VOLUME I

RESEARCH COMPONENT

Suicidality in Neurological Conditions

By

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A thesis submitted to

The University of Birmingham

for the degree of

DOCTORATE IN CLINICAL PSYCHOLOGY

Department of Clinical Psychology

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The University of Birmingham

May 2015

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Overview

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctorate of Clinical Psychology (Clin.Psy.D.) at the University of Birmingham. It consists of two volumes: a research and a clinical volume.

Volume I comprises three chapters. The first chapter is a systematic literature review investigating risk factors associated with suicidality in Huntington's disease. The second chapter is an empirical study of the relationship between disability, depression and suicide ideation in Multiple Sclerosis. The third chapter is an executive summary, which is a public domain briefing document, providing a brief overview of the literature review and the empirical paper.

Volume II comprises five clinical practice reports (CPRs). The first report describes the case of a 24 year old woman presenting with depression, anxiety and low self-esteem. The case is formulated from both a cognitive behavioural and psychodynamic approach. The second report is a single case experimental design evaluating the effectiveness of cognitive behavioural therapy and exposure response prevention for a 42 year old woman presenting with symptoms consistent with body dysmorphia and obsessive compulsive disorder. The third report is a small scale service related piece of research exploring the views of community and inpatient occupational therapy staff working in relation to a new strategy document promoting occupational therapy in mental health services. The fourth report is a case study of a 45 year old woman who named the problem as 'the gremlin' and her story is understood from a social constructionist, narrative perspective. Finally, the fifth report is the abstract of an oral presentation about a 17 year old male diagnosed with cancer in which the

case is formulated utilising a systemic approach. To ensure confidentiality all identifying information in these reports has been anonymised.

Acknowledgements

I would firstly like to thank my research supervisor Dr Theresa Powell whose knowledge, patience, calm and encouraging approach, have contributed to providing me with excellent supervision throughout the whole of the research component.

Thank you to the Multiple Sclerosis team at West Midlands Rehabilitation Centre, especially Dr Chit Ko Ko who provided additional guidance with the research study, as well as with overseeing the recruitment of participants and referrals to the counselling service when required.

At the Queen Elizabeth Hospital Birmingham, I would like to thank Dr John Woolmore for overseeing the recruitment at this site and Dr Inigo Tolosa who supported me in setting up the study, as well as ensuring psychological support would be available to participants if needed.

I am very grateful to Katherine Williams who collected data from a proportion of the participants and to the participants themselves who kindly agreed to take part in the research and spoke so openly about the impact of the condition.

I would also like to thank my appraisal tutor Dr Gary Urquhart Law for his continuous positive feedback and encouragement during each placement and Dr David Rose, an exemplary placement supervisor who has greatly influenced my clinical practice.

A final thank you to my partner, parents and friends, both on the course and outside of the course, who have supported me during the three years.

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Literature Review

What Factors are Associated with Suicidality in Huntington's Disease?

A Systematic Review of the Literature

Abstract

Background: Research has consistently shown that there is a high prevalence of suicide ideation in Huntington's disease ("Huntington's"). In fact, compared with the general population, completed suicide in Huntington's has frequently been shown to occur at a much higher rate. The complex causes and underlying mechanisms for risk are so far poorly understood.

Aim: The aim of this systematic review is to synthesise the findings of research studies which have investigated risk factors associated with suicidality in Huntington's.

Method: Using electronic databases, containing published empirical papers, a systematic search was carried out in order to find relevant studies. Following a strict filtering process, 16 studies were selected. Before collating the main findings, the methodological quality of each study was appraised, utilising a bespoke assessment tool.

Results: The results of this review identify strong evidence suggesting that psychiatric symptoms and/or history are risk factors for both suicide ideation and completed suicide. Additionally, 'mutation' carrier status was indicated for suicide ideation, as well as the suicide of a family member, 'formal' diagnosis and the early stages of Huntington's for completed suicide.

Conclusion: The initial findings provide important information to be considered when developing interventions for reducing suicide risk in Huntington's. Recommendations for future research are suggested in order to further understand risk factors and contribute to the implementation of interventions.

1. Introduction

1.1 Overview

Huntington's disease ("Huntington's") is the most common of all hereditary neurodegenerative illnesses (Martino, Stamelou, & Bhatia, 2013). In the Western world it is estimated that the prevalence of Huntington's is 10-12 per 100 000 (Evans et al., 2013). In the United Kingdom specifically, there are thought to be more than 5700 people aged over 21 with the disease (Evans et al., 2013) with many more 'at risk'. The disease was first described by George Huntington in his paper titled 'On Chorea' (Huntington, 1872) which highlighted the association between the disease and suicide. Suicidal thoughts in Huntington's occur in up to 50% of people (Bloch, Fahy, Fox, Hayden, & Reynolds, 1989; Kessler et al., 1987; Mastromauro, Myers, & Berkman, 1987; Wexler, 1996). Compared to the general population completed suicide rates in Huntington's have been reported to be four to eight times higher (Farrer, Opitz, & Reynolds, 1986; Robins Wahlin et al., 2000; Schoenfeld et al., 1984). More recently, reported prevalence of suicide ideation and suicide attempts have ranged from 8% to 20% (Hubers et al., 2013; Hubers et al., 2012).

A high prevalence of suicide ideation in Huntington's is indisputable (Hubers et al., 2013). However, what is less clear are the complex causes and underlying mechanisms for risk which are so far poorly understood (Bradley, 2004; Craufurd & Snowden, 2014). Suicide is the leading cause of death for the worldwide population; every year approximately one million people commit suicide, equivalent to one death every two minutes (Pompili et al., 2012). Suicides are preventable (Mann et al., 2005) and a national suicide prevention strategy has recently been developed by the World Health Organisation (WHO, 2014) which highlights that several risk factors have been known to act cumulatively to increase an

individual's vulnerability to suicidal behaviour. The aim of this current review is to accumulate and appraise the quality of existing research investigating risk factors associated with suicidality[1] in Huntington's. Identifying common themes or contradictory findings will contribute to a more thorough understanding of the causes associated with suicidality and could provide valuable information to those designing interventions for reducing suicide risk in Huntington's in the future. All identified risk factors will be reported in this review; however the main focus will be on disease-related variables which can potentially be ameliorated with appropriate intervention, for example: psychiatric symptoms. There will also be a focus on identifying 'red flags' for potential difficulties, for example: finding out that the condition has been inherited. An awareness of these factors will mean that clinicians working with people with Huntington's can look out for these 'red flags' and interventions can be provided as preventative measures.

1.2 Huntington's disease

Huntington's is a neurodegenerative condition which affects the brain due to the progressive death of nerve cells; the disorder is characterised by: psychological and psychiatric difficulties, cognitive decline, progressive motor impairments, muscle atrophy and loss of body weight (Novak & Tabrizi, 2010; Quarrell, 2008; Van der Burgh, Björkqvist, & Brundin, 2009; Walker, 2007; Wexler, 2012). The cause is a mutation in a gene known as the huntingtin (HTT) gene which is referred to as an expanded trinucleotide (CAG) repeat (Evans et al., 2013). It is inherited in an autosomal dominant pattern, meaning that one of the two

[1] In this review the term 'suicidality' will refer to: suicide ideation, suicide attempts and completed suicides.

copies of the altered HTT gene mutation is sufficient for the disorder to be passed on from parent to child (Hewitt, 2010).

Children of those with diagnosed Huntington's have a 50% risk of inheriting it (Lawson et al., 1996) and are referred to as 'at risk'. There is currently no cure (Novak & Tabrizi, 2010) or disease modifying treatment (van Duijn et al., 2014) and the progression of the disease occurs without remission until death (Fox, Bloch, Fahy, & Hayden, 1989). The average survival span is approximately 20 years, with onset typically occurring between the ages of 35 and 45 years (Paulsen et al., 2005b).

1.3 Clinical characteristics

The symptoms have been classified as a triad of clinical characteristics: motor, cognitive and psychiatric difficulties (Björkqvist et al., 2006; Larsson, Luszcz, Bui, & Wahlin, 2006; Paulsen, Ready, Hamilton, Mega, & Cummings, 2001) displayed in Table 1 below. They follow a long prodromal period in which cognitive or psychiatric symptoms are evident (Paulsen et al., 2008; Tabrizi et al., 2009). Secondary metabolic symptoms besides the triad of core symptoms and signs are characterised by a decrease in body weight, sleep and autonomic disturbances (Roos, 2014). Currently the onset of Huntington's is defined as when the characteristic motor signs evolve and the gene carrier classification is escalated from "pre-manifest" to "manifest" disease (Novak & Tabrizi, 2010).

Table 1. Triad of clinical characteristics

Type	Symptoms
Motor	Roos (2014) describes the predominant motor behaviour signs as: chorea, meaning unwanted short lasting and accelerated movements; hypokinesia or what is known as Parkinsonian (slowness in starting and executing movements and a decrease in all motor activities); dystonia (laboured twisting and turning movements in voluntary muscles); and rapid tics in both the face and upper limbs.
Cognitive	Slowed thought processing, a deterioration in executive functions, problems with short term memory, concentration, multi-tasking, impulsivity, and a loss of insight (Novak & Tabrizi, 2010). Dementia develops in later stages, although, the degree is difficult to define due to the ability to communicate diminishing in those with the disease (Paulsen et al., 2008).
Psychiatric	For 'mutation' carriers at some point during lifetime psychopathology is experienced (van Duijn et al., 2014). Symptoms include depression, suicidality and non-specific behavioural symptoms such as anxiety, social withdrawal, irritability, agitation, obsessiveness, apathy and personality change (Higgins & Hoblyn, 2014; Naarding, Kremer, & Zitman, 2001).

1.4 Predictive testing and clinical diagnosis

Genetic testing for the disease involves measuring the CAG repeat length in the HTT gene, and predictive testing is used for a person who has no symptoms but is considered 'at risk' due to family history (Novak & Tabrizi, 2010). The results of the test show either an 'increased' or 'decreased' risk, the latter means that they were deemed unlikely to have inherited the genetic mutation (Bloch, Adam, Wiggins, Huggins, & Hayden, 1992). If the predictive test result is positive, this indicates that the person is carrying the expanded HTT gene which means that they will almost certainly develop Huntington's at some point in the future (Robin, 2008; Spinney, 2010). Clinical diagnosis which follows is based upon neurological examination and stage of symptomatology (Roos, 2014).

2. Method

2.1 Initial search for previous systematic reviews

The Cochrane systematic reviews database and Centre for Reviews and Dissemination were searched using the term "Huntington's disease" which revealed zero reviews. Additionally, a further five databases were independently searched with no date limits (PsycINFO, Medline (R), EMBASE, CINAHL PLUS, and AMED). This search revealed two reviews: one titled "To know or not to know: A review of behaviour and suicide ideation in pre-clinical Huntington's disease" (Robins Wahlin, 2007) and another titled: "On suicide in Huntington's disease: A review" (Bindler, Touzeau, Travers, & Millet, 2010) written in French. Both reviews are narrative in nature rather than systematic. The first investigates psychological complications related to predictive testing in Huntington's disease and is therefore only considering one risk factor, unlike this review. The second is more relevant but it only searches one database and it does not specify inclusion criteria or assess the quality of the papers using a quality tool. It was therefore decided that the synthesis and systematic assessment of the planned review was warranted.

2.2 Identification of articles

In order to identify appropriate articles to be included in this systematic review a more precise search strategy and eligibility criteria were designed following the guidance of Tacconelli (2010).

2.2.1 Search strategy for identification of appropriate studies.

Search criteria were generated by identifying keywords from the title of this review, generating synonyms for each of the key words and linking them with logical operators. The

search criteria were then modified using the keywords of identified articles. The same five relevant electronic databases were searched: PsycINFO (1967 – April 2015), Medline (R) (1946 – April 2015), EMBASE (1974 – April 2015), CINAHL PLUS (1937 – April 2015) and AMED (1995 – April 2015) for articles which contained the following key words or text words[2] displayed in Table 2 below.

Table 2. Key words or text words used in search

Key words or text words
A. "huntingtons disease" (term exploded) **or** "huntington* disease" (keyword) **or "**HD" (keyword). B. "suicide" (term exploded) **or** "suicid*" (keyword) **or** "*suicide" (keyword). C. A **and** B were combined.
NB: Utilising * allows for any articles containing words beginning or ending with the search term to be located, for example, suicid* enables the identification of articles including suicide, suicidal, suicidology and suicidality.

Exact searches for each database are detailed in Appendix I.

2.2.2 Inclusion and exclusion criteria.

Table 3 and 4 below contain the inclusion and exclusion criteria.

[2] All search terms were subject headings unless otherwise identified as keywords.

Table 3. Inclusion criteria

Inclusion criteria
1. A peer reviewed empirical publication.
2. Written in English.
3. Studies explicitly investigating Huntington's populations. "Huntington's populations" encompassed those who were: 'at risk', 'decreased risk', or had received 'formal' diagnosis. If specified as 'at risk' this refers to those with a parent who had the disease (Paulsen et al., 2005); they may not yet have been tested, or they have undergone testing and received a 'mutation' carrier result of 'increased' or 'decreased' risk (Hubers et al., 2012). 'Non-mutation' carriers are those who have undergone predictive testing and have received a negative test result (Fiedorowicz et al. 2011). Following genetic testing and the development of symptoms, a neurological examination and the use of a measure such as the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996) can be utilised to determine a 'probable' or 'definite' diagnosis based upon symptomology (Wetzel et al., 2011). It is also possible to be classified into different categories depending upon the level of motor signs for example: 'non-specific motor abnormalities', as well as classified into certain disease stages, dependent upon total overall functioning (Paulsen et al., 2005). Other terminology includes: 'symptomatic' (Almqvist et al., 1999), 'unaffected', 'possibly affected' and affected' (Lipe et al., 1993) and 'suspected' (Schoenfeld et al., 1984).
4. Studies investigating suicide and its relationship to Huntington's disease.
5. Studies defining how suicidal thoughts, suicide intentions, suicide attempts or completed suicide, were identified (for example: a measure of suicide ideation, medical records, death certificates).
6. Studies including a quantitative analysis of factors related to suicide: suicidal thoughts, suicide intentions, suicide attempts or completions.

Table 4. Exclusion criteria

Exclusion criteria
1. Studies where the data for suicidality specifically could not be extracted from the study.
2. Studies measuring solely attitudes to suicide in the future rather than current suicide ideation or physicians attitudes to assisted suicide.
3. Studies not containing an analysis of factors related to suicide.
4. Studies investigating the association between neurobiology and suicide.
5. Studies which were non-empirical, qualitative or case studies.
6. Studies where the participants consisted of children (less than 18 years of age).

2.3 Database search results

574 articles were identified and after initial filtering to inclusion criteria, 42 studies remained. Full article reviews were then undertaken by two researchers and further inclusion criteria applied (see Appendix II), resulting in 16 final studies (see Appendix III). The reference sections of each of the 16 were scrutinised which identified no further studies. The flow chart below (Figure 1) illustrates the overall process.

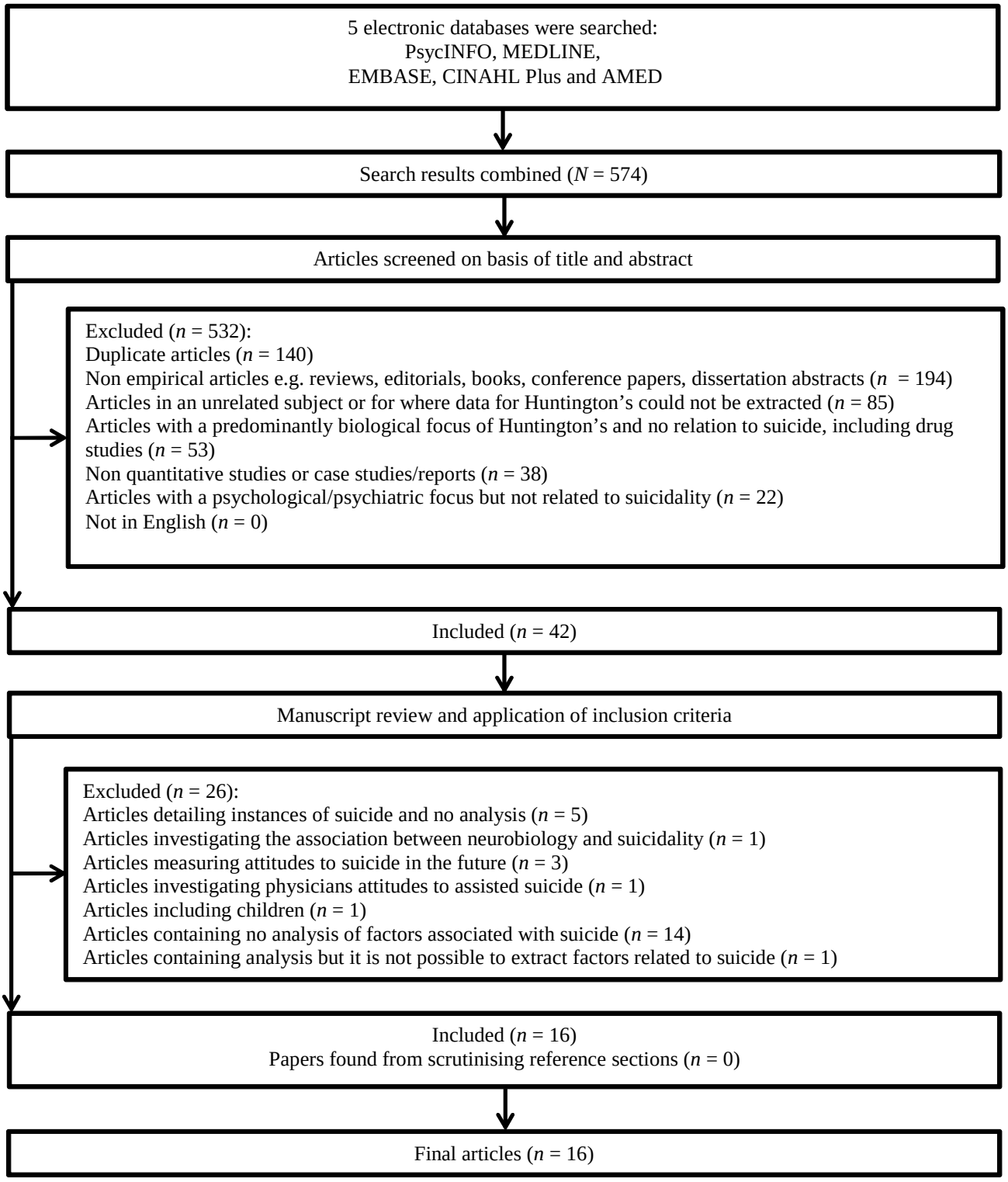


Figure 1. PRISMA diagram of literature search

2.4 Data extraction

A data extraction form was developed in order to ensure that information from each study was collated systematically and in sufficient detail for undertaking quality assessment and data synthesis. Based upon the recommendations of Wright, Brand, Dunn, and Spindler (2007) and Elamin et al. (2009) the data extraction form was designed to meet the requirements of the topic under review. See Appendix IV for a copy of the form.

3. Quality review

3.1 Quality assessment

Consideration of quality assessment tools was carried out in order to identify the most appropriate, including systematic reviews of quality tools for example: Deeks et al. (2003), Katrak, Bialocerkowski, Massy-Westropp, Kumar, and Grimmer (2004) and Sanderson, Tatt, and Higgins (2007). Although, numerous quality tools exist and have been utilised for appraising studies "most omit key quality domains" (Deeks et al., 2003, p. 3) and "there is no gold standard critical appraisal tool for any study design" (Katrak et al., 2004, p. 1). Accordingly, a bespoke quality assessment tool was designed, incorporating questions from several tools, selected as they included questions considered most appropriate to this review. See Appendix V for a copy of the tool and the origin of each criterion.

3.2 Piloting of quality assessment tool

To provide a measure of inter-rater reliability, five studies were chosen at random and reviewed by two researchers independently. The two researchers then discussed the quality ratings and discrepancies were reviewed and agreed upon where possible. Reasons for discrepancies tended to be related to a simple oversight, or a difference in the interpretation of the study information or the quality criteria. The final quality ratings were then compared and inter-rater reliability was calculated using the kappa statistic. This measure was chosen as it is suggested to be more robust than percentage agreements (Uebersax, 1987). A very high level (Landis & Koch, 1977) of inter-rater agreement was achieved: k=0.983, (p< .001), 95% CI (0.95-1.02).

3.3 Quality scoring process and summary table

Each study was assessed and scored using the method described in Table 5 below.

Table 5. Key for Table 6

Key
Yes – GREEN (2)
Partial – ORANGE (1)
No – RED (0)
Not applicable – PURPLE (0)
SCORE (%) = total sum divided by total possible sum x 100

The matrix below in Table 6 illustrates a summary of the quality of each study and scores assigned to each item.

Table 6. Summary table of the quality of the studies

Quality assessment questions & studies in chronological order	**Dorsey et al. (2013)**	**Hubers et al. (2013)**	**Hubers et al. (2012)**	**Fiedorowicz et al. (2011)**	**Wetzel et al. (2011)**	**Larsson et al. (2006)**	**Paulsen et al. (2005)**	**Baliko et al. (2004)**	**Almqvist et al. (2003)**	**Witjés-Ane et al. (2002)**	**Robins et al. (2000)**	**Almqvist et al. (1999)**	**Di Maio et al. (1993)**	**Lipe et al. (1993)**	**Farrer et al. (1986)**	**Schoenfeld et al. (1984)**
1. Are the hypotheses/aims and objectives of the study clearly stated?																
2. Is the rationale for the study clearly outlined?																
3. Is the study design evident and appropriate?																
4. Are the setting, location, recruitment and data collection described?																
5. Is the population identified?																
6. Are main participant characteristics and eligibility clearly described?																
7. Is sample size reported to have sufficient power?																
8. Is response rate reported and non-response considered?																
9. Is proportion and characteristics of those lost to follow-up considered?																

	Dorsey et al. (2013)	Hubers et al. (2013)	Hubers et al. (2012)	Fiedorowicz et al. (2011)	Wetzel et al. (2011)	Larsson et al. (2006)	Paulsen et al. (2005)	Balikо et al. (2004)	Almqvist et al. (2003)	Witjés-Ane et al. (2002)	Robins et al. (2000)	Almqvist et al. (1999)	DiMaio et al. (1993)	Lipe et al. (1993)	Farrer et al. (1986)	Schoenfeld et al. (1984)
10. Is the/are the suicide outcome measure(s) validated and reliable?																
11. Does the sample appear representative of the population?																
12. Are statistical tests used clearly described and appropriate?																
13. If missing data is reported does it describe how it was dealt with?																
14. Are significant effects identified and the importance communicated?																
15. Are confidence intervals or measures of variance reported?																
16. Does the study clearly report key results with reference to objectives?																
17. Do the significant effects provide an idea of the magnitude?																

	Dorsey et al. (2013)	Hubers et al. (2013)	Hubers et al. (2012)	Fiedorowicz et al. (2011)	Wetzel et al. (2011)	Larsson et al. (2006)	Paulsen et al. (2005)	Balikо et al. (2004)	Almqvist et al. (2003)	Wijjés-Ane et al. (2002)	Robins et al. (2000)	Almqvist et al. (1999)	DiMaio et al. (1993)	Lipe et al. (1993)	Farrer et al. (1986)	Schoenfeld et al. (1984)
18. Does the study discuss the generalisability of the results?																
19. Are limitations of the study discussed including potential bias?																
20. Is caution given to the interpretation of results?																
21. Is the conclusion clear and reinforced by the results?																
Score	83%	83%	91%	86%	85%	79%	87%	47%	86%	86%	85%	85%	44%	35%	37%	79%

3.4 Quality scores

Much variation was found in the quality of the papers, from 91% (Hubers et al., 2012) to 35% (Lipe et al., 1993). Out of the 16 papers incorporated in this review, 12 scored 79% and over. Generally, retrospective cohort studies scored the lowest. However, these types of studies have been described as serving a useful purpose (Hess, 2004) and one of them received a quality score of 85% (Almqvist et al., 1999). Irrespective of quality score, a decision was made to include all in the synthesis with consideration given to the quality of each when drawing conclusions. The most prominent methodological issues identified when assessing the studies are described below.

There are possible selection biases because the use of random sampling has not been mentioned in any study and participants have been recruited from either a single hospital (Larsson et al., 2006) or from a voluntary register likely to be acquired from those who attend support groups, where support may be greater than the norm (Haines et al., 1986). With regards to response rate, this was only reported in two studies (Larsson et al. 2006; Almqvist et al., 1999), and the representativeness of the sample is questionable when participants have chosen to undergo predictive testing (Almqvist, Bloch, Brinkman, Craufurd, & Hayden, 1999; Almqvist et al., 2003; Larsson et al., 2006; Witjes-Ané, Zwinderman, Tibben, Van Ommen, & Roos, 2002) because they may well be more confident and capable to deal with possible ‘bad news’ (Codori, Hanson, & Brandt, 1994).

No valid and reliable suicide ideation measure was used by any of the studies and for the retrospective cohort studies (Almqvist et al., 1999; Baliko, Csala, & Czopf, 2004; Di Maio et al., 1993; Farrer et al., 1986; Lipe, Schultz, & Bird, 1993; Schoenfeld et al., 1984) there is concern about whether the data utilised is accurate. Heavy reliance on written records, for

example case notes, means that it is difficult to control for bias and confounding variables (Hess, 2004). In physical health the possibility of suicide can often be ignored and the death classified as due to the disease (Stenager & Stenager, 1992). Additionally, considering death certificates, suicides may be underestimated because those which have been officially reported as accidental may often be suicides (Haines, Conneally, & Rao, 1986). For a more detailed explanation of these issues, please see Appendix VI.

4. Results Part 1 – A summary of the studies and findings

The results section consists of two parts. Firstly, a summary of the findings and characteristics of the 16 studies and secondly, a narrative synthesis to answer the systematic review question: what factors are associated with suicidality in Huntington's disease?

4.1 Summary of studies

A summary of the data extracted from each study including main characteristics, findings and limitations are detailed in Table 8 below, which follows Table 7 listing the abbreviations utilised throughout.

