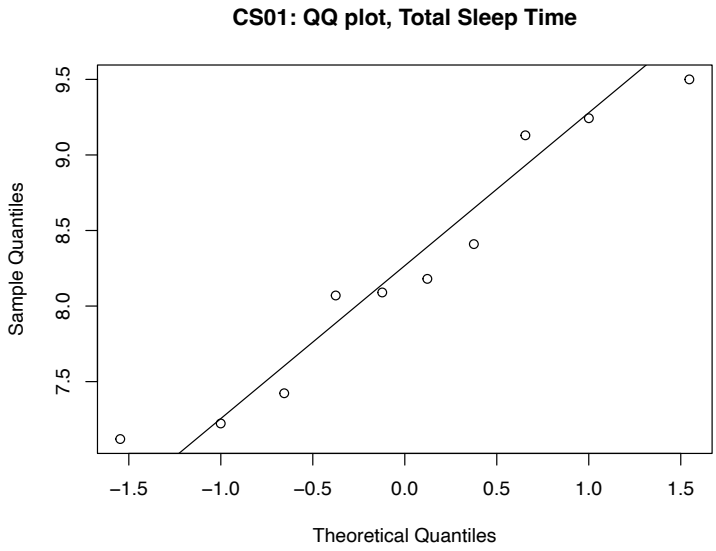
Appendix 4D. Figure 104

CS01: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: $p = 0.417$



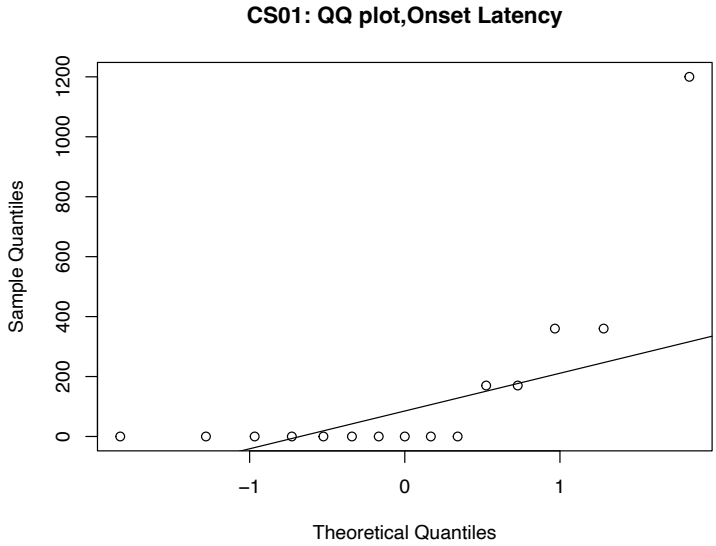
Appendix 4D. Figure 105

CS01: QQ Plot, Total Sleep Time, Shapiro-Wilk Test: p = 0.423



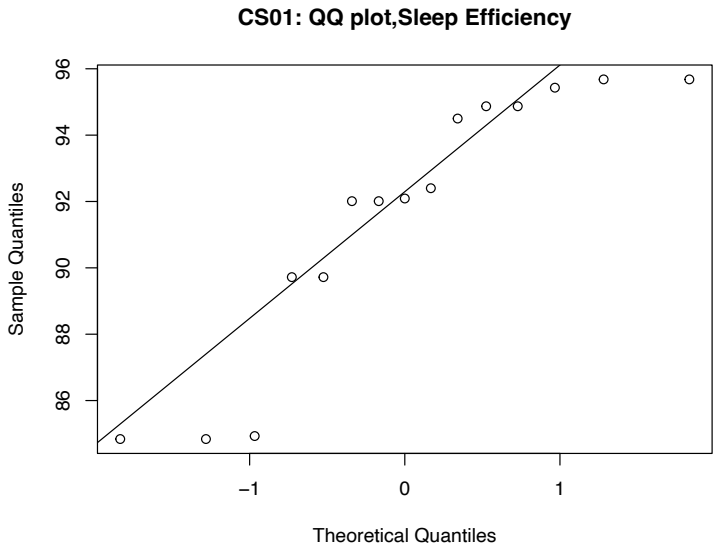
Appendix 4D. Figure 106

CS01: QQ Plot, Sleep Onset Latency, Shapiro-Wilk Test: p = <0.001



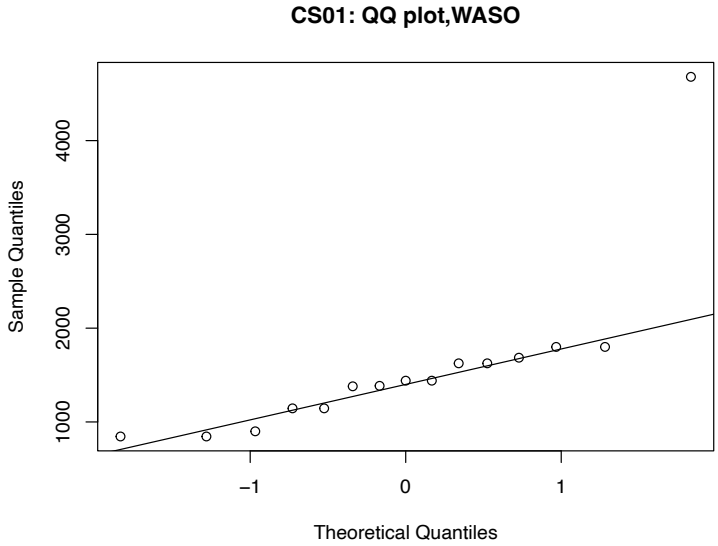
Appendix 4D. Figure 107

CS01: QQ Plot, Sleep Efficiency, Shapiro-Wilk Test: p = 0.014



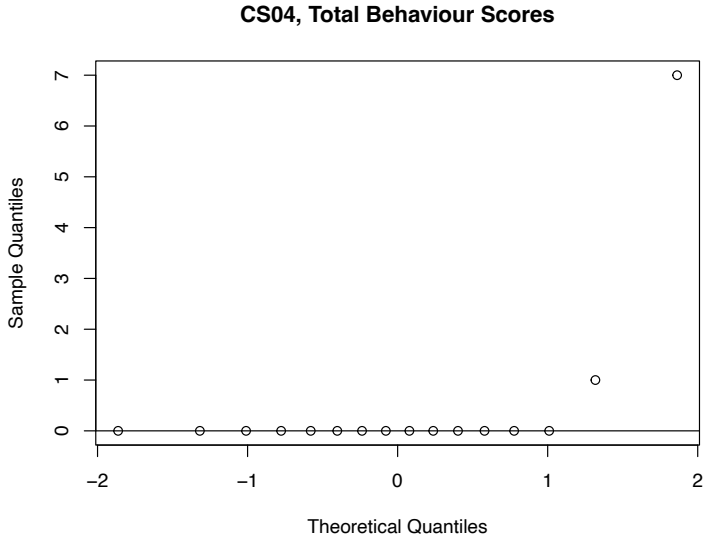
Appendix 4D. Figure 108

CS01: QQ Plot, WASO (Wake After Sleep Onset), Shapiro-Wilk Test: p = <0.001



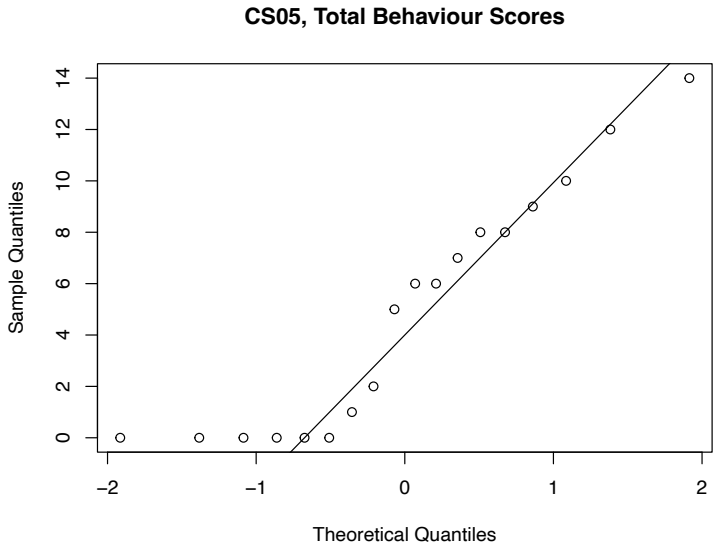
Appendix 4D. Figure 109

CS04: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = <0.001



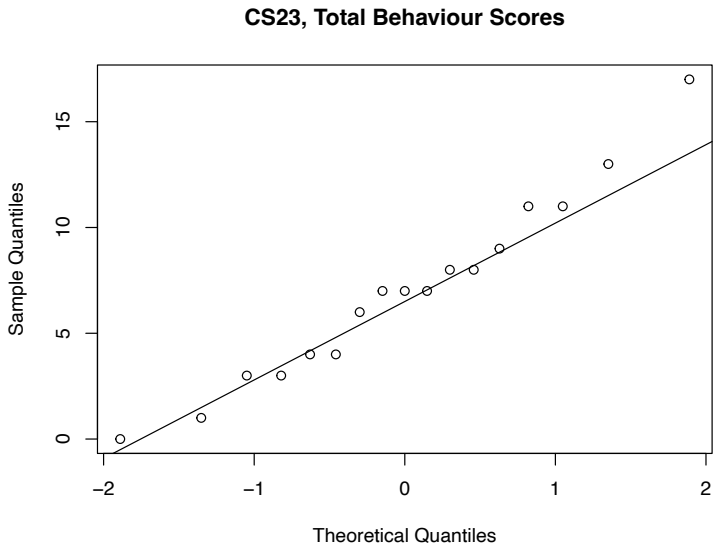
Appendix 4D. Figure 110

CS05: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = 0.029



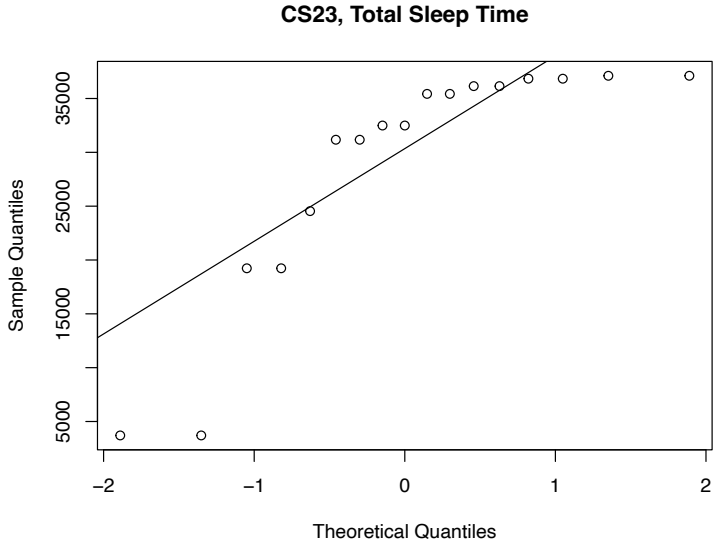
Appendix 4D. Figure 111

CS23: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = 0.829



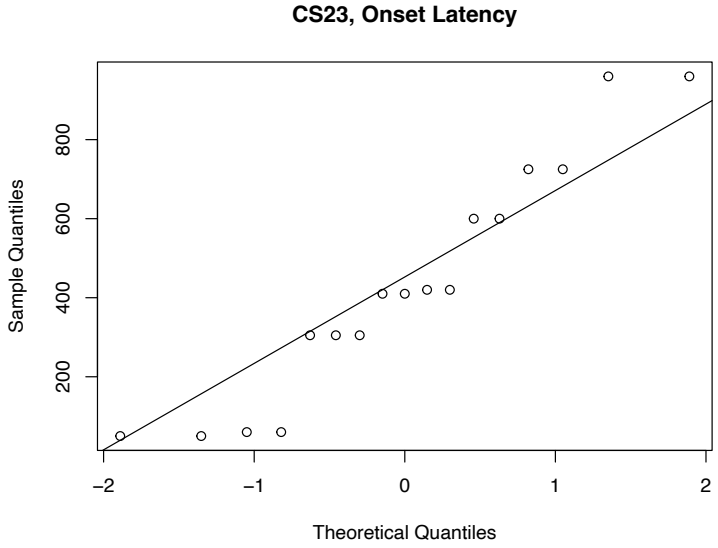
Appendix 4D. Figure 112

CS23: QQ Plot, Total Sleep Time, Shapiro-Wilk Test: p = < 0.001



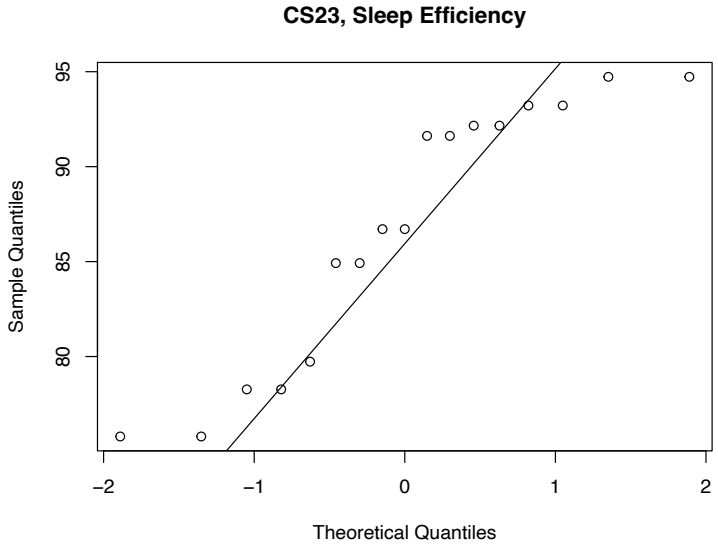
Appendix 4D. Figure 113

CS23: QQ Plot, Sleep Onset Latency, Shapiro-Wilk Test: p = 0.156



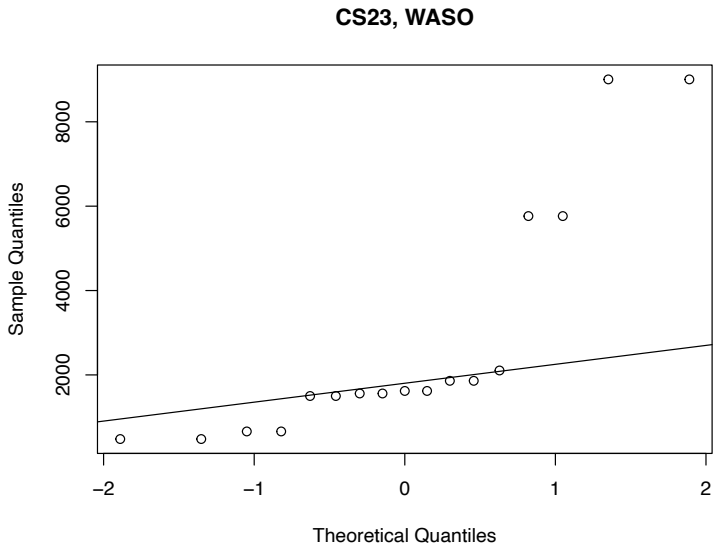
Appendix 4D. Figure 114

CS23: QQ Plot, Sleep Efficiency, Shapiro-Wilk Test: p = 0.026



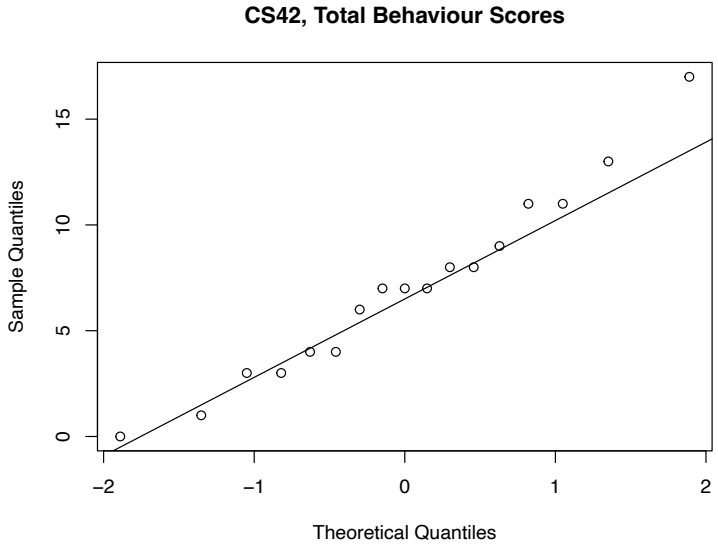
Appendix 4D. Figure 115

CS23: QQ Plot, WASO (Wake After Sleep Onset), Shapiro-Wilk Test: p = < 0.001



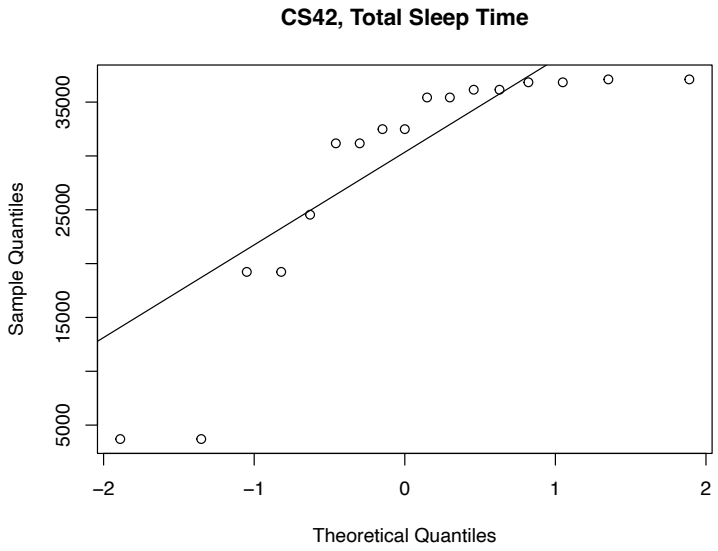
Appendix 4D. Figure 116

CS42: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = 0.829



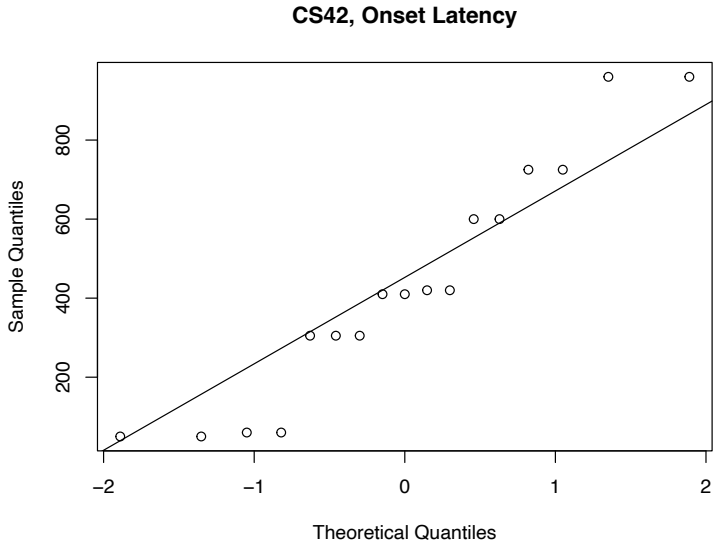
Appendix 4D. Figure 117

CS42 QQ Plot, Total Sleep Time, Shapiro-Wilk Test: p = <0.001



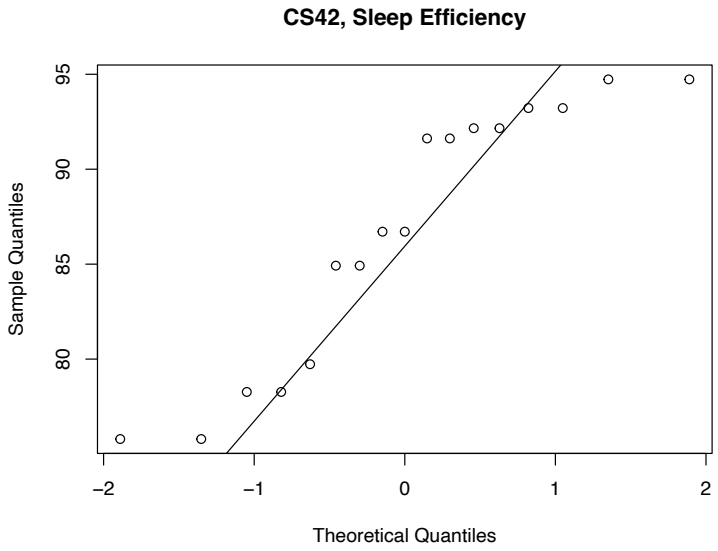
Appendix 4D. Figure 118

CS42 QQ Plot, Sleep Onset Latency, Shapiro-Wilk Test: p = <0.001



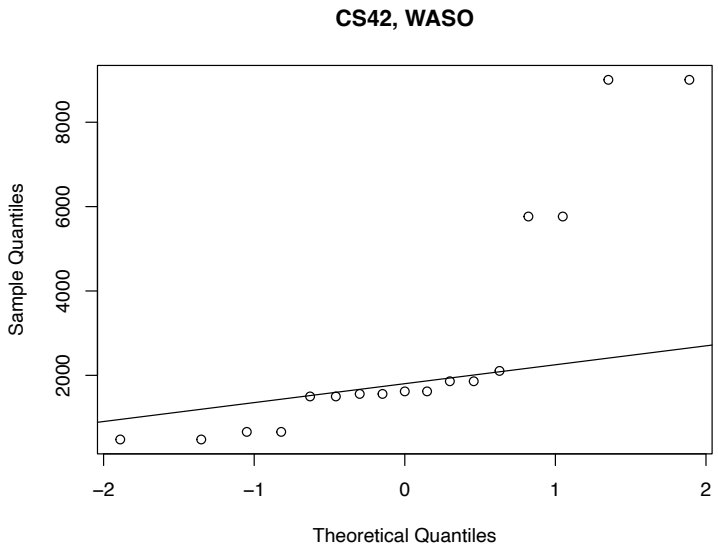
Appendix 4D. Figure 119

CS42: QQ Plot, Sleep Efficiency, Shapiro-Wilk Test: p = 0.026



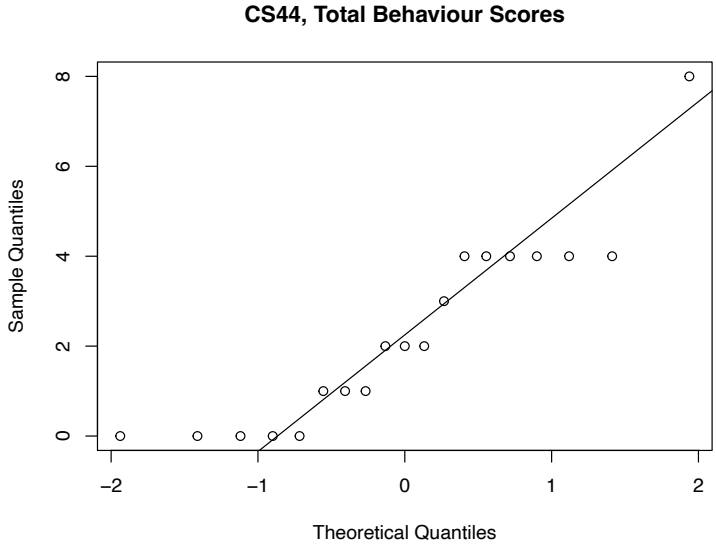
Appendix 4D. Figure 120

C*S42: QQ Plot, WASO (Wake After Sleep Onset), Shapiro-Wilk Test: p = <0.001*



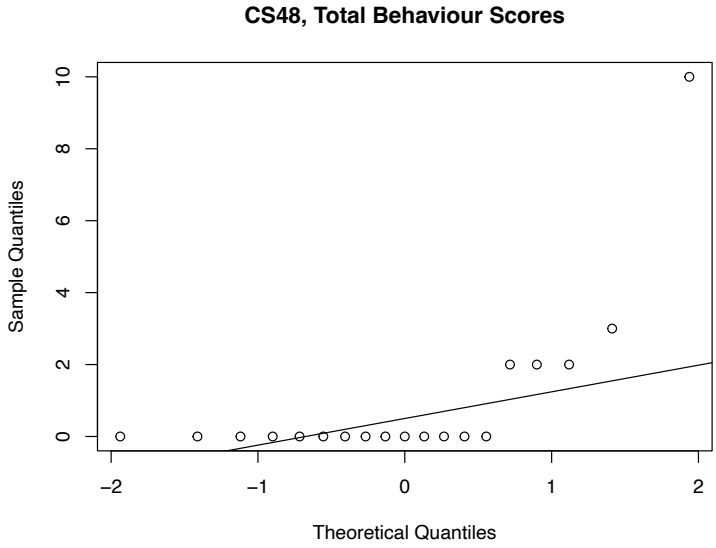
Appendix 4D. Figure 121

CS44: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = <0.001



Appendix 4D. Figure 122

CS48: QQ Plot, Total Behaviour Scores, Shapiro-Wilk Test: p = <0.001



Appendix 5A: Ethical Approval for the Forth Empirical Study of the Thesis

Dear Dr Richards,

Re: "The Behavioural Phenotype of CHARGE Syndrome"

Application for Ethical Review ERN_18-1805

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk.

Kind regards,

Ms Sam Waldron (she/her)

Research Ethics Officer

Appendix 5B: Background Questionnaire

Background Questionnaire

Today's date: _____

Please answer the following about the person you care for:

25. Gender [assigned at birth]

Male o Female o

26. Date of Birth: ___/___/____

27. Age: _____

28. Please indicate which features of CHARGE syndrome the person you care for shows?

(Please include any features your child was born with that have since have been treated)

- o CHD7
- o Coloboma
- o Choanal atresia
- o Missing or reduced sense of smell
- o Facial palsy
- o Feeding and swallowing difficulty
- o External ear anomalies
- o Middle ear anomalies
- o Inner ear anomalies
- o Hearing impairment
- o Heart defects
- o Growth deficiency
- o Genital abnormalities
- o Cleft lip or palate
- o Tracheoesophageal fistula
- o Urinary tract problems
- o Differences in the structure of the brain
- o Skeletal or limb anomalies
- o Developmental delay
- o Intellectual disability
- o Other features not listed here

Please specify the other features of CHARGE syndrome your child shows

_____

_____

29. When was the person you care for diagnosed? _____

30. What is the genetic mechanism causing CHARGE syndrome in the person you care for?

o Frame-shift variant
o Missense variant
o Nonsense variant
o Other
o Deletion
o Unknown

31. Does the person you care for have any additional diagnosis other than CHARGE syndrome?

Yes o No o

If yes, please provide details of the additional diagnosis

_____

32. Who diagnosed the person you care for?

o Paediatrician
o Clinical Geneticist
o GP
o Other

If you selected other, please specify who diagnosed the person you care for

_____

33. Has the person you care for had any medical/health difficulties in the last six months?

Yes o No o

If yes, please provide details of the medical/health difficulties experienced

_____

_____

34. Is the person you care for verbal? (i.e. more than 30 signs/words in their vocabulary)

Yes o No o

If no, are there any alternative ways the person you care for communicates with you?

Yes o No o

Please describe the way the person you care for communicates with you

_____

_____

35. Is the person you care for able to walk unaided?

Yes o No o

36. Is the person you care for able to walk unaided when outdoors?

Yes o No o

If no, is the person you care for able to walk unaided when in a familiar indoor setting?

Yes o No o

If no, Does the person you care for have an alternative way of exploring their environment independently (for example using a walker, five-point-crawling or pushing themselves along the floor on their back)

Yes o No o