Table 7. List of abbreviations

Abbreviations
APA = American Psychiatric Association
AS = The Apathy Scale (Starkstein et al., 1992)
AttQ = Attitude Questionnaire
AQ = Affected Questionnaire (Di Maio et al., 1993; Farrer et al., 1986) used by NHDRR
BDI-II = Beck Depression Inventory (Beck, Steer, & Brown, 1996)
BHS = Beck Hopelessness Scale (Beck & Steer, 1988)
C = Cohort study
CCHD = Chapter of Committee to Combat Huntington's
CCSG = Canadian Collaborative Study Group
CCSPT = Canadian Collaborative Study Predictive Testing Protocol (Fox et al., 1989)
CE = Catastrophic event
CIDI = Composite International Diagnostic Interview (World Health Organisation, 1997) for presence of psychiatric disorder according DSM-IV (APA, 2000)
COHORT = Cooperative Huntington Observational Research Trial (Dorsey et al., 2012)
DSM-IV = Diagnostic Statistic Manual IV (APA, 2000)
CS = Cross-sectional
FHQ = Family History Questionnaire (Di Maio et al., 1993; Farrer et al., 1986)
GHQ = The General Health Questionnaire (Goldberg & Williams, 1988)
GSI = General Severity Index, from the Symptom Check List-90-Revised (SCL90-R) (Derogatis, 1983)
GWB = General Well-being Scale (Dupuy, 1969)
HD = Huntington's disease
HSG = Huntington Study Group, a group of physicians in the United States, Canada, Europe, Australia, New Zealand and South America, dedicated to research in HD
IHA = International Huntington's Association (worldwide)
LES = Life Experiences Survey (Sarason, Johnson, & Siegel, 1978)
L = Longitudinal
LSI = The Life Satisfaction Index (Fox et al., 1989)
LSA = The Life-Styles Assessment (Fox et al., 1989)
MMSE = Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975)
NEHDC = New England Huntington's Disease Centre
NHDRR = National Huntington's Disease Research Roster, a nationwide information resource dedicated to assisting scientific research in HD
PBA = Problem Behaviours Assessment (Craufurd, Thompson, & Snowden, 2001)
PREDICT-HD = Neurobiological Predictors of HD (a multi-site longitudinal observational study used to identify and track markers of HD)
PSS = Psychiatric Status Scale (Spitzer, Endicott, Fleiss, & Cohen, 1970)
REGISTRY = a database of all HD patients throughout Europe collated at University College London (includes genetic status, lifestyle, medical history and disease progression)
SCL90-R = Symptom Check List-90-Revised (Derogatis, 1983)
SD = Standard Deviation
SDMT = Symbol Digit Modalities Test from the cognitive section of the UHDRS-b
SIBS = Self Injurious Behaviour Scale (Fox et al., 1989)
UHDRS-b = Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996)
UK = United Kingdom
USA = United States of America
WFN-HD = World Federation Neurology Huntington's research group

Table 8. Summary table of main characteristics and findings of studies

Author, Year, Journal and Origin	Study Aim(s)	D	Sample	Outcome Measure(s)	Prevalence of suicidality	Main findings	Main limitations	Quality score
1. Dorsey et al. (2013) Journal of Huntington's disease USA, Australia and Canada (48 research centres)	1. To investigate the frequency of depressed mood, suicidal thoughts, suicide attempts, and suicides over 2-3 years in order to evaluate the effects of tetrabenazine*. *Tetrabenazine is used for the treatment of chorea however a serious side effect is that it can increase depression and suicidality.	L	*N* = 1360 All had clinically manifested HD determined by the UHDRS-b & number of CAG repeats. Recruited from COHORT study (HSG COHORT Investigators, 2012). 77 already taking tetrabenazine before entering COHORT. 64 with a new exposure to tetrabenazine during COHORT. 1219 controls never exposed to Tetrabenazine.	UHDRS-b: *one two part question for assessment of suicide ideation.* Study also examined number of suicide attempts and completed suicides, as reported and assessed by site investigators. UHDRS-b: *one two part question for depressed mood.* UHDRS-b: *total functioning section.* UHDRS-b: *motor section.* MMSE Age, education, employment status, history of	1 individual (1.3%) with prior exposure tetrabenazine, 1 with new exposure (1.6%), 35 (2.9%) with no exposure reported suicidal thoughts. Among those with no exposure to tetrabenazine: 17 suicide attempts (1.4%) and 4 suicides (0.3%) occurred. 18.6% reported: a history of suicide ideation.	Tetrabenazine use was associated with: a lower level of suicidal behaviour, less than 2% risk of suicide ideation over 2-3 years of observation. Exposure to tetrabenazine was not associated with: an increased risk of depressed mood or suicidality compared to those with no exposure to the drug.	Generalisability: study examined individuals who volunteered and may have had a lower risk of mental health problems. The rate of prior suicide attempts at baseline was half that of previous research. Low sample sizes of those exposed to the drug meant limited statistical power. Potential confounding variables: participants had higher socio economic status (therefore, increased access to services) and were referred for support during the study if required. It was not possible to extract further information about associations with	86%

			Drug doses were an average of 33-46mg.	mental health support and antipsychotic use.	7.2% reported: a previous suicide attempt.		suicidality as this was not the main focus of the study.	
2. Hubers et al. (2013) Journal of Affective Disorders Netherlands, Germany and the UK (data collected from 15 European countries)	1. To examine predictors of suicidality in HD: at baseline and at 4 year follow-up.	C & L	*N* = 2106 European HD 'mutation' carriers participating in the REGISTRY study (Orth, 2010). 98% were motor symptomatic HD carriers.	UHDRS-b: *one two part question for assessment of suicide ideation.* UHDRS-b: *psychiatric section:* Depressed mood Anxiety Apathy Irritability Aggression UHDRS-b: *total functioning section.* UHDRS-b: *motor section.* Assessment of suicide ideation was carried out by a psychiatrist. Suicide attempts in the past were also recorded. Medication. Age, sex.	At *baseline:* 169 'mutation' carriers (8.0%) endorsed suicide ideation.	At *baseline* correlates with suicidality were: a shorter estimated disease duration, depressed mood, anxiety, apathy, irritability, aggression, higher use of psychotropics and a suicide attempt in the past (all $p < .001$). Age and sex did not correlate with suicidality neither did total and motor functioning, or CAG repeats, or being pre-motor symptomatic. At 4 year *follow-up*: 9.9% had developed suicidal thoughts and predictors of suicidality were: depressed mood (HR=2.73 95% CI 1.57-4.76 $p < .001$), anxiety (HR=1.99 95% CI 1.15-3.42 $p < .01$), apathy (HR=2.27 95% CI 1.30-3.96 $p < .004$). Depressed mood	Suicidal prevalence was much lower than the findings of previous studies e.g. Hubers et al., (2012). Suicide ideation was measured only with one two part question. Attrition bias: Participants attending REGISTRY clinics are likely to be more engaged in support, therefore may have less difficulties. Limited generalisability: a high drop-out rate of 992 participants.	83%

				Estimated disease duration: subtract age at onset from current age.		independently predicted suicide (HR=2.05 95% CI 1.06-3.96 *p*< .03).		
3. Hubers et al. (2012) Journal of Affective Disorders Netherlands	1. To assess prevalence of suicidality in HD. 2. To investigate clinical characteristic associated with suicidality. 3. At 2 year follow-up: to determine potential baseline predictors of suicidality.	CS &L	*N* = 208 192 at initial 50% risk of HD, recruited through Neurology and Clinical Genetics at Leiden University Medical Centre and from a local nursing home. 16 enrolled via Dutch HD patients' association. Cross-sectional analysis: 152 'mutation' carriers and 56 non-carriers.	PBA: *one two part question to assess suicidal ideation and one question to measure depression.* UHDRS-b: *total functioning section.* UHDRS-b: *motor section.* AS CIDI (Dutch translation) for presence of psychiatric disorder. MMSE Medication. Estimated disease duration. Asked when genetic testing result was received.	At *baseline:* 31 'mutation' carriers (20%) were considered suicidal out of 152.	At *baseline*: 20% of 'mutation' carriers were suicidal compared to 0 non-carriers. Associations with suicidality were found to be: apathy (OR=2.84 95% CI 1.27-6.40 *p*< .01), depressed mood (OR=5.92 95% CI 2.26-15.5 *p*< .001) or a DSM-IV diagnosis of depression (OR=4.74 95% CI 1.10-20.3 *p*< .04), and higher use of psychotropics: especially anti-depressants (OR=3.42 (95% CI 2.30-12.3 *p*< .001). No significant differences between suicidal and non-suicidal: demographic variables, place of living, total and motor functioning, being pre-motor symptomatic, number of CAG repeats, estimated disease duration, presence of psychiatric disorder other	The follow-up sample was relatively small. Suicide ideation measured only with one two part question. Variables were dichotomised due to skewed distributions impacting upon statistical power. Variables found to be previously associated with suicide were not measured (e.g. history of suicide attempt). Drop outs: Out of 121 free of suicidality, 21 dropped out after 2 years.	91%

				Sex, age, marital status, children, residential institution.		than depression, when genetic testing result was received, cognitive functioning, marital status and number of children. At 2 year *follow-up:* 7 (7%) became suicidal; these often had depressed mood and a 'formal' DSM-IV diagnosis at baseline. Depressed mood significantly predicted suicidality (OR=1.06 95% CI 1.17-97.0 p< .04).		
4. Fiedorowicz et al. (2011) Neuro-degenerative Diseases USA, Canada, Europe and Australia.	1. To assess risk factors for suicidal behaviour in prodromal* HD over a 3.5 year period. *Prodromal = presence of CAG repeat extension prior to meeting clinical criteria for diagnosis of HD.	L	*N* = 929 Recruited from PREDICT-HD: 735 prior to 'formal' diagnosis and followed for 3.5 years 194 who had a parent with HD were classified as controls and followed for 2.9 years.	UHDRS-b: *one two part suicide question & extrapolated items from BDI-II and BHS & additional questions about frequency of thoughts and a suicide plan*. UHDRS-b: *motor section*. BDI-II Prior history: suicides and	13 (1.6%) participants attempted suicide, 1 of whom attempted twice and 1 who completed suicide.	*Risk factors for suicide ideation*: a history of suicide attempts (HR=8.5 95% CI 2.8-26.1, p< .0002), a score of >13 on the BDI-II (HR=7.2 95% CI 2.3-22.0, p< .0006), incarceration in the previous 2 years (HR=12.5 95% CI 2.7-56.6, p< .002). No association between motor score, number of CAG repeats, demographic variables and suicidality. No controls (those with a	Suicide attempts and completions were combined into a single variable. A low rate of suicidality limited statistical power. Event log unreliable: deaths due to other causes may represent suicide. Selection bias: sample includes only those who have undergone genetic testing.	86%

				attempts were recorded in an event log. PSS LES Age, sex, education. A question about incarceration in the past 2 years. Question about proximity to diagnosis.		parent with HD) displayed suicidal behaviour. Total score of PSS and selected items from LES not significantly associated with suicidality. No significant difference in suicide ideation between controls and others for: proximity to diagnosis.		
5. Wetzel et al. (2011) Psychiatry Research USA, Australia and Europe	1. To assess the relationship between psychiatric difficulties and HD. 2. To investigate how psychiatric symptoms may further contribute to increased suicidality.	CS	*N* = 1941 Recruited from 43 HSG sites with a current diagnosis score of 2 (probably HD) or 3 (definite HD) on the UHDRS-b.	UHDRS-b: *one two part question for assessment of suicide ideation*. UHDRS-b: *psychiatric section:* Factor analysis yielded: 1.Depression/ anxiety 2.Suicidal thoughts 3.Aggression 4.Obsessive/ compulsive behaviour UHDRS-b:	19% (389) endorsed current suicide ideation. 26.5% reported a previous history of suicide ideation. 9.5% reported a history of one attempt (at least). .	*Predictors of suicidality:* higher UHDRS-b score for depression/anxiety (OR=1.14 95% CI 1.12-1.17 $p < .001$), aggression (OR=1.05 95% CI 1.01-1.08 $p < .001$) and a past or current history of alcohol abuse (OR=0.41 95% CI 0.22-0.75 $p < .004$). Not significant predictors: motor or cognitive variables, obsession and compulsions, demographics, tobacco/drug use.	Suicide ideation was measured only with one two part question. The effect sizes describing the associations between psychiatric symptoms and suicide ideation were small. Limited measures of psychiatric symptoms from using UHDRS-b. Actual psychiatric diagnoses were not included.	85%

				motor section. UHDRS-b: *one question (SDMT) from cognitive section.* A question about previous suicide ideation or attempts (to find out prevalence, not included in analysis). Age, sex, education. A question about alcohol, tobacco or drug use.				
6. Larsson et al. (2006) Journal of Genetic Counselling Sweden	1. To explore the psychological and psychosocial health of carriers and non-carriers, pre and post predictive testing with a 2 year follow-up period.	C & L	*N* = 93 35 carriers, 58 non-carriers with a genetic test result from a department of clinical genetics at Karolinska University Hospital.	Battery adopted from CCSPT. SIBS: *to assess suicide ideation including a background questionnaire about previous suicide attempts, psychiatric history and possible future suicidal thoughts.* LSI LSA	12 attempted suicides were recorded over the 2 year period.	At *baseline:* those who had a psychiatric history disclosed a higher level of suicidal thoughts ($p < .05$). At *follow-up:* carriers disclosed higher levels of suicide ideation more often over time, 52% of carriers thought they would consider suicide in the future. A further 30% of carriers said they would consider suicide if they got to middle or advanced stage	Relatively small sample size. Too few attempted suicides to permit reliable multilevel analyses. Participants were undergoing genetic counselling which may have influenced results. Despite the use of several measures, it was not possible to	79%

				GHQ BDI-II Wellbeing measure (Robins Wahlin et al., 2000).		HD. Analyses did not investigate whether other factors predicted suicidality but were focussed on differences between carriers and non-carriers.	extract further information about associations with suicidality as this was not the main focus of the study.	
7. Paulsen, Hoth, Nehl, and Stierman (2005a) The American Journal of Psychiatry USA, Australia and Europe.	1. To examine suicide ideation in individuals 'at risk' and diagnosed with HD and identify critical periods of suicide risk.	CS	*N* = 4171 All recruited from HSG. At risk: 712 with no motor symptoms 363 with non-specific motor abnormalities 408 with motor symptoms which indicated possible HD After diagnosis: 2688 (grouped by stage of disease 1-5).	UHDRS-b: *one two part question for assessment of suicide ideation.* UHDRS-b: *motor section.* UHDRS-b: *cognitive section.* UHDRS-b: *total functioning section.* NB. UHDRS-b: total functional capacity score and motor functioning score determined neurological examination result and stage of disease.	*Endorsement of suicidal thoughts:* Mild 7.2%, moderate 9.0%, severe with intent and plan 1.3%.	*Risk factors:* two critical periods for increased suicide risk were identified: Firstly, in the 'normal' neurological examination phase suicide ideation doubled in those at risk with 'soft motor symptoms' from 9.1% to 19.8% = a significant increase (χ^2=46.8, *df*=2, *p*< .001). Other phases were: 'motor abnormalities indicating possible HD' = 23.5%, 'motor abnormalities indicating definite HD' = 18.5% = a significant decrease (χ^2=5.7, *df*=1, *p*< .05). Secondly, following diagnosis almost 17% in stage 1 endorsed suicidal thoughts compared with 21% in stage 2 = a	Suicide ideation was measured only with one two part question. A longitudinal study is required in order to gather information about the relationship between ideation and actual attempts. Study only uses the UHDRS-b to investigate critical risk periods rather than risk factors associated with suicide (which may have revealed further information).	87%

						significant increase (χ^2=5.5, *df*=1, *p*< .05). Suicide ideation significantly decreased with each further stage: stage 3, 19.5%, stage 4, 14.1%, stage 5, 9.8% (χ^2=13.8, *df*=3, *p*< .01).		
8. Baliko et al. (2004) Neuro-epidemiology Location Hungary	1. To ascertain risk factors for suicide in HD families. 2. To compare the incidence of suicide in those diagnosed with HD with the suicide rate in the general population of Hungary.	CS	*N* = 96 96 families found by clinical examination, medical records, death certificates and reports from relatives (unclear exactly where from).	*Assessment of suicide:* death certificates, medical records and reports from relatives. Stage of disease. Any other suicides in family. Sex, age, age at onset, family size and number of children.	396 deaths were reported in HD families from 1920-1997 and 40 (10%) of these were suicide. Suicide in patients with HD was found to be more common than in the general population (45/100,000 inhabitants per year = 0.0004%).	*Risk factors for suicide:* being at either the early or late stages of the disease, suicide among close relatives was found in 4 of the families with 9 HD cases (i.e. parent/child, brother/sister). 85% were male. Mean age following suicide: 44.2. Mean age following other cause of death: 54.2. Mean age at onset for those who completed suicide: 37.8, mean age at onset for those who did not: 40.4. Suicide occurred more frequently in larger families and those with a lower number of off spring.	Study only records frequencies, no actual statistics carried out. Relatively small sample of suicides *n* = 40. Death certificates and medical records have been found to be unreliable for recording accurate information. Retrospective study.	47%
9. Almqvist et al. (2003)	1. To investigate prospectively the long term (5	C & L	*N* = 202 Asymptomatic	*Assessment of an adverse event:* Clinical chart	3 participants attempted suicide.	*Risk factors:* Risk status: all had received a ‘decreased’	Selection bias: individuals more resilient to cope with	86%

Clinical Genetics Canada and Sweeden.	years) psychological impact of predictive testing. 2. To establish the timing, frequency and predictors of adverse events. An adverse event = clinical depression, psychiatric hospitalisation, suicide or an attempt, a three-fold increase in alcohol use and the breakdown of partner relationship.		individuals from CCSG: 106 individuals were followed up 5 years after initial receipt of test result which indicated a 50% chance of having inherited the gene.	notes and the participant's counsellors were asked to identify if any had occurred. GSI from the SCL90-R ≥63 = psychiatric distress BDI-II ≥10 = depression GWB Timing of adverse event in relation to testing result.		risk result. Results focussed on three individual participants: The first had an elevated GSI and BDI-II score and attempted suicide 4 years after testing, also just after employment was terminated. The second had a BDI-II score suggestive of mild depression and attempted suicide whilst waiting for test results and then again 2 years later. This participant had a psychiatric history and family history of suicide attempts. The third attempted suicide on the day of receiving the test result of a 'decreased' risk. GWB: was not elevated in any of the three who attempted suicide.	bad news may have opted for testing - resulting in less chance of adverse events. People undergoing testing received substantial support and counselling. Suicide ideation has not been measured. Nearly a 50% drop out rate from baseline. Study is not solely investigating suicide and it is not possible to extract information from the different classifications of "adverse event", only from the case reports of the three who attempted suicide.	
10. Witjes-Ané et al. (2002) Journal of Medical	1. To investigate whether there is a difference between carriers and non-carriers	CS & L	*N* = 134 46 carriers 88 non-carriers -	UHDRS-b: *one two part question for assessment of suicide ideation and an*	Mean number of reports of suicidal thoughts on UHDRS-b*,	At *baseline:* no difference in suicide ideation between carriers and non-carriers.	Suicide ideation was measured only with one two part question. Very low level of	88%

Genetics Netherlands	when comparing the outcome of the UHDRS-b assessment over time following predictive testing. 2. To examine whether a history of psychiatric difficulties and the interval between testing and UHDRS-b assessment are associated with UHDRS-b outcome.		recruited from people with HD living in the Netherlands who underwent predictive testing.	*additional question about previous attempts.* UHDRS-b: *psychiatric section.* UHDRS-b: *motor section.* UHDRS-b: *cognitive section.* UHDRS-b: *total functioning section.* Suicide ideation was assessed by a psychologist. A question about psychiatric history. Time interval since DNA testing.	carriers 0.42 (1.64SD), non-carriers 0.03 (0.24SD). *0=absent 4=severe	Suicide ideation in the past was no different when comparing carriers and non-carriers. A history of suicide was never reported. Psychiatric history didn't impact upon UHDRS-b outcome. At *follow-up:* after 18 months changes in UHDRS-b were minimal in in carriers and non-carriers. Time interval since DNA testing: no significant difference between carriers and non-carriers.	suicide ideation in sample – there is a lack of statistical power comparing suicidal thoughts in carriers and non-carriers. Despite the use of several measures, it was not possible to extract further information about associations with suicidality as this was not the main focus of the study	
11. Robins Wahlin et al. (2000) Acta Neurologicala Scandanavia Sweden	1. To examine whether HD gene carriers have an increased risk of suicide and psychological difficulties compared with non-carriers.	C	*N* = 34 Recruited from a HD predictive testing programme in Sweden. 13 gene carriers and 21 non carriers.	*Assessment of suicidality:* SIBS (also assesses previous attempts) Battery adopted from CCSPT *(described in study 5).*	A high frequency of suicidal thoughts and immediate risk found in 4 people (12%) meant genetic testing was postponed	*Risk factors:* carriers exhibited a significantly higher rate of suicidal thoughts on the SIBS than non-carriers ($p < .05$). Scores were significantly higher for carriers when asked about: suicidal thoughts in the past year ($p \leq 0.05$), whether suicide will be attempted when	Small sample size: limits generalisability. Some participants were excluded due to risk. Potential bias: participants may have applied for testing due to unstable life	85%

			Criteria: 50% risk of HD, 25% risk for HD if the parent was deceased or if a parent with 50% risk participated in the study.	*Others:* AttQ A question about suicide attempts in the family.	due to high risk. *Suicide risk:* described as 'very high' in both groups (exact figures unavailable).	symptoms develop ($p \leq 0.05$), and whether suicide will be attempted when reaching middle/advanced stages of the disease ($p \leq 0.10$). 38% of the HD carriers reported previous suicide or suicide attempts in the family. 6 participants had previously attempted suicide however, it is not possible to extract whether they also disclosed suicide ideation at time of study.	circumstances: therefore a self-selected group. Participants were undergoing genetic counselling. There may be other factors associated with suicide but this study focuses on comparing carriers and non-carriers rather than risk factors and it is therefore difficult to extract further information.	
12. Almqvist et al. (1999) American Journal of Human Genetics Canada, Australia, Belgium, German, France, Netherlands, Sweeden, UK, USA.	1. To determine the worldwide frequency of catastrophic events: suicide, suicide attempt or psychiatric hospitalisation, after predictive testing. 2. To investigate factors which may have influenced the occurrence of CE by following up	C &L	*N* = 4527 All had received a predictive testing result. Recruited via: IHA and the WFN-HD research group who wrote to 175 centres in 26 countries and asked them to complete a survey.	*Suicide ideation was measured using a survey of clinical chart notes, recording:* Test results. CE's, clinical status at the time of the CE, test result, timing in relation to receipt of test result. Psychiatric	5 completed suicide, 21 attempted suicide.	*Risk factors for suicide or suicide attempt:* Diagnosis: all who completed suicide were symptomatic (4 were diagnosed, and 1 was probably affected) and all had been very recently diagnosed. Out of 21 who attempted suicide 11 were symptomatic. Time interval after	No direct comparison group of untested at risk persons have been used in this study. Other factors may contribute to a CE which have not been accounted for in this study. Generalisability: complete survey information was received from 100 out of 175 centres.	85%

	after 6-12 months, 1-2 years, 2-3 years, and 3-4 years.			history. Sex. Employment status.		testing: for those who completed suicide it was 18+- 12 months (3-35) months, and for those who attempted suicide it was 9+-8.7 months (0.5-29 months). Psychiatric history: not possible to extract in relation to suicide. Sex: all who completed suicide were female. Employment: all who completed suicide were unemployed.	Sample bias: participants were excluded if they did not receive a follow-up (441/4968= 8.9%). Follow-up occurred after one year, there may be more CEs occurring after one year. There may be more risk factors associated with suicide attempts or suicide ideation however these are not possible to extract from the CE information.	
13. Di Maio et al. (1993) Journal of Medical Genetics USA and Italy	1. To determine suicide frequency in HD families.	C	*N* = 1365 Data on 1365 with a diagnosis of HD on the NHDRR (to be included on the register a first degree relative must complete an AQ and FHQ).	*Assessment of cause of death:* 2793 NHDRR records were examined for the cause of death. Sex, age, age at onset. At risk category was determined from NHDRR information and then classified into:	205 reported suicides in a 5 year period.	*Risk factors for suicide:* Increased risk has been found in all at risk categories: affected 9.3%, possibly affected 21.5%, 50% at risk 4.5%, 25% at risk 2.6%, possibly at risk 7.1% and other 3.2%. 76% were male. Mean age following suicide: 33.5. Mean age following other cause of death: 40.2. Mean age of onset to be similar for both groups.	Attempted suicide has not been measured. Data from NHDRR could be unreliable. Retrospective study. At risk categories appear to have been decided upon by authors rather than a validated/reliable method.	44%

				Affected: clinical examination positive for HD. Possibly affected: clinical examination showed some signs of HD. At 50% risk: children of affected participants. At 25% risk: children of possibly affected participants. Other: spouses and family members with no risk.		Disease duration: significantly lower in those who completed suicide ($p < .0001$). Some data suggest a carrying effect i.e. the occurrence of further cases of suicide in the same family: 28% of the families (40 out of 143) had 48% of the cases of suicide (99 out of 205). Higher occurrences in: parent/child and siblings.		
14. Lipe et al. (1993) Amercican Journal of Medical Genetics USA	1. To examine risk factors for suicide in families with HD.	CS	*N* = 300 Patients were from a Seattle medical centre and University of Washington 18 controls for 9 HD suicides: two disease, age, gender matched participants living with HD	*Assessment of suicide:* Determined via a retrospective questionnaire based on a study by Robins (1981) which involved going through: medical records, social work notes and genetic counselling files. Suicide data	Between 1972 and 1992: there were 11 completed suicides in HD families. 9 with confirmed HD (including 1 at risk). 1 was an	*Risk factors associated with suicide:* 8 were affected with HD, 2 were unaffected and 1 was 'at risk'. 5 of the 9 HD participants completed suicide within 1 year of symptom onset. 73% were male. Mean age at death the same for suicide and other causes of death. None of those who completed suicide	Case notes and medical records may not be reliable. Depression was not measured with a standardised and validated measure, but the presence of three symptoms recorded in notes (e.g. weight loss, insomnia, loss of interest, sadness, feelings of worthlessness).	35%

			were selected randomly from the same population and compared with those who completed suicide.	included: the year of suicide, the method, the duration of time since HD symptom onset and whether there had been any other suicides in the family. Using the same questionnaire the following were also identified: age, sex, number of children, marital status and alcohol misuse.	unaffected spouse. 1 presumed unaffected (as her mother was unaffected).	misused alcohol. Risk factors with odds ratios greater than 1 were: no offspring (OR=13.6), other suicides in the family (OR=1.75), not married (OR=1.6), no contact with other persons who have HD (OR=1.43), living alone (OR=1.26) and depression (OR=1.26). NB. No p values reported.	Relatively small number of suicides. Small control group. Findings based upon frequencies rather than a statistical analysis.	
15. Farrer et al. (1986) American Journal of Medical Genetics USA	1. To identify how many deaths were attributed to suicide. 2. To examine attempted suicides: the number and pattern. 3. To compare these figures with the general population.	CS	*N* = 831 Histories were examined for those on the NHDRR with HD. AQ and FHQ questionnaires were completed by relatives to provide information for the register.	*Assessment of suicide:* Death certificates, medical records and genealogical reports from relatives. Previous suicide attempts. Disease duration. Stage of disease. Sex, age, age of	*Suicide rates:* 147 attempted suicide and 25 completed suicide. *Comparison with general population:* 5.7 suicides per 100 deaths = 4 times higher than the rate of 1.5 for the USA	*Risk factors associated with attempts and completed suicide:* Those who completed suicide had not previously attempted. 72% were male. Disease duration: those who completed suicide lived with their illness 5.8 years less than those that died of other causes. Mean age of onset to be	Suicide rates are likely to be underestimated. Figures related to relatives are thought to be heavily underreported and classified as accidental deaths. Study focusses more on incidences rather than risk factors, there may be more than those identified which have not been	37%

				onset.	caucasian population in 1979.	similar for both groups. Those who completed suicide were more likely to have done so in the early to middle stages of illness.	measured/ analysed. Study only records frequencies, no actual statistics carried out.	
16. Schoenfeld et al. (1984) Journal of Neurology, Neurosurgery and Psychiatry USA	1. To determine factors associated with suicide among patients with HD.	CS	*N* = 1419 149 unrelated HD families = 4919 individuals: 403 deceased and diagnosed with HD, 103 deceased who had suspected HD. From: NEHDC via physicians, health professionals, self referrals and Massachusetts CCHD. Information for the centre was provided by individuals at risk, individuals diagnosed and spouses.	*Assessment of suicide/cause of death:* death certificates, medical records and lay reports from families. Suspected or diagnosed HD. Psychiatric history. History of suicide in the family. Sex, age, marital status, number of children.	Among the 506 (suspected or diagnosed with HD) 20 completed suicide, accounting for 4% of all deaths.	*Risk factors associated with suicide:* Diagnosed: of the 403 deceased and diagnosed with HD there were 9 suicides (2.2%) all were male. Suspected: of the 103 with suspected HD: there were 11 suicides (10.7%) seven were male, four were female. Psychiatric history: of the 11 with suspected HD 2 were in psychiatric hospitals. Out of those who completed suicide: two were sisters and two were uncle and nephew, 80% were male. Mean age following suicide: 47.7. Mean age following other	Suicide rates are most likely underestimated. Only patients whose death was definitely classified as suicide were included in this study. If suicide was suspected these were not included. Information stored at the centre is voluntary. Death certificates, medical records and lay reports may not be reliable.	79%

		cause of death: 54.8. Aged >49 years were three times more likely to commit suicide OR=1.09 than others in the 50-69 year age group OR=8.19. 13 out of 20 who completed suicide had children and were married.

4.1.1 Prevalence of suicidality.

Prevalence rates of suicide ideation in those at risk or diagnosed with Huntington's ranged from 1.6% (Fiedorowicz et al., 2011) to 20% (Hubers et al. 2012). Rates for attempted or completed suicides ranged from 0.6% (Almqvist et al., 1999) to 15% (Di Maio et al., 2003; Farrer et al., 1986). It was not possible to extract prevalence rates from two studies (Witjes-Ané et al. 2002; Robins Wahlin et al., 2000). Table 9 below displays which studies measured suicidal thoughts and/or which measured attempted/completed suicides.

Table 9. Studies measuring suicidal thoughts and/or attempted/completed suicides

Suicidality	Studies
Suicidal thoughts	Dorsey et al. (2013)
	Hubers et al. (2013)
	Hubers et al. (2012)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Larsson et al. (2006)
	Paulsen et al. (2005a)
	Witjes-Ané et al. (2002)
	Robins Wahlin et al. (2000)
Attempted or completed suicide	Dorsey et al. (2013)
	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Larsson et al. (2006)
	Baliko et al. (2004)
	Almqvist et al. (2003)
	Witjes-Ané et al. (2002)
	Almqvist et al. (1999)
	Di Maio et al. (1993)
	Lipe et al. (1993)
	Schoenfeld et al. (1986)
	Farrer et al. (1984)

Some studies measured both suicide ideation and attempted and/or completed suicide. The following sections will summarise further information about the methodologies of the studies and their characteristics.

4.1.2 Study aims and designs.

The aims of the studies included in this review can be categorised into five general

themes, which together with study design can be seen in Table 10.

Table 10. Aims and design of each study

Aim/Design	Studies
Aim	
To investigate the potential side effects of drugs	Dorsey et al. (2013)
To investigate predictors of suicide in Huntington's	Hubers et al. (2013)
	Hubers et al. (2012)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Baliko et al. (2004)*
	Robins Wahlin et al. (2000)
	Di Maio et al. (1993)*
	Lipe et al. (1993)*
To investigate the psychological impact of predictive testing for Huntington's	Larsson et al. (2006)
	Almqvist et al. (2003)
	Witjes-Ané et al. (2002)
	Almqvist et al. (1999)*
To investigate causes of death in Huntington's	Schoenfeld et al. 1984)*
	Farrer et al. (1986)*
To examine critical periods of suicide risk in Huntington's	Paulsen et al. (2005a)
Design	
Cohort	Robins Wahlin et al. (2000)
	Di Maio et al. (1993)
Cross-sectional	Wetzel et al. (2011)
	Paulsen et al. (2005a)
	Baliko et al. (2004)
	Lipe et al. (1993)
	Farrer et al. (1986)
	Schoenfeld et al. (1984)
Longitudinal	Dorsey et al. (2013)
	Hubers et al. (2013)
	Hubers et al. (2012)
	Fiedorowicz et al. (2011)
	Larsson et al. (2006)
	Almqvist et al. (2003)
	Witjes-Ané et al. (2002)
	Almqvist et al. (1999)

*Retrospective cohort studies.

The primary focus of all studies was not specifically to investigate factors associated with suicidality in Huntington's. However, it has been possible to extract some of this information. All of the studies in this review were prospective apart from six which were retrospective cohort studies. In the eight longitudinal studies the length of follow-up varied from six months (Almqvist et al., 1999) to five years (Almqvist et al., 2003). The attrition rates from baseline to final follow-up for six of the longitudinal studies varied from 11%

(Larsson et al., 2006) to 58% (Witjes-Ané et al., 2002); no figure was recorded for Dorsey et al. (2013) or Fiedorowicz et al. (2011).

4.1.3 Study origins and authors.

Most of the studies originated from USA (n = 8) and none originated from the UK. There was overlap in the authors of some of the studies and in the potential sourcing of participants, but it is not stated in the papers whether the same participants have been utilised and should this be the case, it may bias some of the findings by overestimating them. Details are shown in Appendix VII.

4.1.4 Participants.

The total sample size of the 16 studies was N = 23,534. Participants consisted of: people considered 'at risk' who had not yet been tested (for example, an adult child with an affected parent or an unaffected family member); 'mutation' carriers for which test results may have shown an 'increased' risk or 'decreased' risk of developing the disease; people who had undergone genetic testing and received a negative result; referred to as 'non-mutation' carriers and those who had undergone a neurological examination and received a 'formal' diagnosis. Demographic characteristics of all participants are given in Appendix VIII.

4.1.5 Primary outcome measures.

Table 11 below summarises how suicide ideation and attempted/completed suicides were measured. Further details of each measure are given in Appendix IX.

Table 11. Methods used to assess suicidal thoughts and identify completed suicide

Methods	Studies
Suicide ideation	
UHDRS-b	Dorsey et al. (2013)
	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Paulsen et al. (2005a)
	Witjes-Ané et al. (2002)
BDI-II	Fiedorowicz et al. (2011)
BHS	Fiedorowicz et al. (2011)
PBA	Hubers et al. (2012)
SIBS	Larsson et al. (1996)
	Robins Wahlin et al. (2000)
Attempted/completed suicide	
Death certificates	Baliko et al. (2004)
	Farrer et al. (1986)
	Schoenfeld et al.(1984)
Medical records	Baliko et al. (2004)
	Almqvist et al. (2003)
	Almqvist et al. (1999)
	Lipe et al. (1993)
	Schoenfeld et al.(1984)
	Farrer et al. (1986)
Register (NHDRR)	Di Maio et al. (1993)
	Farrer et al. (1986)

The UHDRS-b (Huntington Study Group) has been described by the authors as a valid Huntington's specific measure with high internal consistency and inter-rater reliability (α=0.83) when assessing four domains: motor function, cognitive function, psychiatric function and functional capacity. However, the six studies (Dorsey et al., 2013; Fiedorowicz et al., 2011; Hubers, et al. 2013; Paulsen et al., 2005a; Wetzel et al. 2011; Witjes-Ané et al. 2002) that utilised this measure assessed suicide ideation by asking a one, two-part question from the psychiatric subscale which assesses frequency and severity of suicidal thoughts. Therefore, the validity and reliability ratings no longer apply.

All studies asked an additional question about previous suicide attempts but these were not part of a standardised or validated measure. Two studies (Hubers et al., 2013; Witjes-Ané et al., 2002) described using either a psychiatrist or psychologist to assess suicide ideation, which is a strength. However, it is not clear whether they asked for any additional

information other than that already described. Fiedorowicz et al. (2011) included further questions about suicide risk by extrapolating individual items from the BDI-II (Beck et al., 1996) and the BHS (Beck & Steer, 1988). Although, the BDI-II and BHS are both known to be valid and reliable measures (Beck & Steer, 1991, 1993; Beck, Steer, & Carbin, 1988; Simpson & Tate, 2002), the study only used certain items, the properties of which are unclear.

The PBA (Craufurd et al., 2001) is also a Huntington's specific measure described by the authors to have good inter-rater reliability (α=0.73-0.82) when assessing three dimensions: apathy, depression and irritability. However, the study that used this measure (Hubers et al. 2012) assessed suicide ideation by asking a one, two-part question from the depression dimension, which assesses frequency and severity of suicidal thoughts, for which the properties are unknown.

Two studies (Larsson et al., 2006; Robins Wahlin et al., 2000) used all items from the SIBS (Fox et al., 1989): a Huntington's specific measure of suicide ideation. Whilst this measure has been utilised by other studies not included in this review (Bloch et al., 1989; Fox et al., 1989) and appears the superior, no information about the validity or reliability could be found.

Of the remaining studies (n = 7) reporting attempted/completed suicides, despite concerns about the accuracy of retrospective data (Hess, 2004), the validity of the findings are strengthened for three studies (Baliko et al., 2004; Farrer et al., 1986; Schoenfeld et al., 1984) because they utilised a combination of death certificates, medical records and reports from relatives rather than one sole measure of suicide.

4.1.6 Secondary outcome measures.

Table 12 below summarises the other measures utilised in the sixteen studies. A description of each measure is contained within Appendix X. The secondary measures have been detailed as they are important measurements of potential risk factors.

Table 12: Secondary outcome measures utilised by the studies in this review

Measures	Studies
Alcohol misuse: self designed questionnaire	Lipe et al. (1993)
Apathy: scale	Hubers et al. (2012)
Depressed mood was measured using:	
BDI-II	Fiedorowicz et al. (2011)
	Almqvist et al. (2003)
UHDRS-b	Dorsey et al. (2013)
	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Paulsen et al. (2005a)
	Witjes-Ané et al. (2002)
PBA (includes: apathy & irritability)	Hubers et al. (2012)
Cognitive functioning: UHDRS-b	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Paulsen et al. (2005a)
	Witjes-Ané et al. (2002)
Fox et al. (1989) protocol for predictive testing	Larsson et al. (2006)
(CCSPT programme) which includes:	Robins Wahlin et al. (2000)
LSI (life satisfaction)	
LSA (life style)	
Measure of wellbeing	
BDI-II	
GHQ (psychological health)	
One study included additionally:	
AttQ (attitude to testing)	Robins Wahlin et al. (2000)
Functional (total functioning): UHDRS-b	Dorsey et al. (2013)
	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Paulsen et al. (2005a)
	Witjes-Ané et al. (2002)
Life changes (recent): LES	Fiedorowicz et al. (2011)
Medical records check: self designed questionnaire	Lipe et al. (1993)
Social support	Lipe et al. (1993)
Presence of depression	
Presence of dementia	
Mental state: MMSE	Dorsey et al. (2013)
	Hubers et al. (2012)
Motor functioning: UHDRS-b	Dorsey et al. (2013)
	Hubers et al. (2013)
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
	Paulsen et al. (2005a)

	Witjes-Ané et al. (2002)
Psychiatric disorder:	
CIDI according to DSM-IV	Hubers et al. (2012)
PSS	Fiedorowicz et al. (2011)
Psychiatric distress: GSI from SCL-90	Almqvist et al. (2003)
Psychiatric symptoms: UHDRS-b	Hubers et al. (2013)
	Wetzel et al. (2011)
	Witjes-Ané et al. (2002)
Psychological mood: GWB	Almqvist et al. (2003)
Psychiatric history: SIBS	Larsson et al. (2006)
	Robins Wahlin et al. (2000)

5. Results Part 2 – What factors are associated with suicidality in Huntington's?

A narrative approach will be used to combine, summarise and analyse textually the findings of all 16 studies incorporated in this review, including a consideration of the quality. The narrative synthesis was deemed to be the most appropriate rather than a numerical meta-analysis (Tacconelli, 2010). This was decided *a priori* as the review topic was likely to result in a diverse range of studies, designs, settings and measures (Centre for Reviews and Dissemination, 2008). Risk factors for suicidality for which there is quality evidence will be determined, as well as others that require further research. The main focus will be to identify disease-related variables which can be modified through intervention, and to pinpoint 'red flags' for which preventative measures can be put in place. Demographic variables will follow. For ease of reference, tables detailing the findings for disease-related variables are included in Appendix XI. Each risk factor will be considered in turn looking at both *suicide ideation* and *attempted or completed suicide*.

5.1 Psychiatric symptoms and history

Depressed mood was found to be the most significant correlate and predictor of *suicide ideation* in three longitudinal studies: Hubers et al. (2013) and Hubers et al. (2012) found a significance level of $p < .001$ at baseline and at follow-up it was found to independently predict suicidal thoughts at a level of $p < .03$ and $p < .04$. Over a three and a half year period, Fiedorowicz et al. (2011) reported a BDI-II score >13 to be a risk factor for suicide ideation $p < .0006$. A cross-sectional study confirmed depressed mood to be the strongest predictor of suicidal thoughts in Huntington's ($p < .001$) for those with the highest suicidal ratings (Wetzel et al., 2011).

The quality scores of these studies ranged from 83% to 91%. It is a weakness of all studies that they assessed suicide ideation by extrapolating one item from a full measure. The assessment method by Fiedorowicz et al. (2011) is slightly more credible as they extrapolated items from three separate measures as opposed to one.

Hubers et al. (2013) found additional factors at baseline to be significantly correlated with suicide ideation, namely: anxiety, apathy, irritability and aggression ($p < .001$). Similarly, Wetzel et al. (2011) found anxiety ($p < .001$), aggression ($p < .001$) and alcohol abuse ($p < .04$) to predict suicide ideation (although, the effect sizes were small) but not obsessive/compulsive behaviour or tobacco or drug use. Larsson et al. (2006) found that at baseline, participants with a psychiatric history reported having more suicidal thoughts ($p < .05$) than those who did not. Quality scores for these three studies ranged from 79% to 85%. Again, it is a weakness that the study by Wetzel et al. (2011) measured suicide ideation by using solely one extrapolated item from a full measure. Larsson et al. (2006) used all items from the SIBS, but psychometric properties about this measure could not be found.

Conversely, Fiedorowicz et al. (2011) found no difference in those who were suicidal and those who were not when measuring presence of psychiatric status, for example: anxiety, grandiosity, and alcohol abuse (quality score: 86%). It is a weakness that there was a low rate of suicidality which limits statistical power.

Thus, five studies of higher quality suggested psychiatric symptoms/history are risk factors for suicide ideation; however whilst one disagreed with some of the factors, it is likely that this was due to the low rate of suicidality.

Considering *attempted or completed suicide,* three participants attempted suicide during a five year longitudinal study (Almqvist et al., 2003), one had depressed mood and the

presence of psychiatric distress, one had depressed mood and a psychiatric history and the other had normal scores on the psychological measures (quality score: 86%). Because this group study carried out an analysis followed by the descriptions of only three cases, it may not be generalisable. Lipe et al. (1993) carried out a retrospective cohort study and found that those with depression were found to have higher odds (OR = 1.26) of completing suicide and no evidence of alcohol misuse in those who completed suicide (quality score: 35%). In another retrospective cohort study (Schoenfeld et al., 1984), it was found that out of 11 who completed suicide two were in psychiatric hospitals at the time (quality score: 79%). Although, the quality score of the latter is more acceptable than the study by Lipe et al. (1993) it is important to note that the data for both studies may have come from sources which were potentially inaccurate.

Thus, three studies, two of higher quality, suggest psychiatric symptoms/history to be a risk factor for actual suicide. Further investigation is required however, due to generalisability issues with one of the higher quality studies.

5.2 Suicidality in the past

Hubers et al. (2013) found a suicide attempt in the past to be a significant independent correlate of *suicide ideation* at baseline ($p < .001$) as did the study by Fiedorowicz et al. (2011) ($p < .0002$) (quality scores: 83% to 86%). A further study reported that in those who disclosed higher levels of suicide ideation, 5% reported attempted or completed suicides in family members (quality score: 85%) (Robins Wahlin et al., 2000). However, the sample size of this study was small ($n = 34$), which could limit generalisability.

Considering *attempted or completed suicide,* one participant from the above study (Fiedorowicz et al., 2011) completed suicide following two previous attempts (quality score: 86%). In contrast, a retrospective cohort study (Farrer et al., 1986) reported that out of 25

completed suicides, none had previously attempted suicide. Data came from death certificates and medical records. However, if someone had attempted suicide in the past this may not have been known. In addition, the quality score is low: 37%, which further undermines the findings.

Therefore, two higher quality studies found past suicide attempts to be a risk factor for current suicide ideation. For completed suicide only there is only one study with limited generalisability which found past suicide attempts to be a risk factor and another of low quality which disagreed. This suggests further investigation is required in this area for completed suicides.

Five studies have suggested the occurrence of further cases of suicide in the same family as a risk factor for *completed suicide*. Baliko et al. (2004) found that suicide among close relatives (parent/child, brother/sister) occurred in four families which had nine cases of Huntington's (quality score: 47%). Almqvist et al. (2003) reported that one person who attempted suicide in their sample had a family history of suicide (quality score: 86%). Similarly, Di Maio et al. (1993) found that 28% of the families in the total sample experienced 48% of the cases of suicide (quality score: 44%); Lipe et al. (1993) found that the odds of committing suicide were increased if there had been other suicides in the family OR = 1.75 (quality score: 35%) and Schoenfeld et al. (1984) reported that out of those who completed suicide in their study two were sisters and two were uncle and nephew (quality score: 79%). All studies, however are retrospective cohort studies and therefore could be based upon inaccurate data.

With regards to suicide of a family member being a risk factor for completed suicide, five studies reported this, two with higher quality ratings.

5.3 Proximity to genetic testing

Hubers et al. (2012) found no significant difference in the presence of *suicide ideation* when comparing those who received their genetic test result within the year preceding the study and those who received it more than a year before (quality score: 83%). A limitation though, is that the authors seemed to have assumed that thoughts that occurred after the one year period were associated with something else.

With regards to *completed suicide*, Almqvist et al. (2003) found that in three participants who attempted suicide in their study one attempted suicide on the day of receiving the test result; another attempted suicide whilst waiting for test results and then again two years later; and a third attempted suicide four years after receiving the result (quality score: 86%). In an earlier study by Almqvist et al. (1999) the time period after testing for those who attempted suicide is shorter (0.5-29 months) compared to those who completed suicide (3-35 months) (quality score: 85%). The limitation of both these studies however, is that it is not possible to judge whether the suicide is related to the time period or to other factors.

Given the limitations and the absence of additional evidence, further investigation is required in this area.

5.4 Results of genetic testing

Following genetic testing, carrying the Huntington's gene is determined if there are CAG repeats of $\geq$36 (Fiedorowicz et al. 2011). Three studies found number of CAG repeats not to be associated with *suicide ideation* (Hubers et al. 2013; Hubers et al. 2012; Fiedorowicz et al. 2011).

Robins Wahlin et al. (2000) found that those who received 'mutation' carrier status exhibited a significantly higher rate of suicide ideation ($p < .05$) than those who received 'non-carrier' status (quality score: 85%). Similarly, Hubers et al. (2012) found that 20% of 'mutation' carriers in their study displayed suicide ideation compared to 0% of 'non-mutation' carriers (quality score: 91%) and Larsson et al. (2006) reported that 'mutation' carriers disclosed thinking about suicide more often, over time, than 'non-mutation' carriers (quality score: 79%).

One study (Witjes-Ané et al., 2002) contradicted the above findings and reported no difference between 'mutation' carriers and 'non-mutation' carriers; however, the rate of suicidality in the sample was extremely low resulting in a lack of statistical power (quality score: 88%).

Three higher quality studies found the number of CAG repeats not to be associated with suicide ideation and another three higher quality studies are suggesting 'mutation' carrier status to be a risk factor for suicide ideation, with one contradictory study. Although, it does need to be considered that, the increase in risk could be related to other factors, rather than solely the test result.

One prospective study investigated *completed suicide* (Almqvist et al., 2003) reporting that out of 106 participants who received a 'decreased risk' result three attempted suicide (quality score: 86%). This data, however, has only come from three cases. In retrospective studies: Di Maio et al. (1993) found that out of those who completed suicide, a higher percentage were classified as 'possibly at risk' than 'at risk' and in a further study (Lipe et al. 1993) out of 11 suicides, one person had received an 'at risk' status, compared to eight who were formally diagnosed (quality scores: 35% to 44%). As well as the lower quality score of

the latter two studies, there are also concerns about the accuracy of the data from medical records, registers and death certificates.

In summary, with regards to completed suicide, three studies are suggesting the following results to be risk factors for suicide: 'decreased risk', 'possibly at risk' and 'at risk'. Due to the lack of high quality evidence further investigation is required.

5.5 Age at onset and proximity to 'formal' diagnosis

Three lower quality studies (quality scores: 37% to 47%) investigated age at onset for *completed suicide* (Baliko et al., 1994; Di Maio et al., 1993; and Farrer et al. 1986). The first study suggested mean age at onset to be lower for those who completed suicide when compared to those who did not and the other two studies reported no difference in mean age at onset.

One study asked participants how recently they had received 'formal' diagnosis (>15years, mid 9-15 years, <9 years) and found no significant differences in level of *suicide ideation* (quality score: 86%) (Fiedorowicz et al., 2011). This, however, could be confounded with type of neurological examination diagnosis and symptom severity.

Due to a lack of high quality evidence for both age at onset and formal diagnosis, further investigation is required.

5.6 Results of neurological examination, disease stage and symptom severity

Following genetic testing, 'mutation' carriers can be classified according to neurological examination result and symptoms. A study by Paulsen et al. (2005a) found the highest rates of *suicide ideation* in two classifications: firstly: 'non-specific motor abnormalities' (19.8%) which significantly increased ($p < .001$) from the rate of suicide

ideation in the ‘normal’ category and secondly: ‘motor abnormalities indicating possible Huntington’s’ (23.5%) which significantly decreased ($p < .05$) in the ‘motor abnormalities indicating definite Huntington’s’ classification (quality score: 87%). Based upon level of independence, in the same study, the presence of suicide ideation at different stages of the disease was calculated. Results showed that suicide ideation was most often endorsed in the early stages (for example: 21.6% in stage two compared to 9.8% in stage five $p < .01$). These findings imply that suicide risk is greater during the earlier stages of the disease following the development of symptomatology (quality score: 87%). A clear strength of this study is the large sample size ($n = 4171$).

In contrast, an investigation with ‘asymptomatic’ carriers by Larsson et al. (2006) reported that 52% said they would consider suicide in the future and 30% expected that they would consider it when they reached middle or advanced stages of the disease (quality score: 79%). However, because this is measuring future possible suicidality rather than current suicide ideation in asymptomatic participants, the results of the two cannot be accurately compared. It is also a weakness that the study has a relatively small sample size ($n = 93$).

Looking at symptoms, two studies (Hubers et al., 2012; Wetzel et al., 2011) investigated the association between level of cognitive functioning and suicide ideation. Cognitive functioning was found not to be a significant predictor (quality scores: 85% to 91%). With regards to total level of functioning (overall functioning and independence) and motor symptoms, the same two studies found that they were not significant predictors of suicide ideation. Hubers et al. (2013) and Fiedorowicz et al. (2011) (the latter just looking at motor symptoms) reported the same (quality scores: 83% to 86%). For Hubers et al. (2013) and Fiedorowicz et al. (2011) it is a limitation that prevalence of suicidality in the study is low.

With regards to suicide ideation following neurological examination, experiencing 'non-specific motor abnormalities' and 'motor abnormalities indicating possible Huntington's' were found to be risk factors. Similarly, with regards to level of independence/symptomatology, the earlier stages of the disease have been found to be a risk factor. Although with only one higher quality study, further investigation is required. Two higher quality studies have shown level of cognitive functioning not to be a risk factor, three higher quality studies have found total functioning not to be a risk factor and four higher quality studies have found level of motor functioning not to be a risk factor.

From reviewing medical records, it was found that out of 26 who *attempted or completed suicide* (Almqvist et al., 1999): 16 were 'symptomatic', which included one 'suspected' and four who had been recently diagnosed (quality score: 85%). The findings of this study have considerable worth as it was an international collaborative study with a large sample size (n = 4527). Di Maio et al. (1993) found that those who completed suicide were more likely to be classified as 'possibly affected' and Lipe et al. (1993) found that eight out of ten who completed suicide were classified as 'affected' and two 'unaffected' (quality scores: 35% to 44%). Schoenfeld et al. (1984) reported that nine out of 20 suicides were those who were symptomatic and had been formally diagnosed and the remainder classified as 'suspected' (quality score: 79%).

Looking at stage of disease, the results of four retrospective cohort studies have suggested that the early stages of the disease are when people are more likely to complete suicide. Baliko et al., (2004) reported higher risk in early or later stages, Farrer et al. (1986) reported early to middle stages and Lipe et al. (1993) reported suicide being most common within one year of onset and (quality scores: 35% to 47%). Schoenfeld et al. (1984) with a quality score of 79% agreed, finding early stages of the disease to be a risk factor.

In summary, despite the different use of terminology and lower quality of two studies out of four it appears that those who are 'possibly affected/suspected', 'affected' or 'symptomatic' are most at risk. With regards to stage of disease, despite the quality of three out of four of the studies being lower, all are suggesting being in the early stages of the disease to be a risk factor for completed suicide.

5.7 Estimated disease duration

An estimation of disease duration can be calculated by subtracting age at onset from current age (Vassos, Panas, Kladi, & Vassilopoulos, 2008). Hubers et al. (2013) found that those who reported *suicide ideation* had a significantly shorter estimated disease duration ($p < .01$) (quality score: 83%). Hubers et al. (2012) disagreed, finding no significant difference (quality score: 91%).

Considering *completed suicide,* Di Maio et al. (1993) found disease duration to be significantly lower ($p < .0001$) in those who completed suicide and Farrer et al. (1986) reported that those who completed suicide lived with their illness for 5.8 years less than those who died of other causes (quality scores: 37% to 44%).

Shorter estimated disease duration has been suggested to be a risk factor for suicide ideation by one higher quality study, however another disagreed. With regards to completed suicide two studies of lower quality suggest a shorter disease duration to be a risk factor. It is difficult to know, however, whether disease duration was the risk factor or another variable. Further investigation is required.

5.8 Medication

Dorsey et al. (2013) reported that the use of tetrabenazine for chorea was not associated with an increased risk for *suicide ideation* (quality score: 83%). However, the samples of participants exposed to the drug were low. Hubers et al. (2013) found higher use of psychotropics (anti-depressants, benzodiazepines, mood stabilisers/anti-epileptics) ($p<$ .001) in those with suicide ideation, as did Hubers et al. (2012) who found that the use of anti-depressants was independently associated ($p<$ .001) with suicidal thoughts (quality scores: 83% to 91%).

Further studies are required to investigate potential side effect of an increase in suicide ideation with the use of tetrabenazine. With regards to the use of psychotropics, the quality of the two studies does suggest their use may be a risk factor for suicide ideation. However, depressed mood could be a confounding variable.

5.9 Other

No difference was found in the presence of *suicide ideation* for those who were living in a residential institution or not (Hubers et al., 2012) and no associations were found between recent lifestyle changes and suicide ideation except for those who had been in prison in the past two years ($p<$ .002) Fiedorowicz et al. (2011) (quality scores: 86% to 91%). As there is only one of each study, further investigation is required.

5.10 General demographic variables

Whilst many of the following factors are not those which can be ameliorated, information about general demographics will contribute to highlighting ‘red flags’ for potential difficulties. Four higher quality studies (quality scores: 83% to 91%) showed that

sex was not related to *suicide ideation* (Fiedorowicz et al., 2011; Hubers et al., 2012; Hubers et al., 2013, Wetzel et al., 2011). In four lower quality studies (quality scores: 35% to 47%) over 70% of those who *completed suicide* were male (Baliko et al., 2004; Di Maio et al., 1993; Farrer et al., 1986; Lipe et al., 1993); one with a better quality score of 79% found the same (Schoenfeld et al., 1984) and another with a quality score of 85% disagreed (Almqvist et al., 1999). However, for the studies of better quality, the number of people who completed suicide was small.

Considering age, only one study (Schoenfeld et al., 1984) provided data in relation to age that could in anyway be predictive of *completed suicide* (quality score: 79%) which suggested younger age to be a predictor for actual suicide; other studies only provided average ages at time of participation (Fiedorowicz et al., 2011; Hubers et al., 2012; Hubers et al., 2013, Wetzel et al., 2011) which were found not to be associated with *suicide ideation* (quality scores: 83% to 91%).

With regards to level of education, two higher quality studies (Fiedorowicz et al., 2011; Wetzel, et al., 2011) found no association between education and *suicide ideation* (quality scores: 85% to 86%). Considering employment status for *completed suicide*, one higher quality study (Almqvist et al. 2003) reported that one participant completed suicide just after their employment was terminated and in another higher quality study (Almqvist et al. 1999) all who completed suicide were employed (quality scores: 85% to 86%). In both studies however, the number of people who completed suicide was small.

With regards to family size, one lower quality study (Baliko et al., 2004) reported that *completed suicide* occurred more frequently in larger families and another of lower quality (Lipe et al. 1993) reported that odds for suicide were higher (OR = 1.43) if there was no

contact with other family members with the disease (quality scores: 35% to 47%). Hubers et al. (2012) found no difference in *suicide ideation* depending upon marital status (quality score: 91%), whereas for *completed suicide,* one study (Lipe et al., 1993) found the odds for suicide were higher if the person was not married (OR = 1.06) or living alone (OR = 1.26) (quality score: 35%). In a better quality study, Schoenfeld et al. (1984) reported that 65% of those who completed suicide were married (quality score: 79%). For both studies the number of completed suicides was small.

Hubers et al. (2012) found no difference in *suicide ideation* depending upon the number of children participants had (quality score: 91%). For *completed suicide,* Baliko et al. (2004) reported that suicide occurred more frequently in those with a lower number of children, Lipe et al. (1993) found higher odds for suicide (OR = 13.6) if the person had no children (quality scores: 35% to 47%) and in a better quality study (Schoenfeld et al., 1984) 65% of those who completed suicide had children (quality score: 79%).

In summary, higher quality evidence suggests that suicide ideation does not differ depending on sex and although there is only one study, younger age may be a risk factor for completed suicide. Level of education was found not to be associated with suicide ideation and further investigation is required with regards to employment status and completed suicide. A lack of higher quality evidence and conflicting findings means that further research is needed to investigate whether family size, marital status and number of children are risk factors for suicidality.

6. Discussion

The aim of this review was to present systematically and to synthesise the characteristics and outcomes of quality appraised research studies which have provided findings about the risk factors associated with suicidality in Huntington's, especially those factors that can be ameliorated or used as 'red flags' for clinicians to be aware of when supporting those with Huntington's.

6.1 Findings

The results of this review provide strong evidence suggesting that the following are risk factors for *suicide ideation*: psychiatric symptoms/history, 'mutation' carrier status and the use of psychotropics (although this could be confounded with psychiatric symptoms). Strong evidence suggests that these variables are not risk factors: the number of CAG repeats, cognitive, total and motor functioning, sex and level of education.

For *attempted* or *completed suicide* there is strong evidence for the following: psychiatric symptoms/history, the suicide of a family member, a neurological examination result of: 'suspected' Huntington's or 'symptomatic' and being in the early stages of the disease. Table 13 below, displays the results with additional factors for which there are less evidence and require further investigation.

Table 13. Evidence for risk factors and evidence for factors which do not increase the risk

Factors	Suicide ideation	Attempted/completed suicide
Risk factors		
Strong evidence (≥2studies)	Psychiatric symptoms and history (5 higher quality studies, 1 of higher quality disagreed). Suicidality in the past (2 higher quality studies) Results of genetic testing = 'mutation' carrier status (3 higher quality studies, 1 higher quality contradicts with a small sample) The use of psychotropics (2 higher quality studies).	Psychiatric symptoms and history (2 higher quality studies: 1 study of lower quality). Suicide of a family member in the past (5 studies including: 2 of a higher quality). Results of neurological examination = 'formal' diagnosis of 'symptomatic' or 'suspected' (2 higher quality studies). Being in the early stages of the disease (4 studies, 1 of higher quality). Male (5 studies: 1 higher quality, 4 lower quality, 1 contradictory of higher quality) – requires further investigation. Age of death (4 studies: 1 higher quality, 3 lower quality, 1 contradictory of lower quality) –requires further investigation.
1 higher quality study (further investigation required).	Estimated disease duration being shorter (but 1 higher quality study disagrees). Employment (but 1 higher quality study disagrees). Incarceration in the past 2 years.	Suicidality in the past (but 1 lower quality study disagrees). Closer proximity to receiving genetic testing result (but 1 higher quality study disagrees). Results of genetic testing = 'decreased' risk. Results of neurological examination = 'non-specific motor abnormalities' or 'motor abnormalities indicating possible Huntington's'. The earlier stages of symptomatology. Recent diagnosis. Not married (but 1 study of lower quality disagrees).
1 study of lower quality (further investigation required).	NA	Results of genetic testing = 'at risk'. Results of genetic testing = 'possibly at risk'. Results of examination = 'possibly affected'. Results of examination = 'affected'. Shorter disease duration (2 studies of lower quality) – further investigation required. Mean age at onset for those who completed suicide: 37.8, mean age at onset for those who did not: 40.4 (but 2 of lower quality disagree). Being from a larger family. Not being in contact with other family members with the disease. Having children/ a small number of children (but 1 study of lower quality disagrees).
Not risk factors		
Strong evidence (≥2studies)	Number of CAG repeats (3 higher quality studies). Cognitive functioning (2 higher quality studies). Total functioning (3 higher quality studies). Motor functioning (4 higher quality studies). Sex (4 higher quality studies). Age (4 higher quality studies). Education (2 higher quality studies).	NA

1 higher quality study (further investigation required).	Proximity to genetic testing. Proximity to diagnosis. The use of tetrabenazine. Living in a residential institution. Marital status. Children.	NA

6.2 Methodological issues and weaknesses

It is important to consider that whilst these findings suggest several risk factors for suicidality in Huntington's, the studies included in this review are correlational studies meaning that they are observational rather than experimental. Cohort, cross-sectional and longitudinal studies do not manipulate factors and whilst they can suggest a relationship between variables they have reduced statistical power to ascertain causality (Tooth, Ware, Bain, Purdie, & Dobson, 2005). Other issues which may weaken the reliability of the findings are the use of a non-validated and potentially unreliable primary outcome measures and the conducting of reviews of medical records and death certificates which may not contain accurate information, for example, due to suicide being classified as accidental (Haines et al. (1986). Retrospective study designs were also utilised and generally these are considered as inferior to prospective designs (Hess, 2004).

Additional weaknesses identified in the reviewed studies included: no power calculation to determine the sample size, sample bias mainly due to recruitment from only one site per study or from a voluntary register, losses to follow-up, omitting the reporting of confidence intervals or the magnitude of the effect and a lack of consideration of response rate, study limitations and external validity. Whilst case studies were excluded in the initial search criteria, some group studies have reported results focussing on the individual cases of those who attempted or completed suicide which could limit the generalisability of the findings (Flyvbjerg, 2006). In addition to this, the focus of each study was not always risk

factors associated with suicide and therefore relevant information could not always be extracted from the findings.

6.3 Limitations of the review

There are some limitations to this systematic review. Centre for Reviews and Dissemination (2008) propose that the best quality evidence possible should be used when writing a systematic review, however, the quality of the quantitative studies used in this review range from 35% to 91%. Qualitative research has been postulated to have an important role in systematic review findings (Jackson & Waters, 2005) and may have contributed to the understanding of risk factors for suicide, but was excluded. Findings from unpublished studies which can be included in reviews (Altman, 2001) have also been omitted. Ideally, in order to avoid publication bias, a review should include all studies of relevance, regardless of publication status (Centre for Reviews and Dissemination, 2008). The overlap of authors who have written papers included in this review may also mean an overestimation of findings if the data has been analysed for more than one study.

No single quality tool has been identified for widespread use within systematic reviews of observational studies (Sanderson et al., 2007). However, a limitation of the bespoke tool utilised in this review is that the scoring of it implies that each assessed component has an equal weighting. For example, the reporting of a clear hypothesis was allocated the same weighting as the use of appropriate statistical tests. What is not reflected in the weighting of each component of the tool is that the use of an appropriate analysis could be argued to be more critical than if the study had reported the hypotheses or not. This may have resulted in an over-reliance on the subjective rating of the researcher in defining the degree of overall methodological weakness.

Additionally, whilst this review has been carried out in a rigorous and transparent manner, narrative synthesis has inherently been proposed to be a more subjective process than meta-analysis which has greater power and precision (Centre for Reviews and Dissemination, 2008).