Please describe how the person you care for explores their environment

_____

_____

The following questions ask for background information about you and your family:

21. What was your age in years on your last birthday? _____

22. Please select the highest level of your educational qualifications

o No formal educational qualifications

o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma

o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent

o 3 or more 'A' Levels, NVQ 3, BTEC National, or equivalent

o Polytechnic/University degree, NVQ 4, or equivalent

o Masters/Doctoral degree, NVQ 5, or equivalent

23. What is your relationship to your child with CHARGE syndrome (e.g. mother, father, stepmother, grandmother, adoptive parent)? _____

24. In total how many people currently live in your home?

Children o Adults o

25. Does the person you care for normally live with you?

Yes o No o

If no, where do they live?

_____

26. What is your current marital status?

o Married, and living with spouse

o Living with partner

o Divorced/Separated/Widowed/Single and NOT living with a partner

If you are married / living with spouse / partner:

27. What was your partner/spouse's age in years on their last birthday? _____

28. Please select the highest level of your partner/spouse's educational qualifications

o No formal educational qualifications

o Fewer than 5 GCSE's or O Level's (grades A-C), NVQ 1, or BTEC First Diploma

o 5 or more GCSE's or O Level's (grades A-C), NVQ 2, or equivalent

- o 3 or more ‘A’ Levels, NVQ 3, BTEC National, or equivalent
- o Polytechnic/University degree, NVQ 4, or equivalent
- o Masters/Doctoral degree, NVQ 5, or equivalent

29. What is your partner/spouse’s relationship to your child with CHARGE syndrome (e.g., mother, father, stepmother, adoptive parent)? _____

Recent data from research with families of children with special needs has shown that a family’s financial resources are important in understanding family member’s views and experiences. With this in mind, we would be very grateful if you could answer the additional question below. We are not interested in exactly what your family income is, but we would like to be able to look at whether those with high versus lower levels of financial resources have different experiences. However, we would like to reassure you that the question below is optional.

30. What is your current total annual family income? Please include a rough estimate of total salaries and other income (including benefits) before tax and national insurance/pensions. Please tick one box:

o Less than £15,000

o £15,001 to £25,000

o £25,001 to £35,000

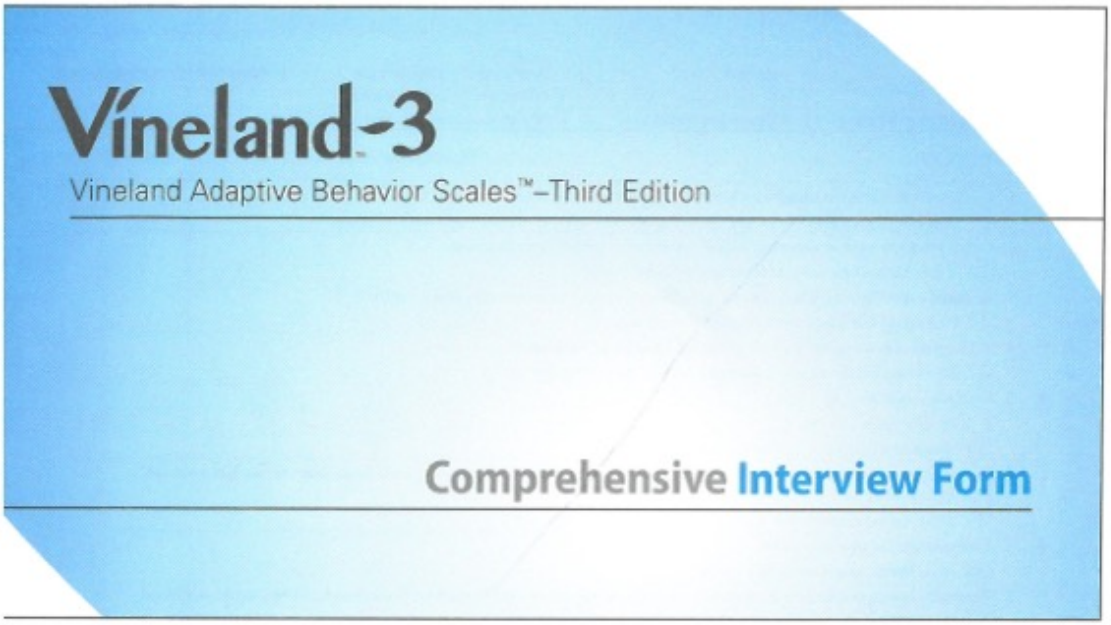
o £35,001 to £45,000

o £45,001 to £55,000

o £55,001 to £65,000

o £65,001 or more

Appendix 5C: Vineland Adaptive Behavior Scales - III (VABS: (Sparrow et al., 2016)



kaminee's Name: _____ Today's Date: _____ Examinee's Birth Date: _____
(first, middle, last) (month, day, year) (month, day, year)

kaminee's Age: _____ Examinee's Sex: ☐ Female ☐ Male Respondent's Name: _____

espondent's Relationship to the Examinee: ☐ Mother ☐ Father ☐ Other _____ Interviewer's Name: _____

IRECTIONS

omplete instructions for administering this form are provided in Chapter of the Vineland–3 Manual. The Manual also includes a list of suggested terview questions and scoring criteria for the items in Appendix G, hich you may wish to have available when conducting the interview.

eep in mind that the Coping Skills subdomain does not begin until ge 2; the Written, Domestic, and Community subdomains do not begin ntil age 3; and the optional Maladaptive Behavior domain does not begin ntil age 3.

CORING THE ITEMS

ore each item 2, 1, or 0 as follows:

ircle 2 if, when the behavior is needed or appropriate, the individual *ually* performs it without help or prompting (or if he/she performed e behavior when younger, but has now outgrown it).

ircle 1 if, when the behavior is needed or appropriate, the individual *metimes* performs it without help or prompting.

ircle 0 if the individual *never* performs the behavior, or never performs without help or prompting. Whether he/she hasn't learned the behavior, not physically able to perform it, is not expected or allowed to perform or chooses not to perform it, circle 0.

Some items use a different scoring system: 2 = Yes, 0 = No. This is indicated in the booklet.

If the respondent has not had the opportunity to observe a behavior, ask him/her to estimate a score for that item. In addition to marking the item score, also check the box to the right of the item score, in the column labeled **Check if Est**.

If the individual performed a behavior when he/she was younger, but has now outgrown it, circle 2. Do not check the Estimated box.

Some items include a Scoring Tip, indicated with the symbol ☑. Use the tips to help you score those items.

BASAL AND CEILING RULES

A basal is established when there are *four consecutive items* with scores of 2. A ceiling is established when there are *four consecutive items* with scores of 0. Continue administering Interview Topics until you have established a basal and a ceiling, and all items between the basal and ceiling have been scored. If there is no basal, you must score all items from the first item in the subdomain up to the ceiling. If there is no ceiling, you must score all items from the last item in the subdomain back to the basal.