6.4 Future research

As well as the requirements already mentioned in Table 13 above, this review has highlighted other areas for further investigation. Hubers et al. (2013) proposed how the investigation of trajectories of suicidality is needed, especially the extent to which suicide ideation is related to actual suicide at each stage of the disease (Witjes-Ané et al., 2002). Few studies have demonstrated the weight of each predictor of suicide (Paulsen et al., 2005a). With regards to assessment measures, Hubers et al. (2012) and Wetzel et al. (2011) suggested that instead of a general medical questionnaire, the use of a detailed psychopathology interview should be incorporated. A lack of diagnostic criteria and adequate rating scales are still a problem and were initially raised in an earlier review by Naarding et al. (2001). Valid and reliable outcome measures for suicide ideation are essential. With regards to predictive testing, Almqvist et al. (1999) suggested that the use of a control group of individuals who have chosen not to undergo testing could be followed whilst monitoring suicidality. No studies have investigated whether suicidal thoughts predict completed suicide, whilst this seems obvious, specific research in this population is required. Future research could also investigate which variables prevent individuals with Huntington's from considering or completing suicide.

6.5 Clinical relevance

The reviewed research has made recommendations for amendments to clinical practice to work towards reducing suicidality in Huntington's. Several studies including Hubers et al. (2012) and Robins Wahlin et al. (2000) described the importance of screening suicide ideation at all stages of the disease, especially including careful follow-up after genetic testing and when individuals become 'symptomatic' (Almqvist et al., 1999; Schoenfeld et al., 1984). Individuals with depressive symptoms should be prioritised (Fiedorowicz et al., 2011; Paulsen et al., 2005a). Furthermore clinicians should carefully monitor those who have carried out previous suicide attempts (Fiedorowicz et al., 2011), where there has been a suicide in the family (Baliko et al., 2004; Schoenfeld et al., 1984), those with psychiatric symptoms (Wetzel et al., 2011; Witjes-Ané et al., 2002) and those in the early stages of the disease following formal diagnosis (Schoenfeld et al., 1984).

During the assessment of individuals with Huntington's, an awareness of risk factors for suicide is essential (Almqvist et al., 1999). Additionally, the identification of 'red flags' will help clinicians to know what to look out for and interventions can be put in place in order to reduce risk. Consideration of support strategies such as referrals to mental health professionals and counselling (for example: Hubers et al., 2012; Larsson et al., 2006) are required for all including those undergoing genetic testing; as are taking the necessary steps to ensure the safety of any individual who discloses suicide ideation (Wetzel et al., 2011). Before testing and in order to identify those who may require additional support, a baseline assessment should be carried out (Almqvist et al., 2003).

7. Conclusion

Despite some limitations, this current review contributes to the body of research examining suicidality in Huntington's and provides important findings for individuals with the disease, researchers and service commissioners. Further research is required in this area to focus on reducing prevalence rates of suicide, to further understand the risk factors and to develop and implement appropriate interventions to ameliorate and address them.

8. References

Alderson, M.R., & Meade, T.W. (1967). Accuracy of diagnosis on death certificates compared with that in hospital records. *British Journal of Preventive & Social Medicine, 21*(1), 22-29.

Almqvist, E.W., Bloch, M., Brinkman, R., Craufurd, D., & Hayden, M.R. (1999). A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease. *The American Journal of Human Genetics, 64*(5), 1293-1304.

Almqvist, E.W., Brinkman, R.R., Wiggins, S., Hayden, M.R., Nicolson Klimek, M.L., Trew, M., . . . Shokeir, M.H.K. (2003). Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease. *Clinical Genetics, 64*(4), 300-309. doi: 10.1034/j.1399-0004.2003.00157.x

Alonso, M.E., Ochoa, A., Boll, M.C., Sosa, A.L., Yescas, P., López, M., . . . Rasmussen, A. (2009). Clinical and genetic characteristics of Mexican Huntington's disease patients. *Movement Disorders, 24*(13), 2012-2015. doi: 10.1002/mds.22737

Altman, D.G. (2001). Systematic reviews in health care: Systematic reviews of evaluations of prognostic variables. *BMJ: British Medical Journal, 323*(7306), 224.

APA. (2000). *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders* (4 ed.). Washington, DC: American Psychiatric Association.

Baliko, L., Csala, B., & Czopf, J. (2004). Suicide in Hungarian Huntington's disease patients. *Neuroepidemiology, 23*(5), 258-260. doi: DOI:10.1159/000079953

Beck, A.T., & Steer, R.A. (1988). Beck Hopelessness Scale. *The Psychological Corporation, San Antonio*.

Beck, A.T., & Steer, R.A. (1991). *Manual for Beck Scale for Suicide Ideation*. San Antonio: Psychological Corporation.

Beck, A.T., & Steer, R.A. (1993). *Beck Scale for Suicide Ideation*. United States of America: Pearson.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Beck Depression Inventory-II* (2nd ed.). United States of America: Pearson.

Beck, A.T., Steer, R.A., & Carbin, M.G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review, 8*(1), 77-100.

Bindler, L., Touzeau, T., Travers, D., & Millet, B. (2010). Le Suicide dans la maladie de Huntington: état actuel des connaissances. *Annales Medico-Psychologiques: Revue Psychiatrique, 168*(5), 338-342.

Björkqvist, M., Petersén, Å., Bacos, K., Isaacs, J., Norlén, P., Gil, J., . . . Tabrizi, S.J. (2006). Progressive alterations in the hypothalamic-pituitary-adrenal axis in the R6/2 transgenic mouse model of Huntington's disease. *Human Molecular Genetics, 15*(10), 1713-1721. doi: 10.1093/hmg/ddl094

Bloch, M., Adam, S., Wiggins, S., Huggins, M., & Hayden, M. R. (1992). Predictive testing for Huntington disease in Canada: The experience of those receiving an increased risk. *American Journal of Medical Genetics, 42*(4), 499-507.

Bloch, M., Fahy, M., Fox, S., Hayden, M.R., & Reynolds, J.F. (1989). Predictive testing for Huntington disease: II. Demographic characteristics, life-style patterns, attitudes, and psychosocial assessments of the first fifty-one test candidates. *American Journal of Medical Genetics, 32*(2), 217-224.

Booij, S.J., Tibben, A., Engberts, D.P., Marinus, J, & Roos, R.A.C. (2014). Thinking about the end of life: a common issue for patients with Huntington's disease. *Journal of Neurology, 261*(11), 2184-2191. doi: 10.1007/s00415-014-7479-4

Bradley, W.G. (2004). *Neurology in clinical practice: principles of diagnosis and management* (Vol. 1). Philadelphia: Elsevier Inc.

Bryois, C. (1988). The length of survival and cause of death in Huntington chorea. *Schweizer Archiv für Neurologie, 140*(2), 101-115.

Caldwell, K., Henshaw, l., & Taylor, G. (2011). Developing a framework for critiquing health research: an early evaluation. *Nurse Education Today, 31*(8), e1-e7. doi: 10.1016/j.nedt.2010.11.025

Centre for Rewiews and Dissemination. (2008). *Systematic Reviews: CRD's guidance for undertaking reviews in health care.* York: University of York.

Codori, A.M., Hanson, R., & Brandt, J. (1994). Self-selection in predictive testing for Huntington's disease. *American Journal of Medical Genetics, 54*(3), 167-173.

Craufurd, D., & Snowden, J. S. (2014). Neuropsychiatry and Neuropsychology. In G. Bates, S. J. Tabrizi, S. Tabrizi & L. Jones (Eds.), *Huntington's Disease* (pp. 36-65): Oxford University Press.

Craufurd, D., Thompson, J.C., & Snowden, J.S. (2001). Behavioral changes in Huntington disease. *Cognitive and Behavioral Neurology, 14*(4), 219-226.

De la Cadena, C. G., Alonso. Ma, E., Ochoa, A., & Martinez, C. (1997). Attitudes regarding molecular diagnosis in Mexican families at risk of inheriting Huntington's disease. *Archives of Medical Research, 28*(4), 513-516.

Deeks, J.J., Dinnes, J., D'amico, R., Sowden, A.J., Sakarovitch, C., Song, F., . . . Altman, D.J. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment, 7*(27), 1-179. doi: 10.3310/hta7270

Derogatis, L.R. (1983). SCL-90-R administration, scoring and procedures manual—II, 1983. *Clinical Psychometric Research, Towson, MD.*

Di Maio, L., Squitieri, F., Napolitano, G., Campanella, G., Trofatter, J.A., & Conneally, P.M. (1993). Suicide risk in Huntington's disease. *Journal of Medical Genetics, 30*(4), 293-295.

Dorsey, E.R., Brocht, A.F.D., Nichols, P.E., Darwin, K.C., Anderson, K.E., Beck, C.A., . . . Shoulson, I. (2013). Depressed Mood and Suicidality in Individuals Exposed to Tetrabenazine in a Large Huntington Disease Observational Study. *Journal of Huntington's disease, 2*(4), 509-515. doi: 10.3233/JHD-130071

Dorsey, E.R., & The Huntington Study Group COHORT Investigators (2012). Characterisation of a large group of individuals with Huntington disease and their relatives enrolled in the COHORT study. *Public Library of Science One, 7*(2), e29522. doi: 10.1371/journal.pone.0029522

Downs, S.H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *Journal of Epidemiology and Community Health, 52*(6), 377-384.

Dufrasne, S., Roy, M., Galvez, M., & Rosenblatt, D.S. (2011). Experience over fifteen years with a protocol for predictive testing for Huntington disease. *Molecular Genetics and Metabolism, 102*(4), 494-504. doi: 10.1016/j.ymgme.2010.12.001

Dupuy, H. (1969). The psychological examination: cycle IV. *Washington, DC: National Center for Health Statistics.*

Elamin, M.B., Flynn, D.N., Bassler, D., Briel, M., Alonso-Coello, P., Karanicolas, P.J., . . . Kunz, R. (2009). Choice of data extraction tools for systematic reviews depends on

resources and review complexity. *Journal of Clinical Epidemiology, 62*(5), 506-510. doi: 10.1016/j.jclinepi.2008.10.016
Epping, E. A., Mills, J. A., Beglinger, L. J., Fiedorowicz, J. G., Craufurd, D., Smith, M. M., . . . Paulsen, J. S. (2013). Characterization of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study. *Journal of Psychiatric Research, 47*(10), 1423-1431. doi: 10.1016/j.jpsychires.2013.05.026
Evans, S.J.W., Douglas, I., Rawlins, M.D., Wexler, N.S., Tabrizi, S.J., & Smeeth, L. (2013). Prevalence of adult Huntington's disease in the UK based on diagnoses recorded in general practice records. *Journal of Neurology, Neurosurgery & Psychiatry*, jnnp-2012-304636.
Farrer, L.A., Opitz, J.M., & Reynolds, J.F. (1986). Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. *American Journal of Medical Genetics, 24*(2), 305-311.
Fiedorowicz, J.G., Mills, J.A., Ruggle, A., Langbehn, D., Paulsen, J.S., & Group, Predict-HD Investigators of the Huntington Study. (2011). Suicidal behavior in prodromal Huntington disease. *Neurodegenerative Diseases, 8*(6), 483-490. doi: 10.1159/000327754
Flyvbjerg, B. (2006). Five misunderstandings about case-study research. *Qualitative Inquiry, 12*(2), 219-245. doi: 10.1177/1077800405284363
Folstein, M.F., Folstein, S.E., & McHugh, P.R. (1975). “Mini-mental state”: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research, 12*(3), 189-198.
Fowkes, F.G., & Fulton, P.M. (1991). Critical appraisal of published research: introductory guidelines. *BMJ: British Medical Journal, 302*(6785), 1136.
Fox, S., Bloch, M., Fahy, M., & Hayden, M.R. (1989). Predictive testing for Huntington disease: I. Description of a pilot project in British Columbia. *American Journal of Medical Genetics, 32*(2), 211-216.
Gielen, A.C., & Roche, K.A. (1979). Death anxiety and psychometric studies in Huntington's disease. *Omega: Journal of Death and Dying, 10*(2), 135-145.
Glasser, J.H. (1981). The quality and utility of death certificate data. *American Journal of Public Health, 71*(3), 231-233.
Goldberg, D., & Williams, P. (1988). A user's guide to the General Health Questionnaire. 1988. *NFER-Nelson, Windsor*.
Haines, J.L., Conneally, P.M., & Rao, D.C. (1986). Causes of death in Huntington disease as reported on death certificates. *Genetic Epidemiology, 3*(6), 417-423. doi: 10.1002/gepi.1370030606
Hayden, M.R., Berkowicz, A.L., Beighton, P.H., & Yiptong, C. (1981). Huntington’s chorea on the island of Mauritius. *South African Medical Journal, 60*(26), 1001-1002.
Hess, D.R. (2004). Retrospective studies and chart reviews. *Respiratory care, 49*(10), 1171-1174.
Hewitt, J. (2010). *Huntington's Disease Causes, Tests and Treatments* (M. Gabata Ed.). United States of America: Kenrose Media.
Higgins, A., & Hoblyn, J. . (2014). A review of psychiatric and behavioural manifestations and interventions for patients with Huntington's Disease in a long term care setting. *Journal of Neurology, Neurosurgery and Neuropsychiatry, 85*, A89. doi: 10.1136/jnnp-2014-309032.256
Hubers, A., Mast, R.C., Pereira, A.M., Roos, R.A.C., Veen, L.J.,Cobbert, C.M., Duijn, E., Giltay, E.J. (2015). Hypothalamic-pituitary-adrenal axis functioning in Huntington's

disease and its association with depressive symptoms and suicidality. *Journal of Neuroendocrinology, (27)*3, 234-244. doi: 10.1111/jne.12255

Hubers, A. , van Duijn, E., Roos, R.A.C., Craufurd, D., Rickards, H., Bernhard Landwehrmeyer, G., . . . Giltay, E.J. (2013). Suicidal ideation in a European Huntington's disease population. *Journal of Affective Disorders, 151*(1), 248-258. doi: 10.1016/j.jad.2013.06.001

Hubers, A., Reedeker, N., Giltay, E., Roos, R., van Duijn, E., & van der Mast, R. (2012). Suicidality in Huntington's disease. *Journal of Affective Disorders, 136*(3), 550-557. doi: 10.1016/j.jad.2011.10.031

Huntington, G. (1872). On Chorea. *The Medical and Surgical Reporter, 26*(15), 217-321.

Huntington Study Group (1996). The Unified Huntington's Disease Rating Scale: Reliability and Consistency. *Movement Disorders, 11,* 136-142.

Jackson, N., & Waters, E. (2005). Criteria for the systematic review of health promotion and public health interventions. *Health Promotion International, 20*(4), 367-374. doi: 10.1093/heapro/dai022

Katrak, P., Bialocerkowski, A.E., Massy-Westropp, N., Kumar, V.S.S., & Grimmer, K.A. (2004). A systematic review of the content of critical appraisal tools. *BMC Medical Research Methodology, 4*(22), 1-11. doi: 10.1186/1471-2288-4-22

Kessler, S. (1987). Psychiatric implications of presymptomatic testing for Huntington's disease. *American Journal of Orthopsychiatry, 57*(2), 212-219.

Kessler, S., Field, T., Worth, L., Mosbarger, H., Opitz, J.M., & Reynolds, J.F. (1987). Attitudes of persons at risk for Huntington disease toward predictive testing. *American Journal of Medical Genetics, 26*(2), 259-270.

Kmet, L.M., Lee, R.C., & Cook, L.S. (2004). *Standard quality assessment criteria for evaluating primary research papers from a variety of fields*: Alberta Heritage Foundation for Medical Research.

Landis, J.R., & Koch, G.G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, 159-174.

Lanska, D.J., Lanska, M.J., Lavine, L., & Schoenberg, B.S. (1988). Conditions associated with Huntington's disease at death: a case-control study. *Archives of Neurology, 45*(8), 878-880.

Larsson, M.U., Luszcz, M.A., Bui, T.H., & Wahlin, T.B. (2006). Depression and Suicidal Ideation After Predictive Testing for Huntington's Disease: A Two-Year Follow-up Study. *Journal of Genetic Counseling, 15*(5), 361-374. doi: 10.1007/s10897-006-9027-6

Lawson, K., Wiggins, S., Green, T., Adam, S., Bloch, M., Hayden, M. R., . . . Ives, E. (1996). Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. *Journal of Medical Genetics, 33*(10), 856-862. doi: 10.1136/jmg.33.10.856

Lindblad, A., Juth, N., Fürst, C.J., & Lynöe, N. (2010). Continuous deep sedation, physician-assisted suicide, and euthanasia in Huntington's disorder. *International Journal of Palliative Nursing, 16*(11), 527-533. doi: 10.12968/ijpn.2010.16.11.80019

Lipe, H., Schultz, A., & Bird, T.D. (1993). Risk factors for suicide in Huntingtons disease: A retrospective case controlled study. *American Journal of Medical Genetics, 48*(4), 231-233.

Mandich, P., Jacopini, G., Di Maria, E., Sabbadini, G., Chimirri, F., Bellone, E., . . . Frontali, M. (1998). Predictive testing for Huntington's disease: ten years' experience in two Italian centres. *The Italian Journal of Neurological Sciences, 19*(2), 68-74.

Mann, J.J., Apter, A., Bertolote, J., Beautrais, A., Currier, D., Haas, A., . . . Marusic, A. (2005). Suicide prevention strategies: a systematic review. *Journal of Amercian Medical Association, 294*(16), 2064-2074. doi: 10.1001/jama.294.16.2064

Marteau, T.M., & Croyle, R.T. (1998). The new genetics: psychological responses to genetic testing. *BMJ: British Medical Journal, 316*(7132), 693.

Martino, D., Stamelou, M., & Bhatia, K.P. (2013). The differential diagnosis of Huntington's disease-like syndromes:'red flags' for the clinician. *Journal of Neurology, Neurosurgery & Psychiatry, 84*(6), 650-656. doi: 10.1136/jnnp-2012-302532

Mastromauro, C., Myers, R. H., & Berkman, B. (1987). Attitudes toward presymptomatic testing in Huntington disease. *American Journal of Medical Genetics, 26*(2), 271-282. doi: 10.1002/ajmg.1320260205

Naarding, P., Kremer, H.P.H., & Zitman, F.G. (2001). Huntingtonˈs disease: a review of the literature on prevalence and treatment of neuropsychiatric phenomena. *European Psychiatry, 16*(8), 439-445. doi: 10.1016/S0924-9338(01)00604-6

Nehl, C., & Paulsen, J.S. (2004). Cognitive and Psychiatric Aspects of Huntington Disease Contribute to Functional Capacity. *Journal of Nervous and Mental Disease, 192*(1), 72-74. doi: 10.1097/01.nmd.0000106004.67587.57

NICE. (2012). *Methods for the development of NICE public health guidance: process and methods guides*. NICE.

Novak, M.J., & Tabrizi, S.J. (2010). Huntington's disease. *British Medical Journal, 340*(4), c3109. doi: 10.1136/bmj.c3109

Orth, M. (2010). Observing Huntington's disease: the European Huntington's disease network's REGISTRY. *Journal of Neurology, Neurosurgery & Psychiatry*. doi: 10.1371/currents.RRN1184

Paulsen, J.S, Ready, R.E., Hamilton, J.M., Mega, M.S., & Cummings, J.L. (2001). Neuropsychiatric aspects of Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 71*(3), 310-314.

Paulsen, J.S., Hoth, K.F., Nehl, C., & Stierman, L. (2005a). Critical periods of suicide risk in Huntington's disease. *American Journal of Psychiatry, 162*(4), 725-731. doi: 10.1176/appi.ajp.162.4.725

Paulsen, J.S., Langbehn, D.R., Stout, J.C., Aylward, E., Ross, C.A., Nance, M., . . . Beglinger, L.J. (2008). Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(8), 874-880. doi: 10.1136/jnnp.2007.128728

Paulsen, J.S., Nehl, C., Hoth, K.F., Kanz, J.E., Benjamin, M., Conybeare, R., . . . Turner, B. (2005b). Depression and stages of Huntington's disease. *Journal of Neuropsychiatry and Clinical Neurosciences, 17*(4), 496-502. doi: 10.1176/jnp.17.4.496

Pompili, M., Forte, A., Palermo, M., Stefani, H., Lamis, D. A., Serafini, G., . . . Girardi, P. (2012). Suicide risk in multiple sclerosis: A systematic review of current literature. *Journal of Psychosomatic Research, 73*(6), 411-417. doi: 10.1016/j.psychores.2012.09.011

Quarrell, O.W. (2008). *Huntington's Disease: The Facts* (Second edition ed.). New York: Oxford University Press.

Ribai, P., Nguyen, K., Hahn-Barma, V., Gourfinkel-An, I., Vidailhet, M., Legout, A., . . . Durr, A. (2007). Psychiatric and cognitive difficulties as indicators of juvenile Huntington disease onset in 29 patients. *Archives of Neurology, 64*(6), 813-819. doi: 10.1001/archneur.64.6.813

Rickards, H., De Souza, J., van Walsem, M., van Duijn, E., Simpson, S. A., Squitieri, F., & Landwehrmeyer, B. (2011). Factor analysis of behavioural symptoms in Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 82*(4), 411-412. doi: 10.1136/jnnp.2009.181149

Robin, N.H. (2008). *Medical Genetics. It's application to Speech, Hearing and Craniofacial Disorders.* Oxfordshire: Plural Publishing Inc.

Robins, E. (1981). *The Final Months: A Study Of The Lives Of 134 Persons Who Committed Suicide* Oxford: Oxford University Press.

Robins Wahlin, T.B. (2007). To know or not to know: A review of behaviour and suicidal ideation in preclinical Huntington's disease. *Patient Education and Counseling, 65*(3), 279-287. doi: 10.1016/j.pec.2006.08.009

Robins Wahlin, T.B., Bäckman, L., Lundin, A., Haegermark, A., Winblad, B., & Anvret, M. (2000). High suicidal ideation in persons testing for Huntington's disease. *Acta Neurologica Scandinavica, 102*(3), 150-161. doi: 10.1034/j.1600-0404.2000.102003150.x

Roos, R.A.C. (2014). Clinical Neurology. In G. Bates, S. J. Tabrizi, S. Tabrizi & L. Jones (Eds.), *Huntington's Disease* (pp. 25-35): Oxford University Press.

Sainsbury, P., & Jenkins, J.S. (1982). The accuracy of officially reported suicide statistics for purposes of epidemiological research. *Journal of Epidemiology and Community Health, 36*(1), 43-48.

Sanderson, S., Tatt, I.D., & Higgins, J.P.T. (2007). Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. *International Journal of Epidemiology, 36*(3), 666-676. doi: 10.1093/ije/dym018

Sarason, I.G., Johnson, J.H., & Siegel, J.M. (1978). Assessing the impact of life changes: development of the Life Experiences Survey. *Journal of Consulting and Clinical Psychology, 46*(5), 932.

Saugstad, L., & Odegard, O. (1986). Huntington's chorea in Norway. *Psychological Medicine, 16*(1), 39-48. doi: 10.1017/S0033291700002518

Schoenfeld, M., Myers, R.H., Cupples, L.A., Berkman, B., Sax, D.S., & Clark, E. (1984). Increased rate of suicide among patients with Huntington's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 47*(12), 1283-1287.

Schwarz, N. (1999). Self-reports: how the questions shape the answers. *American Psychologist, 54*(2), 93.

Sepčić, J., Antonelli, L., Šepić-Grahovac, D., & Materljari, E. (1989). Epidemiology of Huntington's disease in Rijeka district, Yugoslavia. *Neuroepidemiology, 8*(2), 105-108. doi: 10.1159/000110172

Shen, Y.C. (2008). Lamotrigine in motor and mood symptoms of Huntington's disease. *World Journal of Biological Psychiatry, 9*(2), 147-149. doi: 10.1080/15622970701332520

Simpson, G., & Tate, R. (2002). Suicidality after traumatic brain injury: demographic, injury and clinical correlates. *Psychological Medicine, 32*(04), 687-697. doi: 10.1017/S0033291702005561

Smith, T. (2009). Critical appraisal of quantitative and qualitative research literature. *Journal of Medical Radiation Sciences, 56*(3), 6-10.

Sorensen, S.A., & Fenger, K. (1992). Causes od death in patient's with Huntington's disease and in unffected first degree relaties. *Journal of Medical Genetics, 29*(12), 911-914.

Spinney, L. (2010). Uncovering the true prevalence of Huntington's disease. *The Lancet Neurology, 9*(8), 760-761. doi: 10.1016/S1474-4422(10)70160-5

Spitzer, R.L., Endicott, J., Fleiss, J.L., & Cohen, J. A. (1970). The Psychiatric Status Schedule: A technique for evaluating psychopathology and impairment in role functioning. *Archives of General Psychiatry, 23*(1), 41-55.

Starkstein, S.E., Mayberg, H.S., Preziosi, T.J., Andrezejewski, P., Leiguarda, R., & Robinson, R.G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *Journal of Neuropsychiatry and Clinical Neuroscience, 4*(2), 134-139.

Steed, L. (2001). Further validity and reliability evidence for Beck Hopelessness Scale scores in a nonclinical sample. *Educational and Psychological Measurement, 61*(2), 303-316. doi: 10.1177/00131640121971121

Stenager, E.N., & Stenager, E. (1992). Suicide and patients with neurologic diseases: methodologic problems. *Archives of Neurology, 49*(12), 1296-1303.

Tabrizi, S.J., Langbehn, D.R., Leavitt, B.R., Roos, R.A.C., Durr, A., Craufurd, D., . . . Scahill, R.I. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. *The Lancet Neurology, 8*(9), 791-801. doi: 10.1016/S1474-4422(09)70170-X

Tacconelli, E. (2010). Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases, 10*(4), 226.

Thomas, B.H., Ciliska, D., Dobbins, M., & Micucci, S. (2004). A process for systematically reviewing the literature: providing the research evidence for public health nursing interventions. *Worldviews on Evidence-Based Nursing, 1*(3), 176-184. doi: 10.1111/j.1524-475X.2004.04006.x

Thompson, Bruce, Diamond, Karen E, McWilliam, Robin, Snyder, Patricia, & Snyder, Scott W. (2005). Evaluating the quality of evidence from correlational research for evidence-based practice. *Exceptional Children, 71*(2), 181-194.

Thompson, J.C., Harris, J., Sollom, A.C., Stopford, C.L., Howard, E., Snowden, J.S., & Craufurd, D. (2012). Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease. *Journal of Neuropsychiatry and Clinical Neuroscience, 24*(1), 53-60. doi: 10.1176/appi.neuropsych.11030057

Tibben, A., Duivenvoorden, H.J., Vegter-van der Vlis, M., Niermeijer, M F., Frets, P.G., van de Kamp, J.J., . . . Verhage, F. (1993). Presymptomatic DNA testing for Huntington disease: identifying the need for psychological intervention. *American Journal of Medical Genetics, 48*(3), 137-144. doi: 10.1002/ajmg.1320480305

Tooth, L., Ware, R., Bain, C., Purdie, D.M., & Dobson, A. (2005). Quality of reporting of observational longitudinal research. *American Journal of Epidemiology, 161*(3), 280-288. doi: 10.1093/aje/kwi042

Van der Burgh, J.M., Björkqvist, M., & Brundin, P. (2009). Beyond the brain: widespread pathology in Huntington's disease. *The Lancet Neurology, 8*. doi: 10.1016/S1474-4422(09)70178-4

van Duijn, E., Craufurd, D., Hubers, A.A.M., Giltay, E.J., Bonelli, R. M., Rickards, H., . . . Orth, M. (2014). Neuropsychiatric symptoms in a European Huntington's disease cohort (REGISTRY). *Journal of Neurology, Neurosurgery & Psychiatry*, jnnp-2013-307343. doi: 10.1136/jnnp-2013-307343

Vassos, E., Panas, M., Kladi, A., & Vassilopoulos, D. (2008). Effect of CAG repeat length on psychiatric disorders in Huntington's disease. *Journal of Psychiatric Research, 42*(7), 544-549. doi: 10.1016/j.jpsychires.2007.05.008

Von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., & Vandenbroucke, J.P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology

(STROBE) statement: guidelines for reporting observational studies. *Preventive Medicine, 45*(4), 247-251. doi: 10.1136/bmj.39335.541782.AD

Walker, F.O. (2007). Huntington's Disease *Lancet, 369*, 218-228. doi: 10.1016/S0140-6736(07)60111-1

Wetzel, H., Gehl, C.R., Dellefave-Castillo, L., Schiffman, J.F., Shannon, K.M., Paulsen, J.S., & Huntington Study, Group. (2011). Suicidal ideation in Huntington disease: the role of comorbidity. *Psychiatry Research, 188*(3), 372-376. doi: 10.1016/j.psychres.2011.05.006

Wexler, A. (1996). Genetic testing of families with hereditary diseases. *Journal of American Medical Association, 276*(14), 1139-1140.

Wexler, N.S. (2012). Huntington's disease: advocacy driving science. *Annual Review of Medicine, 63*, 1-22. doi: 10.1146/annurev-med-050710-134457

WHO. (2014). *Preventing Suicide: A Global Imperative.* Luxemborg: WHO Library Cataloguing-in-Publication Data.

Witjes-Ané, M.N.W., Zwinderman, A.H., Tibben, A., Van Ommen, G.J.B., & Roos, R.A.C. (2002). Behavioural complaints in participants who underwent predictive testing for Huntington's disease *Journal of Medical Genetics, 39*(11), 857-862. doi: 10.1136/jmg.39.11.857

Wong, M.T., Chang, P.C., Yu, Y.L., Chan, Y.W., & Chan, V. (1994). Psychosocial impact of Huntington's disease on Hong Kong Chinese families. *Acta Psychiatrica Scandinavica, 90*(1), 16-18. doi: 10.1111/j.1600-0447.1994.tb01549.x

Wright, R.W., Brand, R.A., Dunn, W., & Spindler, K.P. (2007). How to write a systematic review. *Clinical Orthopaedics and Related Research, 455*, 23-29. doi: 10.1097/BLO.0b013e31802c9098

Empirical Paper

Disability, Depression and Suicide Ideation in Multiple Sclerosis

Abstract

Background: Research has found depressive symptoms to occur frequently in people with Multiple Sclerosis (MS). Rates of suicide ideation are also increased in this population. 'Rational suicide' is a concept used to describe the presence of suicide ideation in the absence of major depression. It has been suggested as a way of gaining a sense of mastery over the disease.