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PsychCorp

Product Number 31321

RECEPTIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Responding
B Understanding Words
C Understanding Nonverbal Communication
D Identifying Things
E Following Basic Instructions
F Understanding Questions
G Understanding Implied Messages
H Attending to Entertaining Material
I Following Complex Instructions
J Attending to Informational Material

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

0	A	1. Looks toward parent or caregiver when hearing parent's or caregiver's voice. ? How can you tell that he/she hears your voice or the voice of someone else he/she knows?	2 1 0	☐
	A	2. Looks toward parent or caregiver who is gesturing to get his/her attention. ? What about when you gesture to get his/her attention?	2 1 0	☐
	A	3. Responds upon hearing his/her name called (for example, turns toward speaker, smiles). ? How does he/she react when you call his/her name?	2 1 0	☐
	C	4. When parent or caregiver looks or points at something, looks in that direction. ? What does he/she do when you point or look toward something?	2 1 0	☐
	B	5. Understands at least 10 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she understand?	2 0	☐
	C	6. Responds appropriately to at least three basic gestures (for example, head nod for *yes*, head shake for *no*, hand out for *give me*, reaching, waving, clapping). ? What about simple gestures like this one [shake your head "no"]?	2 1 0	☐
	B	7. Understands the meaning of *no*. ? What about simple words like *yes* and *no*?	2 1 0	☐
	C	8. Responds appropriately to at least three facial expressions being made by others (for example, frown, smile, surprised look, angry face). ? How does he/she respond to your facial expressions, for example, when you frown or look sad?	2 1 0	☐
	B	9. Understands the meaning of *yes*. ? What about simple words like *yes* and *no*?	2 1 0	☐
	E	10. Follows instructions requiring only one action (for example, "Sit down"; "Come here"). ? How about one-step instructions, like "Sit down" or "Come here"?	2 1 0	☐
	D	11. Identifies at least three *actual* objects when asked (for example, points to a dog, car, cup, key, etc.). ? What about real life objects?	2 1 0	☐
	B	12. Understands at least 50 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she understand?	2 0	☐
	G	13. Responds to the tone of spoken words (for example, approaches eagerly when "Come here" is spoken lovingly, but hesitantly when "Come here" is spoken sharply). ? What about when you change the tone of your voice to emphasize what you mean, like the difference between saying "Come here" in a loving way and an angry way?	2 1 0	☐
	D	14. Identifies at least three body parts on self when asked (for example, points to own nose, mouth, hands, feet, etc.). ? What about his/her own body parts?	2 1 0	☐
	E	15. Follows instructions with one action and one object (for example, "Bring me the book"; "Close the door"). ? What about instructions that include one action and one object, like "Bring me the book" or "Close the door"?	2 1 0	☐
	C	16. Responds appropriately to at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning *be quiet*, hands apart to show *this big*). ? What about more advanced gestures like this one [motion "come here"]?	2 1 0	☐
	D	17. Identifies at least three objects pictured in a book, magazine, or electronic screen when asked (for example, points to a dog, car, cup, key, etc.). ? What about objects shown in pictures, like when you are reading together?	2 1 0	☐
1	D	18. Identifies at least three body parts pictured in a book, magazine, or electronic screen when asked (for example, points to a nose, a mouth, hands, feet, etc.). ? What about body parts shown in pictures?	2 1 0	☐
	F	19. Responds to questions that use *what* (for example, when asked "What is this?" replies "A ball"). ? How about questions that use *what*?	2 1 0	☐
	F	20. Responds to questions that use *who* (for example, when asked "Who is that?" replies "Auntie Kesha"). ? How about questions that use *who*?	2 1 0	☐
	D	21. Identifies at least three basic actions pictured in a book, magazine, or electronic screen when asked (for example, points to someone eating, sitting, jumping, etc.). ? What kinds of actions does he/she identify when they are shown in pictures, like when you are reading together?	2 1 0	☐

RECEPTIVE — COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

	F	22. Responds to questions that use *where* (for example, when asked "Where did Felipe go?" points where Felipe went). ? How about questions that use *where*?	2 1 0	☐
	E	23. Follows instructions with two related actions (for example, "Pick up those toys and put them away"; "Get your coat and put it on"). ? What about instructions to do two things that go together, like "Get your coat and put it on"?	2 1 0	☐
	E	24. Follows instructions with one action and two objects (for example, "Bring me the crayons and the ball"; "Put on your shirt and your shoes"). ? What about instructions that include one action and two objects, like "Bring me the crayons and the ball" or "Put on your shirt and your shoes"?	2 1 0	☐
	E	25. Follows instructions in "if–then" form (for example, "If you're thirsty, then get a drink"; "If you are cold, then get a sweatshirt"). ? What about if–then instructions, like "If you're thirsty, then get a drink" or "If you are cold, then get a sweatshirt"?	2 1 0	☐
	H	26. Pays attention to a story for at least 15 minutes. ☑ Score 2 if the individual did this when younger, but has now outgrown listening to stories. ? For how long does he/she listen to a story?	2 1 0	☐
2	F	27. Responds to questions that use *why* (for example, when asked "Why are you crying?" replies "My toy broke"). ? How about questions that use *why*?	2 1 0	☐
	E	28. Follows instructions with two unrelated actions (for example, "Turn off the TV and get my keys"). ? What about instructions to do two things that don't go together, like "Turn off the TV and get my keys"?	2 1 0	☐
	F	29. Responds to questions that use *when* (for example, when asked "When do you eat breakfast?" replies "In the morning"). ? How about questions that use *when*?	2 1 0	☐
	H	30. Pays attention to a show for at least 30 minutes and understands what is happening. ? For how long does he/she pay attention to a TV show, movie, or live performance, and how can you tell if he/she understands what is happening?	2 1 0	☐
	I	31. Identifies left and right on own body (for example, hands, feet, arms). ? What about identifying left and right on his/her own body?	2 1 0	☐
	I	32. Follows instructions requiring three actions (for example, "Get dressed, eat breakfast, and brush your teeth"). ? What about three-step instructions, like "Get dressed, eat breakfast, and brush your teeth"?	2 1 0	☐
3+	H	33. Pays attention to a show for at least 60 minutes and understands what is happening. ? For how long does he/she pay attention to a TV show, movie, or live performance, and how can you tell if he/she understands what is happening?	2 1 0	☐
	G	34. Understands sarcasm (for example, understands when a comment such as "That's just great!" really means "That's awful!"). ? What about understanding sarcasm?	2 1 0	☐
	J	35. Pays attention to a 15-minute informational presentation and understands what is being said. ? For how long does he/she pay attention to information being presented that's serious or educational, and how can you tell if he/she understands what is being said?	2 1 0	☐
	I	36. Follows instructions involving left and right (for example, "Go to the left"; "Look to the right"). ? How does he/she respond to directions that involve left and right?	2 1 0	☐
	I	37. When instructed to do something up to an hour later, remembers to do it (for example, "When your show is over, put your dishes in the sink"). ? How often does he/she remember to do something meant to be done a little later, like something you've asked him/her to do after a show that he/she is watching is over?	2 1 0	☐
	I	38. When instructed to do something several hours later, remembers to do it (for example, "When you get home from school, let the dog out"). ? How often does he/she remember to do something that you ask to be done much later that day, for example, letting the dog out after school?	2 1 0	☐
	J	39. Pays attention to a 30-minute informational presentation and understands what is being said. ? For how long does he/she pay attention to information being presented that's serious or educational, and how can you tell if he/she understands what is being said?	2 1 0	☐

)mments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest Numbered Basal Item ____ × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**rec** Raw Score	C + D

EXPRESSIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Beginning Sounds & Gestures
B Beginning Speech
C Vocabulary
D Using Gestures
E Communicating Names & Age
F Using Simple Grammatical Forms
G Using Intermediate Grammatical Forms
H Using Pronouns
I Asking Questions
J Using Complex Grammatical Forms
K Expressing Ideas & Experiences
L Stating Age, Birthday, & Address
M Giving Directions

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0	A	1. Makes sounds of pleasure (for example, coos, laughs). ? What sounds does he/she make when happy?	2 1 0	☐
	A	2. Cries or fusses when uncomfortable (thirsty, hungry, wet, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about when he/she is uncomfortable, maybe hungry, thirsty, or wet?	2 1 0	☐
	A	3. Vocalizes or gestures (for example, cries or waves arms) to get parent's or caregiver's attention. ? What does he/she do to get your attention when you are not paying attention to him/her?	2 1 0	☐
	A	4. Makes at least three one-syllable speech sounds (for example, "Mah," "Bah," "Ee," "Oh"). ☑ Score 2 if the individual did this when younger, but now says words. ? What about making one-syllable sounds, like "Mah," "Bah," or "Oh"?	2 1 0	☐
	A	5. Babbles in strings of sounds (for example, "Ba-ba-ba-ba," "Ma-ma-ma-ma," "Da-da-da-da"). ☑ Score 2 if the individual did this when younger, but now says words. ? What about making strings of sounds, like "Ba-ba-ba-ba," "Ma-ma-ma-ma," or "Da-da-da-da"?	2 1 0	☐
	A	6. Vocalizes or gestures if he/she wants an activity to keep going or stop (for example, says "Again," shakes head *no*). ? What does he/she do if he/she wants an activity to stop or keep going?	2 1 0	☐
	B	7. Says "Dada," "Mama," or another name for parent or caregiver (including parent's or caregiver's first name or nickname). ? What about words to represent Mom or Dad?	2 1 0	☐
	D	8. Uses at least three basic gestures (for example, head nod for *yes*, head shake for *no*, reaching or pointing toward something desired, waving, clapping). ? How does he/she gesture when he/she wants something or wants to express himself/herself?	2 1 0	☐
	B	9. Repeats or tries to repeat common words immediately upon hearing them (for example, *ball*, *car*, *more*). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about repeating words that he/she hears?	2 1 0	☐
	B	10. Says "No"; must actually mean *no*, not just repeat the word. ? What does he/she say if he/she doesn't want something?	2 1 0	☐
	C	11. Names at least three objects (for example, ball, dog, favorite toy). ? What about common objects, such as a ball, dog, or favorite toy?	2 1 0	☐
1	B	12. Says one-word requests (for example, "Want," "More," "Open"). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she express what he/she wants, such as being picked up or having more of something?	2 1 0	☐
	C	13. Names at least 10 objects. ☑ Score 2 for Yes or 0 for No. ? About how many objects can he/she label?	2 0	☐
	B	14. Says "Yes"; must actually mean *yes*, not just repeat the word. ? What does he/she say if you say "Do you want this," and he/she does want it?	2 1 0	☐
	C	15. Names at least three actions (for example, drink/drinking, eat/eating, play/playing). ? What about labeling actions, like drinking, eating, or playing?	2 1 0	☐
	E	16. Calls brothers, sisters, or friends by their name or nickname. ? Whose names or nicknames does he/she use?	2 1 0	☐
	C	17. Says at least 50 words. ☑ Score 2 for Yes or 0 for No. ? About how many total words does he/she say?	2 0	☐

EXPRESSIVE — COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check If Est

F	18. Uses phrases with a noun and a verb (for example, "Mommy stay," "Give ball"). ? What about using both a noun and a verb, such as "Mommy stay" or "Give ball"?	2 1 0	☐
E	19. Says own first name or nickname. ? What about his/her own name or nickname?	2 1 0	☐
H	20. Uses pronouns to refer to self; grammar need not be correct (for example, "Give me," "Me want," "Mine toy"). ? What about using pronouns to refer to himself/herself, such as "I want" or "Give me"?	2 1 0	☐
F	21. Uses simple adjectives to describe things (for example, *dirty*, *pretty*, *big*, *loud*). ? What about using adjectives to describe things, such as "Pretty picture" or "Big doggie"?	2 1 0	☐
F	22. Says what he/she is doing using simple sentences; grammar need not be correct (for example, "Ginger and me play," "Dan read me a book"). ? Can you give me some examples of how he/she talks about what he/she is doing?	2 1 0	☐
D	23. Uses at least three more advanced gestures (for example, motioning *come here*, finger over lips meaning *be quiet*, hands apart to show *this big*). ? What about more advanced gestures like this one [motion *come here*]?	2 1 0	☐
F	24. Uses negatives in sentences; grammar need not be correct (for example, "I won't drink it," "Me no go"). ? What about using negatives in sentences, such as "I won't drink it" or "Me no go"?	2 1 0	☐
E	25. Says correct age when asked; holding up correct number of fingers counts. ? What about when you ask how old he/she is?	2 1 0	☐
G	26. Uses possessives in phrases or sentences; grammar need not be correct (for example, "This is mine," "Your book," "This is Carol's desk"). ? What about using possessives, words like "mine," "Mommy's," or "your"?	2 1 0	☐
G	27. Uses *and* in phrases or sentences (for example, "Mom and Dad," "I want ice cream and cake"). ? How about using the word *and* in phrases or sentences, such as "Mom and Dad" or "I want ice cream and cake"?	2 1 0	☐
I	28. Asks questions beginning with *who* (for example, "Who's that?"; "Who went to the store?"); just asking "Who?" (one word) doesn't count. ? How about questions beginning with *who*, like "Who's that?" or "Who went to the store?"	2 1 0	☐
2 G	29. Uses plural nouns (for example, "Two cats," "More crackers," "Those flowers"). ? What does he/she say to mean more than one of something, like more than one cat or more than one cracker?	2 1 0	☐
H	30. Uses pronouns to refer to others; pronoun gender and grammar need not be correct (for example, "You want?"; "Her happy"; "Him ball"). ? What about using pronouns to refer to others, such as "You want" or "Give him"?	2 1 0	☐
G	31. Uses *in*, *on*, and *under* correctly in phrases or sentences (for example, "In the box," "Ball go under table"). ? How about using the words *in*, *on*, and *under*?	2 1 0	☐
I	32. Asks questions beginning with *why* (for example, "Why do I have to go?"; "Why did you put my stuff away?"); just asking "Why?" (one word) doesn't count. ? How about questions beginning with *why*, like "Why do I have to go?" or "Why did you put my stuff away?"	2 1 0	☐
E	33. Says first and last name when asked; saying first name only doesn't count. ? What about when you ask for his/her full name?	2 1 0	☐
H	34. Uses pronouns correctly; pronoun gender and grammar must be correct (for example, "I want," "Their ball," "Call her"). ? What about using pronouns correctly?	2 1 0	☐
I	35. Asks questions beginning with *when* (for example, "When is dinner?"; "When can we go home?"); just asking "When?" (one word) doesn't count. ? How about questions beginning with *when*, like "When is dinner?" or "When can we go home?"	2 1 0	☐
J	36. Uses *because* in phrases or sentences (for example, "Because I want to," "Kathy went home because she was sick"). ? How about using the word *because*?	2 1 0	☐
L	37. Says his/her age at next birthday correctly when asked; holding up correct number of fingers counts. ? What about his/her age at his/her next birthday?	2 1 0	☐

EXPRESSIVE — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Beginning Sounds & Gestures
B Beginning Speech
C Vocabulary
D Using Gestures
E Communicating Names & Age
F Using Simple Grammatical Forms
G Using Intermediate Grammatical Forms
H Using Pronouns
I Asking Questions
J Using Complex Grammatical Forms
K Expressing Ideas & Experiences
L Stating Age, Birthday, & Address
M Giving Directions

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
J	38. Uses past tense verbs (for example, *walked*, *baked*). ? How does he/she use verbs to mean that something happened in the past?	2 1 0	☐
K	39. Tells the basic parts of a familiar story or book or movie plot (the characters, what happens, how it ends, etc.). ? How much detail does he/she tell about a familiar story when asked?	2 1 0	☐
J	40. Uses *behind*, *in front of*, and *between* correctly in phrases or sentences (for example, "Terrell is behind you," "I walked in front of her," "The ball went between the cars"). ? How about using the words *behind*, *in front of*, and *between*?	2 1 0	☐
M	41. Gives simple directions involving one or two steps (for example, how to make, find, or do something). ? What about giving simple directions, like how to make something or find something?	2 1 0	☐
J	42. Uses compound sentences joined by *and* or *but* (for example, "She asked me, and I told her no"; "Jerome wanted to go, but I didn't"). ? How about putting sentences together using *and* or *but*, for example, "She asked me, and I told her no"?	2 1 0	☐
3+ K	43. Uses own knowledge or opinions to comment on things, situations, and emotions (for example, "I think he's mad at her because she said mean things about him"). ? What about using his/her own knowledge or opinions to comment on things, for example, why a friend is mad at someone?	2 1 0	☐
K	44. Tells about everyday (i.e., routine) experiences in detail (for example, when asked what he/she did with a friend today, tells who was involved, where the activity took place, etc.). ? How much detail does he/she give when he/she talks about everyday experiences, like what happened at a friend's house?	2 1 0	☐
K	45. Tells about one-time (i.e., non-routine) experiences in detail (for example, when asked to describe a trip, tells who was involved, where the activity took place, etc.). ? What about when you ask about one-time experiences, like what he/she did on a recent vacation?	2 1 0	☐
L	46. Says both the month and day of his/her birthday when asked. ? How about the month and day of his/her birthday?	2 1 0	☐
K	47. Clarifies by restating with different words when he/she is not fully understood at first. ? If he/she is telling you something, and you aren't quite following, what does he/she do to help you understand what he/she is trying to say?	2 1 0	☐
L	48. Says complete home address correctly when asked (that is, street or rural route, apartment number, city, and state, with or without zip code). ? What about his/her complete home address?	2 1 0	☐
M	49. Gives complex directions involving three or more steps in logical order (for example, to a distant location, for a recipe requiring many steps). ? What about giving multiple-step directions, like how to get somewhere or prepare a recipe?	2 1 0	☐

Comments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**exp** Raw Score	C + D

WRITTEN — COMMUNICATION DOMAIN

NTERVIEW TOPICS

A Identifying Signs & Letters
B Understanding How Writing Works
C Copying
D Beginning Reading
E Beginning Writing
F Working With Written Information
G Personal Writing
H Reading Level
I Advanced Writing
J Forms & Business Letters

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0–2	B	1. Holds a book correctly for reading and turns the pages from front to back. ? How does he/she hold a book and turn the pages?	2 1 0	☐
	A	2. Recognizes one or more simple signs and icons/symbols (for example, STOP signs, bathroom door signs, arrows, smiley face). ? What about familiar signs, symbols, and icons, like STOP signs, bathroom door signs, and arrows?	2 1 0	☐
	A	3. Identifies one or more alphabet letters. ? What letters of the alphabet does he/she identify?	2 1 0	☐
	A	4. Recognizes own name in printed form. ? What about recognizing his/her own name in printed form?	2 1 0	☐
	A	5. Identifies at least 10 alphabet letters. ☑ Score 2 for Yes or 0 for No. ? What letters of the alphabet does he/she identify?	2 0	☐
3	B	6. Understands what direction his/her language is written in (for example, from left to right in English; in other languages from right to left or top to bottom). ? What does he/she understand about writing going from left to right? [Or a substitution appropriate to the individual's language]	2 1 0	☐
	B	7. Writes in the correct direction (for example, from left to right in English; in other languages from right to left or top to bottom). ? How often does he/she write words from left to right? [Or a substitution appropriate to the individual's language]	2 1 0	☐
	C	8. Copies own first name without mistakes. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy his/her first name?	2 1 0	☐
4	C	9. Copies simple words from an example without mistakes (for example, *cat, see, go*); copying name doesn't count. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy simple words like *cat, see, go*?	2 1 0	☐
	D	10. Identifies all alphabet letters, both uppercase and lowercase. ☑ Score 2 for Yes or 0 for No. ? For how many letters does he/she recognize both uppercase and lowercase?	2 0	☐
	E	11. Writes alphabet letters using the correct orientation (that is, not reversed or upside down). ? How many alphabet letters does he/she write correctly, not backwards or upside down?	2 1 0	☐
	D	12. Reads at least 10 words. ☑ Score 2 for Yes or 0 for No. ? About how many words does he/she read out loud?	2 0	☐
	E	13. Writes own first and last name from memory; writing first name only doesn't count. ? How often does he/she write both his/her first and last name without copying and without help?	2 1 0	☐
5	D	14. Reads simple sentences of three or more words out loud. ? How long are the sentences that he/she reads out loud?	2 1 0	☐
	C	15. Copies phrases or sentences of four or more words without mistakes. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How well does he/she copy phrases or sentences with four words or more?	2 1 0	☐
	E	16. Writes at least 10 simple words from memory (for example, *hat, ball, the*); may make small spelling errors. ☑ Score 2 for Yes or 0 for No. ? What words does he/she write from memory, other than his/her name?	2 0	☐

WRITTEN — COMMUNICATION DOMAIN

INTERVIEW TOPICS

A Identifying Signs & Letters	D Beginning Reading	G Personal Writing	J Forms & Business Letters
B Understanding How Writing Works	E Beginning Writing	H Reading Level	
C Copying	F Working With Written Information	I Advanced Writing	

		Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
	D 17. Reads simple stories out loud. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about reading simple stories?	2 1 0	☐
	E 18. Writes simple sentences of three or more words; may make small errors in spelling or grammar. ? How long are the sentences that he/she writes?	2 1 0	☐
	E 19. Writes at least 20 words from memory; may make small spelling errors. ☑ Score 2 for Yes or 0 for No. ? What words does he/she write from memory, other than his/her name?	2 0	☐
	H 20. Reads and understands material of a second-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
	G 21. Writes simple notes, letters, emails, or texts that include at least three sentences (for example, thank you notes, postcards, invitations); may use abbreviated words and make small errors in spelling or grammar. ☑ Score 2 for Yes or 0 for No. ? How long are the simple notes, letters, emails, or texts that he/she writes?	2 0	☐
	F 22. Finds or sorts things in alphabetical order (for example, finds a name in an alphabetized address book or list of phone numbers, finds a word in a dictionary, alphabetizes a list of words or movie titles). ? How often is he/she able to find things that are in alphabetical order—for example, words in a dictionary—or put words or actual things like books or music in alphabetical order himself/herself?	2 1 0	☐
	F 23. Accurately interprets information presented in simple tables, graphs, or charts. ? How accurately does he/she read tables, graphs, or charts?	2 1 0	☐
	I 24. Writes short reports or summaries (for example, a summary of something read) at least three sentences long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports or summaries. ? What about writing a short report or summary of three sentences or more?	2 1 0	☐
6–7	F 25. Accurately interprets visual instructions (for example, assembly instructions, directions shown on a map). ? How well does he/she understand and follow visual instructions, such as assembly instructions, diagrams, or directions on a map?	2 1 0	☐
	F 26. Uses a table of contents or index to find information within a book or electronic resource. ? What about using a table of contents or index to find information within a book or electronic file?	2 1 0	☐
	H 27. Reads and understands material of a fourth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
	G 28. Writes emails, stories, letters, journal entries, etc. at least 10 sentences long; may use abbreviated words and make small errors in spelling or grammar. ☑ Score 2 for Yes or 0 for No. ? How long are the emails, stories, letters, or other longer things that he/she writes?	2 0	☐
	F 29. Uses the Internet or a library to find information for writing a paper or completing a job assignment. ? How does he/she go about finding information that he/she needs to write a paper or complete a job assignment?	2 1 0	☐
8+	I 30. Writes reports, papers, or essays at least one page long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports, papers, or essays. ? How long are the reports, papers, or essays that he/she writes using his/her own words, not just copying something?	2 1 0	☐
	G 31. Writes or draws instructions for others (for example, how to do something, how to get somewhere). ? What about writing or drawing instructions or directions for someone, like how to do something or get somewhere?	2 1 0	☐

WRITTEN COMMUNICATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

I	32. Edits or corrects own written work before handing it in (for example, checks punctuation, spelling, grammar, etc.); use of computer spell-checker is okay. ? What does he/she do to check and correct his/her written work before handing it in?	2 1 0	☐
J	33. Accurately completes paper or electronic forms of one page or less (for example, forms for school or work). ? How long are the paper or electronic forms that he/she completes accurately on his/her own, such as forms for school or work?	2 1 0	☐
H	34. Reads and understands material of a sixth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
I	35. Writes reports or compositions at least three pages long; must use own words rather than simply borrowing or copying from other sources. ☑ Score 2 if the individual did this when younger, but now no longer needs to write reports or compositions. ? How long are the reports or compositions that he/she writes using his/her own words, not just copying something?	2 1 0	☐
H	36. Reads and understands material of a ninth-grade level or higher. ☑ Score 2 for Yes or 0 for No. ? At about what grade level is he/she reading and comprehending?	2 0	☐
J	37. Accurately completes paper or electronic forms of two pages or more (for example, a job, college, or credit application). ? How long are the paper or electronic forms that he/she completes accurately on his/her own, such as a job, college, or credit application?	2 1 0	☐
J	38. Writes business or application letters (for example, requests information, makes a complaint, applies for a job or to a school). ? What kinds of business or application letters does he/she write?	2 1 0	☐

mments or Observations: _____

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Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**wrn** Raw Score	C + D

PERSONAL — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Eat	D Using Spoon & Fork	G Cleaning Hands & Face	J Fastening Fasteners	M Using Knives When Eating	P Health Care
B Cooperating in Dressing & Washing	E Removing Clothing	H Putting on Clothes & Shoes	K Bathing	N Eating & Exercise Choices	
C Beginning to Drink	F Toilet Training	I Hygiene	L Using the Bathroom	O Preparing for Weather	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

0	A	1. Opens mouth when food is offered. ☑ Score 2 if the individual did this when younger, but has now outgrown being fed. ? What does he/she do when you put some food in front of his/her mouth?	2 1 0 ☐
	C	2. Drinks from a bottle or spill-proof drinking cup (often called a "sippy cup"); must hold the bottle or cup himself/herself. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How much help does he/she need with a bottle or a "sippy cup?"	2 1 0 ☐
	A	3. Sucks or chews on finger foods (for example, crackers, cookies, toast). ? What about finger foods like small crackers or cookies?	2 1 0 ☐
	A	4. Eats solid foods (for example, cooked vegetables, chopped meats). ? What about solid foods like cooked vegetables or chopped meat?	2 1 0 ☐
	B	5. Cooperates actively in undressing and dressing (raises arms for removing top, holds out feet for putting on pants or shoes, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about undressing and getting dressed?	2 1 0 ☐
	B	6. Cooperates actively in washing of hands and face (holds out hands, turns face toward parent or caregiver, etc.). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about when someone washes his/her hands and face?	2 1 0 ☐
	D	7. Feeds self with a spoon; may spill. ? How about using a spoon?	2 1 0 ☐
	E	8. Removes shoes and socks. ? What about shoes and socks?	2 1 0 ☐
1	C	9. Drinks from a regular cup or glass (sippy cups don't count); some spilling may occur. ? What about a regular glass or cup?	2 1 0 ☐
	D	10. Feeds self with a fork; may spill. ? How about using a fork?	2 1 0 ☐
	E	11. Removes clothing that opens in the front (for example, a coat or jacket); does not have to unbutton or unzip the clothing. ? What about a jacket or something else that opens in the front?	2 1 0 ☐
	F	12. Lets someone know when he/she has a wet or soiled diaper or pants (for example, points, vocalizes, pulls at diaper). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What does he/she do when he/she has a wet or dirty diaper or pants?	2 1 0 ☐
	H	13. Pulls up clothing with elastic waistbands (for example, underwear, sweatpants). ? What about clothes that have elastic waistbands?	2 1 0 ☐
	C	14. Drinks from a regular cup or glass without spilling (sippy cups don't count). ? What about a regular glass or cup?	2 1 0 ☐
	F	15. Urinates in a toilet or potty chair; parent or caregiver may initiate. ? How is he/she using the toilet or a potty chair?	2 1 0 ☐
	G	16. Washes hands using soap and water and dries them; does not need to turn the water on and off or adjust the temperature. ? What about washing his/her hands?	2 1 0 ☐
	D	17. Feeds self with a spoon without spilling. ? How about using a spoon?	2 1 0 ☐
	E	18. Removes pullover garments (for example, T-shirt, sweatshirt, dress). ? What about a T-shirt or something else that he/she has to pull off over his/her head?	2 1 0 ☐

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

H	19. Puts on shoes; may be on the wrong feet and does not need to tie or fasten. ? Who puts on his/her shoes?	2 1 0	☐
H	20. Puts on clothing that opens in the front (for example, a coat or jacket); does not need to zip or button. ? What about a jacket or something else that opens in the front?	2 1 0	☐
F	21. Defecates in a toilet or potty chair; parent or caregiver may initiate. ? How is he/she using the toilet or a potty chair?	2 1 0	☐
F	22. Is toilet-trained during the day; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet.* ? What happens during the day?	2 1 0	☐
H	23. Puts on pullover garments (for example, T-shirt, sweatshirt, dress). ? What about a T-shirt or something else that he/she has to put on over his/her head?	2 1 0	☐
I	24. Wipes or blows nose using tissue, napkin, toilet paper, or other appropriate material. ? What about wiping and blowing his/her nose?	2 1 0	☐
2 G	25. Washes and dries face; does not need to turn the water on and off or adjust the temperature. ? What about washing his/her face?	2 1 0	☐
G	26. Wipes or cleans face and hands as needed during or after meals. ? What about wiping or cleaning his/her face and hands while eating and afterwards?	2 1 0	☐
H	27. Puts clothing on with the right side forward and correct side out. ? What about putting his/her clothes on with the right side forward and the correct side out?	2 1 0	☐
F	28. Is toilet-trained during the night; may require help with undressing, flushing, wiping, or washing hands, *but must initiate using the toilet.* ? What about accidents during the night?	2 1 0	☐
I	29. Covers mouth and nose when coughing or sneezing. ? What does he/she do when he/she coughs or sneezes?	2 1 0	☐
F	30. Uses the toilet during the day and at night without help; must wipe, flush, and wash hands by himself/herself. ? How much help does he/she need?	2 1 0	☐
J	31. Fastens snaps. ? What about snaps?	2 1 0	☐
I	32. Brushes teeth; must put toothpaste on toothbrush, brush adequately, and rinse. ? What about brushing his/her teeth?	2 1 0	☐
3 J	33. Buttons large buttons, in the correct buttonholes (for example, coat buttons). ? How about big buttons, like on a coat?	2 1 0	☐
I	34. Changes clothing that has become dirty, wet, muddy, or smelly. ? What about changing clothes if they've gotten dirty, wet, muddy, or smelly?	2 1 0	☐
J	35. Connects and zips zippers that are not already fastened at the bottom (for example, on a coat or jacket). ? What about zippers that are not already fastened at the bottom, like on a coat or jacket?	2 1 0	☐
K	36. Bathes or showers and dries self; does not need to turn the water on and off or adjust the temperature. ? What about taking a bath or a shower?	2 1 0	☐
H	37. Puts shoes on the correct feet and securely ties or fastens them. ? What about tying or fastening his/her shoes?	2 1 0	☐
M	38. Spreads food with a table knife (for example, butter, jam, mustard). ? How does he/she use a table knife?	2 1 0	☐
J	39. Buttons small buttons, in the correct buttonholes (for example, shirt buttons). ? How about small buttons, like on a shirt?	2 1 0	☐
N	40. Shows awareness that some foods are healthier than others (for example, states that fruits and vegetables are healthier than foods high in sugar or fat). ? What does he/she know about healthy and unhealthy foods?	2 1 0	☐

PERSONAL — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Eat	D Using Spoon & Fork	G Cleaning Hands & Face	J Fastening Fasteners	M Using Knives When Eating	P Health Care
B Cooperating in Dressing & Washing	E Removing Clothing	H Putting on Clothes & Shoes	K Bathing	N Eating & Exercise Choices	
C Beginning to Drink	F Toilet Training	I Hygiene	L Using the Bathroom	O Preparing for Weather	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
L	41. Finds and uses an appropriate restroom when away from home. ? What happens if he/she needs to use the bathroom away from home?	2 1 0	☐
K	42. Turns faucets on and adjusts the water temperature. ? What about turning faucets on and adjusting the water temperature?	2 1 0	☐
O	43. Selects appropriate clothing during wet or cold weather (for example, raincoat, boots, sweater). ? What kind of clothes does he/she choose if it's rainy or cold?	2 1 0	☐
M	44. Cuts easy-to-cut food with a table knife (for example, fish, pancakes, butter). ? How does he/she use a table knife?	2 1 0	☐
4+ N	45. Shows awareness that physical exercise is good for people (for example, states that exercise is healthy, that people should exercise, etc.). ? What does he/she know about the health benefits of exercise?	2 1 0	☐
K	46. Washes and rinses hair; does not need to turn the water on and off or adjust the temperature. ? Who washes his/her hair?	2 1 0	☐
N	47. Chooses to exercise for health and/or enjoyment. ? How often does he/she choose to exercise on his/her own?	2 1 0	☐
L	48. Uses the toilet before going out if uncertain about the availability of a restroom. ? What about using the toilet before going out if there might not be a bathroom at his/her destination?	2 1 0	☐
N	49. Makes healthy eating choices (eats a balanced diet, eats unhealthy foods in moderation, etc.). ? How often does he/she choose to eat healthy foods?	2 1 0	☐
M	50. Cuts harder-to-cut food with a sharp knife (for example, meat, raw vegetables). ? How does he/she use a sharp knife?	2 1 0	☐
O	51. Plans for changes in weather by taking along an umbrella, a sweater, etc. ? What does he/she do to prepare for a change in the weather while he/she is out?	2 1 0	☐
P	52. Takes own temperature when needed. ? What about taking his/her own temperature?	2 1 0	☐
P	53. Takes medicine as directed on his/her own. ? What about taking medicine?	2 1 0	☐
P	54. Goes to the doctor when needed (that is, when illness or injury requires professional care). ? What happens when he/she is sick or hurt enough that he/she needs to see a doctor or nurse?	2 1 0	☐
P	55. Monitors supply of medications (nonprescription and prescription) and replaces them as needed. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What about keeping track of and refilling any medicines that he/she takes?	2 1 0	☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation		
	No. of Est	A	Highest-Numbered Basal Item	× 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling		D
	(A ÷ B) × 100 =	% Est	**per** Raw Score		C + D

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DOMESTIC — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning Home Safety
B Cleaning Up After Self
C Putting Clothes, etc. Where They Belong
D Food Preparation Basics
E Advanced Home Safety
F Basic Household Chores
G Cleaning Up After Meals
H More Complex Food Preparation
I Advanced Household Chores

		Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0–2	A 1. Is careful around hot objects (for example, the stove or oven, an open fire). ? What about safety concepts like being careful around hot objects?	2 1 0	☐
	A 2. Is careful when using sharp objects (for example, scissors, knives). ? What about sharp things like knives or scissors?	2 1 0	☐
	B 3. Wipes up own spills; must get wiping material and clean the spill adequately. ? What does he/she do if he/she spills something?	2 1 0	☐
	C 4. Puts dirty clothes in the proper place to be washed (for example, a laundry basket or chute). ? What about his/her dirty clothes?	2 1 0	☐
3–4	B 5. Removes dirty shoes or wipes them on a doormat before entering a residence. ? What does he/she do if his/her shoes are dirty when he/she is going into someone's house?	2 1 0	☐
	B 6. Puts away his/her books, toys, etc. when done using them. ? What about after he/she is done using things like toys, books, or magazines?	2 1 0	☐
	D 7. Washes hands before preparing food. ? What about washing his/her hands before preparing food?	2 1 0	☐
	B 8. Fully clears own dishes, utensils, napkins, cups, etc. after eating. ? What about clearing his/her own dishes and things after eating?	2 1 0	☐
	F 9. Does at least two simple household chores (for example, dusts, empties trash cans, feeds pet). ? What simple chores does he/she do?	2 1 0	☐
5–6	D 10. Prepares a simple snack or meal (for example, a sandwich, cheese and crackers, microwave foods). ? What about preparing a simple snack or meal like a sandwich, cheese and crackers, or microwave food?	2 1 0	☐
	E 11. Understands what to do in dangerous situations (for example, when to get help, when to call 911, how to distance self from danger). ? What does he/she understand about what to do in dangerous situations, for example, when to get help or call 911?	2 1 0	☐
	C 12. Hangs wet towel on a towel rack or hook, or puts in the proper place to be washed. ? What about his/her wet towels?	2 1 0	☐
	C 13. Puts clean clothes away where they belong (for example, in drawers or closet, on hooks). ? What about his/her clean clothes after they've been washed?	2 1 0	☐
	D 14. Uses at least two simple kitchen appliances (for example, toaster, microwave, electric can opener). ? What kitchen appliances does he/she use, things like a toaster, microwave, or electric can opener?	2 1 0	☐
	D 15. Washes fruits and vegetables before eating or cooking them. ? What about washing fruits and vegetables before eating or cooking them?	2 1 0	☐
	E 16. Secures home against intruders when home (keeps doors locked, finds out who is at the door before opening it, etc.). ? What does he/she do to keep intruders out when he/she is home, things like locking the doors and asking who's at the door before opening it?	2 1 0	☐
	D 17. Uses at least three kitchen utensils to prepare food (for example, knives, tongs, spatula, vegetable peeler). ? What kitchen utensils does he/she use, things like knives, spatulas, and vegetable peelers?	2 1 0	☐
7–8	E 18. Is careful when operating household appliances or equipment (for example, vacuum cleaner, lawnmower, iron, power tools). ? How careful is he/she when using household appliances or equipment like a vacuum cleaner, lawnmower, iron, or power tools?	2 1 0	☐
	D 19. Prepares and eats leftovers. ? What about preparing leftovers?	2 1 0	☐

DOMESTIC — DAILY LIVING SKILLS DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

F	20. Uses household products correctly (for example, laundry detergent, furniture polish, glass cleaner). ? What about using household products like cleaners correctly?	2 1 0	☐
G	21. Puts dishes away when clean and dry. ? What about putting away clean dishes when he/she is supposed to?	2 1 0	☐
E	22. Secures home against intruders when leaving home (locks doors, closes windows, turns on alarm, etc.). ? What does he/she do to keep intruders out when he/she leaves home?	2 1 0	☐
G	23. Washes dishes (either by hand, or by loading and running the dishwasher when needed). ? What about washing dishes when he/she is supposed to?	2 1 0	☐
F	24. Cleans floors thoroughly (sweeps, vacuums, mops, etc.). ? What about cleaning floors when he/she is supposed to?	2 1 0	☐
9+ G	25. Puts leftover food away (for example, in plastic bags or wrap, in containers). ? What about putting away leftover food when he/she is supposed to?	2 1 0	☐
H	26. Uses the stove or oven for cooking or baking (turns burners on and off, sets oven temperature, etc.). ? What about using the stove or oven?	2 1 0	☐
I	27. Recognizes when simple maintenance tasks need to be done and does them (for example, replaces light bulbs, batteries, filters, or vacuum cleaner bag). ? What about noticing when things like light bulbs or batteries need changing and doing it on his/her own?	2 1 0	☐
I	28. Cleans bathroom (toilet, sink, tub or shower, etc.). ? What about cleaning a bathroom when he/she is supposed to?	2 1 0	☐
I	29. Does laundry; must wash, dry, and fold/hang. ? What about doing laundry when he/she is supposed to?	2 1 0	☐
H	30. Prepares a full meal consisting of three or more food items. ? What's an example of a big meal that he/she prepares by himself/herself?	2 1 0	☐

mments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**dom** Raw Score	C + D