Rationale: In MS, evidence has been found for a direct association between disability and depression, disability and suicide ideation, and depression and suicide ideation. However, all three variables have not yet been investigated altogether.

Aims: This study therefore explored the relationship between all three variables, examined differences in types of progressive MS, types of disability, and looked for a sub-group of individuals who displayed what is referred to as 'rational suicide'.

Method: Using a cross-sectional study design, standardised questionnaires measuring: disability, depression and suicide ideation were administered to those attending MS out-patient clinics.

Results: Depressive symptoms were found to mediate the relationship between both *perceived* and *actual* physical disability and suicide ideation. There were no differences between types of MS; however, there were significant differences in levels of suicide ideation for different disability types and an identified sub-group of individuals displaying 'rational suicide' for those with lower levels of *perceived* disability.

Conclusion: The findings clearly suggest that as part of routine clinical practice, regular screening is required for both depression and suicide ideation, whilst bearing in mind the disability types for which a higher level of suicide ideation was found.

1. Introduction

1.1 Overview

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system which affects more than two million people worldwide (Kingwell et al., 2013). In the Western world it has been identified as the most frequent cause of progressive neurological disability in young adults (Gunzler et al., 2015). In Europe, for the past three decades, a prevalence rate of 83 people per 100,000 has been estimated (Pugliatti et al., 2006). In the United Kingdom specifically, Mackenzie, Morant, Bloomfield, MacDonald & O'Riordan (2014) identified approximately 236,669 (203.4 per 100,000 population) living with MS in 2010, including 6,003 newly diagnosed that year (9.64 per 100,000 per year). MS has a unique geographical distribution and higher prevalence rates have been found in areas further away from the equator which suggests an environmental influence (Simpson et al., 2011).

The present study explores the relationship between disability, depression and suicide ideation in people with progressive MS. Although the relationship between disability and depression (Smith & Arnett, 2013) and disability and suicide ideation (Viner et al., 2014) and depression and suicide ideation (Turner et al., 2006) have been explored discretely, no studies to date have explored all three factors together, or specifically, whether depression mediates the relationship between disability and suicide ideation. Of additional interest is whether people with specific types of disability report higher levels of suicide ideation and whether there is a sub-group of people with MS who display what is referred to as ‘rational suicide’ (Mayo, 1986). The present paper will begin by outlining the nature of MS.

1.2 Multiple Sclerosis

This progressive, neurodegenerative, immune-mediated disorder, characterised by deterioration of the myelin sheath, is potentially highly disabling and has no known etiology (Pugliatti et al., 2006). Although, an interplay between genetic factors, immune system (Gourraud, Harbo, Hauser, & Baranzini, 2012) and environmental factors have frequently been suggested (Alla & Mason, 2014). The condition is diagnosable via magnetic resonance imaging (MRI) scan, cerebrospinal fluid (CSF) examination or the use of McDonald criteria (Polman et al., 2011).

The disease course is most often categorised into four different types (Hooper, 2013) and irrespective of type, symptoms can vary considerably. Primarily they include: debilitating fatigue, weakness, numbness, tremors, blurred or double vision, pain, problems with mobility and balance, bladder, bowel and sexual dysfunction, mood changes and cognitive deterioration (Hooper, 2013; Hyphantis et al., 2008). The onset of MS typically starts between the ages of 20 and 40 years, it can affect people of all ethnic and cultural backgrounds but is most common in the caucasian race (Bailey, 2010). Women are more than twice as likely to develop the disease as men (Beal, Stuifbergen, & Brown, 2007). Table 1 below describes the different subtypes, followed by an illustration of the pattern of clinical courses in Figure 1.

Table 1. Clinical course of MS

Type	Disease course
Relapsing Remitting Multiple Sclerosis (RRMS)	A purely relapsing–remitting disease course, including minor remissions (Pugliatti et al., 2006). Outside of individual relapses it is characterised by the absence of worsening neurological function (Tutuncu et al., 2012). RRMS can include full recovery in between relapses (Feinstein, 2007). 85% begin their disease course with this form (Hooper, 2013).
Primary Progressive Multiple Sclerosis (PPMS)	Progression/increasing disability from onset with plateaus and possible minor improvements (Pugliatti et al., 2006). 10% (approx.) of people with MS are diagnosed with PPMS (Hooper, 2013). It has been suggested that this type portends a worse prognosis than other disease courses (Kantarci et al., 1998).
Secondary Progressive Multiple Sclerosis (SPMS)	If a progressive disease course follows a period of symptomatic relapses (RRMS) this is referred to as SPMS (Tutuncu et al., 2012). Two thirds (approx.) of those diagnosed with RRMS will transition to SPMS, usually 10-15 years after diagnosis (Hooper, 2013).
Progressive Relapsing Multiple Sclerosis (PRMS)	Progressive disease from onset: there are clear acute relapses of which there may or may not be a full recovery and periods between relapses which are characterised by continuing progression (Pugliatti et al., 2006). This is a rare form of MS affecting approximately 5% (Hooper, 2013). NB. The disease course is often more simply categorised into RRMS, SPMS and PPMS - it can be unclear however, as to whether PRMS courses are classified as RRMS or PPMS (Pugliatti et al., 2006).

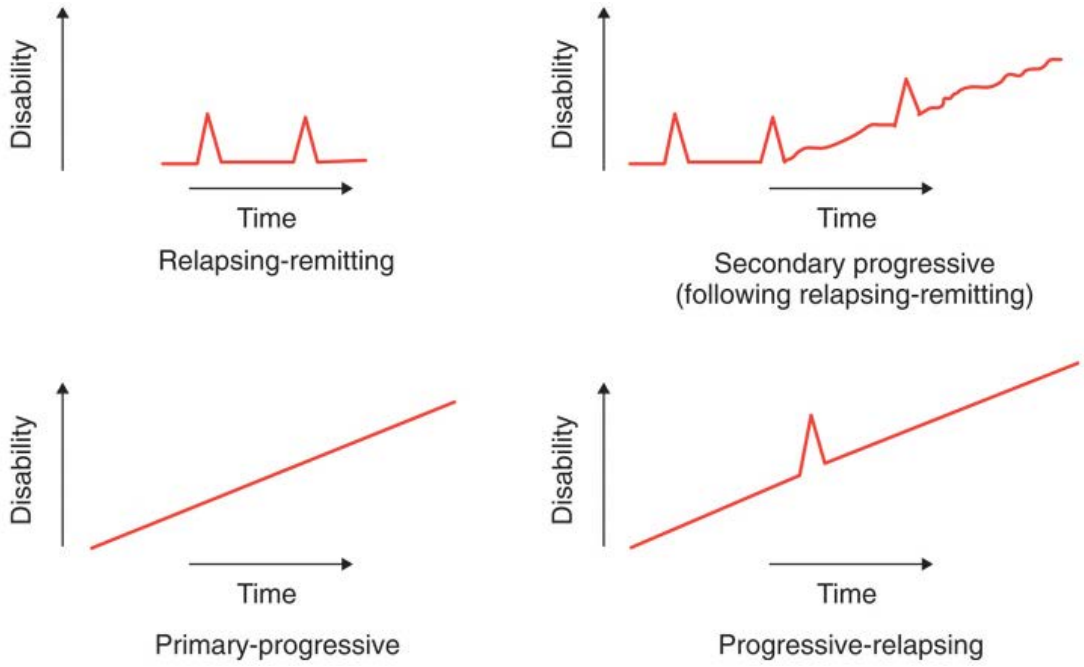


Figure 1. The four different clinical courses of MS from Lublin and Reingold (1996)

Disease modifying drugs which target inflammation, are immunosuppressive and reduce relapses for those with RRMS; however, the same drugs are not effective with

progressive MS disease types (Coetzee, Zaratin & Gleason, 2015). For these types where the management of the disease involves the use of alternative drugs and rehabilitation, the main aim is to improve function and minimise symptoms, rather than to reduce progression (Feinstein, Freeman & Lo, 2015).

As those with SPMS initially experience definite periods of relapse, for which there is disease modifying treatment, this suggests that there could be a difference in the emotional adaption between those with PPMS and SPMS. Only one study appears to have investigated this (Vleugels et al., 1998) and found that those with SPMS were experiencing higher levels of depression. Two explanations were suggested for the significant difference. Firstly because the period of RRMS is substantial (often around 15 years) this means that those with SPMS may have had less time to adjust to the progressive diagnosis. Secondly, because those with SPMS had experienced relapses for which the occurrence was uncertain, those with PPMS were more likely to have known the rate at which the condition was likely to deteriorate and therefore knew what to expect (Vleugels et al., 1998). A weakness of that study however is that that when comparing the two groups, those with PPMS were older, had experienced MS for longer and reported a higher level of disability. Therefore, the present study will also examine differences in levels of depressive symptoms and suicide ideation for different MS types.

With regards to the pathology, PPMS has been reported to resemble SPMS although there is known to be a higher level of inflammation in SPMS (Revesz, Kidd, Thompson, Barnard, & McDonald, 1994). In PPMS, an unfavourable outcome is predicted due to the rapid progression of disability (Ebers, 2004). With regards to both PPMS and SPMS, the rate of disease progression in both has actually been found to be comparable (Kuhlman, 2013; Soldán et al., 2015). In progressive MS types, where there is a higher level of increasing

disability compared to RRMS, this has been associated with higher levels of depression and suicide ideation (Chwastiak et al., 2002; Dennis et al., 2009; Sarısoy, Terzi, Gümüş, & Pazvantoğlu, 2013; Turner et al., 2006). For this reason, the progressive MS types will be the focus of investigation in this research study.

1.3 Depression and suicide in MS

Depressive symptoms occur frequently in people with MS (Dalgas et al., 2014) and are referred to as a significant problem in this condition (Gay, Vrignaud, Garitte & Meunier, 2010). Around half of people with MS will develop depression at some point in their lifetime (Minden & Schiffer, 1990; Sadovnick et al., 1996). This is three times higher than the risk of depression reported in the general population (Kessler et al., 1994). Explanations for such high rates in this population have been linked to: an early age of onset, increased social stressors and a lack of family and community support (Feinstein, Kartsounis, Miller, Youl & Ron, 1992). Fatigue and cognitive impairment have also been implicated as factors; however, findings are conflictual (Siegert & Abernethy, 2005).

Other risk factors in this population associated with depression include: hopelessness, a history of alcohol abuse, relationship difficulties, ineffective coping strategies (Feinstein et al., 1992); the psychosocial effects of disability, brain lesions on structures involved in mood regulation and immune dysfunction (Wallin, Wilken, Turner, Williams & Kane, 2006). Elevated levels of cytokines which coordinate communication between cells of the immune system (Imitola, Chitnis, & Khoury, 2005) are implicated in higher degrees of disability associated with MS (Kaplin, 2011) and the development of depressive symptoms in adults in the general population (Gold & Irwin, 2006). It has been debated as to whether the effects of disease modifying drugs such as interferons (IFNs) can cause both depression and suicide ideation. However, despite initial concerns (Multiple Sclerosis Study Group, 1993) the major

risk factor has been suggested to be a history of depression prior to use of IFNs (Feinstein, O'Connor & Feinstein, 2002; Mohr et al., 1999).

Suicide rates in the MS population have been found to be twice the rate of the general population (Bronnum-Hansen, Stenager, Stenager & Kock-Henriksen, 2005; Koch-Henriksen, Brønnum-Hansen & Stenager, 1998; Stenager et al., 1992). One study reported completed suicide in MS to occur at a rate 7.5 times higher (Sadovnick, Eisen, Ebers & Paty, 1991) and another reported that over a quarter of people with MS experience suicide ideation (Feinstein, 2002). In retrospective cohort studies the risk of suicide was found to be higher for males (Bronnum-Hansen et al., 2005; Fredrikson, Cheng, Jiang & Wasserman, 2002), males with onset before the age of 30, males and females over 40 (Stenager et al., 1992), those with previous suicidal behaviour (Stenager, Koch-Henriksen & Stenager, 1996), within one year of diagnosis (Fredrikson et al., 2002), within the first five years of the disease (Bronnum-Hansen et al., 2005) and for those reporting anxiety (Korostil & Feinstein, 2007).

To date, there are only three prospective studies investigating risk factors for suicide ideation in MS. Feinstein (2002) found that those with suicide ideation were more likely to live alone, report higher anxiety and social stress, misuse alcohol and have a lifetime diagnosis of major depression. Turner et al. (2006) found depression to be the single best predictor of suicide ideation in MS and the following to be significantly associated: a younger age, an earlier disease course, progressive disease type, a lower income, being unmarried, lower social support, not being ablt to drive and higher levels of depression and physical disability (mobility, bowel and bladder difficulties). However, Viner et al. (2014) highlighted weaknesses in the latter study because it used a cross-sectional design and identified no modifiable determinants (except potentially for bowel incontinence) which persisted after adjustment for depression. They therefore carried out a study which included a six month

follow-up, adjusted for depressive symptoms and found the following to be significantly associated with suicide ideation: being aged 65 or over, having lower self-efficacy, lower levels of coping, self reported bladder and bowel symptoms and difficulties with speaking and swallowing (Viner et al., 2014). There is also a weakness in this study because a standardised and validated measure of disability was not utilised.

It is of concern that depression in MS, which has been linked to suicidality (Carson, Best, Warlow & Sharpe, 2000), can often be left undetected and untreated (Feinstein, 2004; Patten, Beck, Williams, Barbui & Metz, 2003). This may be due to a difficulty in distinguishing depression from the common symptoms of MS, for example, fatigue and cognitive dysfunction, both of which can be observed in MS without the presence of depressive symptoms (Siegert & Abernethy, 2005). Similarly, Caine and Schwid (2002) postulated that cases of suicidal ideation in MS may also remain unidentified because the assessment process can be complicated by patients superficially reassuring clinicians that they will not harm themselves, because they do not wish to disclose suicide ideation.

1.4 The impact of disability on depression in MS

The findings of a systematic review by Arnett, Barwick and Beeney (2008) investigating the relationship between physical disability and depression in MS suggested equivocal findings. Null findings were reported by eleven studies and for five of these studies the main weakness was small sample size. One study used a non-standardised measure of disability but five used standardised measures and had a reasonable sample size. Conversely, eleven studies reported statistically significant findings suggesting increased disability is related to depression with effect sizes in the moderate range. Since this review, several other studies have confirmed this finding (Anhoque, Domingues, Carvalho, Teixeira & Domingues,

2011; Arnett et al., 2008; Beal et al., 2007; da Silva et al., 2011; Gay et al., 2010; Sarısoy et al., 2013; Smith & Arnett, 2013).

1.5 The impact of disability on suicide ideation in MS

In the general population, evidence for a linear relationship between disability and suicide ideation has been found (Dennis et al., 2009; Meltzer et al., 2012; Park et al., 2014). Those with major disabling conditions, such as MS, have an increased risk of suicide as touched upon above (Giannini et al., 2010). However, there is a lack of research investigating the association between disability and suicide ideation in MS. Two studies which investigated risk factors associated with completed suicide, found that those with a moderate level of disability were most at risk (Stenager et al., 1996) as well as those who were more severely disabled (Berman & Samuel, 1993).

The more recent of two studies investigating the association between disability and suicide ideation reported self-reported bladder or bowel difficulties, and communication and swallowing difficulties to be risk factors (Viner et al., 2014). The earlier study by Turner et al. (2006) found mobility, bladder and bowel functioning to be associated with suicide ideation as well as a higher level of *perceived* physical disability. In fact, assessing a person's own perspective of disability is important (Turk, Okifuji & Scharff, 1995) and there are an increasing number of studies incorporating these measures (Freeman et al., 2001). For example, it has been found in a study exploring obesity related disability, that level of *perceived* disability can be different to *actual* physical limitation (Larsson & Mattsson, 2001). Therefore, the present study will explore both self-reported disability and the degree to which this is seen as a problem for the person.

1.6 Rational suicide

It has been suggested that people can freely desire suicide or a hastened death, based upon a logical, carefully contemplated decision in the absence of depression or psychiatric difficulties, referred to as 'rational suicide' (Onkay-Ho, 2014). Further criteria for rational suicide have been defined as: "(i) the presence of an unremittingly hopeless condition, (ii) a suicidal decision made as a free choice and (iii) the presence of an informed decision-making process" (Werth & Cobia, 1995, p. 1). It is well recognised that suicide ideation is a core symptom of major depression (Pompili et al., 2012). However, in the MS population not all suicides have been found to occur in the context of depressive symptoms (Sadovnick et al., 1991). Caine and Schwid (2002) advised that the absence of suicide ideation should not be presumed if there is no evidence of depression. In fact, suicide ideation has been found to be present in a psychiatric population with even very mild forms of depression (Babigian & Odoroff, 1969).

In a MS specific study, Gaskill, Foley, Kolzet and Picone (2011) found a perceived loss of control to be associated with suicide ideation and suggested that suicide ideation could provide a fall back means of still feeling in control for people faced with the burden of an unpredictable disease. This supports earlier research with a Huntington's population (Lipe, Schultz & Bird, 1993) explaining suicide as a rational but extreme decision to escape the disease. Similarly, Siegel and Meyer (1999) described suicide ideation following diagnosis of Human Immunodeficiency Virus (HIV), as a way of gaining a sense of mastery to overcome the potentially debilitating and life threatening diagnosis. Therefore, this present study will also explore whether there is a subgroup of people with suicide ideation with only a minimal or mild level of depression.

1.7 Summary

The relationship between all three variables together (disability, depression and suicide ideation) has not been investigated in the MS population although, Meltzer et al. (2012) found depression to mediate the relationship between disability and suicide ideation in the general population. Previous research has reported the relationship between disability and depression to be robust. However, the literature investigating the association between disability and suicide ideation and depression and suicide ideation in MS is sparse. There are only three studies looking at the direct relationships.

With regards to depression and suicide ideation, all three found a significant association. However, looking at the relationship between disability and suicide ideation one did not find a significant association between level of disability and suicide ideation (Feinstein, 2002) and there are methodological weaknesses with the other two, which did find significant associations. Feinstein (2002) measured suicide ideation by using three self-report questions derived from the Beck Suicide Scale (Beck and Steer, 1993), the psychometric properties for extracting these three questions are unknown. Similarly, Viner et al. (2014) used a self-designed measure for disability rather than a standardised and validated measure and both (Turner et al., 2006; Viner et al., 2014) assessed suicide ideation by selecting one single item from the Patient Health Questionnaire (PHQ-9) (Kroenke & Spitzer, 2002), a measure for which good psychometric properties are only applicable when all items are administered.

1.8 Aims of the present study

1. To explore the relationship between disability, depression and suicide ideation, specifically, do depressive symptoms mediate the relationship between *perceived* disability and suicide ideation?
2. To explore the relationship between disability, depression and suicide ideation, specifically, do depressive symptoms mediate the relationship between *actual* physical disability and suicide ideation?
3. Based on the work of Vleugels et al. (1998) do levels of depressive symptoms and suicidal ideation differ between certain types of progressive MS?
4. Based on the work of Turner et al. (2006) and Viner et al. (2014) is any specific area of disability related to suicide ideation?
5. Based on the work of Onkay-Ho (2014) is there a sub-group of individuals who report suicide ideation with only a minimal or mild level of depressive symptoms?

1.9 Clinical relevance

Suicide ideation in people with disabilities is a complex and imperative health concern (Giannini et al., 2010). Specifically in those with MS, the presence of depression is known to have a significant impact upon both quality of life, general health (Feinstein, 2007; Fruewald, Loeffler-Stastka, Eher, Saletu & Baumhacki, 2001; Lester, Stepleman & Hughes, 2007) and adherence to treatment (Mohr, Goodkin, Gatto & Van Der Wende, 1997). Depression is a key predictor of suicide risk in MS (Paparrigopoulos, Ferentinos, Kouzoupis, Koutsis & Papadimitriou, 2010). Attending to depression and suicidality in MS is therefore, a medical priority, to the extent that suicide may be an avoidable tragedy (Faber, 2003). Suicide ideation can be an experience which is highly distressing and clinical research in this area is

crucial (Coughlin & Sher, 2013). If increasing levels of disability are found to be important or any specific type of MS or area of disability found to be a ‘red flag’ for depression and hence suicide, it will be important for clinicians to screen this group in particular in the future.

2. Method

2.1 Design

A cross-sectional study design was utilised.

2.2 Ethical approval

Full ethical approval was received from the West Midlands branch of National Research Ethics Committee and the Research and Development departments of the trusts from which participants were recruited. See Appendices I and II.

2.3 Participants

Participants were recruited from two local out-patient MS clinics in Birmingham. The first was a MS specialist rehabilitation clinic for people with complex needs which had increased following a progression of their condition, warranting a specialist referral from a medical professional for disability management. The team consisted of: a consultant in rehabilitation medicine; MS nurses; physiotherapists; and occupational therapists. The second clinic was a specialist MS clinic in an acute hospital which monitored all patients in the local area with MS. The team consisted of: neurologists; MS nurses; physiotherapists; occupational therapists; dieticians; and speech and language therapists. At both clinics, the regularity of appointments varied depending upon the needs of the patient and the severity of the condition, with some patients only requiring annual review.

Seventy-five participants with progressive MS participated in the study. Information about response rate and non-responders was not available. All participants were asked to provide the following information: sex, ethnicity, age, age at onset, age at diagnosis, marital and living status, education and employment details, type of MS, the use of a catheter and/or

wheelchair, the use of disease modifying medication or anti-depressants, a history of depression or suicidality, family history of depression or suicidality, current or history of alcohol misuse, a history of mental health problems and current physical co-morbid conditions. This was collated and is summarised in the results section.

2.4 Inclusion and exclusion criteria

See Table 2 below.

Table 2. Inclusion and exclusion criteria

Criteria
Inclusion
1. A diagnosis of progressive MS following neurological examination, CSF examination or MRI scan and determined by the McDonald criteria (Polman et al., 2011).
2. Cognitive ability to provide informed consent to participate in the study.
3. Sufficient command of English language to complete the study measures with the researcher.
4. Age at least 16 years.
Exclusion
1. Current severe mental health problems other than depression (which could impact upon ability to provide fully informed consent to participate).

2.5 Recruitment

Participants were recruited between March 2013 and March 2015 from the MS specialist rehabilitation clinic (n = 70) and between August 2014 and March 2015 (n = 5) from the MS clinic in the acute hospital. MS clinic staff used an NHS database listing patient information to identify those who met the inclusion criteria. Potential participants were then invited to participate in the research by one of the clinicians, either in person during attendance at a review appointment, over the telephone or by postal invite. In all cases, a

participant information sheet and expression of interest form were provided by the clinicians (Appendices III and IV). If participants expressed an interest to the clinician in taking part then they were telephoned by a researcher no sooner than 48 hours later and were offered an appointment if they wished to proceed.

2.6 Measures

Beck Suicide Scale (BSS) (Beck & Steer, 1993) (Appendix V) was used to measure suicide ideation. The highest total possible score is 42 and the higher the score the higher the level of suicide ideation.

Beck Depression Inventory (BDI-II) (Beck, Steer & Brown, 1996) (Appendix VI) was used to measure depressive symptoms. The highest total possible score is 63 and the higher the score the higher the level of depressive symptoms. There are clinical cut off points to categorise the level of depression: mild = 14-19, moderate = 20-28. Severe = 29-63.

Multiple Sclerosis Impact Scale (MSIS-29) (Hobart, Lamping, Fitzpatrick, Riazi & Thompson, 2001) (Appendix VII) was used to measure *perceived* disability assessing how much the respondent is 'bothered' by specific areas of disability. The highest total possible score is 145, the higher the score the higher the level of disability. *Perceived* physical impact is assessed in 20 questions (highest possible score: 100) and *perceived* psychological impact is assessed in 9 questions (highest possible score: 45).

Guys Neurological Disability Scale (GNDS) (Sharrack & Hughes, 1999a) (Appendix VIII) was used to measure *actual* disability, the highest total possible score is 60. All measures have been used previously in MS research and are described in further detail in Appendix IX. Each measure was chosen based upon its clinical relevance, applicability and robust psychometric properties, details of which are detailed in Appendix X.

2.7 Procedure

Data collection was carried out either at the MS clinic or at the participant's own home. Each participant was given an opportunity to ask questions and then asked to sign a consent form (Appendices XI). Demographic data was collected followed by the four measures assessing: suicide ideation, depression, *perceived* disability and *actual* physical disability, in this order. Many participants had visual difficulties and so each question was read out by the researcher. One participant with a hearing impairment required the use of an interpreter. All other participants completed the measures independently.

Following completion of the suicide ideation measure, if any suicidal thoughts were disclosed a thorough risk assessment was completed by the researcher, including clinical questions used to determine the level of suicide ideation and whether the participant had formulated a plan to take their own life. When there was an immediate concern, the participant was not left alone and a duty psychiatrist was contacted via the participant's general practitioner (GP) and requested to visit the participant. When there was concern but not of such an immediate level, the respective clinic was informed on the same day and a decision was made as to whether to: contact the participant's GP and/or make a referral for talking therapy. A referral for the latter was offered to 13 participants. One participant was already receiving therapeutic support.

2.8 Analysis

IBM SPSS: version 21 was used to analyse the data. The main analysis was a mediation model (Preacher & Hayes, 2008; Preacher & Hayes, 2004).

3. Results

3.1 Demographic and clinical characteristics

The sample consisted of 31 males and 44 females, with an average age of 55 years (*SD* = 10.08, range: 38-79). The average age of onset was 33 years (*SD* = 11.62, range: 13-68) and the average time since onset was 23 years (*SD* = 12.48, range: 5-55). Table 3 below displays additional demographic and clinical characteristics.

Table 3. Demographic and clinical characteristics of participants

Demographic/clinical characteristics	*n* =
Marital status:	
Married	33
Separated	3
Divorced	16
Widowed	5
Partner	3
Single	15
Living status:	
Alone	22
With at least one other	53
Education:	
<12 years	45
≥12 years	30
Employment:	
Employed (part or full time)	11
Long term sick	1
Volunteer	2
Unemployed	61
Urinary catheter (permanent or temporary)	35
Wheelchair:	
All the time	31
For going out	31
Disease modifying medication	1
Anti-depressants	15
A history of depression	47
A history of suicidality:	
Suicide ideation	11
One attempt	4
Three attempts	2
Eleven attempts	1
A family history of depression	22
A family history of suicidality*	13
A current or history of alcohol misuse	8
A history of mental health problems:	
Psychosis	1
Anxiety	4

Co-morbid condition:	1
Arthritis & scoliosis	1
Asthma	1
Type one diabetes	1
Type two diabetes	1
Epilepsy and Meniere's disease	2
Heart problems	1
High blood pressure	1
Osteoarthritis	3
Mild stroke >6months ago	1
Parkinson's disease	2
Underactive thyroid	

*Thoughts, attempts, or completions.

There were 26 participants with a diagnosis of PPMS and 49 had a diagnosis of SPMS. The PPMS sample consisted of 14 males and 12 females, with an average age of 55 years (*SD* = 9.66, range: 38-79). The average age of onset was 30 years (*SD* = 9.72, range: 13-58) and the average time since onset was 19 years (*SD* = 15.00, range: 5-55). The SPMS sample consisted of 20 males and 29 females, with an average age of 58 years (*SD* = 10.67, range: 38-76). The average age of onset was 39 years (*SD* = 12.9, range: 15-68) and the average time since onset was 25 years (*SD* = 10.64, range: 5-55).

3.2 Descriptive statistics

Table 4 below shows descriptive statistics for each measure including Cronbach's alpha (for all participants, PPMS and SPMS). Excellent internal reliability was found for all measures, the lowest being for the GNDS.

Table 4. Measures of central tendency and reliability

Measure	*M*	*SD*	*Mdn*	Mode	Range	Cronbach's alpha
All participants (N = 75):						
BSS (*max score 42)*	2.44	5.67	0.00	0.00	0.00-35.00	0.93
BDI-II *(max score 63)*	13.8	8.88	13.00	9.00	0.00-39.00	0.88
MSIS-29 *(max score 145)*	86.75	25.36	88.00	71.00	14.00-22.00	0.93
MSIS (physical subscale) *(max score 100)*	64.71	19.27	65.00	46.00	0.00-96.00	0.91
MSIS (psychological subscale) *(max score 45)*	21.91	8.32	20.00	19.00	9.00-41.00	0.85
GNDS *(max score 60)*	24.73	8.92	24.00	23.00	1.00-49.00	0.71
PPMS (n = 26):						
BSS (*max score 42)*	0.92	2.98	0.00	0.00	0.00-15.00	0.93
BDI-II *(max score 63)*	13.31	7.97	13.50	60.0	1.00-32.00	0.86
MSIS-29 *(max score 145)*	83.30	26.19	88.50	60.0	2.00-126.00	0.93
MSIS (physical subscale) *(max score 100)*	62.31	21.43	60.00	65.00	0.00-91.00	0.92
MSIS (psychological subscale) *(max score 45)*	21.04	8.17	20.50	22.00	10.00-37.00	0.89
GNDS *(max score 60)*	23.08	10.55	22.00	20.00	1.00-49.00	0.81
SPMS (n = 49):						
BSS (*max score 42)*	3.24	6.56	0.00	0.00	0.00-35.00	0.94
BDI-II *(max score 63)*	14.06	9.40	13.00	9.00	0.00-39.00	0.89
MSIS-29 *(max score 145)*	88.55	25.00	87.00	71.00	45.00-140.00	0.93
MSIS (physical subscale) *(max score 100)*	34.00	18.12	65.00	46.00	36.00-69.00	0.91
MSIS (psychological subscale) *(max score 45)*	22.37	8.44	19.00	19.00	9.00-41.00	0.84
GNDS *(max score 60)*	25.60	7.91	26.00	26.00	9.00-43.00	0.62

Following the same procedure described in previous studies, for example Crane, Shah, Barnhofer and Holmes (2012) participants were split into two groups according to their BSS score: 49 participants reported no suicide ideation (BSS score = 0) and 26 reported some level of suicide ideation (BSS score ≥1). The mean score of depressive symptoms for all

participants just meets the clinical category of 'mild' according to the BDI-II manual. The numbers of participants in each clinical category were: minimal = 37, mild = 21, moderate = 11 and severe = 6. Table 5 and 6 below, display descriptive statistics for each item of the MSIS-29 and the GNDS.

Table 5. Descriptive statistics for MSIS-29 areas of *perceived* disability

Area of disability	*M*	*SD*
Physical subscale:		
Physically demanding tasks	3.99	1.21
Gripping things tightly	3.13	1.43
Carrying things	3.93	1.32
Balancing	3.48	1.62
Moving about indoors	3.23	1.57
Being clumsy	3.21	1.39
Stiffness	3.47	1.34
Heavy limbs	3.45	1.45
Tremors	2.53	1.44
Spasms	2.95	1.34
Body not doing what you want	3.76	1.31
Having to depend on others	3.75	1.40
Limitations in social/leisure	3.17	1.57
Being stuck at home	3.03	1.59
Difficulty using hands	3.33	1.52
Having to cut down on things	3.09	1.55
Problems using transport	2.52	1.70
Taking longer to do things	3.32	1.46
Difficulty doing things spontaneously	3.55	1.39
Toilet urgency	2.71	1.56
Psychological subscale:		
Feeling unwell	2.52	1.37
Problems sleeping	2.17	1.37
Mental fatigue	2.61	1.32
Worries about MS	2.51	1.42
Anxiety and tension	2.36	1.40
Irritability	2.60	1.32
Problems concentrating	2.57	1.38
Lack of confidence	2.57	1.47
Feeling depressed	1.99	1.22

Table 6. Descriptive statistics for GNDS areas of *actual* physical disability

Area of disability	*M*	*SD*
Memory	1.81	1.64
Mood	1.43	1.47
Vision	0.87	0.91
Speech	0.92	1.12
Swallowing	1.24	1.47
Arms	2.90	1.50
Mobility	4.01	1.05
Bladder	2.93	1.81
Bowel	1.75	1.81
Fatigue	2.19	1.70
Sexual	3.21	2.06
Other[3]	1.47	1.33

3.3 Preparation for analysis

Kolomogorov-Smirnov (K-S) tests were used to see if the distribution of scores for each measure differed significantly from a normal distribution. Scores from the BSS and BDI-II were not normally distributed and scores from the MSIS-29 and GNDS were normally distributed. In the PPMS sample distributions of scores were normally distributed for all measures except the BSS and in the SPMS sample distributions of scores were normally distributed for all measures except the BSS and BDI-II. Demographic variables were normally distributed. See Appendix XII for SPSS outputs.

3.4 Results for each aim

The results for each aim will be reported one by one in the next section.

[3] The item 'other' refers to any other types of problems not already asked about. Responses included: pain, dizziness, spasms, balance and stiffness.

3.4.1 Aim 1: do depressive symptoms mediate the relationship between perceived disability and suicide ideation?

In order to explore the relationship between disability, depressive symptoms and suicide ideation, mediation analysis procedures were used to examine the potential mediating effects of depressive symptoms (Preacher & Hayes, 2008; Preacher & Hayes, 2004). This particular strategy reports bias corrected bootstrap confidence intervals which are robust to violation of parametric inference assumptions and therefore overcomes the problem of non-normality as described above and provides robust confidence intervals in smaller sample situations (Hardle & Marron, 1991; Moore & McCabe, 2005). Furthermore, given this is a clinical population, it cannot be assumed that the reference population itself has a normal distribution of scores so the decision was taken that it would be inappropriate to correct the sample distributions for normality.

Traditionally, the use of non-parametric statistical procedures has been recommended for such data (Coolican, 2014; Giles, 2014). However, for inferential tests, non-parametric procedures are associated with a loss of statistical power (Howell, 2012) and there is no direct non-parametric equivalent test for mediation analysis. A loss of statistical power can increase substantially the risk of type II errors in smaller samples (Heiman, 2001). Therefore, in this analysis where variables show deviation from normality, traditional asymptotic probability estimates will be strengthened by bootstrap parameter estimates and associated 95% confidence intervals.

The model calculates the tests of significance of the mediation pathway and the coefficient. If the 95% confidence intervals of the parameter and the mediation test do not pass through zero, then they can be considered statistically significant. Prior to the analysis,

in order to standardise the regression parameters and to enable direct comparison between parameter coefficients within the mediation model, all of the variables were transformed into *z* scores ($M = 0$, $SD = 1$).

Table 7 below displays the outcomes of the mediation analysis for *perceived* disability and Figure 2 below displays the model. SPSS outputs are included in Appendix XIII.

Table 7. Outcome of mediation analysis for *perceived* disability

	Path Estimate β	Standard Error SE	p value	Lower 95% Bootstrap Confidence Interval	Upper 95% Bootstrap Confidence Interval
Model: *Perceived* disability -> Depression -> Suicide ideation					
Direct effect in the unmediated model=**C**	0.42	0.16	0.01	0.9	0.74
Direct effect in the mediated model =**C′**	0.10	0.11	0.40	-0.13	0.33
Mediator (depression) =**M1**	0.32	0.15	NA	0.12	0.73
Path to mediator =**A1**	0.66	0.10	0.00	0.46	0.87
Path from mediator =**B1**	0.48	0.22	0.03	0.05	0.91

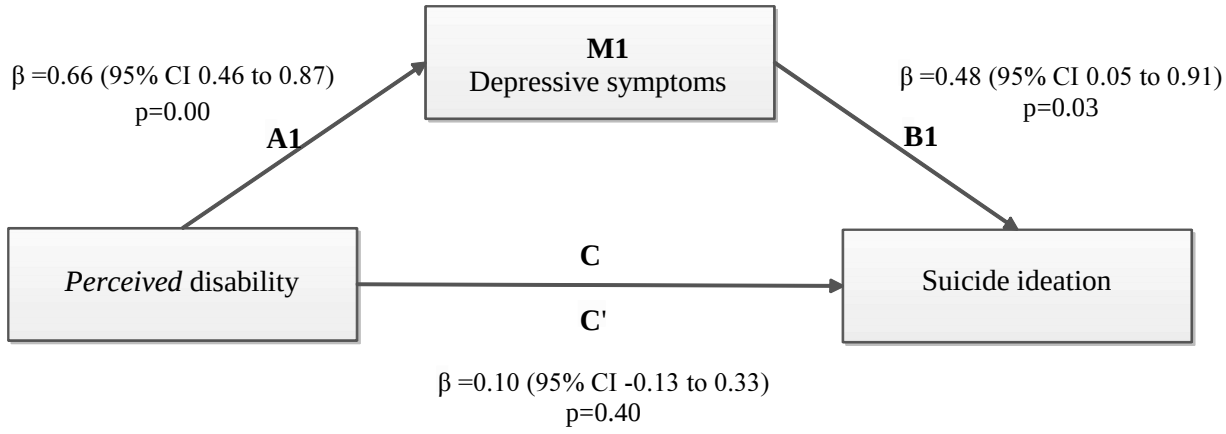


Figure 2. The mediating effect of depressive symptoms upon *perceived* disability and suicide ideation

In the unmediated model, the effect of *perceived* disability on suicide ideation was significant (**C**). This was reduced (**C′**) when the mediating effect of depressive symptoms was included in the analysis, accounting for approximately 32% of the original relationship

between *perceived* disability and suicide ideation (**M1**). Significant path coefficients were reported for both the path to the mediator variable (**A1**) and from the mediator variable to suicide ideation (**B1**). Accordingly, a complete mediation effect was observed.

3.4.2 Aim 2: do depressive symptoms mediate the relationship between *actual* physical disability and suicide ideation?

Table 8 below displays the outcomes of the mediation analysis for *actual* physical disability and Figure 3 displays the model. SPSS outputs are included in Appendix XIV.

Table 8. Outcome of mediation analysis for *actual* disability

	Path Estimate β	Standard Error SE	p value	Lower 95% Bootstrap Confidence Interval	Upper 95% Bootstrap Confidence Interval
Model: *Actual* disability -> Depression -> Suicide ideation					
Direct effect in the unmediated model =**C**	0.36	0.18	0.05	0.04	0.72
Direct effect in the mediated model =**C′**	0.05	0.11	0.63	-0.17	0.28
Mediator (depression) =**M1**	0.31	0.12	NA	0.13	0.61
Path to mediator =**A1**	0.60	0.10	0.00	0.41	0.80
Path from mediator =**B1**	0.51	0.19	0.01	0.14	0.89

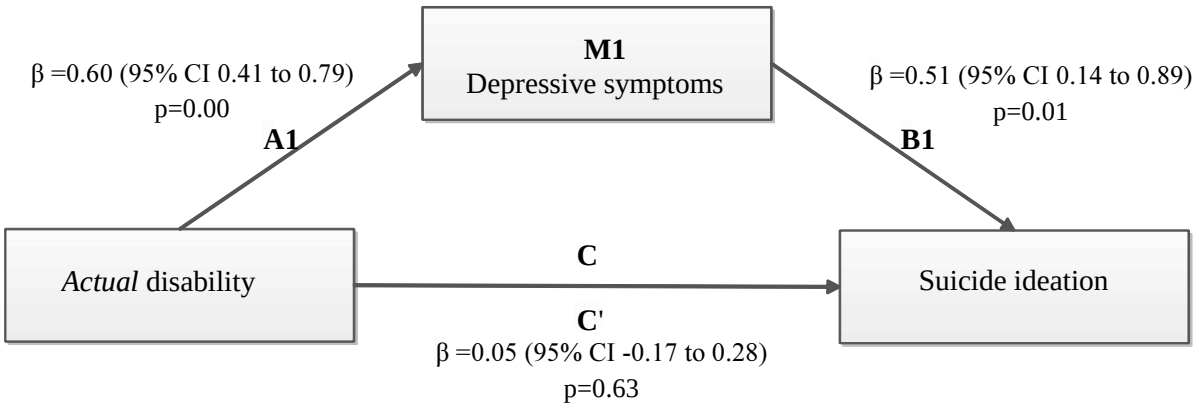


Figure 3. The mediating effect of depressive symptoms upon *actual* physical disability and suicide ideation

In the unmediated model, the effect of *actual* disability on suicide ideation was significant (**C**). This was reduced (**C′**) when the mediating effect of depressive symptoms was included in the analysis, accounting for approximately 31% of the original relationship between *actual* physical disability and suicide ideation (**M1**). Significant path coefficients were reported for both the path to the mediator variable (**A1**) and from the mediator variable to suicide ideation (**B1**). Accordingly, a complete mediation effect was observed.

3.4.3 Post-hoc power analysis.

Fritz and MacKinnon (2007) provide a Monte Carlo simulation of the sample size required to detect mediation effects using a range of different methodologies for estimating mediation for example Baron and Kenny (1986) and Sobel (1982). Additionally, this paper provides sample size estimates for percentile bootstrap and bias corrected bootstrap estimation, see Appendix XV.

Using bias corrected bootstrap:

1. A sample size of 54 participants would provide power of 0.8 to detect a mediated relationship with one medium and one large effect path coefficient.
2. A sample size of 71 would allow for the detection of two medium path sizes.
3. A sample size of 34 individuals would allow the detection of two large path sizes.
4. Small associations of lesser magnitude would not be considered of clinical relevance.

Accordingly, a sample size of 75 provided a good compromise between efficiency and clinical utility. For *perceived* disability the path sizes were: $\beta = 0.66$ (large) and $\beta = 0.48$ (medium). For *actual* physical disability the path sizes were: $\beta = 0.60$ (large) and $\beta = 0.51$ (medium).

3.4.4 Aim 3: based on the work of Vleugels et al. (1998) do levels of depressive symptoms and suicidal ideation differ between certain types of progressive MS?

Two Mann-Whitney tests were carried out as the distributions for depressive symptoms and suicide ideation were non-normal. Tests showed that there were no significant differences in BSS and BDI-II scores between PPMS (n = 26) and SPMS (n = 49). In order to check for any other differences between the two groups, independent t-tests were carried out as distributions for disability and demographics were normal. There were no other significant differences between disability and demographics for PPMS and SPMS.

3.4.5 Aim 4: based on the work of Turner et al. (2006) and Viner et al. (2014) is any specific area of disability related to suicide ideation?

As distributions for disability measures were normal, a series of independent-sample t-tests were carried out. Bonferroni adjustments to account for multiple testing were not administered as this is an exploratory question (Bender and Lange, 1999). Participants were categorised as either: no suicide ideation (a score of 0 on the BSS, n = 49); or suicide ideation (a score ≥1 on the BSS, n = 26). Table 9 below displays the significant and non-significant differences for *perceived* disability. The higher the score, the higher the impact of disability.

Table 9. Comparing no suicide ideation and suicide ideation for areas of *perceived* disability

Area of disability	*M*	*SD*	*t*(73)	*p*
Physical subscales:				
Physically demanding tasks				
No suicide ideation	3.96	1.22	-0.27	0.98
Suicide ideation	4.03	1.22		
Gripping things tightly				
No suicide ideation	3.08	1.44	-0.43	0.76
Suicide ideation	3.23	1.42		
Carrying things				
No suicide ideation	4.00	1.32	0.60	0.69
Suicide ideation	3.81	1.33		
Problems with balance				
No suicide ideation	3.39	1.64	-0.67	0.64
Suicide ideation	2.65	1.60		
Moving about indoors				

No suicide ideation	2.98	1.66	-1.90	0.02*
Suicide ideation	3.69	1.29		
Being clumsy				
No suicide ideation	3.08	1.37	-1.13	0.55
Suicide ideation	3.46	1.42		
Being stiff				
No suicide ideation	3.49	1.23	0.21	0.08
Suicide ideation	3.42	1.58		
Heavy limbs				
No suicide ideation	3.20	1.43	-2.10	0.35
Suicide ideation	3.92	1.38		
Tremors				
No suicide ideation	2.33	1.30	-1.74	0.03*
Suicide ideation	2.92	1.62		
Spasms				
No suicide ideation	2.33	2.73	-1.91	0.26
Suicide ideation	2.92	3.35		
Body not doing what you want				
No suicide ideation	3.63	1.36	-1.16	0.90
Suicide ideation	4.00	1.20		
Depending on others				
No suicide ideation	3.65	1.49	-1.20	0.12
Suicide ideation	3.92	1.20		
Limitations in social and leisure				
No suicide ideation	3.12	1.56	-0.38	0.94
Suicide ideation	3.27	1.61		
Being stuck at home				
No suicide ideation	2.89	1.60	-1.12	0.44
Suicide ideation	3.31	1.54		
Difficulty using hands				
No suicide ideation	3.20	1.58	-1.01	0.35
Suicide ideation	3.58	1.39		
Cutting down on work/social life				
No suicide ideation	2.86	1.62	-1.84	0.11
Suicide ideation	3.54	1.33		
Problems using transport				
No suicide ideation	2.33	1.63	-1.36	0.71
Suicide ideation	2.88	1.82		
Taking longer to do things				
No suicide ideation	3.10	1.57	-1.80	0.01*
Suicide ideation	3.73	1.15		
Difficulty doing things spontaneously				
No suicide ideation	3.29	1.50	-2.30	0.00*
Suicide ideation	4.03	1.00		
Toilet urgency				
No suicide ideation	2.45	1.50	-2.01	0.98
Suicide ideation	3.19	1.58		
<u>Psychological subscales:</u>				
Feeling unwell				
No suicide ideation	2.27	1.25	-2.28	0.34
Suicide ideation	3.00	1.47		
Problems sleeping				
No suicide ideation	2.00	1.24	-1.52	0.02*
Suicide ideation	2.50	1.56		
Mental Fatigue				
No suicide ideation	2.31	1.12	-2.90	-0.52
Suicide ideation	3.49	1.36		

Worries about MS				
No suicide ideation	2.22	1.31	-2.44	0.66
Suicide ideation	3.04	1.48		
Anxiety and tension				
No suicide ideation	2.16	1.26	-1.70	0.01*
Suicide ideation	2.73	1.56		
Irritability				
No suicide ideation	2.43	1.34	-1.60	0.47
Suicide ideation	2.92	1.23		
Problems concentrating				
No suicide ideation	2.35	1.32	-2.00	0.84
Suicide ideation	3.00	1.41		
Lack of confidence				
No suicide ideation	2.16	1.34	-3.56	0.67
Suicide ideation	3.34	1.41		
Feeling depressed				
No suicide ideation	1.69	2.54	-2.99	0.00*
Suicide ideation	2.54	1.48		

*Significant differences

No significant differences were found when comparing *actual* physical disability items from the GNDS between no suicide ideation and suicide ideation, as displayed in Appendix XVI.

3.4.6 Aim 5: based on the work of Onkay-Ho (2014) is there a sub-group of individuals who report suicide ideation with only a minimal or mild level of depressive symptoms?

As described above, some participants showed no suicide ideation at all (65%). Further exploration of the data was therefore warranted, especially the relationship between BSS and BDI-II scores. Figure 4 below shows the relationship between BSS and BDI-II, visual inspection of which suggests that in those who do report some level of suicide ideation this is associated with increasing levels of depressive symptoms. However, a number of people who reported suicide ideation have minimal (a score of ≤13) or mild (a score between 14 and 19) depressive symptoms (namely: participants 5, 6, 7, 11, 14, 16, 18, 19, 25, 37, 46, 66, 72, 74) according to BDI-II scores, see appendix XVII. Conversely, some people with higher levels of depression show no suicide ideation.

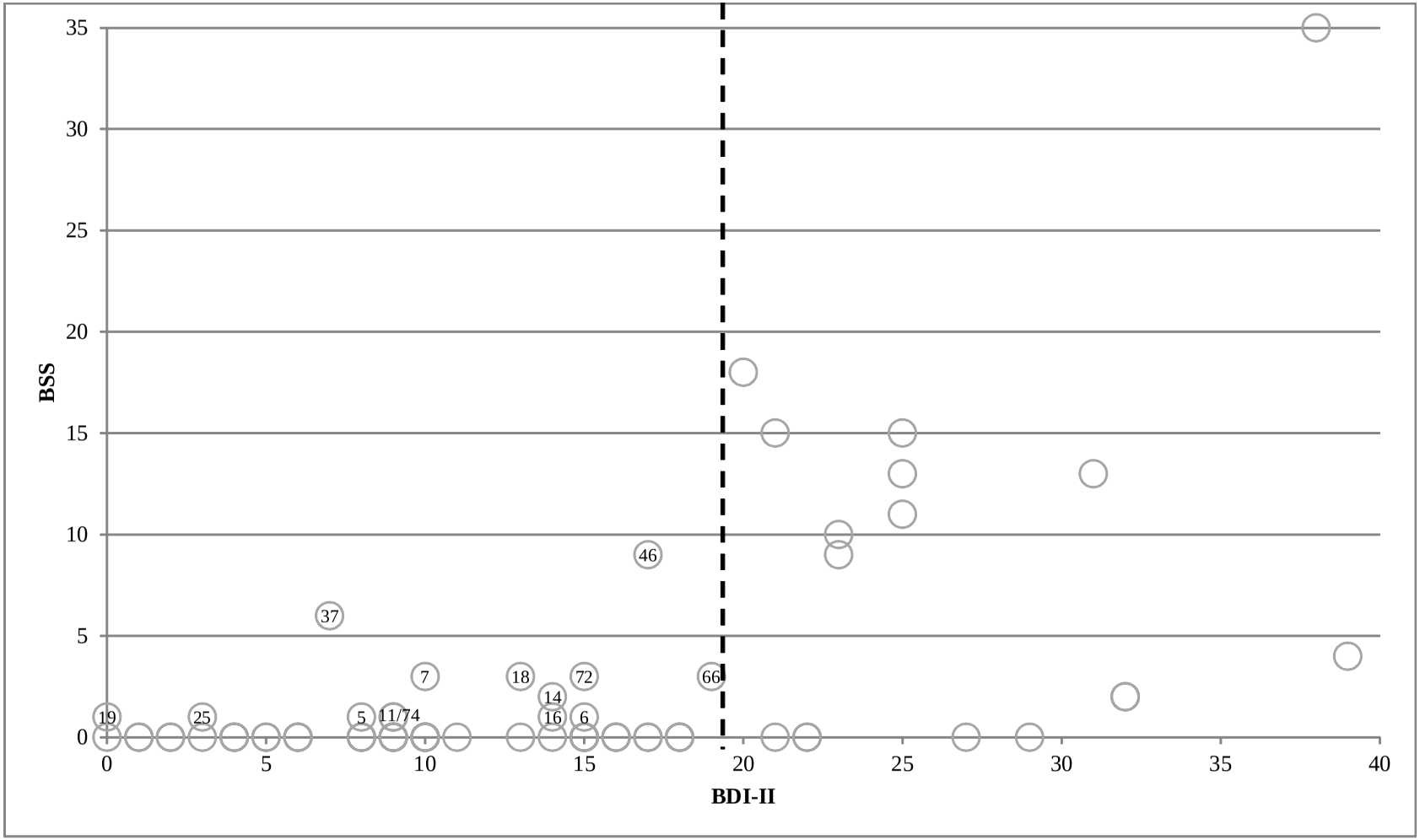


Figure 4. The relationship between BSS and BDI-II scores and participant numbers of individuals displaying what is referred to as rational suicide

As rational suicide is one of the interests of the present study, comparisons between those with suicide ideation but minimal or mild levels of depressive symptoms (referred to as rational suicide ideation, $n = 14$) and those with suicide ideation and higher levels of depressive symptoms (referred to as suicide ideation, $n = 11$) were carried out. K-S tests revealed all distributions to be normal except for GNDS in the rational suicide ideation group and the BDI-II in the suicide ideation group (see Appendix XVIII).

Using a series of independent-sample *t*-tests, to compare level of *perceived* disability and demographic variables, the only significant difference was found between the rational suicide ideation group ($M = 77.86$, $SD = 19.25$) and the suicide ideation group ($M = 112.27$, $SD = 11.95$) in the overall level of *perceived* disability, $t(23) = -0.52$, $p < .00$. Therefore, participants displaying rational suicide ideation reported a lower level of *perceived* disability. Using Mann Whitney tests for the non-normally distributed data, no significant differences were found in the overall level of *actual* physical disability. However, as expected, a significant difference was found between the rational suicide ideation ($Mdn = 9.50$) and the suicide ideation group ($Mdn = 25.0$) in level of depressive symptoms $U = 1.00$, $p < .00$ with participants displaying what is referred to as rational suicide ideation reporting lower levels of depressive symptoms.

4. Discussion

The present study looked at the relationship between three variables: disability, depression and suicide ideation in MS. The main aim of the study was to explore the relationship between all three variables together, including a measure of *perceived* and *actual* physical disability. The study also aimed to find out whether there were differences between: certain types of progressive MS and specific areas of disability. Finally the study was interested in the concept of rational suicide and examined whether there were a sub-group of individuals who displayed what is referred to as 'rational suicide'.

The prevalence of suicidality was 35%, slightly higher than the findings of Feinstein (2002) and Turner et al. (2006). Out of a total sample of 75, four participants had previously attempted suicide on one occasion, two had made three previous attempts and one had attempted suicide on eleven occasions. Four described the trigger for the first attempt as the MS diagnosis. The overall mean total BDI-II score was found to be similar to that of other MS studies for example: Pujol et al. (2000). The observed scores on the MSIS-29 physical and psychological subscales were also found to be similar to previous studies, for example Forbes, While, Mathes, and Griffiths (2006), Motl, Suh, and Weikert (2010); as were the GNDS scores for example: Nicholl, Lincoln, Francis, and Stephan (2001).

4.1 Findings

The relationship between *perceived* disability and suicide ideation was found to be mediated by depressive symptoms, and the relationship between *actual* physical disability and suicide ideation was mediated by depressive symptoms. When comparing PPMS and SPMS, there were no significant differences in the level of depressive symptoms and suicide ideation. When investigating the impact of different types of disability, there were significant

differences between those with no suicide ideation and those with suicide ideation for several of the *perceived* disability items, but none for *actual* physical disability. Finally, there was a small (19%) sub-group of individuals who reported suicide ideation but only minimal or mild levels of depressive symptoms, therefore displaying what is referred to as rational suicide. Each finding will be discussed below in relation to previous literature.

4.1.1 Aim 1: do depressive symptoms mediate the relationship between *perceived* disability and suicide ideation?

Depressive symptoms were found to mediate the relationship between *perceived* disability and suicide ideation. This is a brand new finding and it is the first time it has been investigated in MS. It is consistent with the findings of Meltzer et al. (2012) who found that the relationship between limitations of daily living activities in adults from the general population and suicidality were mediated by depression. Their measure of disability was not asking how much the limitation 'bothered' the participant but was a self-report measure of actual limitation. In the present study, however a direct relationship has been found between *perceived* disability and depressive symptoms, as well as *perceived* disability and suicide ideation. The latter finding is similar to the study by Turner et al. (2006) who also found a direct relationship between *perceived* disability and suicide ideation in a sample of veterans who had received services for MS in the United States of America. It seems that there is a lack of research investigating the impact of *perceived* disability in MS despite Turk et al. (1995) advocating for its use in disability research generally. In the present study at least 30% of the direct relationship between *perceived* disability and suicide ideation was accounted for by depressive symptoms, suggesting that interventions could be put in place to ameliorate them.

4.1.2 Aim 2: do depressive symptoms mediate the relationship between *actual* physical disability and suicide ideation?

Depressive symptoms were found to mediate the relationship between *actual* physical disability and suicide ideation. Again, this is another new finding and a concept which has not been investigated in MS before. Consistent with the findings of Meltzer et al. (2012) depressive symptoms had an indirect effect upon the direct relationship between *actual* physical disability and suicide ideation in MS. In the present study, depressive symptoms accounted for at least 30% of the relationship. They are a modifiable contributory factor to suicide ideation and therefore need to be addressed. Finding a significant direct relationship between *actual* disability and depressive symptoms has mirrored the findings of several other studies in this population, most recently the study by Smith and Arnett (2013). The finding of a significant relationship between depressive symptoms and suicide ideation has contributed to the few studies in this area which reported similar (Feinstein, 2002; Turner et al., 2006; Viner et al., 2014).

4.1.3 Aim 3: based on the work of Vleugels et al. (1998) do levels of depressive symptoms and suicidal ideation differ between certain types of progressive MS?

In the present study levels of depression symptoms and suicide ideation did not differ between certain types of progressive MS and there were no other significant differences between the two groups. Although Vleugels et al. (1998) found a significant difference in PPMS and SPMS using the BDI-II, it is a weakness of the study that the two groups differed in age, duration of disease and disability level. In the present study there were no differences between the two groups, suggesting that the study by Vleugels et al. (1998) may have been

confounded. As there are only two studies comparing emotional adaption in progressive MS types, further research in this area is required.

4.1.4 Aim 4: based on the work of Turner et al. (2006) and Viner et al. (2014) is any specific area of disability related to suicide ideation?

Using validated and standardised measures, no differences were found between individuals with and without suicide ideation in terms of areas of *actual* physical disability; however, there were several differences for *perceived* disability. Namely: 'moving about indoors', 'tremors', 'taking longer to do things' and 'difficulty doing things spontaneously' for the physical subscale; 'problems sleeping', 'anxiety and tension' and 'feeling depressed' for the psychological subscale. Tremors have been referred to as one of the most physically disabling manifestations of MS (Thompson et al., 2001). Participants who reported being more 'bothered' by tremors and the other specific areas of disability also disclosed higher levels of suicide ideation. Using non-validated measures for disability, previous literature found mobility, bladder and bowel functioning (Turner et al., 2006); bladder or bowel functioning, communication and swallowing difficulties (Viner et al., 2014) to be associated with suicide ideation. As there are few studies investigating types of both *perceived* and *actual* physical disability as risk factors for suicide ideation, further investigation is required.

4.1.5 Aim 5: based on the work of Onkay-Ho (2014) is there a sub-group of individuals who report suicide ideation with only a minimal or mild level of depressive symptoms?

The present study found that there was a sub-group of individuals who reported suicide ideation with only a minimal or mild level of depressive symptoms. As the inclusion of the mediated variable between disability and suicide ideation meant that the path estimate

reduced to not quite zero, for both *perceived* and *actual* disability, it could be suggested that the residual amount accounted for the sub-group of participants who reported suicide ideation but only a minimal or mild level of depression.

This finding supports the theory for what is referred to as rational suicide suggesting that those without co-morbid psychiatric disorders may consider suicide as a method of finding a way to avoid the pain or suffering (Onkay-Ho, 2014), or in order to gain a sense of mastery over the condition (Siegel & Meyer, 1999). Findings of the present study could also be in agreement with the results of a qualitative analysis by Gaskill et al. (2011), suggesting that perceived loss of control is the major disease-related variable associated with suicide ideation in MS. Those in the group of participants reporting what is referred to as rational suicide had a significantly lower overall score on the *perceived* disability measure than the suicide ideation group. This suggests that those in the rational suicide sub-group were therefore, less bothered by the level of *perceived* disability associated with MS. A possible explanation for the lower scores for the rational suicide ideation group could be that suicide ideation has provided a method for mastering or avoiding the impact and therefore, the disability is *perceived* as less concerning. Further research is required in this area.

4.2 Limitations

All participants recruited in the present study were attending MS outpatient clinics for review appointments and/or rehabilitation support. This suggests that there may be a sample bias in the study as those attending clinics are engaged in support and may not represent the whole population. In order to account for this, ethical approval was sought to advertise the study on the MS society website with a view to administering the measures with additional participants over the telephone. The rationale for this was to target potential participants in a

wider geographical area and those who may not have been engaged in support from MS clinicians. The request however was rejected due to concerns about the management of suicide risk should a concern have arisen.

Furthermore, previous research has suggested that higher levels of suicide ideation are present within the first year after diagnosis (Fredrikson et al., 2002) as well as the following four years (Bronnum-Hansen et al., 2005). No participants in the present study had been diagnosed less than five years ago and therefore could potentially be better adjusted to their condition. This suggests that the rates of depressive symptoms and suicide ideation in this sample group could be under representative, additionally some participants (n = 15) were taking antidepressants which could have reduced depressive symptoms and suicide ideation. Attempts to recruit participants in the earlier stages of their disease from the MS clinic in the acute hospital proved a challenge. Despite substantial progress in the diagnosis of MS within the last decade (Karussis, 2014) the pressure for physicians to ensure an accurate diagnosis (Cohen & Rae-Grant, 2012) may still result in a reluctance to diagnose hastily and therefore finding suitable participants within the early stages of the disease with a definite progressive diagnosis was not achieved.

Finally, with regards to the measures, it can be seen from Appendix XIX that the MSIS-29 and GNDS did not measure all the same items. It could therefore be argued that the differences in types of *perceived* disability for some items on the MSIS-29 were found without their being direct comparisons on the GNDS. As there are not two equivalent measures which are reliable and validated, one measuring *perceived* disability and another measuring *actual physical* disability, this issue is not easy to overcome.