COMMUNITY — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Basic Money Skills	D Basic Rights & Responsibilities	G Using Money	J Advanced Safety Outside the Home	M Achieving Goals	P Earning Money
B Basic Safety Outside the Home	E Calendar Basics	H Using Technology	K Being On Time	N Understanding Rights	Q Managing Money
C Telling Time	F Telephone Use	I Eating Out	L Shopping Skills	O Traveling	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	F	1. Talks to a familiar person using a phone, computer, or other electronic device; does not need to place the call. ? How often does he/she talk with someone he/she knows?	2 1 0 ☐
0–2	A	2. Understands that money is used to buy things. ? How can you tell that he/she understands what money is used for?	2 1 0 ☐
	A	3. Counts at least 10 objects, one by one. ? To use money, you have to be able to count things. How many things like blocks or other objects does he/she count correctly?	2 1 0 ☐
	B	4. Remains within safe distance of caregiver when in public places; being carried, pushed in a stroller, etc. doesn't count. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about staying within a safe distance from you when you are out in public?	2 1 0 ☐
	B	5. Understands and follows safety precautions while riding in a car (for example, keeps seat belt on, refrains from unnecessarily distracting the driver). ? What about staying safe in the car, for example, keeping his/her seatbelt on and not distracting the driver?	2 1 0 ☐
	C	6. Understands that a clock is used to tell time. ? How can you tell if he/she knows what a clock is used for?	2 1 0 ☐
	H	7. Operates at least two technology devices for entertainment (for example, a television, DVD player, music player, handheld game, computer used for entertainment). ? What electronic devices does he/she use for entertainment?	2 1 0 ☐
	I	8. Uses appropriate manners when eating in public (for example, uses utensils, sits properly, doesn't disrupt others). ? How are his/her manners when eating out?	2 1 0 ☐
	E	9. Says all seven days of the week in order when asked. ? If you ask him/her to say the days of the week in order, how often does he/she get it right?	2 1 0 ☐
3–4	B	10. Looks both ways when crossing streets or roads. ? What does he/she do in terms of safety when crossing streets or roads?	2 1 0 ☐
	D	11. Respects the right to personal privacy for self and others (for example, while using the restroom or changing clothes; not opening others' mail). ? What about people's right to privacy?	2 1 0 ☐
	A	12. Names a penny, nickel, dime, and quarter when asked; does not need to know the value of the coins. ? What coins does he/she identify?	2 1 0 ☐
5	E	13. Says the current day of the week when asked. ? What if you ask him/her "What day of the week is it today?"	2 1 0 ☐
	A	14. Understands that some items cost more than others (for example, might say "I have enough money to buy stickers but not a book" or "Which pens cost less?"). ? What does he/she understand about some things costing more than others?	2 1 0 ☐
	F	15. Knows what phone number to call in an emergency and how to make the call (for example, knows how to call 911 or an emergency contact). ? What does he/she know about making a call in an emergency?	2 1 0 ☐
	B	16. Obeys traffic lights and *Walk/Don't Walk* signs when crossing streets or roads. ? What about crossing when there's a light or a *Walk/Don't Walk* sign?	2 1 0 ☐
	C	17. Tells time using a digital clock or watch. ? What kinds of clocks or watches can he/she tell time on?	2 1 0 ☐
	D	18. Understands and follows community rules and laws (for example, rules and laws regarding littering, pet control, respecting others' property, etc.). ? What about community rules and laws, like those regarding littering, pet control, and respecting others' property?	2 1 0 ☐
	F	19. Makes calls to others using a phone, computer, or other electronic device. ? How often does he/she call someone on his/her own?	2 1 0 ☐
	G	20. Knows the difference between bills of different values ($1, $5, $10 bills, etc.). ? What does he/she know about the values of different bills, for example, the difference between a one-dollar bill and a ten-dollar bill?	2 1 0 ☐

		Response Options: 2 = Usually, 1 = Sometimes, 0 = Never	Check if Est
B	21. Understands signs or symbols used to indicate danger (for example, skull and crossbones for poison, circle with slash for "don't do"). ? What does he/she know about signs or symbols that are used to indicate danger, like the warning sign that's a circle with a slash through it?	2 1 0	☐
E	22. Identifies a specific date (either the current date or another) on a calendar when asked. ? What if you ask him/her to find a specific date on a calendar, like today's date or his/her birthday?	2 1 0	☐
G	23. Says the value of a penny (1 cent), nickel (5 cents), dime (10 cents), and quarter (25 cents) when asked. ? What does he/she know about how much different coins are worth?	2 1 0	☐
J	24. Chooses to avoid dangerous or risky activities or situations (for example, walking in an unsafe area, jumping off high places, picking up a hitchhiker). ? How often does he/she do something risky, like walking in an unsafe area, jumping off high places, or picking up a hitchhiker?	2 1 0	☐
G	25. Makes small purchases at a store (for example, candy, stickers). ? How often does he/she make purchases by himself/herself?	2 1 0	☐
G	26. Combines coins to equal a specific amount (for example, 87 cents). ? What if he/she needs to combine coins to equal a specific amount, 87 cents for example?	2 1 0	☐
J	27. Follows safety precautions in work and/or leisure activities (for example, wears safety equipment, uses caution when operating tools and machinery). ? What does he/she do to stay safe when working or having fun?	2 1 0	☐
H	28. Watches or listens to TV or radio or uses the Internet to obtain current information (for example, news, weather report, traffic conditions). ? How often does he/she use a technology device to get current information like news, weather, or traffic conditions?	2 1 0	☐
K	29. Uses a clock to keep track of when to do something (for example, watch a TV show, meet a friend). ? How well does he/she use a clock to keep track of when to do something?	2 1 0	☐
M	30. Sets a short-term goal and achieves it (for example, completes all homework by Thursday night in order to have the weekend free). ? What are some short-term goals that he/she has achieved recently?	2 1 0	☐
F	31. Finds a needed phone number (for example, uses a contact list, the Internet, a phone book, 411). ? What does he/she do if he/she needs to find a phone number?	2 1 0	☐
J	32. Keeps personal belongings secure (wallet, purse, phone, etc.) when away from home (for example, when shopping, eating out, or traveling). ? What does he/she do to keep his/her money, phone, and other belongings from being lost or stolen when he/she is away from home?	2 1 0	☐
K	33. Gets up on time when needed (for example, sets alarm, arranges to be awakened). ? What does he/she do when he/she needs to get up at a certain time?	2 1 0	☐
L	34. Carries or stores money/debit card/credit cards safely, without losing (for example, in a wallet, purse, or money belt). ? What does he/she do to keep his/her money, debit card, and credit cards safe when out in public?	2 1 0	☐
H	35. Operates technology to accomplish at least two kinds of tasks (for example, writing documents, school-related email, organizing information, finding information on the Internet). ? How does he/she use technology to get tasks done, such as schoolwork?	2 1 0	☐
N	36. Understands the right to vote. ? What about the right to vote?	2 1 0	☐
H	37. Uses at least two social interaction technologies (for example, personal email, texting, social media, Skype™; telephone calls don't count). ? How does he/she use technology for social purposes?	2 1 0	☐
L	38. Checks change to make sure it is correct after buying something. ? How often does he/she check his/her change after buying something to make sure it's correct?	2 1 0	☐
L	39. Evaluates quality and price when deciding what to buy. ? What factors does he/she consider in deciding what to buy?	2 1 0	☐
N	40. Understands the right to begin or discontinue services (for example, telephone or Internet service). ? What about the right to start or stop a service, for example, phone service?	2 1 0	☐
N	41. Understands the right to report legitimate problems with products, services, living situation, etc. ? What about the right to report a problem with a product, a service, or his/her living situation?	2 1 0	☐

COMMUNITY — DAILY LIVING SKILLS DOMAIN

INTERVIEW TOPICS

A Basic Money Skills	D Basic Rights & Responsibilities	G Using Money	J Advanced Safety Outside the Home	M Achieving Goals	P Earning Money
B Basic Safety Outside the Home	E Calendar Basics	H Using Technology	K Being On Time	N Understanding Rights	Q Managing Money
C Telling Time	F Telephone Use	I Eating Out	L Shopping Skills	O Traveling	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
K	42. Notifies an appropriate person when he/she will be late or absent for school, work, an appointment, etc. ? What about calling in on his/her own if he/she will be late or absent for school, work, or an appointment?	2 1 0	☐
M	43. Sets a goal that can be done in six months or more and achieves it (for example, works and saves money to buy something expensive, gets in better physical shape). ? How about any goals that need six months or more to achieve?	2 1 0	☐
12+ O	44. Travels at least one mile to a familiar destination when needed (using public transportation, walking, biking, driving, etc.). ? What about traveling to places where he/she has gone many times?	2 1 0	☐
P	45. Has worked to earn money outside the home (for example, babysitting or yard work for a neighbor, having a job). ☑ Score 2 for Yes or 0 for No. ? What has he/she done to earn money outside the home, like babysitting or yard work for a neighbor, or having a job?	2 0	☐
I	46. At a restaurant, gets seating, chooses what to order, places order, and pays for meal. ? What parts of eating in a restaurant does he/she do completely on his/her own, like getting a place to sit, ordering, and paying?	2 1 0	☐
N	47. Understands the right to access records and information (for example, school or medical records, credit history). ? What about the right to see records or other information about him/her, like school or doctor's records?	2 1 0	☐
O	48. Travels at least one mile to an unfamiliar destination when needed (using public transportation, walking, biking, driving, etc.). ? What about traveling to new places?	2 1 0	☐
M	49. Sets a long-range goal requiring two years or more and achieves it (for example, makes a sports or academic team, gets into college). ? How about any goals that need two years or more to achieve?	2 1 0	☐
O	50. Uses a city, highway, bus, or electronic map (or GPS) to figure out how to reach a destination when needed. ? What does he/she do to figure out how to get somewhere?	2 1 0	☐
L	51. Buys groceries and household supplies when needed. ? How often does he/she get groceries and household supplies?	2 1 0	☐
Q	52. Manages daily expenses responsibly (for example, meals, bus fare). ? What about planning for daily expenses like meals and bus fare and sticking to that plan?	2 1 0	☐
Q	53. Uses a bank account responsibly (keeps money in the account, keeps tracks of the balance, doesn't overdraw, etc.). ? What about using a bank account responsibly?	2 1 0	☐
P	54. Has held a job (10 hours or more a week) for at least one month. ☑ Score 2 for Yes or 0 for No. ? What's the longest he/she has held a job?	2 0	☐
Q	55. Uses a credit or debit card in his/her name responsibly (for example, does not exceed credit limit, pays on time). ? What about using a credit or debit card responsibly?	2 1 0	☐
Q	56. Manages monthly expenses responsibly (for example, rent, utilities). ? What about planning for monthly expenses like rent and utilities and sticking to that plan?	2 1 0	☐
Q	57. Pays bills on time. ? How often does he/she pay his/her bills on time?	2 1 0	☐
P	58. Has held the same job (10 hours or more a week) for at least one year. ☑ Score 2 for Yes or 0 for No. ? What's the longest he/she has held a job?	2 0	☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**cmm** Raw Score	C + D

INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning Social Behavior
B Responding to Familiar People
C Expressing & Recognizing Emotions
D Identifying Self & Others
E Imitating Others
F Interpersonal Appropriateness
G Friendships
H Demonstrating Caring
I Conversational Skills
J Taking Others' Perspective
K Interpersonal Flexibility

			Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*	Check if Est
0	A	1. Looks at the face of parent or caregiver. (?) When does he/she look at your face?	2 1 0	☐
	A	2. Smiles in response to a smile or a friendly voice. (?) What does he/she do when you smile at him/her or speak pleasantly to him/her?	2 1 0	☐
	B	3. Recognizes family members or other significant people. (?) How can you tell when he/she recognizes family members or other people who he/she knows well?	2 1 0	☐
	B	4. Smiles or makes sounds when approached by a familiar person. (?) What does he/she do when someone who he/she knows comes up to him/her?	2 1 0	☐
	C	5. Shows at least three different emotions (for example, happiness, sadness, surprise, fear). (?) What kinds of emotions does he/she show?	2 1 0	☐
	A	6. Tries to interact with others (for examples, smiles or makes noises at someone, reaches for someone). (?) How do you know if he/she wants to interact with you?	2 1 0	☐
	B	7. Reaches for familiar person when that person holds out arms to him/her. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What does he/she do when you hold out your arms to pick him/her up?	2 1 0	☐
	B	8. Shows affection to familiar people (for example, touches, hugs, kisses, cuddles). (?) How does he/she show affection to familiar people?	2 1 0	☐
	A	9. Shows interest in children the same age, other than brothers or sisters (for example, watches them, smiles at them). (?) What does he/she do around other children his/her age, apart from his/her brothers or sisters?	2 1 0	☐
	B	10. Looks around from time to time to check that parent, caregiver, or other familiar person is nearby. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) How typical is it of him/her to look around from time to time to be sure that someone familiar is nearby?	2 1 0	☐
	D	11. Identifies self while looking at own image in mirror or photo. (?) What does he/she do when he/she sees himself/herself in a mirror or photo?	2 1 0	☐
	C	12. Smiles in response to praise or compliments (for example, "Good job," "That's a nice shirt"). (?) How does he/she respond when someone praises him/her or gives him/her a compliment?	2 1 0	☐
	E	13. Imitates or tries to imitate parent's or caregiver's facial expressions (for example, when parent or caregiver makes a happy, sad, or surprised face). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What about copying your facial expressions, for example, when you make a happy, sad, or surprised face?	2 1 0	☐
1	C	14. Recognizes emotions in others (for example, might say "You look sad" or "Rachel is happy"). (?) How can you tell that he/she knows what other people are feeling?	2 1 0	☐
	E	15. Imitates relatively complex actions as they are being performed by another person (for example, shaving, putting on makeup, vacuuming, hammering nails). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) What about copying an activity while you or someone else is doing it, like pretending to shave, put on makeup, or vacuum?	2 1 0	☐
	H	16. Uses actions or words to show happiness, sympathy, or concern for others on own initiative (for example, hugs, holds hands, asks "Are you okay?"). (?) How does he/she show other people that he/she feels happy for them, sad for them, or concerned about them?	2 1 0	☐
	G	17. Tries to make friends with others his/her age (that is, shows particular interest in interacting with certain other children). (?) How does he/she try to make friends with others his/her age?	2 1 0	☐

INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning Social Behavior	D Identifying Self & Others	G Friendships	J Taking Others' Perspective
B Responding to Familiar People	E Imitating Others	H Demonstrating Caring	K Interpersonal Flexibility
C Expressing & Recognizing Emotions	F Interpersonal Appropriateness	I Conversational Skills	

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
D	18. Says the relationship of family members to self (for example, "That's my mom," "He's my brother"); simply calling parents Mom, Dad, or equivalent doesn't count. ? How does he/she describe how family members are related to him/her, things like "that's my mom" or "he's my brother"?	2 1 0	☐
C	19. Uses words to express own emotions (for example, "I'm happy," "I'm scared," "I don't like him"). ? What words does he/she use to show his/her emotions?	2 1 0	☐
F	20. Maintains culturally appropriate eye contact during social interactions. ? What about making proper eye contact when he/she interacts with people?	2 1 0	☐
F	21. Answers politely when familiar adults make small talk (for example, if asked "How are you?" says "I'm fine"; if told "You look nice," says "Thank you"). ? How does he/she respond when adults who he/she knows make "chit chat" or small talk, like asking "How are you?" or saying "You look nice"?	2 1 0	☐
E	22. Imitates relatively complex actions several hours after watching someone else perform them (for example, shaving, putting on makeup, vacuuming, hammering nails). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about copying an activity several hours after seeing you or someone else do it, like pretending to shave, put on makeup, or vacuum?	2 1 0	☐
2 F	23. Speaks using a loudness, speed, and level of excitement that is appropriate for the conversation. ? What about adjusting his/her voice to the proper loudness, talking speed, and level of excitement for the conversation?	2 1 0	☐
H	24. Does things to try to please others on own initiative (for example, makes someone a card or gift, helps without being asked). ? How often does he/she do things to try to please others, like making them a card or gift or helping with something without being asked?	2 1 0	☐
G	25. Has a best friend or a few good friends. ☑ Score 2 for Yes or 0 for No. ? What about a best friend or a few really good friends?	2 0	☐
F	26. Maintains an acceptable distance between self and others in social situations (for example, does not get too close to another person when talking). ? What about not standing too close or too far away from other people in social situations?	2 1 0	☐
G	27. Is a good friend: Treats his/her friends fairly and with respect, is supportive, etc. ? How does he/she usually treat his/her friends?	2 1 0	☐
I	28. Talks with others about shared interests (for example, sports, TV shows, summer plans). ? What about talking with someone about things that they're both interested in?	2 1 0	☐
G	29. Maintains friendships over time (for example, has had the same good friend for over a year). ? How long have his/her best friendships lasted?	2 1 0	☐
J	30. Recognizes that the likes and dislikes of others can differ from his/her own (for example, might say "Kelly likes pizza, but I don't"; "I liked that movie, but Gretchen hated it"). ? How well does he/she realize that other people might not like and dislike the same things that he/she does, for example, movies or kinds of food?	2 1 0	☐
3 I	31. Starts small talk when he/she meets people he/she knows (for example, says "How are you?"; "What's up?"). ? How often does he/she start "chit chat" or small talk when seeing people who he/she knows, like asking "How are you?"	2 1 0	☐
G	32. Chooses friends with good qualities: Friends who treat him/her with respect, are supportive, stay out of trouble, etc. ? What kinds of friends does he/she usually choose in terms of how they treat him/her, if they're troublemakers, and so on?	2 1 0	☐
I	33. Moves easily from one topic to another in conversation when needed; does not "get stuck" on one topic. ? How flexible is he/she at moving from one topic to another in conversations?	2 1 0	☐