4.3 Clinical Implications

The present study has identified several important factors which may be useful for reducing suicide ideation and preventing suicide in people with MS in the future. The relationship found between all three variables (disability, depressive symptoms and suicide ideation) suggests that it is particularly important to screen for depression in those with more severe disability either *perceived* or *actual*. This is consistent with suggestions from previous research that providers who care for those with MS must closely monitor depressive symptoms and suicide ideation (Coughlin & Sher, 2013). Depression is a modifiable factor in MS which can be treated effectively with antidepressants (Arciniegas & Anderson, 2002) or psychological therapy and if not ameliorated can lead to suicidality (Paparrigopoulos et al., 2010; Raskind, 2008). Suicidal behaviour in the general population has been conceptualised as existing on a continuum from suicide ideation, to formulation of a plan, to attempted or completed suicide; additionally, levels of suicide ideation have been found to be transient and fluctuate, suggesting the process before attempting suicide to be complex (Kessler, Berglund, Borges, Nock & Wang, 2005).

The suggestion that suicide may be rational is both sensitive in nature and has been a controversial one. Werth (1998) believes that rational suicide could be considered as an intervention, in other words thinking about suicide may provide an individual with a way of gaining power over their life situation. Werth (1998) has developed criteria to be used in clinical practice for screening out irrational suicidality and delaying an impulsive act. However, whilst some propose that current guidelines and legal statutes fail to consider the complexity of suicide, which has been suggested to be completed under free will and in the absence of psychiatric disorder (Onkay-Ho, 2014), others disagree. Lokhandwala and Westefeld (1998) have argued that acceptance of rational suicide may prevent individuals

from taking the time to think through the decision carefully. Furthermore, Maltsberger (1998) believes that the conditions required for a suicide to be labelled as rational are ambiguous and presume many moral and ethical assumptions.

What is evident from the findings of this present study is that screening for suicide ideation is of utmost importance and that absence of minimal or mild depressive symptoms cannot be presumed to be indicative of no suicide ideation. Clinicians need to be asking all those with MS whether they have or are experiencing any thoughts about harming themselves, whilst remaining aware of the types of *perceived* disabilities associated with suicide ideation rather than solely *actual* disability. Suicide ideation clinical assessment instruments for use with those with neurological conditions have been suggested by Lewis, Anderson and Feuchtinger (2014) and include and a suicide risk assessment and management protocol (New South Wales Department of Health, 2004) and the Nurses' Global Assessment of Suicide Risk (NGASR) (Cutcliffe & Barker, 2004). Both are said to be used widely in clinical practice and are suggested for use as a guide to inform clinical decision making (Lynch, Howard, El-Mallakh & Matthews, 2008).

Previous research has reported that the therapeutic relationship between the clinician and individual experiencing suicide ideation is critical to the initial screening and assessment (Lynch et al., 2008; Maris, 1992). Whilst referrals for psychiatric or psychological support need to be considered carefully, reacting to the disclosure of suicide ideation by conceptualising it as a ‘psychiatric emergency’ could give the message that conversations are taboo, whereas, allowing individuals to share their innermost thoughts in a therapeutic milieu, may contribute to some emotional relief (Gaskill et al., 2011). Further supportive interventions with counsellors, psychologists and talking therapists can encourage open

discussions and work towards ameliorating modifiable risk factors (Arciniegas & Anderson, 2002; Feinstein, 2002; Wallin et al., 2006).

Other than the suggestions already mentioned, future research could also focus on those with MS who do not experience depressive symptoms and what it is that helps them to manage. Gaining a more thorough understanding of additional risk factors which are known to contribute to the direct relationship between disability and suicide ideation is also needed for example: lack of social support, poor coping mechanisms. Finally, if rational suicide is a response to a perceived loss of control in MS, then further research is required in order to find ways of increasing levels of perceived control.

5. Conclusion

Suicide ideation in MS is potentially a treatable cause of both morbidity and mortality (Feinstein, 1997; 2002). Given that suicide ideation is associated with an increased risk for making plans, attempting suicide and completing suicide (Kessler et al., 2005; Nock et al., 2008), regular screening in clinical practice alongside further research in this area is imperative, especially taking into consideration the impact of *perceived* disability. Whether suicide ideation in this population is considered rational or not, what is clear from the present study is that prevalence rates remain high and steps need to be taken towards reducing them and the distress which has been found to accompany suicide ideation in those with MS (Coughlin & Sher, 2013).

6. References

Alla, S., & Mason, D. (2014). Multiple sclerosis in New Zealand. *Journal of Clinical Neuroscience, 21*(8), 1288-1291. doi: 10.1016/j.jocn.2013.09.009

Anhoque, C.F., Domingues, S.C.A., Carvalho, T., Teixeira, A.L., & Domingues, R.B. (2011). Anxiety and depressive symptoms in clinically isolated syndrome and multiple sclerosis. *Arquivos de neuro-psiquiatria, 69*(6), 882-886. doi: 10.1590/S0004-282X2011000700006

Arciniegas, D.B., & Anderson, C.A. (2002). Suicide in neurologic illness. *Current treatment options in neurology, 4*(6), 457-468.

Arnett, P.A., Barwick, F.H., & Beeney, J.E. (2008). Depression in multiple sclerosis: review and theoretical proposal. *Journal of the International Neuropsychological Society, 14*(05), 691-724. doi: 10.10170S1355617708081174

Babigian, H.M., & Odoroff, C.L. (1969). The mortality experience of a population with psychiatric illness. *American journal of Psychiatry, 126*(4), 470-480.

Bailey, J. (2010). What is multiple sclerosis? *Multiple Sclerosis Society*.

Baron, R.M., & Kenny, D.A. (1986). The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology, 51*(6), 1173.

Beal, C.C., Stuifbergen, A.K., & Brown, A. (2007). Depression in multiple sclerosis: a longitudinal analysis. *Archives of psychiatric nursing, 21*(4), 181-191. doi: 10.1016/j.apnu.2007.02.008

Beck, A.T., Kovacs, M., & Weissman, A. (1979). Assessment of suicidal intention: the Scale for Suicide Ideation. *Journal of consulting and clinical psychology, 47*(2), 343.

Beck, A.T., & Steer, R.A. (1991). *Manual for Beck scale for suicide ideation*. San Antonio: Psychological Corporation.

Beck, A.T., & Steer, R.A. (1993). *Beck Scale for Suicide Ideation*. United States of America: Pearson.

Beck, A.T., Steer, R.A., & Brown, G.K. (1996). *Beck Depression Inventory-II* (2nd ed.). United States of America: Pearson.

Beck, A.T., Steer, R.A., & Ranieri, W.F. (1988). Scale for suicide ideation: psychometric properties of a self report version. *Journal of Clinical Psychology, 44*, 499-505.

Bender, R., & Lange, S. (1999). Multiple test procedures other than Bonferroni's deserve wider use. *BMJ: British Medical Journal, 318*(7183), 600.

Berman, A.L., & Samuel, L. (1993). Suicide among people with multiple sclerosis. *Neurorehabilitation and Neural Repair, 7*(2), 53-62. doi: 10.1177/136140969300700202

Bronnum-Hansen, H., Stenager, E., Stenager, E.N, & Kock-Henriksen, N. (2005). Suicide among Danes with multiple sclerosis. *Journal of Neurology, Neuropsychiatry and Psychiatry, 76*, 1457-1459. doi: 10.1136/jnnp.2004.056747

Caine, E. D., & Schwid, S. R. (2002). Multiple sclerosis, depression, and the risk of suicide. *Neurology, 59*(5), 662-663. doi: 10.1212/WNL.59.5.662

Carson, A.J., Best, S., Warlow, C., & Sharpe, M. (2000). Suicidal ideation among outpatients at general neurology clinics: prospective study. *BMJ, 320*(7245), 1311-1312. doi: 10.1136/bmj.320.7245.1311

Cella, D.F., Dineen, K., Arnason, B., Reder, A., Webster, K.A., Karabatsos, G., . . . Stewart, J. (1996). Validation of the functional assessment of multiple sclerosis quality of life instrument. *Neurology, 47*(1), 129-139.

Cheng, E.M., Hays, R.D., Myers, L.W., Ellison, G.W., Beckstrand, M., & Vickrey, B.G. (2001). Factors related to agreement between self-reported and conventional Expanded Disability Status Scale (EDSS) scores. *Multiple sclerosis, 7*(6), 405-410.

Chwastiak, L., Ehde, D.M. , Gibbons, L.E., Sullivan, M., Bowen, J.D., & Kraft, G.H. (2002). Depressive symptoms and severity of illness in multiple sclerosis: Epidemiological study of a large community sample. *American Journal of Psychiatry, 159*, 1862-1868. doi: 10.1176/appi.ajp.159.11.1862

Coetzee, T., Zaratin, P., & Gleason, T. L. (2015). Overcoming barriers in progressive multiple sclerosis research. *The Lancet Neurology, 14*(2), 132-133.

Cohen, J. A., & Rae-Grant, A. (2012). *Handbook of Multiple Sclerosis*. London: Springer Healthcare Ltd.

Coolican, H. (2014). *Research Methods and Statistics in Psychology*: Psychology Press.

Coughlin, S.S., & Sher, L. (2013). Suicidal behavior and neurological illnesses. *Journal of depression & anxiety*(1). doi: 10.4172/2167-1044.S9-001

Crane, C., Shah, D., Barnhofer, T., & Holmes, E.A. (2012). Suicidal imagery in a previously depressed community sample. *Clinical Psychology & Psychotherapy, 19*(1), 57-69. doi: 10.1002/cpp.741

Cutcliffe, J.R., & Barker, P. (2004). The Nurses' Global Assessment of Suicide Risk (NGASR): developing a tool for clinical practice. *Journal of psychiatric and mental health nursing, 11*(4), 393-400. doi: 10.1111/j.1365-2850.2003.00721.x

da Silva, A.M., Vilhena, E., Lopes, A., Santos, E., Gonçalves, M.A., Pinto, C., . . . Cavaco, S. (2011). Depression and anxiety in a Portuguese MS population: associations with physical disability and severity of disease. *Journal of the neurological sciences, 306*(1), 66-70. doi: 10.1016/j.jns.2011.03.042

Dalgas, U., Stenager, E., & Sloth, M. (2014). The effect of exercise on depressive symptoms in multiple sclerosis based on a meta-analysis and critical review of the literature. *European Journal of Neurology*. doi: 10.1111/ene.12576

Dennis, M., Baillon, S., Brugha, T., Lindesay, J., Stewart, R., & Meltzer, H. (2009). The influence of limitation in activity of daily living and physical health on suicidal ideation: results from a population survey of Great Britain. *Social Psychiatry and Psychiatric Epidemiology, 44*(8), 608-613.

Derogatis, L.R. (1983). SCL-90-R administration, scoring and procedures manual—II, 1983. *Clinical Psychometric Research,* Towson, MD: Clinic Psychometric Research.

Ebers, G.C. (2004). Natural history of primary progressive multiple sclerosis. *Multiple Sclerosis, 10*(3 suppl), S8-S15.

Faber, R.A. (2003). Suicide in neurological disorders. *Neuroepidemiology, 22*(2), 103-105. doi: 10.1159/000068751

Feinstein, A. (1997). Multiple sclerosis, depression, and suicide. Clinicians should pay more attention to psychopathology. *British Medical Journal, 315*(7110), 691-692.

Feinstein, A. (2002). An examination of suicidal intent in patients with multiple sclerosis. *Neurology, 59*(5), 674-678. doi: 10.1212/WNL.59.5.674

Feinstein, A. (2004). The neuropsychiatry of multiple sclerosis. *Canadian Journal of Psychiatry, 49*, 157-163.

Feinstein, A. (2007). *The Clinical Neuropsychiatry of Multiple Sclerosis*. Cambridge: Cambridge University Press.

Feinstein, A., Freeman, J., & Lo, A.C. (2015). Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. *The Lancet Neurology, 14*(2), 194-207.

Feinstein, A., Kartsounis, L.D., Miller, D.H., Youl, B.D., & Ron, M.A. (1992). Clinically isolated lesions of the type seen in multiple sclerosis: a cognitive, psychiatric, and MRI follow up study. *Journal of Neurology, Neurosurgery & Psychiatry, 55*(10), 869-876. doi: doi:10.1136/jnnp.55.10.869

Feinstein, A., O'Connor, P., & Feinstein, K. (2002). Multiple sclerosis, interferon beta-1b and depression: A prospective investigation. *Journal of Neurology, 249*(7), 815-820.

Forbes, A., While, A., Mathes, L., & Griffiths, P. (2006). Health problems and health-related quality of life in people with multiple sclerosis. *Clinical Rehabilitation, 20*(1), 67-78. doi: 10.1191/0269215506cr880oa

Fraser, C., & McGurl, J. (2007). Psychometric testing of the Americanized version of the Guy's Neurological Disability Scale. *Journal of Neuroscience Nursing, 39*(1), 13-20.

Fredrikson, S., Cheng, Q., Jiang, G.X., & Wasserman, D. (2002). Elevated suicide risk among patients with multiple sclerosis in Sweden. *Neuroepidemiology, 22*(2), 146-152. doi: 10.1159/000068746

Freeman, J.A., Thompson, A.J., Fitzpatrick, R., Hutchinson, M., Miltenburger, C., Beckmann, K., . . . Pozzilli, C. (2001). Interferon-β1b in the treatment of secondary progressive MS Impact on quality of life. *Neurology, 57*(10), 1870-1875.

Fritz, M.S., & MacKinnon, D.P. (2007). Required sample size to detect the mediated effect. *Psychological science, 18*(3), 233-239. doi: doi:10.1111/j.1467-9280.2007.01882.x

Fruewald, S., Loeffler-Stastka, H., Eher, R., Saletu, B., & Baumhacki, U. (2001). Depression and quality of life in multiple sclerosis. *Acta Neurologica Scandinavica, 104*(5), 257-261. doi: 10.1034/j.1600-0404.2001.00022.x

Gaskill, A., Foley, F.W., Kolzet, J., & Picone, M.A. (2011). Suicidal thinking in multiple sclerosis. *Disability and Rehabilitation, 33*(17-18), 1528-1536. doi: 10.3109/09638288.2010.533813

Gay, M.C., Vrignaud, P., Garitte, C., & Meunier, C. (2010). Predictors of depression in multiple sclerosis patients. *Acta Neurologica Scandinavica, 121*(3), 161-170. doi: 10.1111/j.1600-0404.2009.01232.x

Giannini, M. J., Bergmark, B., Kreshover, S., Elias, E., Plummer, C., & O'Keefe, E. (2010). Understanding suicide and disability through three major disabling conditions: Intellectual disability, spinal cord injury, and multiple sclerosis. *Disability and Health Journal, 3*(2), 74-78. doi: 10.1016/j.dhjo.2009.09.001

Giles, D. (2014). *Advanced Research Methods in Psychology*. Oxfordshire: Psychology Press.

Gold, S.M., & Irwin, M.R. (2006). Depression and immunity: inflammation and depressive symptoms in multiple sclerosis. *Neurologic Clinics, 24*(3), 507-519. doi: 10.1016/j.iac.2009.02.008

Goldberg, D.P., & Hillier, V.F. (1979). A scaled version of the General Health Questionnaire. *Psychological Medicine, 9*(01), 139-145.

Gourraud, P.A., Harbo, H.F., Hauser, S.L., & Baranzini, S.E. (2012). The genetics of multiple sclerosis: an up-to-date review. *Immunological Reviews, 248*(1), 87-103.

Gunzler, D.D., Perzynski, A., Morris, N., Bermel, R., Lewis, S., & Miller, D.H. (2015). Disentangling Multiple Sclerosis and depression: an adjusted depression screening score for patient-centered care. *Journal of Behavioral Medicine*, 1-14. doi: 10.1007/s10865-014-9574-5

Hardle, W., & Marron, J.S. (1991). Bootstrap simultaneous error bars for nonparametric regression. *The Annals of Statistics*, 778-796. doi: doi:10.1214/aos/1176348120
Hawton, A., Green, C., Telford, C., Zajicek, J., & Wright, D. (2012). Using the Multiple Sclerosis Impact Scale to estimate health state utility values: mapping from the MSIS-29, version 2, to the EQ-5D and the SF-6D. *Value in Health, 15*(8), 1084-1091. doi: 10.1016/j.jval.2012.07.007
Heiman, G.W. (2001). *Understanding Research Methods and Statistics: An Integrated Introduction for Psychology*. Boston: Houghton Mifflin Boston.
Hobart, J. (2011). The Multiple Sclerosis Impact Scale: Initial development, subsequent revision, lessons learned. In C. Jenkinson, M. Peters & M. B. Bromberg (Eds.), *Quality of Life Measurement in Neurodegenerative and Related Conditions* (pp. 24-38). Cambridge: Cambridge University Press.
Hobart, J., & Cano, S. (2009). *Improving the Evaluation of Therapeutic Interventions in Multiple Sclerosis: The Role of New Psychometric Methods*: Prepress Projects.
Hobart, J., Lamping, D., Fitzpatrick, R., Riazi, A., & Thompson, A. (2001). The multiple sclerosis impact scale (MSIS-29). A new patient-based outcome measure. *Brain, 124*, 962-973.
Hoogervorst, E.L.J., Eikelenboom, M.J., & Polman, C.H. (2003). One year changes in disability in multiple sclerosis: neurological examination compared with patient self report. *Journal of Neurology, Neurosurgery & Psychiatry, 74*(4), 439-442.
Hooper, K. (2013). *Managing Progressive Multiple Sclerosis*. New York: National Multiple Sclerosis Society.
Howell, D. (2012). *Statistical Methods for Psychology*: Cengage Learning.
Hyphantis, T.N., Christou, K., Kontoudaki, S., Mantas, C., Papamichael, G., Goulia, P., . . . Mavreas, V. (2008). Disability status, disease parameters, defense styles, and ego strength associated with psychiatric complications of multiple sclerosis. *The International Journal of Psychiatry in Medicine, 38*(3), 307-327. doi: 10.2190/PM.38.3.g
Imitola, J., Chitnis, T., & Khoury, S.J. (2005). Cytokines in multiple sclerosis: from bench to bedside. *Pharmacology & Therapeutics, 106*(2), 163-177. doi: 10.1016/j.pharmthera.2004.11.007
Kantarci, O., Siva, A., Eraksoy, M., Karabudak, R., Sütlaş, N., Ağaoğlu, J., . . . Demirkiran, M. (1998). Survival and predictors of disability in Turkish MS patients. *Neurology, 51*(3), 765-772. doi: 10.1212/WNL.51.3.765
Kaplin, A. (2011). Depression in Multiple Sclerosis. In J. A. Cohen & R. A. Rudick (Eds.), *Multiple Sclerosis Therapeutics* (pp. 823-844). Cambridge: Cambridge University Press.
Karussis, D. (2014). The diagnosis of multiple sclerosis and the various related demyelinating syndromes: a critical review. *Journal of Autoimmunity, 48-49*, 132-142. doi: 10.1016/j.jaut.2014.01.022
Kessler, R.C., Berglund, P., Borges, G., Nock, M., & Wang, P.S. (2005). Trends in suicide ideation, plans, gestures, and attempts in the United States, 1990-1992 to 2001-2003. *Jama, 293*(20), 2487-2495. doi: 10.1001/jama.293.20.2487.
Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., . . . Kendler, K.S. (1994). Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States: results from the National Comorbidity Survey. *Archives of General Psychiatry, 51*(1), 8-19. doi: 10.1001/archpsyc.1994.03950010008002

Kileff, J., & Ashburn, A. (2005). A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clinical Rehabilitation, 19*(2), 165-169. doi: 10.1191/0269215505cr839o

Kingwell, E., Marriott, J.J., Jetté, N., Pringsheim, T., Makhani, N., Morrow, S.A., . . . Kulaga, S. (2013). Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *Bio Med Central Neurology, 13*(1), 128. doi: 10.1186/1471-2377-13-128

Koch-Henriksen, N., Brønnum-Hansen, H., & Stenager, E. (1998). Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. *Journal of Neurology, Neurosurgery & Psychiatry, 65*(1), 56-59. doi: 10.1136/jnnp.65.1.56

Korostil, M., & Feinstein, A. (2007). Anxiety disorders and their clinical correlates in multiple sclerosis patients. *Multiple Sclerosis, 13*(1), 67-72.

Kroenke, K., & Spitzer, R.L. (2002). The PHQ-9: a new depression diagnostic and severity measure. *Psychiatric Annals, 32*(9), 1-7.

Kuhlman, T. (2013). Relapsing–remitting and primary progressive MS have the same cause(s): the neuropathologist's view: 2. *Multiple Sclerosis Journal, 19*(3), 268-269. doi: 10.1177/1352458513476563

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis an expanded disability status scale (EDSS). *Neurology, 33*(11), 1444-1444.

Larsson, U.E., & Mattsson, E. (2001). Perceived disability and observed functional limitations in obese women. *International Journal of Obesity and Related Metabolic Disorders, 25*(11), 1705-1712. doi: 10.1038/sj.ijo.0801805

Lester, K., Stepleman, L., & Hughes, M. (2007). The association of illness severity, self-reported cognitive impairment, and perceived illness management with depression and anxiety in a multiple sclerosis clinic population. *Journal of Behavioral Medicine, 30*(2), 177-186. doi: 10.1007/s10865-007-9095-6

Lewis, D.S., Anderson, K.H., & Feuchtinger, J. (2014). Suicide prevention in neurology patients: evidence to guide practice. *Journal of Neuroscience Nursing, 46*(4), 241-248. doi: 10.1097/JNN.0000000000000062

Lipe, H., Schultz, A., & Bird, T.D. (1993). Risk factors for suicide in Huntingtons disease: A retrospective case controlled study. *American Journal of Medical Genetics, 48*(4), 231-233.

Lipps, G.E., Lowe, G.A., De La Haye, W., Longman-Mills, S., Clarke, T.R., Barton, E.N., & Bain, B. (2010). Validation of the Beck Depression Inventory II in HIV-positive patients. *West Indian Medical Journal, 59*(4), 374-379.

Lokhandwala, T.M., & Westefeld, J.S. (1998). Rational suicide and the crisis of terminal illness. *Journal of Personal & Interpersonal Loss, 3*(2), 143-159.

Lublin, F.D., & Reingold, S.C. (1996). Defining the clinical course of multiple sclerosis results of an international survey. *Neurology, 46*(4), 907-911. doi: 10.1212/WNL.46.4.907

Lynch, M.A., Howard, P.B., El-Mallakh, P., & Matthews, J.M. (2008). Assessment and management of hospitalized suicidal patients. *Journal of Psychosocial Nursing and Mental Health Services, 46*(7), 45-52.

Mackenzie, I.S., Morant, S.V., Bloomfield, G.A., MacDonald, T.M., & O'Riordan, J. (2014). Incidence and prevalence of multiple sclerosis in the UK 1990–2010: a descriptive study in the General Practice Research Database. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(1), 76-84. doi: 10.1136/jnnp-2013-305450

Maltsberger, J.T. (1998). An explication of rational suicide: Its definitions, implications, and complications. *Journal of Personal & Interpersonal Loss, 3*(2), 177-192.
Maris, R.W. (1992). *Assessment and Prediction of Suicide* (Vol. 21): Guilford Press.
Mayo, D.J. (1986). The concept of rational suicide. *Journal of medicine and philosophy, 11*(2), 143-155.
McCullagh, R., Fitzgerald, A.P., Murphy, R.P., & Cooke, G. (2008). Long-term benefits of exercising on quality of life and fatigue in multiple sclerosis patients with mild disability: a pilot study. *Clinical Rehabilitation, 22*(3), 206-214.
Meltzer, H., Brugha, T., Dennis, M.S., Hassiotis, A., Jenkins, R., McManus, S., . . . Bebbington, P. (2012). The influence of disability on suicidal behaviour. *ALTER-European Journal of Disability Research, 6*(1), 1-12. doi: 10.1016/j.alter.2011.11.004
Minden, S.L., & Schiffer, R.B. (1990). Affective disorders in multiple sclerosis review and recommendations for clinical research. *Archives of Neurology, 47*(1), 98-104. doi: 10.1001/archneur.1990.00530010124031
Mohr, D.C., Goodkin, D.E., Gatto, N., & Van Der Wende, J. (1997). Depression, coping and level of neurological impairment in multiple sclerosis. *Multiple sclerosis, 3*(4), 254-258. doi: 10.1177/13524585970030040
Mohr, D.C., Likosky, W., Dwyer, P., Van Der Wende, J., Boudewyn, A.C., & Goodkin, D.E. (1999). Course of depression during the initiation of interferon beta-1a treatment for multiple sclerosis. *Archives of Neurology, 56*(10), 1263-1265. doi: 10.1001/archneur.56.10.1263
Moore, D.S., & McCabe, G.P. (2005). *Introduction to the Practice of Statistics*: WH Freeman/Times Books/Henry Holt & Co.
Motl, R.W., Suh, Y., & Weikert, M. (2010). Symptom cluster and quality of life in multiple sclerosis. *Journal of Pain and Symptom Management, 39*(6), 1025-1032. doi: 10.1016/j.jpainsymman.2009.11.312
Multiple Sclerosis Study Group (1993). Interferon beta-1b is effective in relapsing–remitting multiple sclerosis: Clinical results of a multi-centre, randomized, double-blind placebo controlled trail. *Neurology, 43*, 655–661.
New South Wales Department of Health. (2004a). Suicide risk assessment and management protocols: For NSW health staff. Retrieved from: http://www.health.nsw.gov.au/mhdao/programs/mh/Publications/framework-suicide-risk-assess.pdf
Nicholl, C.R., Lincoln, N.B., Francis, V.M., & Stephan, T.F. (2001). Assessment of emotional problems in people with multiple sclerosis. *Clinical Rehabilitation, 15*(6), 657-668. doi: 10.1191/0269215501cr427oa
Nock, M.K., Borges, G., Bromet, E.J., Alonso, J., Angermeyer, M., Beautrais, A., . . . Gluzman, S. (2008). Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *The British Journal of Psychiatry, 192*(2), 98-105. doi: 10.1192/bjp.bp.107.040113
Onkay-Ho, A. (2014). Suicide: rationality and responsibility for life. *Canadian Journal of Psychiatry, 59*(3), 141-147.
Paparrigopoulos, T., Ferentinos, P., Kouzoupis, A., Koutsis, G., & Papadimitriou, G.N. (2010). The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. *International Review of Psychiatry, 22*(1), 14-21. doi: 10.3109/09540261003589323

Park, J.I., Han, M., Kim, M.S., Yoon, M.S., Ko, S.H., Cho, H.C., & Chung, Y.C. (2014). Predictors of suicidal ideation in older individuals receiving home-care services. *International Journal of Geriatric Psychiatry, 29*(4), 367-376. doi: 10.1002/gps.4012

Patten, S.B., Beck, C.A., Williams, J.V.A., Barbui, C., & Metz, L.M. (2003). Major depression in multiple scleosis. *Neurology, 61*, 1524-1527. doi: 10.1212/01.WNL.0000095964.34294.B4

Polman, C.H., Reingold, S.C., Banwell, B., Clanet, M., Cohen, J.A., Filippi, M., . . . Kappos, L. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology, 69*(2), 292-302.

Pompili, M., Forte, A., Palermo, M., Stefani, H., Lamis, D. A., Serafini, G., . . . Girardi, P. (2012). Suicide risk in multiple sclerosis: A systematic review of current literature. *Journal of Psychosomatic Research, 73*(6), 411-417. doi: 10.1016/j.psychores.2012.09.011

Preacher, K.J, & Hayes, A.F. (2008). Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behaviour Research Methods, 40*(3), 879 - 891. doi: doi:10.3758/BRM.40.3.879

Preacher, K.J., & Hayes, A.F. (2004). SPSS and SAS procedures for estimating indirect effects in simple mediation models. *Behavior Research Methods, Instruments, & Computers, 36*(4), 717-731. doi: 10.3758/BF03206553

Prinz, U., Nutzinger, D.O., Schulz, H., Petermann, F., Braukhaus, C., & Andreas, S. (2013). Comparative psychometric analyses of the SCL-90-R and its short versions in patients with affective disorders. *BMC psychiatry, 13*(1), 104.

Pugliatti, M., Rosati, G., Carton, H., Riise, T., Drulovic, J., Vécsei, L., & Milanov, I. (2006). The epidemiology of multiple sclerosis in Europe. *European Journal of Neurology, 13*(7), 700-722. doi: 10.1111/j.1468-1331.2006.01342.x

Pujol, J., Bello, J., Deus, J., Cardoner, N., Martí-Vilalta, J.L., & Capdevila, A. (2000). Beck Depression Inventory factors related to demyelinating lesions of the left arcuate fasciculus region. *Psychiatry Research: Neuroimaging, 99*(3), 151-159. doi: 10.1016/S0925-4927(00)00061-5

Radloff, L.S. (1977). The CSES-D Scale: a self-report depression scale for research in the general population. *Journal of Applied Psychological Measurement, 1*, 385-401.

Raskind, M.A. (2008). Diagnosis and treatment of depression comorbid with neurologic disorders. *The American Journal of Medicine, 121*(11), S28-S37. doi: 10.1016/j.amjmed.2008.09.011

Revesz, T., Kidd, D., Thompson, A.J., Barnard, R.O., & McDonald, W.I. (1994). A comparison of the pathology of primary and secondary progressive multiple sclerosis. *Brain, 117*(4), 759-765.

Riazi, A., Hobart, J.C., Lamping, D.L., Fitzpatrick, R., & Thompson, A.J. (2002). Multiple Sclerosis Impact Scale (MSIS-29): reliability and validity in hospital based samples. *Journal of Neurology, Neurosurgery & Psychiatry, 73*(6), 701-704.

Richard, J., Werth, J. L., & Rogers, J. R. (2000). Rational and assisted suicidal communication on the Internet: A case example and discussion of ethical and practice issues. *Ethics & Behavior, 10*(3), 215-238.

Rossier, P., & Wade, D.T. (2002). The Guy's Neurological Disability Scale in patients with multiple sclerosis: a clinical evaluation of its reliability and validity. *Clinical rehabilitation, 16*(1), 75-95.

Sadovnick, A.D., Eisen, K., Ebers, G.C., & Paty, D.W. (1991). Cause of death in patients attending multiple sclerosis clinics. *Neurology, 41*(8), 1193-1193. doi: 10.1212/WNL.41.8.1193

Sadovnick, A.D., Remick, R.A., Allen, J., Wartz, E.A., Yee, I.M., Eisen, K., . . . Paty, D.W. (1996). Depression and multiple sclerosis. *Neurology, 46*, 628-632. doi: 10.1212/WNL.46.3.628

Sarısoy, G., Terzi, M., Gümüş, K., & Pazvantoğlu, O. (2013). Psychiatric symptoms in patients with multiple sclerosis. *General Hospital Psychiatry, 35*(2), 134-140. doi: 10.1016/j.genhosppsych.2012.10.011

Sharrack, B., & Hughes, R.A.C. (1999a). The Guy's Neurological Disability Scale (GNDS): a new disability measure for multiple sclerosis. *Multiple Sclerosis 5*, 223-233.