3132\1-2/9/9/

INTERPERSONAL RELATIONSHIPS — SOCIALIZATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	I 34. Talks with others without interrupting or being rude. ? What about talking with others without interrupting or being rude?	2 1 0	☐
	J 35. Tells others what he/she is thinking and feeling instead of assuming that they know. ? How often does he/she tell people what he/she is thinking and feeling, instead of assuming that they know?	2 1 0	☐
4	I 36. Stays on topic in conversations when needed; does not digress. ? What about staying on topic in conversations, rather than getting off track?	2 1 0	☐
	H 37. Responds positively to the good fortune of others on own initiative (for example, congratulates a friend who receives an award). ? What does he/she do when something good has happened to someone, like when a friend gets an award?	2 1 0	☐
	H 38. Gives cards and/or gifts to immediate family members on "special days" on own initiative. ? What about giving cards or gifts to family members on special days like birthdays or holidays without being reminded or told?	2 1 0	☐
	K 39. Will engage in activities suggested by friends, even if not preferred. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? How often does he/she do something suggested by friends when he/she would rather do something else?	2 1 0	☐
5+	J 40. Starts conversations with others by talking about things that interest them (for example, "Tyrone tells me you like cars"). ? How often does he/she start a conversation with someone by bringing up something that he/she knows that the other person is interested in?	2 1 0	☐
	K 41. Participates in conversations on a topic not of interest to him/her. ? What about talking with others about things that they're interested in, even though he/she really isn't?	2 1 0	☐
	J 42. Responds to hints or indirect cues in conversation (for example, knows that a yawn may mean "I'm bored," an abrupt change of subject may mean "I don't want to talk about that," looking at the time may mean "I need to end this conversation"). ? When someone he/she is talking with drops a hint like yawning because they're bored, looking at the time, or changing the subject, how often does he/she get the hint and react appropriately to it?	2 1 0	☐
	J 43. Provides additional explanation when needed in order for someone to follow what he/she is saying (for example, "In case you missed what I said…," "What we were talking about was…"). ? What about recognizing when someone he/she is talking with needs some background information or something explained in order to follow what's being said?	2 1 0	☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**ipr** Raw Score	C + D

PLAY AND LEISURE — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Beginning to Play
B Playing With Others
C Make-Believe
D Sharing
E Responding to Social Cues
F Following Rules in Games & Sports
G Playing Games
H Doing Things With Peers
I Planning Activities

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

0	A	1. Responds when parent or caregiver is playful (for example, smiles, laughs, claps hands). ? How does he/she respond when you act playful with him/her?	2 1 0	☐
	A	2. Shows interest in surroundings (for example, looks or moves around, touches objects or people). ? What does he/she do that shows that he/she is interested in the things around him/her?	2 1 0	☐
	A	3. Plays simple interaction games with others (for example, peek-a-boo, patty-cake). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about playing baby games like peek-a-boo and patty-cake?	2 1 0	☐
	A	4. Plays near another child, each doing different things. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about playing near another child who is playing, even if they're not playing together?	2 1 0	☐
	A	5. Copies the play of a child playing nearby with little or no interaction between the two. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about copying what a child playing nearby is doing, even though they're not really playing together?	2 1 0	☐
	B	6. Plays interactively with one or more children for at least 5 minutes with someone older supervising. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How long does he/she play interactively with one or more other children when someone older is supervising?	2 1 0	☐
1	B	7. Chooses to join other children who are playing rather than watching them or playing alone. ? When you let him/her decide, how often does he/she choose to join other children who are playing, versus just watching them or playing by himself/herself?	2 1 0	☐
	C	8. Uses common household objects or other objects for make-believe activities (for example, pretends a block is a car or a box is a house). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about using things around the house for make-believe, like pretending a big box is a house?	2 1 0	☐
	D	9. Shares toys or possessions when told to do so. ? How often does he/she share when he/she is told to?	2 1 0	☐
	E	10. Joins in with a group when verbal cues indicate that he/she is welcome. ? What does he/she do when asked to join a group activity?	2 1 0	☐
	B	11. Plays interactively with one or more children for at least 30 minutes with someone older supervising. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How long does he/she play interactively with one or more other children when someone older is supervising?	2 1 0	☐
	B	12. Protects self by moving away from those who try to hurt others or destroy things (those who bite, hit, throw things, smash things, etc.). ? What does he/she do when a child nearby is acting aggressive by trying to hurt other children or destroy things?	2 1 0	☐
	C	13. Plays simple make-believe activities with other children (for example, plays "dress-up," pretends to be superheroes). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of make-believe games does he/she play with other children?	2 1 0	☐
	G	14. Plays with others at simple outdoor group games with no score (for example, tag, jump rope, catch). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about outdoor group games where you don't keep score, like tag, jump rope, or catch?	2 1 0	☐
	B	15. Seeks out others for play or companionship (for example, asks others to play or spend time together). ? How often does he/she take the initiative to ask other children to play?	2 1 0	☐
	B	16. Plays with other children with minimal supervision. ? How about playing interactively with one or more other children without someone older supervising?	2 1 0	☐
	F	17. Takes turns when asked while playing games or sports. ? How often does he/she take turns when he/she is asked to?	2 1 0	☐
	C	18. Engages with other children in elaborate make-believe activities involving more than one role (for example, plays "school" or "restaurant," enacts a TV show or movie). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of make-believe games does he/she play with other children?	2 1 0	☐
2	D	19. Shares toys or possessions without having to be told to do so. ? How often does he/she share without having to be told to?	2 1 0	☐

31321-2/8/9/

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

	E	20. Joins in with a group when nonverbal cues indicate that he/she is welcome. ? What does he/she do when a group lets him/her know without words that they want him/her to join in, like motioning "come join us" or pointing to an empty chair?	2 1 0	☐
	F	21. Takes turns without having to be asked while playing games or sports. ? How often does he/she take turns without having to be asked?	2 1 0	☐
3	G	22. Plays with others at simple indoor or outdoor games where the players keep score (for example, tic-tac-toe, kickball, card games). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about simple indoor or outdoor games where the players keep score?	2 1 0	☐
	F	23. Follows rules in games or sports without being told to do so. ? How often does he/she follow rules in games or sports without being told to?	2 1 0	☐
	G	24. Plays with others at simple card or board games based only on chance (for example, Candyland®, the card game "war"). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What kinds of card or board games does he/she play without anyone helping him/her?	2 1 0	☐
	E	25. Refrains from entering a group when verbal cues indicate that he/she is not welcome. ? What does he/she do when told that he/she is not welcome to join a group activity?	2 1 0	☐
	D	26. Asks permission before using things that belong to or are being used by another. ? How often does he/she ask permission before using something that belongs to someone else or that someone else is using?	2 1 0	☐
	F	27. Shows good sportsmanship in games or sports: Plays fair, is not overly aggressive, congratulates winning players, does not act mean when he/she loses, etc. ? What about showing good sportsmanship, like playing fair, congratulating other players when they win, and not getting mad when he/she loses?	2 1 0	☐
4+	H	28. Gets together with two or more peers at someone's home. ? How often does he/she get together with a group at someone's home?	2 1 0	☐
	E	29. Refrains from entering a group when nonverbal cues indicate that he/she is not welcome. ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What does he/she do when a group lets him/her know without words that they *don't* want him/her to join in, like ignoring his/her presence?	2 1 0	☐
	H	30. Goes places with peers during the day or evening with someone supervising (for example, shopping, a movie, a sports event). ☑ Score 2 if the individual did this when younger, but has now outgrown the need to be supervised. ? What places does he/she go with others his/her age with someone supervising, either during the day or at night?	2 1 0	☐
	G	31. Plays with others at two or more board, card, or electronic games requiring skill and decision making (for example, Monopoly™, poker, Scrabble®, interactive video games). ? What board or card or electronic games requiring skill does he/she play without anyone helping him/her?	2 1 0	☐
	I	32. Plans ahead to do things with peers on his/her own. ? What kinds of activities does he/she plan ahead with others his/her age?	2 1 0	☐
	I	33. Obtains schedule information for movies, sports events, concerts, etc. (for example, looks at a newspaper or on the Internet, phones a movie theater). ? What about looking up schedule information for movies, sports events, concerts, and so on?	2 1 0	☐
	H	34. Goes places with peers during the day without someone supervising (for example, a shopping mall, park, community center). ? What places does he/she go during the day with others his/her age without someone supervising?	2 1 0	☐
	I	35. Plans fun activities with more than two things to be arranged (for example, birthday party, group outing). ? What about activities that require a lot of things to be planned, like a birthday party or group outing?	2 1 0	☐
	H	36. Goes places with peers in the evening without someone supervising (for example, a concert, lecture, sports event, movie). ? What places does he/she go at night with others his/her age without someone supervising?	2 1 0	☐

Comments or Observations: _____

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**pla** Raw Score	C + D

COPING SKILLS — SOCIALIZATION DOMAIN

INTERVIEW TOPICS

A Handling Transitions
B Beginning Emotional Control
C Good Manners
D Asking For & Accepting Help
E Adapting Behavior to the Situation
F Respecting Others
G Controlling Anger
H Obeying Time Limits
I Managing Social Risks
J Making Decisions

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

				Check if Est
0	B	1. Seeks comfort from parent, caregiver, or other when hurt or upset. (?) What does he/she do to try to feel better when he/she gets hurt or upset?	2 1 0	☐
	A	2. Looks or moves toward parent or caregiver when approached by an unfamiliar person. ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) How often does he/she look or move toward you when someone he/she doesn't know approaches?	2 1 0	☐
	A	3. Separates easily from parent or caregiver when left with another person (that is, does not have a temper tantrum, sulk, etc. when parent or caregiver leaves or attempts to leave). (?) How often are you able to leave him/her with another person without him/her getting upset?	2 1 0	☐
	A	4. Transitions easily from one activity to another. (?) How often is he/she able to change from one activity to another, like playtime to bath time, without getting upset?	2 1 0	☐
	C	5. Responds politely when given something (that is, expresses thanks either verbally or nonverbally). (?) How often does he/she remember to say *thank you* when given something?	2 1 0	☐
1	C	6. Is polite when asking for something (that is, uses *please* or an appropriate nonverbal gesture). (?) How often does he/she remember to say *please* when asking for something?	2 1 0	☐
	A	7. Handles changes in routine without becoming overly distressed. (?) How does he/she usually react to changes in his/her everyday routine?	2 1 0	☐
	B	8. Recovers quickly from a minor setback or disappointment (for example, doesn't pout for long after losing a game or not getting something that he/she wants). (?) How long does it usually take him/her to get over a small disappointment, like losing a game or not getting something that he/she wants?	2 1 0	☐
	B	9. Uses words or gestures to express distress rather than screaming, hitting, throwing something, etc. (?) What about using words or gestures when he/she is upset rather than screaming, hitting, throwing something, and so on?	2 1 0	☐
	F	10. Apologizes for small, unintentional mistakes (for example, burping, bumping into someone). (?) What does he/she do if he/she makes a small, accidental mistake like burping or bumping into someone?	2 1 0	☐
	C	11. Acts appropriately when introduced to new people (for example, smiles, shakes hands, says "Happy to meet you"). (?) What does he/she do when introduced to someone new?	2 1 0	☐
	D	12. Requests help when encountering a problem beyond own capability to solve (for example, a computer problem, fixing something). (?) How often does he/she ask for help when he/she can't figure out how to do something?	2 1 0	☐
	E	13. Changes behavior intentionally depending on how well he/she knows another person (for example, acts more formally with someone new than with a friend or family member). (?) What about understanding that people are usually expected to act differently with someone they've just met than with a friend or family member?	2 1 0	☐
2	D	14. Accepts helpful suggestions or solutions from others. (?) How is he/she about accepting helpful suggestions from others?	2 1 0	☐
	F	15. Apologizes with sincerity after hurting another's feelings. (?) What does he/she do if he/she hurts someone's feelings?	2 1 0	☐
	E	16. Copies appropriate behavior of others when in a new situation and unsure how to act. (?) What does he/she do when he/she is in a new situation where he/she is not sure how to act?	2 1 0	☐
3	F	17. Is willing to compromise in order to get along with peers. (?) How often is he/she willing to compromise in order to get along with others his/her age?	2 1 0	☐
	G	18. Controls anger or hurt feelings when plans change for reasons that can't be helped (for example, an event cancelled due to bad weather, a trip postponed due to car trouble). (?) How does he/she usually respond when plans change for reasons that can't be helped, like when something he/she is looking forward to has to be called off because of bad weather?	2 1 0	☐
	H	19. Follows time limits imposed by parent or caregiver (for example, amount of time allowed to watch TV, play a game, use the Internet, or play outside). ☑ Score 2 if the individual did this when younger, but has now outgrown it. (?) When you tell him/her that he/she is only allowed to do something for a limited amount of time, how often does he/she obey that time limit without having to be reminded; for example, "You can watch TV until this show is over, then you have to turn it off"?	2 1 0	☐

31321-2 / 7 / 19 /

COPING SKILLS — SOCIALIZATION DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	G	20. Understands that when someone does or says something that hurts, it may be accidental rather than intentional. ? What about understanding that when someone does or says something that hurts, it might have been an accident or mistake, and that the person may not have been trying to hurt him/her?	2 1 0 ☐
	E	21. Adjusts behavior to keep from disrupting others nearby (for example, is quiet near others who are working, listening to a show, etc.). ? What about realizing when he/she needs to adjust his/her behavior so that he/she doesn't disturb others nearby, like someone who is working or listening to a show?	2 1 0 ☐
4–5	G	22. Controls anger or hurt feelings when he/she does not get his/her way (for example, when not allowed to watch television or attend a party, when a suggestion is rejected by a friend or supervisor). ? How does he/she usually respond when he/she doesn't get his/her way, like not being allowed to do something that he/she wants to?	2 1 0 ☐
	F	23. Keeps promises. ? How often does he/she keep his/her promises, like paying back money or returning things that he/she borrows, without having to be reminded?	2 1 0 ☐
	G	24. Controls anger or hurt feelings when given constructive criticism (for example, correction of misbehavior, discussion of a test score or grade, a performance review). ? How does he/she usually respond when someone criticizes him/her in a way that's intended to be helpful, like suggesting how to do something better next time?	2 1 0 ☐
	I	25. Understands that a friendly appearing person may actually intend harm. ? What does he/she understand about how a friendly acting person may actually want to take advantage of him/her?	2 1 0 ☐
	F	26. Respects others' time (for example, doesn't keep others waiting or interrupt others who are busy). ? What about respecting other people's time, like not keeping them waiting or interrupting them when they're busy?	2 1 0 ☐
	I	27. When possible, avoids or leaves harmful relationships or situations (for example, being bullied, coerced into breaking the law, taken advantage of sexually or financially). ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? What about staying away from or leaving a relationship or situation where he/she or someone else might get hurt?	2 1 0 ☐
6+	I	28. Avoids being manipulated, dominated, or taken advantage of by others. ? What does he/she do to keep others from controlling or taking advantage of him/her?	2 1 0 ☐
	J	29. Thinks through the consequences of his/her actions before acting (for example, refrains from acting impulsively, considers relevant information). ? How often does he/she think through the consequences before doing something?	2 1 0 ☐
	H	30. Obeys curfews (that is, comes home when he/she is told to, during the day or at night). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? When you tell him/her that he/she needs to be home at a certain time, how often is he/she home at that time?	2 1 0 ☐
	I	31. Is aware of and uses caution when encountering risky social situations (for example, Internet solicitations, a stranger's offer of a ride or money, "binge" drinking parties, social media, personal ads). ☑ If the respondent has not had the opportunity to observe this, estimate a score and check the Estimated box. ? How is he/she at being cautious when people he/she doesn't know well try to get him/her to do something risky, either in person or through the Internet?	2 1 0 ☐
	H	32. Informs parent or caregiver about his/her plans when he/she goes out (for example, what time he/she is leaving and returning, where he/she is going). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about telling you about his/her plans when he/she goes out, like where he/she is going and when he/she will be home?	2 1 0 ☐
	J	33. Recognizes that advertising messages may not be accurate. ? What about understanding that the purpose of advertising is to influence our decisions, and that everything in ads isn't always totally true?	2 1 0 ☐

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation	
	No. of Est	A	Highest-Numbered Basal Item × 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling	D
	(A ÷ B) × 100 =	% Est	**cop** Raw Score	C + D

GROSS MOTOR — MOTOR SKILLS DOMAIN

INTERVIEW TOPICS

A Sitting
B Pre-Walking Mobility
C Standing
D Walking
E Ball Activities
F Climbing
G Running
H Using Stairs
I Jumping & Hopping
J Catching a Ball
K Riding a Tricycle or Bicycle

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
0	A	1. Sits supported (for example, in a chair, with pillows, etc.) for at least 1 minute. ? How long does he/she sit with his/her back supported, like in a chair with a back or propped up by pillows?	2 1 0 ☐
	B	2. Rolls over from back onto stomach. ? How about rolling over from his/her back onto his/her stomach?	2 1 0 ☐
	A	3. Sits unsupported for at least 1 minute. ? How long does he/she sit without anything supporting his/her back?	2 1 0 ☐
	B	4. Moves, scoots, or crawls across the floor. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about moving, scooting, or crawling across the floor?	2 1 0 ☐
	A	5. Sits unsupported for at least 10 minutes. ? How long does he/she sit without anything supporting his/her back?	2 1 0 ☐
	C	6. Stands holding on to a stable object for at least 5 seconds. ☑ Score 2 if the individual did this when younger, but now stands without holding on to anything. ? How long does he/she stand while holding on to something?	2 1 0 ☐
	C	7. Pulls self up to standing position. ? What about pulling himself/herself up to standing?	2 1 0 ☐
	C	8. Stands supported with one hand and reaches for an object with the other hand without falling. ☑ Score 2 if the individual did this when younger, but now stands without holding on to anything. ? What happens if he/she is standing holding on to something with one hand and reaches for something with his/her other hand?	2 1 0 ☐
	D	9. Takes steps while supporting self using furniture or another stable object. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about taking steps while holding on to furniture or something else?	2 1 0 ☐
	B	10. Crawls up stairs. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go up stairs?	2 1 0 ☐
	C	11. Stands unsupported for at least 1 minute. ? How long does he/she stand without holding on to anything?	2 1 0 ☐
	D	12. Takes at least two steps without support. ? How many steps does he/she take without holding on to anything?	2 1 0 ☐
	C	13. Stands unsupported and reaches for an object without falling. ? What happens if he/she is standing without holding on to anything and reaches for something?	2 1 0 ☐
	D	14. Walks to get around; does not need to hold on to anything. ? How often does he/she walk to get around rather than crawling?	2 1 0 ☐
	F	15. Safely climbs on and off low objects (for example, child's chair, step stool, low bench). ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How about low objects like a child's chair?	2 1 0 ☐
	B	16. Goes down stairs by crawling backwards or scooting on bottom. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go down stairs?	2 1 0 ☐
	C	17. Squats or bends down to pick up objects without falling. ? What happens when he/she needs to pick up something off the ground?	2 1 0 ☐
	E	18. Throws a ball with one hand; accuracy not important. ? How about throwing a ball with one hand?	2 1 0 ☐
	F	19. Safely gets on and off an adult-sized chair. ? How about an adult-sized chair?	2 1 0 ☐
1	G	20. Runs without falling; may be awkward and uncoordinated. ? How smoothly does he/she run, and how often does he/she fall?	2 1 0 ☐
	H	21. Walks up stairs, putting both feet on each step; may use railing. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go up stairs?	2 1 0 ☐
	E	22. Kicks a ball while standing; accuracy not important. ? How about kicking a ball while standing?	2 1 0 ☐

31321-2/6/9/

GROSS MOTOR — MOTOR SKILLS DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never* — Check if Est

D	23. Walks two or more blocks without having to rest or needing physical support. ? What about walking two or more blocks without needing to rest or be helped?	2 1 0	☐
H	24. Walks down stairs, facing forward, putting both feet on each step; may use railing. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How does he/she go down stairs?	2 1 0	☐
I	25. Jumps off the ground with both feet without falling. ? How about jumping off the ground with both feet without falling?	2 1 0	☐
G	26. Runs smoothly without falling. ? How smoothly does he/she run, and how often does he/she fall?	2 1 0	☐
F	27. Safely climbs up and down high objects (for example, jungle gym, ladder, tree). ? What about high objects like a jungle gym, a ladder, or a tree?	2 1 0	☐
D	28. Walks carefully on a sidewalk or road that is slippery or uneven. ? What does he/she do if he/she is walking outside and the sidewalk or road is slippery or uneven?	2 1 0	☐
I	29. Jumps forward at least three times with both feet without falling. ? How many times can he/she jump forward with both feet without falling?	2 1 0	☐
G	30. Runs smoothly, changing speed and direction (for example, when playing tag or sports, or chasing a pet). ? How about changing his/her speed and direction while running, like when playing tag or sports?	2 1 0	☐
J	31. Catches a beach ball-sized ball from a distance of 2 or 3 feet. ? What about a beach ball-sized ball thrown from 2 or 3 feet away?	2 1 0	☐
H	32. Walks up stairs, alternating feet; may use railing. ? How does he/she go up stairs?	2 1 0	☐
2 H	33. Walks down stairs, alternating feet; may use railing. ? How does he/she go down stairs?	2 1 0	☐
H	34. Climbs a flight of eight or more stairs at a normal pace; may use railing. ? How fast does he/she go up a flight of eight or more stairs?	2 1 0	☐
K	35. Pedals a tricycle or other three-wheeled vehicle for at least 6 feet. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How far does he/she pedal a tricycle or other three-wheeled vehicle?	2 1 0	☐
I	36. Hops on one foot at least once without falling; may hold on to something for balance. ? How about hopping on one foot while holding on to something?	2 1 0	☐
K	37. Pedals a tricycle or other three-wheeled vehicle around corners. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? What about pedaling a tricycle or other three-wheeled vehicle around corners?	2 1 0	☐
3+ J	38. Catches a beach ball-sized ball from at least 6 feet away. ? What about a beach ball-sized ball thrown from 6 feet away or more?	2 1 0	☐
I	39. Hops forward on one foot with ease without holding on (for example, during hopscotch). ? How about hopping forward on one foot multiple times without holding on?	2 1 0	☐
J	40. Catches a tennis- or baseball-sized ball from a distance of 2 or 3 feet, using one or both hands extended away from body. ? What about a tennis- or baseball-sized ball thrown from 2 or 3 feet away?	2 1 0	☐
K	41. Rides a balance bike or bicycle with training wheels for at least 10 feet. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How far does he/she ride a balance bike or a bicycle with training wheels?	2 1 0	☐
J	42. Catches a tennis- or baseball-sized ball from a distance of at least 10 feet, moving to catch it if necessary. ? What about a tennis- or baseball-sized ball thrown from 10 feet away or more when he/she needs to move to catch it?	2 1 0	☐
K	43. Rides a regular bicycle without training wheels without falling. ? What about riding a regular bicycle without falling?	2 1 0	☐

Office Use Only

Calculation of % Est *(see Manual)*		Raw Score Calculation	
No. of Est	A	Highest-Numbered Basal Item ____ × 2 =	C
No. of Items Answered	B	Points Between Basal and Ceiling	D
(A ÷ B) × 100 =	% Est	**gmo** Raw Score	C + D

FINE MOTOR — MOTOR SKILLS DOMAIN

INTERVIEW TOPICS

A Beginning to Handle Objects
B Manipulating Things
C Opening Doors
D Beginning Crayon/Pen Use
E Hand Coordination
F Drawing
G Coloring
H Using Scissors
I Tying
J Precise Movements

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

				Check if Est
0	A	1. Reaches for a toy or object. ? How often does he/she reach to try to grab a toy or other object?	2 1 0	☐
	A	2. Picks up objects; may use both hands. ? How does he/she pick up things like a toy or a ball?	2 1 0	☐
	A	3. Moves an object from one hand to the other. ? What about moving an object from one hand to the other?	2 1 0	☐
	B	4. Removes an object (for example, a block or small toy) from a box or other container with no lid. ? How about taking something out of a box or other container?	2 1 0	☐
	A	5. Picks up small objects (no larger than 2 inches on any side) with thumb and fingers (for example, raisins, beads, small blocks). ? How does he/she pick up small objects?	2 1 0	☐
	A	6. Picks up a small toy or object with one hand and hands it to someone without dropping it. ? How does he/she pick up something small and hand it to someone?	2 1 0	☐
	B	7. Puts an object (for example, a block or small toy) into a box or other container with no lid. ? How about putting something into a box or other container?	2 1 0	☐
	D	8. Marks on paper with a crayon, pen, or pencil; method of grasping the crayon, pen, or pencil is not important. ? What about making marks on paper with a crayon, pen, or pencil?	2 1 0	☐
	C	9. Opens doors that require only pushing or pulling (for example, cabinet, refrigerator, sliding, or swinging doors). ? What about opening doors that only need to be pushed or pulled, like cabinet doors or sliding doors?	2 1 0	☐
1	B	10. Stacks at least four small blocks or other small objects; alignment need not be perfect, but the stack must remain upright. ☑ Score 2 if the individual did this when younger, but has now outgrown it. ? How many blocks or other small objects does he/she stack before they fall?	2 1 0	☐
	B	11. Turns book or magazine pages one by one; books with cardboard pages don't count. ? How about turning book or magazine pages one at a time?	2 1 0	☐
	E	12. Unwraps small objects (for example, gum or candy). ? How often does he/she unwrap small objects like a piece of candy or gum by himself/herself?	2 1 0	☐
	C	13. Opens doors by turning a doorknob or handle. ? What about opening doors by turning a doorknob or handle?	2 1 0	☐
2	E	14. Uses a twisting hand–wrist motion (for example, winds up a toy or music box, screws/unscrews the lid of a jar). ? What about holding something in one hand and twisting with the other, like winding up a toy or music box, or unscrewing the lid of a jar?	2 1 0	☐
	D	15. Holds a crayon, pen, or pencil in proper position (that is, using a tripod grasp, not with fist) for writing or drawing. ? How does he/she hold a crayon, pen, or pencil?	2 1 0	☐
	E	16. Presses buttons accurately on a small keyboard or touch screen (for example, on a calculator, cell phone, or other handheld device). ? What about pressing buttons on a small keyboard or touchscreen, like on a cell phone or calculator?	2 1 0	☐
	H	17. Opens and closes scissors with one hand; does not have to cut with them. ? What about opening and closing scissors with one hand?	2 1 0	☐
	F	18. Draws a circle freehand while looking at an example. ? What about copying a circle?	2 1 0	☐
	G	19. Colors simple shapes or animals; more coloring is inside the lines than outside. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0	☐
3	F	20. Draws more than one recognizable form (for example, a person, house, tree). ? What does he/she draw well enough that you can recognize what it is?	2 1 0	☐
	E	21. Pours liquid from one container to another with little or no spilling (for example, pouring milk or juice into a glass). ? What happens when he/she tries to pour liquid, like pouring milk or juice into a glass?	2 1 0	☐
	F	22. Draws a square freehand while looking at an example. ? What about copying a square?	2 1 0	☐
	H	23. Uses scissors to cut along a straight line across a standard sheet of paper. ? How far does he/she cut with scissors on a straight line across a sheet of paper?	2 1 0	☐

31321-2 / 5 / 9 /

FINE MOTOR — MOTOR SKILLS DOMAIN

Response Options: 2 = *Usually*, 1 = *Sometimes*, 0 = *Never*

			Check if Est
	F	24. Draws a triangle freehand while looking at an example. ? What about copying a triangle?	2 1 0 ☐
	F	25. Uses an eraser without tearing the paper. ? How about using an eraser without tearing the paper?	2 1 0 ☐
4	H	26. Cuts out simple shapes (circles, squares, rectangles, etc.). ? What kinds of things does he/she cut out?	2 1 0 ☐
	G	27. Colors simple pictures with all coloring inside the lines. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0 ☐
	G	28. Colors a full-page drawing or scene using two or more colors; all coloring is inside the lines. ☑ Score 2 if the individual did this when younger, but has now outgrown coloring. ? What kinds of things does he/she color, and how much coloring is inside the lines?	2 1 0 ☐
	F	29. Draws a straight line using a ruler or straightedge. ? What about drawing a straight line using a ruler or straightedge?	2 1 0 ☐
5+	I	30. Ties a knot. ? What about tying a knot without help?	2 1 0 ☐
	H	31. Cuts out complex shapes (for example, stars, animals, alphabet letters). ? What kinds of things does he/she cut out?	2 1 0 ☐
	I	32. Ties a secure bow (for example, shoe laces, gift wrapping). ? What about tying a secure bow without help, for example, shoe laces or a gift wrapping bow?	2 1 0 ☐
	J	33. Manipulates very small objects (for example, sets hands on a watch, threads a sewing needle, glues miniature model parts). ? What about working with very small objects, like setting the hands on a watch, threading a sewing needle, or gluing tiny model parts?	2 1 0 ☐
	J	34. Assembles, builds, or creates complex building toy structures, model sets, homemade jewelry, arts and crafts, etc. ? What kinds of complex building toy structures, model sets, homemade jewelry, arts and crafts, and things like that does he/she make?	2 1 0 ☐

Comments or Observations: _____

Office Use Only	Calculation of % Est *(see Manual)*		Raw Score Calculation		
	No. of Est	A	Highest-Numbered Basal Item	× 2 =	C
	No. of Items Answered	B	Points Between Basal and Ceiling		D
	(A ÷ B) × 100 =	% Est	**fmo** Raw Score		C + D

MALADAPTIVE BEHAVIOR DOMAIN

Unlike the adaptive behavior items that you have just completed, the maladaptive behavior items are read directly to the respondent. Read (or paraphrase) each item as it is written, clarify if needed, and ask the respondent to tell you how often the behavior happens:

2 = *Often*, **1** = *Sometimes*, **0** = *Never*

SUGGESTED INTRODUCTION

Say to the respondent, "We're going to finish by talking about problem behaviors that [name] may or may not be exhibiting. This time I'm going to read you a description of each behavior and ask you to tell me if it happens often, happens sometimes, or never happens."

INTERNALIZING — MALADAPTIVE BEHAVIOR DOMAIN

	Response Options: 2 = Often, 1 = Sometimes, 0 = Never			Check if Est
1.	Is overly needy or dependent (for example, insists on help even when he/she does not need it, clings to parent or teacher).	2	1 0	☐
2.	Has eating problems (for example, overeats, refuses to eat, will only eat one or two things, hoards food).	2	1 0	☐
3.	Has sleep problems (for example, walks in his/her sleep, has a lot of nightmares, sleeps way more or less than others his/her age).	2	1 0	☐
4.	Refuses to go to school or work, or has to come home, because of worrying, sadness, nervousness, etc.	2	1 0	☐
5.	Is extremely anxious or nervous.	2	1 0	☐
6.	Cries or is sad for no clear reason.	2	1 0	☐
7.	Avoids interacting with others (withdraws, prefers to be alone, etc.).	2	1 0	☐
8.	Lacks interest in doing things that he/she enjoys or used to enjoy.	2	1 0	☐
9.	Is extremely fearful of one or more common objects or situations (for example, heights, snakes, elevators).	2	1 0	☐
10.	Worries for no clear reason.	2	1 0	☐
11.	Is very irritable or moody.	2	1 0	☐
12.	Feels helpless or hopeless (for example, says that things are bad and will never get better).	2	1 0	☐
13.	Complains of feeling sick, exhausted, or in pain, even though there is no medical reason.	2	1 0	☐

Office Use Only — **Internalizing** Raw Score ☐

EXTERNALIZING — MALADAPTIVE BEHAVIOR DOMAIN

	Response Options: 2 = Often, 1 = Sometimes, 0 = Never			Check if Est
1.	Has temper tantrums: Screams, cries, kicks, etc.	2	1 0	☐
2.	Disobeys those in authority.	2	1 0	☐
3.	Bullies others physically or with words.	2	1 0	☐
4.	Lies, cheats, or steals.	2	1 0	☐
5.	Is physically aggressive (for example, hits, kicks, bites).	2	1 0	☐
6.	Is stubborn or argues.	2	1 0	☐
7.	Is verbally abusive (that is, hurts others on purpose with insults, put-downs, etc.).	2	1 0	☐
8.	Breaks rules or laws because of peer pressure.	2	1 0	☐
9.	Is much more active or restless than others his/her age (for example, moves all the time, cannot sit still, fidgets).	2	1 0	☐
10.	Takes or uses school or work property when not allowed (for example, books, office supplies).	2	1 0	☐
11.	Destroys his/her own or someone else's possessions on purpose.	2	1 0	☐

Office Use Only — **Externalizing** Raw Score ☐

313212/1491

CRITICAL ITEMS — MALADAPTIVE BEHAVIOR DOMAIN

Response Options: 2 = *Often*, 1 = *Sometimes*, 0 = *Never*

		Check if Est
1. Gets fixated on objects or parts of objects (for example, stares at spinning wheels or fan blades, lines up objects, flips light switches over and over).	2 1 0	☐
2. Talks about hearing voices that others do not hear, or seeing things that others do not see.	2 1 0	☐
3. Harms himself/herself (for example, bangs his/her head, hits or bites self, cuts self, tears at skin, pulls out his/her hair).	2 1 0	☐
4. Uses strange or repetitive speech (for example, has conversations with himself/herself in public, says things that make no sense, repeats the same thing over and over).	2 1 0	☐
5. Loses awareness of what is happening around him/her (for example, seems to be "in a fog," "zones out").	2 1 0	☐
6. Repeats physical movements over and over (for example, rocks back and forth, spins, flaps hands).	2 1 0	☐
7. Has toileting accidents (that is, wets or soils self when not in diapers).	2 1 0	☐
8. Eats non-food items such as dirt, paste, or soap.	2 1 0	☐
9. Engages in compulsive behavior (for example, repeated hand washing, repeatedly checking and rechecking something, other compulsive rituals).	2 1 0	☐
10. Shows far more interest in weapons or extreme violence than others his/her age.	2 1 0	☐
11. Harms animals (for example, tortures or kills pets or wild animals).	2 1 0	☐
12. Has beliefs that are not true (for example, believes he/she has a "true" identity or "special" powers, believes that others secretly want to cause harm).	2 1 0	☐
13. Gets so fixated on a particular topic that it annoys others (for example, trains, reptiles, maps, subway systems).	2 1 0	☐
14. Talks about killing himself/herself or has tried to kill self.	2 1 0	☐
15. Has no response to pain (for example, does not cry or seek help when cut, bruised, or badly hurt).	2 1 0	☐
16. Wanders, darts away, or takes off from home, school, or someone watching him/her without regard for safety.	2 1 0	☐
17. Threatens to hurt or kill someone.	2 1 0	☐
18. Is tricked by others into doing something that could seriously harm him or her, or someone else.	2 1 0	☐
19. Gets fixated on a person in a way that is annoying or intrusive to that person.	2 1 0	☐
20. Engages in unwanted sexual behavior (for example, unwanted comments, unwanted physical contact, exposing himself/herself, masturbating in public, having sex at school or work).	2 1 0	☐

GENERAL COMMENTS

Use this space to record any general comments about the interview that you want included in the test record.

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01-21-2015

Vineland-3

Comprehensive Interview Form Score Report

Examinee's Name:

Examiner's Name:

Interview Respondent's Name:

Calculation of Examinee's Age	Year	Month	Day
Test Date			
Birth Date			
Test Age			

Score Summary

	Subdomains				
	Raw Score	v-Scale Score	Age Equivalent (AE)	Growth Scale Value (GSV)	% Est
Receptive (rec)					
Expressive (exp)					
Written (wrn)					
COMMUNICATION (COM) Sum of v-Scale Scores:		1			
Personal (per)					
Domestic (dom)					
Community (cmm)					
DAILY LIVING SKILLS (DLS) Sum of v-Scale Scores:		2			
Interpersonal Relationships (ipr)					
Play and Leisure (pla)					
Coping Skills (cop)					
SOCIALIZATION (SOC) Sum of v-Scale Scores:		3			
Gross Motor (gmo)					
Fine Motor (fmo)					
MOTOR SKILLS (MOT) Sum of v-Scale Scores:		4			

	Domains and Adaptive Behavior Composite			
	Sum of v-Scale Scores	Standard Score	85% 90% 95% Confidence Interval	Percentile Rank
Communication (COM)	1		—	
Daily Living Skills (DLS)	2		—	
Socialization (SOC)	3		—	
Sum of Domain Standard Scores				
See Table B.3 to convert to ABC		▼		
Adaptive Behavior Composite (ABC)			—	
Motor Skills (MOT)	4		—	

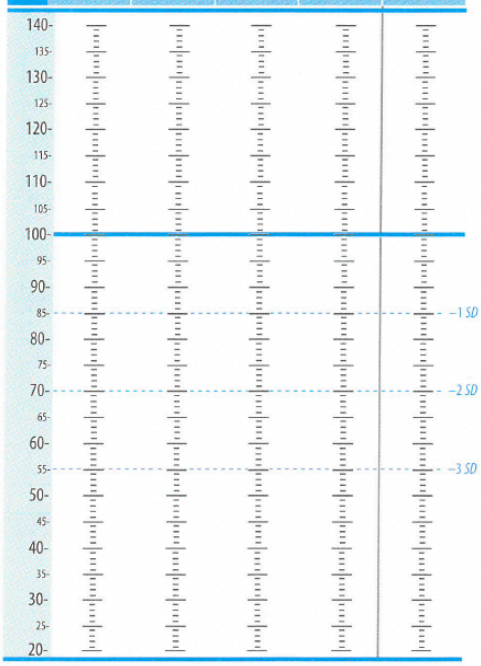
PEARSON

PsychCorp

Subdomain v-Scale Score Profile

	COMMUNICATION			DAILY LIVING SKILLS			SOCIALIZATION			MOTOR SKILLS		
	rec	exp	wrn	per	dom	cmm	ipr	pla	cop	gmo	fmo	
24	•	•	•	•	•	•	•	•	•	•	•	24
23	•	•	•	•	•	•	•	•	•	•	•	23
22	•	•	•	•	•	•	•	•	•	•	•	22
21	•	•	•	•	•	•	•	•	•	•	•	21
20	•	•	•	•	•	•	•	•	•	•	•	20
19	•	•	•	•	•	•	•	•	•	•	•	19
18	•	•	•	•	•	•	•	•	•	•	•	18
17	•	•	•	•	•	•	•	•	•	•	•	17
16	•	•	•	•	•	•	•	•	•	•	•	16
15	•	•	•	•	•	•	•	•	•	•	•	15
14	•	•	•	•	•	•	•	•	•	•	•	14
13	•	•	•	•	•	•	•	•	•	•	•	13
12	•	•	•	•	•	•	•	•	•	•	•	12
11	•	•	•	•	•	•	•	•	•	•	•	11
10	•	•	•	•	•	•	•	•	•	•	•	10
9	•	•	•	•	•	•	•	•	•	•	•	9
8	•	•	•	•	•	•	•	•	•	•	•	8
7	•	•	•	•	•	•	•	•	•	•	•	7
6	•	•	•	•	•	•	•	•	•	•	•	6
5	•	•	•	•	•	•	•	•	•	•	•	5
4	•	•	•	•	•	•	•	•	•	•	•	4
3	•	•	•	•	•	•	•	•	•	•	•	3
2	•	•	•	•	•	•	•	•	•	•	•	2
1	•	•	•	•	•	•	•	•	•	•	•	1

Domain and ABC Standard Score Profile



MALADAPTIVE BEHAVIOR

	Raw Score	v-Scale Score	Critical Items (Circle all item scores of 2 or 1)
Internalizing			1. 2 1 2. 2 1 3. 2 1 4. 2 1 5. 2 1 6. 2 1 7. 2 1 8. 2 1 9. 2 1 10. 2 1
Externalizing			11. 2 1 12. 2 1 13. 2 1 14. 2 1 15. 2 1 16. 2 1 17. 2 1 18. 2 1 19. 2 1 20. 2 1

STRENGTH/WEAKNESS ANALYSIS

Domains	Standard Score (SS)	SS Minus Mean SS	.10 or .05 Critical Value	Strength or Weakness	Base Rate
COM				S or W	
+					
DLS				S or W	
+					
SOC				S or W	
+					
MOT				S or W	
=					
	Sum of SS	÷ No. of domains (3 or 4)	= Mean SS (one decimal)	Calculation of Mean Domain Standard Score	

Subdomains	v-Scale Score (vS)	vS Minus Mean vS	.10 or .05 Critical Value	Strength or Weakness	Base Rate
rec				S or W	
+					
exp				S or W	
+					
wrn				S or W	
+					
per				S or W	
+					
dom				S or W	
+					
cmm				S or W	
+					
ipr				S or W	
+					
pla				S or W	
+					
cop				S or W	
+					
gmo				S or W	
+					
fmo				S or W	
=					
	Sum of vS	÷ No. of subdomains	= Mean vS (one decimal)	Calculation of Mean Subdomain v-Scale Score	

PAIRWISE DIFFERENCE COMPARISONS

Domain Comparisons	Standard Score	<, >, or =	Standard Score	Standard Score Difference	.10 or .05 Critical Value	Statistically Significant	Base Rate
COM		_	DLS			Y or N	
COM		_	SOC			Y or N	
DLS		_	SOC			Y or N	
COM		_	MOT			Y or N	
DLS		_	MOT			Y or N	
SOC		_	MOT			Y or N	

Subdomain Comparisons	v-Scale Score	<, >, or =	v-Scale Score	v-Scale Score Difference	.10 or .05 Critical Value	Statistically Significant	Base Rate
Communication							
rec		_	exp			Y or N	
rec		_	wrn			Y or N	
exp		_	wrn			Y or N	
Daily Living Skills							
per		_	dom			Y or N	
per		_	cmm			Y or N	
dom		_	cmm			Y or N	
Socialization							
ipr		_	pla			Y or N	
ipr		_	cop			Y or N	
pla		_	cop			Y or N	
Motor Skills							
gmo		_	fmo			Y or N	
Across-Domain Comparisons							
		_				Y or N	
		_				Y or N	
		_				Y or N	

Abbreviations

COM	Communication	DLS	Daily Living Skills	SOC	Socialization	MOT	Motor Skills
rec	Receptive	per	Personal	ipr	Interpersonal Relationships	gmo	Gross Motor
exp	Expressive	dom	Domestic	pla	Play and Leisure	fmo	Fine Motor
wrn	Written	cmm	Community	cop	Coping Skills		

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Appendix 5D: Questions About Behaviour Function QABF: Matson & Vollmer, 1995)

QABF (Matson & Vollmer, 1995) V1.0 20/01/21

Richards Lab
Birmingham

Behaviour in CHARGE Syndrome
Study 1
Questions About Behavioural Function (QABF)

The Cerebra Network for Neurodevelopmental Disorders

UNIVERSITY OF BIRMINGHAM

Researcher Instructions: Ask participant each question referring to the behaviour categories identified for this participant in part 2 of the Challenging Behaviour Interview (CBI). When aggression and an additional behaviour of concern were identified in part 2 of the CBI there should be 2 answer provided for each of the following 40 questions.

Participant Instructions: "*Rate how often the person you care for demonstrates [Insert behaviour] behaviours in situations where they might occur. Be sure to rate how often each behaviour occurs, not what you think a good answer would be*".

		Does not apply	Never	Rarely	Some	Often
1	Engages in the behaviour to get attention.	X	0	1	2	3
2	Engages in the behaviour to escape work or learning situations.	X	0	1	2	3
3	Engages in the behaviour as a form of 'self-stimulation'.	X	0	1	2	3
4	Engages in the behaviour because he/she is in pain.	X	0	1	2	3
5	Engages in the behaviour to get access to items such as preferred toys, food, or beverages.	X	0	1	2	3
6	Engages in the behaviour because of the sensory input in the environment	X	0	1	2	3
7	Engages in the behaviour because a routine has been interrupted	X	0	1	2	3
8	Engages in the behaviour to escape from a social situation	X	0	1	2	3
9	Engages in the behaviour because he/she likes to be reprimanded.	X	0	1	2	3
10	Engages in the behaviour when asked to do something (get dressed, brush teeth, work, etc.).	X	0	1	2	3
11	Engages in the behaviour even if he/she thinks no one is in the room.	X	0	1	2	3
12	Engages in the behaviour more frequently when he/she is ill.	X	0	1	2	3
13	Engages in the behaviour when you take something away from him/her.	X	0	1	2	3
14	Engages in the behaviour because of sound or light from the environment	X	0	1	2	3
15	Engages in the behaviour when you prevent him/her from completing a routine or ritual	X	0	1	2	3
16	Engages in the behaviour when you interact socially with him/her	X	0	1	2	3
17	Engages in the behaviour to draw attention to him/herself.	X	0	1	2	3
18	Engages in the behaviour when he/she does not want to do something.	X	0	1	2	3
19	Engages in the behaviour because there is nothing else to do.	X	0	1	2	3
20	Engages in the behaviour when there is something bothering him/her physically.	X	0	1	2	3
21	Engages in the behaviour when you have something he/she wants.	X	0	1	2	3
22	Engages in this behaviour to be removed from a noisy or bright environment	X	0	1	2	3
23	Engages in this behaviour when there has been an interruption or change to his/her routine	X	0	1	2	3
24	Engages in this behaviour when he/she does not want social attention	X	0	1	2	3
25	Engages in the behaviour to try and get a reaction from you.	X	0	1	2	3
26	Engages in the behaviour to try and get people to remove a task or demand	X	0	1	2	3
27	Engages in the behaviour in a highly repetitive manner, ignoring his/her surroundings.	X	0	1	2	3
28	Engages in the behaviour because he/she is physically uncomfortable.	X	0	1	2	3
29	Engages in the behaviour when a peer has something he/she wants.	X	0	1	2	3

30	Engages in the behaviour to reduce noise or light	X	0	1	2	3
31	Engages in the behaviour to try to re-establish a preferred routine or ritual	X	0	1	2	3
32	Engages in the behaviour to try to get people to leave him/her alone.	X	0	1	2	3
33	Does he/she seem to be saying 'come see me' or 'look at me' when engaging in the behaviour?	X	0	1	2	3
34	Does he/she seem to be saying 'stop asking me to do this' when engaging in the behaviour?	X	0	1	2	3
35	Does he/she seem to enjoy the behaviour, even if no one is around?	X	0	1	2	3
36	Does the behaviour seem to indicate to you that he/she is not feeling well?	X	0	1	2	3
37	Does he/she seem to be saying 'give me that (toy item, food item) when engaging in the behaviour?	X	0	1	2	3
38	Does he/she seem to be saying 'this place is too noisy/bright'?	X	0	1	2	3
39	Does he/she seem to be saying 'let me finish my routine or ritual' when engaging in this behaviour?	X	0	1	2	3
40	Does he/she seem to be saying 'leave me alone' when engaging in this behaviour?	X	0	1	2	3

Appendix 5E: The Challenging Behaviour Interview (CBI: Oliver et al., 2003)

Challenging Behaviour Interview

ID: Date of interview:

CHALLENGING BEHAVIOUR INTERVIEW (PART I)

1. Which of the following behaviours have occurred in the last month? (See appendix for definitions and examples)

Challenging Behaviour Category	List behaviours from examples in appendix
☐ Self –Injury (SIB)	**Description:** Non-accidental behaviours which producing temporary marks or reddening of the skin or cause bruising, bleeding or other temporary or permanent tissue damage. **Example:** Self-biting, head banging, head-punching or slapping, removing hair, self-scratching, body biting, eye poking or pressing.
☐ Physical aggression (PAG)	**Description:** A non-accidental, physical act involving physical contact with another person likely to result in pain or distress. **Example: Punching, pushing, kicking, tripping, pulling hair, scratching, throwing objects, using objects as weapons, grabbing clothing.**
☐ Verbal aggression (VAG)	**Description:** Verbal statements that are likely to induce fear or distress. **Example: Threats, insults etc.**
☐ Disruption and destruction of property or the environment (DST)	**Description:** A non-accidental physical act which results in disruption or superficial or substantial damage to any property or the environment. **Example: Tearing or chewing own clothing, tearing newspapers, notes, books, breaking windows or furniture, slamming doors, pulling pictures from walls, spoiling a meal, throwing objects, knocking objects to the floor.**
☐ Anal poking (AP)	**Description:** Insertion of objects, fingers or hand into the anus.
☐ Stereotyped behaviours (STB)	**Description:** Apparently meaningless, repetitive movements, executed in an almost identical way each time. **Example: Rocking, hand regard, twiddling objects, strobing, patting or tapping part of the body, spinning, head weaving or rolling, constant hand movements, hand sucking and eye pressing (when there is no tissue damage).**
☐ Inappropriate vocalisations (IV)	**Description:** Shouting, screaming, repetitive groaning or moaning, growling.
☐ Inappropriate removal of clothing (IRC)	**Description:** Inappropriate removal of clothing.
☐ Pica (PIC)	**Description:** Eating inedible substances. **Example: Eating paper, leaves, discarded food etc.**
☐ Inappropriate or unacceptable sexual behaviour (ISB)	**Description:** Inappropriate or unacceptable sexual behaviour.
☐ Smearing (SMR)	**Description:** Smearing of faeces.
☐ Stealing (STL)	**Description:** Intentionally stealing object.
☐ Self-induced vomiting and regurgitation (SIV)	**Description:** The act of intentionally making themselves vomit.

CHALLENGING BEHAVIOUR INTERVIEW (PART II)

In each box, enter the category of challenging behaviour that is being considered	Agression	SIB

1. Think about how often this behaviour occurred in the last month. If there was no change and you watched this person now, then would you *definitely* see the behaviour:

⑤	④	③	②	①		
In the next 15 minutes	In the next hour	By this time tomorrow	By this time next week	By this time next month		

2. In the last month, for how long did the *longest* episode or burst of this behaviour last?

①	②	③	④	⑤		
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour		

3. In the last month, for how long have episodes or bursts of this behaviour *typically* lasted or lasted on average?

①	②	③	④	⑤		
Less than a minute	Less than 5 minutes	Less than 15 minutes	Less than an hour	More than an hour		

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4. For the worst episode of behaviour in the last month, what response was necessary[1]?

⓪	①	②	③	④		
Nothing	Verbal discouragement or reminder	Informal physical intervention by one member of staff e.g. blocking, holding an arm briefly, taking objects from an individual Removal to a safe environment Removal of staff or others from immediate environments	Informal physical intervention by more than one member of staff Formal restraint procedure Protective or restrictive devices employed	Seclusion PRN medication Legal involvement or legal advice has been sought Section of MHA invoked		

[1] To score, identify any items which have occurred and take highest scoring item.

5. In the last month, what has been the worst effect of this behaviour on the individual's *physical health*?

⓪	①	②	③
No effect at all	**Minor, temporary injury,** such as reddening of the skin, but *no* bruising or tissue damage	**Moderate injury,** such as bruising , cuts or abrasions **or illness lasting less than a day,** e.g. brief stomach upset, a single episode of vomiting	**Significant injury** e.g. fractured bones, sutures required, minor or major operation required **or illness lasting more than a day**

6. In the last month, what has been the worst *direct* effect of this behaviour on the *physical health* of staff or carers?

⓪	①	②	③
No effect at all	**Minor, temporary injury,** such as reddening of the skin, but *no* bruising or tissue damage	**Moderate injury,** such as bruising , cuts or abrasions **or illness lasting less than a day,** e.g. brief stomach upset, a single episode of vomiting	**Significant injury** e.g. fractured bones, sutures required, minor or major operation required **or illness lasting more than a day**

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7. In the last month, what has been the worst *direct* effect of this behaviour on the *physical health* of other service users?

⓪	①	②	③
No effect at all	**Minor, temporary injury,** such as reddening of the skin, but *no* bruising or tissue damage	**Moderate injury,** such as bruising , cuts or abrasions **or illness lasting less than a day,** e.g. brief stomach upset, a single episode of vomiting	**Significant injury** e.g. fractured bones, sutures required, minor or major operation required **or illness lasting more than a day**

8. Throughout the whole of the last month, has the behaviour had any negative effects on the well-being of other service users e.g. disruption to planned activities, service users are frightened or upset, belongings or clothing are damaged or lost, meals are spoiled etc.?

⓪	①	②	③	④
No effect at all on the well-being of other service users	Effect on the well-being of other service users **about once in the last month**	Effect on the well-being of other service users **about once a week**	Effect on the well-being of other service users **about once every 3 days**	Effect on the well-being of other service users **nearly every day**

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9. In the last month, what has been the *direct* effect of this behaviour on the environment in which the individual lives?

⓪	①	②	③	④		
No damage or loss at all	**Disruption or mild damage** to property or the living areas e.g., objects thrown, furniture tipped, doors slammed, meals spoiled, paint scratched. **Item does not require repair or replacement.**	**Moderate damage** to property or living areas e.g. curtains torn, furniture partly broken. **Item requires repair but can be used.**	**Significant damage** to property and living areas. **Item requires repair and cannot be used.**	**Extreme damage** to property or living areas. **Item requires replacement and cannot be used or repaired** e.g. windows broken, furniture unusable.		

10. In the last month, as a result of this behaviour, have restrictive or protective devices (e.g. arm splints, helmet) or specially designed clothing (e.g. all-in-one suit) been worn by the individual?

⓪	①	②	③	④		
Never	**Some of the time**	**About half the time**	**Most of the time**	**Almost continuously**		

(If so was it: Arm splint(s)☐ Helmet or headgear☐ Gloves/mittens/other items on hands☐ Specially designed clothing☐ Other☐, (please specify)_____)

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11. Has the environment in which the individual currently lives been modified because of this behaviour (examples of modification are given in the box below)?

⓪	①	②	③		
No modifications	**Modifications to the person's possessions but not elsewhere** e.g. padding on a wheel chair, clothing which is strengthened	**Modifications have been made to the environment but are not noticeable unless pointed out e.g. curtains on Velcro, window locks**	**Modifications have been made to the environment and are noticeable**		

Examples of modification to the environment: windows are not made of glass, TV is in a protective cabinet or out of reach, furniture is secured, a cupboard door is secured, a door is secured, curtains are absent (because they will be torn down), pictures are out of reach, hard or sharp surfaces are padded, service users are always visible, a room is out of bounds, cutlery is plastic, furniture is deliberately heavy, door closers are fitted to prevent slamming, wallpaper is washable in rooms apart from kitchen and bathroom, fridge is secured, ornaments are out of reach, furniture or fittings have been removed, furniture is chosen because it has particular qualities e.g. no sharp edges etc.

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12. In the last month, as a result of this behaviour, has a verbal response by staff or carers been necessary e.g. discouraging the behaviour, distraction to another activity, reminder, reprimand?

⓪	①	②	③	④		
Never	**At least once a month**	**At least once a week**	**At least once a day**	**At least once an hour**		

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13. In the last month, as a result of this behaviour, has physical contact or prevention or restraint by staff or carers been necessary e.g. blocking, taking objects from an individual, temporary restraint of an arm?

⓪	①	②	③	④		
Never	**At least once a month**	**At least once a week**	**At least once a day**	**At least once an hour**		

(If so was it a written procedure ☐ or an informal procedure ☐, please tick.)

14. In the last month, for this behaviour, was it necessary for more than one member of staff to respond when the behaviour occurred?

⓪	①	②	③	④		
Never	**At least once a month**	**At least once a week**	**At least once a day**	**At least once an hour**		

15. In the last month, has there been any contact with any of the following regarding this behaviour?

		Name and Contact Number
☐	Clinical Psychologist or Psychology Assistant working with a Clinical Psychologist	
☐	Psychiatrist	
☐	General Practitioner	
☐	Challenging Behaviour specialist or team	
☐	Speech and language therapist	
☐	Legal advisor	
☐	Other	
☐	Other	
☐	Other	

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