Sharrack, B., & Hughes, R.A.C. (1999b). Scale development and Guy's neurological disability scale. *Journal of Neurology, 246*(3), 226-226.

Siegel, K., & Meyer, I.H. (1999). Hope and resilience in suicide ideation and behavior of gay and bisexual men following notification of HIV infection. *AIDS Education and Prevention, 11*, 53-64.

Siegert, R., & Abernethy, D. (2005). Depression in multiple sclerosis: A review. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(4), 469-475. doi: 10.1136/jnnp.2004.054635

Simpson, S., Blizzard, L., Otahal, P., Van der Mei, I., & Taylor, B. (2011). Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry, 82*(10), 1132-1141.

Smith, M.M., & Arnett, P.A. (2013). Perfectionism and physical disability predict depression in multiple sclerosis. *Journal of Psychosomatic Research, 75*(2), 187-189. doi: 0.1016/j.jpsychores.2013.06.001

Sobel, M.E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leinhardt (Ed.), *Sociological Methodology* (Vol. 13, pp. 290-312).

Soldán, M.M.P., Novotna, M., Zeid, N.A., Kale, N., Tutuncu, M., Crusan, D.J., . . . Pirko, I. (2015). Relapses and disability accumulation in progressive multiple sclerosis. *Neurology, 84*(1), 81-88.

Steer, R.A.J., Rissmiller, D., Ranieri, W.F., & Beck, A.T. (1993). Dimensions of suicidal ideation in psychiatric inpatients. *Behaviour Research and Therapy, 31*(2), 229-236.

Stenager, E.N., Koch-Henriksen, N., & Stenager, E. (1996). Risk factors for suicide in multiple sclerosis. *Psychotherapy and Psychosomatics, 65*(2), 86-90. doi: 10.1159/000289052

Stenager, E.N., Stenager, E., Koch-Henriksen, N., Brønnum-Hansen, H., Hyllested, K., Jensen, K., & Bille-Brahe, U. (1992). Suicide and multiple sclerosis: an epidemiological investigation. *Journal of Neurology, Neurosurgery & Psychiatry, 55*(7), 542-545. doi: 10.1136/jnnp.55.7.542

Stewart, A.L., Hays, R.D., & Ware, J.E. (1988). The MOS short-form general health survey: reliability and validity in a patient population. *Medical care*, 724-735.

Thompson, A.J. (2001). Symptomatic management and rehabilitation in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry, 71*(supplement 2), ii22-ii27.

Turk, D.C., Okifuji, A., & Scharff, L. (1995). Chronic pain and depression: role of perceived impact and perceived control in different age cohorts. *Pain, 61*(1), 93-101. doi: 10.1016/0304-3959(94)00167-D

Turner, A.P, Hambridge, J., White, J., Carter, G., Clover, K., Nelson, L., & Hackett, M. (2012). Depression Screening in Stroke A Comparison of Alternative Measures With

the Structured Diagnostic Interview for the Diagnostic and Statistical Manual of Mental Disorders, (Major Depressive Episode) as Criterion Standard. *Stroke, 43*(4), 1000-1005.

Turner, A.P, Williams, R.M, Bowen, J.D, Kivlahan, D.R, & Haselkorn, J.K. (2006). Suicidal Ideation in Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation, 87*(8), 1073-1078. doi: 10.1016/j.apmr.2006.04.021

Tutuncu, M., Tang, J., Zeid, N.A., Kale, N., Crusan, D.J., Atkinson, E.J., . . . Keegan, B.M. (2012). Onset of progressive phase is an age-dependent clinical milestone in multiple sclerosis. *Multiple Sclerosis Journal*, 1352458512451510. doi: 10.1177/1352458512451510

Viner, R., Patten, S.B., Berzins, S., Bulloch, A.G.M., & Fiest, K.M. (2014). Prevalence and risk factors for suicidal ideation in a multiple sclerosis population. *Journal of psychosomatic research, 76*(4), 312-316. doi: 10.1016/j.jpsychores.2013.12.010

Vleugels, L., Pfennings, L., Pouwer, F., Cohen, L., Ketelaer, P., Polman, C., . . . Ploeg, H. (1998). Psychological functioning in primary progressive versus secondary progressive multiple sclerosis. *British Journal of Medical Psychology, 71*(1), 99-106.

Wade, D.T., & Collin, C. (1988). The Barthel ADL Index: a standard measure of physical disability? *Disability & Rehabilitation, 10*(2), 64-67.

Wallin, M. T., Wilken, J. A., Turner, A. P., Williams, R. M., & Kane, R. (2006). Depression and multiple sclerosis: Review of a lethal combination. *Journal of Rehabilitation Research and Development, 43*(1), 45-62.

Werth, J.L. (1998). Using rational suicide as an intervention to prevent irrational suicide. *Crisis: The Journal of Crisis Intervention and Suicide Prevention, 19*(4), 185.

Werth, J.L., & Cobia, D.C. (1995). Empirically based criteria for rational suicide: A survey of psychotherapists. *Suicide and Life-Threatening Behavior, 25*(2), 231-240. doi: 10.1111/j.1943-278X.1995.tb00922.x

Whitaker, J.N., McFarland, H.F., Rudge, P., & Reingold, S.C. (1995). Outcomes assessment in multiple sclerosis clinical trials: a critical analysis. *Multiple Sclerosis, 1*(1), 37-47.

Williams, J.R., Hirsch, E.S., Anderson, K., Bush, A.L., Goldstein, S.R., Grill, S., . . . Palanci, J. (2012). A comparison of nine scales to detect depression in Parkinson disease Which scale to use? *Neurology, 78*(13), 998-1006.

Executive Summary

1. Public Dissemination Document

This document provides an overview of the thesis submitted in partial fulfilment of the requirements for the degree of Doctorate in Clinical Psychology (Clin.Psy.D.) at the University of Birmingham. The research comprises two papers. The first paper is a review of the literature examining factors which are associated with suicidal thoughts and actual suicide in people with Huntington's disease. The second paper investigates whether depression forms an important link between disability and suicidal thoughts in people with Multiple Sclerosis.

1. Literature review: What factors are associated with suicidality in Huntington's disease? A systematic review of the literature.

The aim of this review was to inspect and combine the findings of all previous research papers that have examined factors related to suicidal thoughts and/or actual suicide in people with Huntington's disease. Factors may include: experiencing depression, the result of genetic testing and the severity of the disease.

Huntington's disease is an inherited neurological health condition which damages nerve cells in the brain and gradually gets worse over time (Kingma, van Duijn, Timman, van der Mast, & Roos, 2008). Children of those with diagnosed Huntington's have a 50% risk of inheriting the condition (Lawson et al., 1996) and genetic testing can be carried out to find out whether the gene has been inherited (Fox, Bloch, Fahy, & Hayden, 1989). Some of the features of the disease include: problems with movement, memory or concentration difficulties and mental health problems, for example anxiety, depression and thoughts about no longer wanting to live (Paulsen et al., 2008). In fact, several research studies have found that people with Huntington's disease are more likely to experience these thoughts than the general population (Farrer, Opitz, & Reynolds, 1986; Hubers et al., 2013; Wetzel et al., 2011).

Several factors (many of which can be improved with psychological support) have been suggested to increase the risk or predict whether suicide will be considered and carried out. It is important to identify and combine these findings so that people supporting those with Huntington's disease can be aware of what these factors are and signpost patients to help. Previous research papers which have examined these factors were therefore searched for and relevant papers were then screened to evaluate how well the research had been carried out and reported. Finally the findings of each study were collated altogether.

The main findings of this review were that psychiatric symptoms and/or history, for example, anxiety and depression, were most often found to be related to suicidal thoughts in Huntington's disease. The factors related to actual suicide were: psychiatric symptoms and/or history, the suicide of a family member, finding out from genetic testing that the gene had been inherited, being formally diagnosed with Huntington's and being in the early stages of the disease. Other factors were suggested, but a lack of higher quality research in these areas indicates that further research is required.

This review has shown that there are clear factors which have been found to be related to suicidal thoughts and actual suicide in higher quality research studies. It is important that awareness of these factors is increased in clinicians who work with people with Huntington's disease. This will enable clinicians to look out for these factors and routinely check whether their patients are having any thoughts of harming themselves and refer them for psychological support when necessary.

2. Empirical paper: Disability, depression and suicide ideation in Multiple Sclerosis.

Multiple Sclerosis is another neurological condition and involves inflammation of the central nervous system (Kingwell et al., 2013). There are different disease course types and

symptoms include disability related to: fatigue, weakness, pain, problems with sight, memory and concentration, mobility and balance, bladder, bowel and sexual dysfunction and mood changes (Hooper, 2013; Hyphantis et al., 2008).

Previous research has shown that in Multiple Sclerosis: disability is related to depression (Smith & Arnett, 2013); disability is related to suicidal thoughts (Viner, Patten, Berzins, Bulloch, & Fiest, 2014) and depression is related to suicidal thoughts (Turner, Williams, Bowen, Kivlahan & Haselkorn, 2006). However, no research has yet investigated the relationship between all three variables together, to find out whether depression forms an important link between disability and suicidal thoughts. Despite depression being found to be related to suicidal thoughts, some other research has reported that suicidal thoughts in Multiple Sclerosis have been found to occur without the person experiencing any symptoms of major depression (Sadovnick, Eisen, Ebers & Paty, 1991). It has also been suggested that people can freely desire suicide or a hastened death, based upon a carefully contemplated decision, which is referred to as 'rational suicide' (Onkay-Ho, 2014).

The aim of this research was to find out whether depression formed an important link between disability and suicidal thoughts. Additionally, to find out: if there were differences in levels of depression and suicidal thoughts in different types of Multiple Sclerosis; whether those with certain types of disabilities (for example, mobility, difficulties with using their hands, problems with vision) experienced more suicidal thoughts than those who did not and finally, whether there were a sub-group of individuals who displayed 'rational suicide'.

Out-patients from Multiple Sclerosis clinics were asked to complete four questionnaires measuring: suicidal thoughts, depression, physical disability and how much the severity of their disability 'bothered' them.

The main findings of the research were that depression was an important link between disability and suicidal thoughts and when comparing different types of Multiple Sclerosis, there were no differences in levels of depression and suicidal ideation. However, there were differences found in levels of suicidal thoughts for those who reported being bothered by different types of disability for example tremors and not being able to do things spontaneously. Finally, a sub-group of individuals displaying 'rational suicide' and only minimal or mild symptoms of depression were identified.

The conclusion of the research, therefore, was that it is of vital importance for clinicians working with people with Multiple Sclerosis to regularly check whether patients are experiencing depression or any thoughts about harming themselves. The different types of disability found in this research for those who reported higher levels of suicidal thoughts need to be used as 'red flags', meaning that if patients are experiencing them, it could lead to depression and hence suicide. Therefore, these patients require careful monitoring.

2. References

Farrer, L.A., Opitz, J.M., & Reynolds, J.F. (1986). Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk. *American Journal of Medical genetics, 24*(2), 305-311.

Fox, S., Bloch, M., Fahy, M., & Hayden, M.R. (1989). Predictive testing for Huntington disease: I. Description of a pilot project in British Columbia. *American Journal of Medical Genetics, 32*(2), 211-216.

Hooper, K. (2013). *Managing Progressive Multiple Sclerosis*. New York: National Multiple Sclerosis Society.

Hubers, A. , van Duijn, E., Roos, R.A.C., Craufurd, D., Rickards, H., Bernhard Landwehrmeyer, G., . . . Giltay, E.J. (2013). Suicidal ideation in a European Huntington's disease population. *Journal of Affective Disorders, 151*(1), 248-258. doi: 10.1016/j.jad.2013.06.001

Hyphantis, T.N., Christou, K., Kontoudaki, S., Mantas, C., Papamichael, G., Goulia, P., . . . Mavreas, V. (2008). Disability status, disease parameters, defense styles, and ego strength associated with psychiatric complications of multiple sclerosis. *The International Journal of Psychiatry in Medicine, 38*(3), 307-327. doi: 10.2190/PM.38.3.g

Kingma, E. M., van Duijn, E., Timman, R., van der Mast, R. C., & Roos, R. A. C. (2008). Behavioural problems in Huntington's disease using the Problem Behaviours Assessment. *General Hospital Psychiatry, 30*(2), 155-161.

Kingwell, E., Marriott, J.J., Jetté, N., Pringsheim, T., Makhani, N., Morrow, S.A., . . . Kulaga, S. (2013). Incidence and prevalence of multiple sclerosis in Europe: a systematic review. *Bio Med Central Neurology, 13*(1), 128. doi: 10.1186/1471-2377-13-128

Lawson, K., Wiggins, S., Green, T., Adam, S., Bloch, M., Hayden, M. R., . . . Ives, E. (1996). Adverse psychological events occurring in the first year after predictive testing for Huntington's disease. *Journal of Medical Genetics, 33*(10), 856-862. doi: 10.1136/jmg.33.10.856

Onkay-Ho, A. (2014). Suicide: rationality and responsibility for life. *Canadian Journal of Psychiatry. Revue Canadienne de Psychiatrie, 59*(3), 141-147.

Paulsen, J.S., Langbehn, D.R., Stout, J.C., Aylward, E., Ross, C.A., Nance, M., . . . Beglinger, L.J. (2008). Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(8), 874-880. doi: 10.1136/jnnp.2007.128728

Sadovnick, A.D., Eisen, K., Ebers, G.C., & Paty, D.W. (1991). Cause of death in patients attending multiple sclerosis clinics. *Neurology, 41*(8), 1193-1193. doi: 10.1212/WNL.41.8.1193

Smith, M.M., & Arnett, P.A. (2013). Perfectionism and physical disability predict depression in multiple sclerosis. *Journal of Psychosomatic Research, 75*(2), 187-189. doi: 0.1016/j.jpsychores.2013.06.001

Turner, A.P, Williams, R.M, Bowen, J.D, Kivlahan, D.R, & Haselkorn, J.K. (2006). Suicidal Ideation in Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation, 87*(8), 1073-1078. doi: 10.1016/j.apmr.2006.04.021

Viner, R., Patten, S.B., Berzins, S., Bulloch, A.G.M., & Fiest, K.M. (2014). Prevalence and risk factors for suicidal ideation in a multiple sclerosis population. *Journal of Psychosomatic Research, 76*(4), 312-316. doi: 10.1016/j.jpsychores.2013.12.010

Wetzel, H., Gehl, C.R., Dellefave-Castillo, L., Schiffman, J.F., Shannon, K.M., Paulsen, J.S., & Huntington Study, Group. (2011). Suicidal ideation in Huntington disease: the role of comorbidity. *Psychiatry Research, 188*(3), 372-376. doi: 10.1016/j.psychres.2011.05.006

Literature Review Appendices

Appendix I. Search strategy for each database

OVID PsycINFO 1967 to April Week 2 2015 (final search 18.4.2015)

Subject headings:

Exp huntingtons disease (huntingtons chorea, chorea, genetic disorders)

Key words:

Huntington* disease

HD

Subject headings:

Exp suicide (includes: self destructive behaviour, assisted suicide, attempted suicide, death and dying, mental disorders, psychological autopsy, self injurious behaviour, suicide ideation, suicide prevention, suicidology)

Key words:

Suicid*

*Suicide

Search strategy:

#	Searches	Results
1	exp huntingtons disease/	2413
2	huntington* disease.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	3352
3	HD.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	3072
4	exp suicide/	21517
5	suicid*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]	47796
6	*suicide/	18133
7	1 or 2 or 3	4814
8	4 or 5 or 6	47796
9	7 and 8	64

OVID MEDLINE(R) 1946 to April Week 2 2015 (final search 18.4.2015)

Subject headings:

Exp Huntington disease

Key words:

Huntington* disease

HD

Subject headings:

Exp suicide (includes: suicide ideation, suicide-assisted, suicide-attempted)

Key words:

Suicid*

*Suicide

Search strategy:

#	Searches	Results
1	exp Huntington Disease/	9664
2	huntington* disease.mp.	12463
3	HD.mp.	25083
4	exp Suicide/	49209
5	suicid*.mp.	66023
6	*suicide/	22485
7	1 or 2 or 3	32749
8	4 or 5 or 6	66023
9	7 and 8	138

OVID EMBASE 1974 to April Week 2 2015 (final search 18.4.2015)

Subject headings:

Exp huntingtons disease (huntingtons chorea, chorea, genetic disorders)

Key words:

Huntington* disease

HD

Subject headings:

Exp suicide (includes: self destructive behaviour, assisted suicide, attempted suicide, death and dying, mental disorders, psychological autopsy, self injurious behaviour, suicide ideation, suicide prevention, suicidology)

Key words:

Suicid*

*Suicide

Search strategy:

Search Strategy:

#	Searches	Results
1	exp huntingtons disease/	19061
2	huntington* disease.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	14236
3	HD.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	39824
4	exp suicide/	44166
5	suicid*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	95369
6	*suicide/	26028
7	1 or 2 or 3	53772
8	4 or 5 or 6	95369

9	7 and 8	359

EBSCO CINAHL PLUS 1937 to April week 2 2015 (final search 18.4.2015)

Subject terms:

Huntington’s disease

Key words:

Huntington*

HD

Subject terms: Exp Suicide ideation (includes: suicide-attempted, suicide-assisted, suicide, suicide-risk)

Key words:

Suicid*

*Suicide

Search strategy:

#	Query	Limiters/Expander	Last Run Via	Result
S7	S3 AND S6	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	5
S6	S4 OR S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	3,365
S5	"suicid* OR *suicide"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	244
S4	(MH "Suicide ideation")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	3,176
S3	S1 OR S2	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	1,179

			Search Screen - Advanced Search Database - CINAHL Plus	
S2	"huntington* or HD"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	284
S1	(MH "Huntington's Disease")	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Plus	1,148

EBSCO AMED 1995 to April week 2 2015 (final search 18.4.2015)

Subject terms:

Huntington disease

Huntington’s disease

Huntingtons disease

Huntington’s chorea

Huntingtons

Key words:

Huntington*

HD

Subject terms:

Suicide

Suicide ideation

Suicide attempt

Suicide risk factors

Assisted suicide

Attempted suicide

Suicid*

*Suicide

Search strategy:

#	Query	Limiters/Expander	Last Run Via	Result
S18	S8 AND S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	8
S17	S9 OR S10 OR S11 OR S12 OR S13 OR	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	1,275

	S14 OR S15 OR S16		Database - AMED - The Allied and Complementary Medicine Database	
S16	*suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	1,225
S15	suicid*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	1,275
S14	attempted suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	49
S13	assisted suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	831
S12	suicide risk factors	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	12
S11	suicide attempt	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	49
S10	suicide ideation	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	50
S9	Suicide	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	1,225

S8	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	732
S7	HD	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	583
S6	huntington*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	180
S5	huntingtons	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	167
S4	huntingtons chorea	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	1
S3	huntingtons disease	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	24
S2	huntington's disease	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	72
S1	huntington disease	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - AMED - The Allied and Complementary Medicine Database	87

Appendix II. Full text papers considered and excluded

Articles detailing instances of suicide only (*n* = 5)

1. Causes of death in patients with Huntington's disease and in unaffected first degree relatives (Sorensen et al., 1992)

2. Epidemiology of Huntington's disease in Rijeka district, Yugoslavia (Sepčić, Antonelli, Šepić-Grahovac, & Materljari, 1989).

3. The length of survival and causes of death in Huntington's disease (Bryois, 1988)

4. Causes of death in Huntington's disease as reported on death certificates (Haines et al., 1986)

5. Huntington's Chorea in Norway (Saugstad & Odegard, 1986).

Articles investigating the association between neurobiology and suicidality (*n* = 1)

1. Hypothalamic-pituitary-adrenal axis functioning in Huntington's disease and its association with depressive symptoms and suicidality (Hubers et al., 2015).

Articles measuring attitudes to suicide in the future (*n* = 3)

1. Attitudes toward presymptomatic testing in Huntington disease (Mastromauro et al., 1987).

2. Death anxiety and psychometric studies in Huntington's disease (Gielen & Roche, 1979).

3. Psychosocial impact of Huntington's disease on Hong Kong families (Wong, Chang, Yu, Chan, & Chan, 1994).

Articles investigating physicians attitudes to assisted suicide (*n* = 1)

1. Continuous deep sedation, physician-assisted suicide, and euthanasia in Huntington's disorder (Lindblad, Juth, Fürst, & Lynöe, 2010)

Articles including children (*n* = 1)

1. Psychiatric and cognitive difficulties as indicators for juvenile Huntington's disease (Ribai et al., 2007).

Articles containing no analysis of factors associated with suicide (*n* = 14)

1. Thinking about end of life: a common issue for patients with Huntington's disease (Booij, Tibben, Engberts, Marinus, & Roos, 2014).

2. Characterisation of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study (Epping et al., 2013).

3. Longitudinal evaluation of neuropsychiatric symptoms in Huntington's disease (Thompson et al., 2012).

4. Experience over fifteen years with a protocol for predictive testing for Huntington disease (Dufrasne, Roy, Galvez, & Rosenblatt, 2011)

5. Factor analysis of behavioural symptoms in Huntington's disease (Rickards et al., 2011)

6. Clinical and genetic characteristics of Mexican Huntington's disease patients (Alonso et al., 2009).

7. Lamotrigine in motor and mood symptoms of Huntington's disease (Shen, 2008).

8. Depression and stages of Huntington's disease (Paulsen et al., 2005b).

9. Cognitive and Psychiatric Aspects of Huntington Disease Contribute to Functional Capacity (Nehl & Paulsen, 2004).

10. Attitudes regarding molecular diagnosis in Mexican families at risk of inheriting Huntington's disease (De la Cadena, Alonso. Ma, Ochoa, & Martinez, 1997).

11. Pre-symptomatic DNA testing for Huntington disease: identifying the need for psychological intervention (Tibben et al., 1993).

12. Predictive testing for Huntington's disease: ten years' experience in two Italian centres (Mandich et al., 1998).

13. Conditions associated with Huntington's disease at death: a case-control study (Lanska, Lanska, Lavine, & Schoenberg, 1988)

14. Psychiatric implications of presymptomatic testing for Huntington's disease (Kessler, 1987).

Articles containing analysis but not possible to extract factors related to suicide (*n* = 1)

1. Adverse psychological events occurring in the first year after predictive testing for Huntington disease (Lawson et al., 1996).

Appendix III. Final papers included in the review

1. Depressed Mood and Suicidality in Individuals Exposed to Tetrabenazine in a Large Huntington Disease Observational Study (Dorsey et al., 2013).
2. Suicide ideation in a European Huntington's disease population (Hubers et al., 2013).
3. Suicidality in Huntington's disease (Hubers et al., 2012).
4. Suicidal behavior in prodromal Huntington disease (Fiedorowicz et al., 2011).
5. Suicide ideation in Huntington disease: the role of comorbidity (Wetzel et al., 2011).
6. Depression and Suicide ideation After Predictive Testing for Huntington's Disease: A Two-Year Follow-up Study (Larsson et al., 2006).
7. Critical periods of suicide risk in Huntington's disease (Paulsen et al., 2005a).
8. Suicide in Hungarian Huntington's disease patients (Baliko et al., 2004).
9. Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease (Almqvist et al., 2003).
10. Behavioural complaints in participants who underwent predictive testing for Huntington's disease (Witjes-Ané et al., 2002).
11. High suicide ideation in persons testing for Huntington's disease (Robins Wahlin et al., 2000).
12. A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease (Almqvist et al., 1999).
13. Onset symptoms in 510 patients with Huntington's disease (Di Maio et al., 1993).
14. Risk factors for suicide in Huntingtons disease: A retrospective case controlled study (Lipe et al., 1993).
15. Suicide and attempted suicide in Huntington disease: implications for preclinical testing of persons at risk (Farrer, et al., 1986).

16. Increased rate of suicide among patients with Huntington's disease (Schoenfeld et al., (1984).

Appendix IV. Data extraction form

General Information

Study ID:

Quality criteria score:

Authors:

Year:

Title:

Location of study:

Focus of study:

The psychological impact of genetic testing □

Suicide ideation over stages of HD □

Risk factors associated with suicide □

To assess the prevalence of suicidality □

Study Eligibility

Aims/objectives:

Hypothesis:

Rationale:

Design: Cross sectional □ Cohort □ Longitudinal □

Inclusion/Exclusion criteria:

Participants

Population description:

At risk (first degree relative) □

'Mutation' carrier/CAG repeat extraction/Expanded CAG repeat (increased risk) / Normal CAG length (decreased risk) □

‘Non-mutation’ carrier □

Minor soft signs □

Motor symptoms □

Definite diagnosis □

Any additional information:

Method of recruitment:

Number of participants invited to participate:

Number of participants who participated:

Response rate:

Age:

Gender:

Ethnicity:

Other relevant socio-demographic variables:

Times of follow-up:

Number of participant lost at follow-up:

Procedure

Method for data collection:

Outcome measures

Suicide:

Validity/Reliability:

Other measures:

Analyses

Statistical procedure:

Missing data? Yes □ No □ Not mentioned □

How was missing data accounted for?

Results

Dichotomous outcome (e.g. odds ratio, risk ratio, confidence intervals, p-value) □

Continuous outcome (e.g. mean difference, confidence intervals) □

Key significant results:

Importance of significance:

Magnitude of effect:

Additional information:

Conclusions

Main findings:

Limitations:

Generalisability:

Implications for clinical practice:

Appendix V. Quality assessment tool (self designed)

Key:

NICE (2012) ♦

Caldwell, Henshaw, and Taylor (2011) ∅

Smith (2009) ♠

Von Elm et al. (2007) ♣

Thompson, Diamond, McWilliam, Snyder, and Snyder (2005) ∗

Kmet, Lee, and Cook (2004) ⊗

Thomas, Ciliska, Dobbins, and Micucci (2004) ♥

Downs and Black (1998) ⊕

Fowkes and Fulton (1991) #

Objective and rationale
1. Are the hypotheses/aims and objectives of the study clearly stated? # • **Yes** – Identified clearly in the introduction or method section conveying what the study is aiming to achieve. • **Partially** – Vague description, unclear objective, or not easily identifiable in introduction or method section. • **No –** No reporting of hypotheses/aims or objectives. • **NA –** Question not applicable to this study.
2. Is the rationale for the study clearly outlined? ∅ • **Yes –** Clear rationale described in the context of current issues and previous research. • **Partially –** Vague rationale or missing context of current issues. • **No –** Inappropriate rationale or none described. • **NA –** Question not applicable to this study.
Design and setting
3. Is the study design evident and appropriate? ⊗ • **Yes** – Easily identifiable and appropriate choice of design in introduction or method. • **Partially –** Not easily identifiable or reported in discussion section. • **No –** Not evident or inappropriate. • **NA –** Question not applicable to this study.
4. Is the setting, location, period(s) of recruitment, and data collection described? ♣ • **Yes** – Clear description and thoroughly detailed. • **Partially** – Not all aspects described or confusing. • **No** – No description or only one of the above. • **NA –** Question not applicable to this study.

Study sample and representativeness
5. Is the population identified? ∅ • **Yes –** Yes clearly identified with sources of recruitment reported. • **Partially –** Unclear description, some information omitted or does not include all populations recruited from. • **No –** Not reported. • **NA –** Question not applicable to this study.
6. Are the main characteristics of the participants clearly described, including eligibility criteria of the sample (if appropriate)? ⊗ • **Yes –** Eligibility criteria are easily identified and the main characteristics are clearly provided (e.g. gender, age) or there is reference to a previous study cited. • **Partially –** Incomplete or unclear reporting of characteristics and eligibility criteria. • **No –** Baseline, eligibility criteria and categorisation omitted. • **NA –** Question not applicable to this study.
7. Is it reported that the sample size is considered to have sufficient power to detect a clinically relevant result? # • **Yes –** It is reported that the sample size has sufficient power, at a certain level of significance and this is why it was selected. • **Partially –** Power is considered when reporting results and is sufficient or a large sample size is reported as a strength of the study. • **No –** No reference as to whether sample size is considered to have enough power or sample size reported to be too small. • **NA –** Question not applicable to this study e.g. retrospective review of case notes.
8. Are the response rates reported and the impact of non-respondents considered? # • **Yes –** Response rate is reported and the impact of non-respondents is considered. • **Partially –** Response rate is reported but non-respondents are not considered. • **No –** No reporting of response rate and no reporting about non-respondents. • **NA –** Question not applicable to this study e.g. retrospective review of case notes.
Internal validity
9. Have the proportion and characteristics of participants lost to follow-up been described and considered? ⊕ • **Yes –** Proportion of drop outs and characteristics reported, with possible reasons described in order to consider bias. • **Partially –** Proportion to follow-up reported but no possible biases discussed. • **No –** No reporting of proportion or characteristics. • **NA –** Question not applicable to this study e.g. cross sectional study.
10. Is the/are the suicide outcome measure(s) validated and reliable? ♦ • **Yes –** Widely used standardised and validated measure(s) with good reliability. • **Partially –** Validated measure but one or two items extrapolated, or whole non-validated measure which has been used by other studies, or suicide information has come from potentially unreliable data e.g. death certificate, case notes, medical records. • **No –** Unreliable measure, prone to subjectivity and possible error e.g. self designed interview or question. • **NA –** Question not applicable to this study.
11. Does the sample appear representative of the population? ♥ • **Yes –** Sample appears representative of the population from which it is drawn and

typical of wider population e.g. nationwide or worldwide recruitment.
- **Partially –** Unclear or possible bias: recruited from a voluntary register or referred from one source e.g. one local clinic or similar.
- **No –** Sample does not appear representative of population, or not enough information provided.
- **NA –** Question not applicable to this study.

Data analysis

12. Are the statistical tests used to analyse data clearly described and appropriate? ⊕
- **Yes –** Statistical tests are described and appropriate.
- **Partially –** Complex description, or had to be guessed at but probably appropriate, or minor flaws identified.
- **No –** Obviously inappropriate methods utilised.
- **NA –** Question not applicable to this study e.g. frequencies reported only.

13. If missing data is reported is there a description for how this was considered and accounted for? #
- **Yes –** Missing data was reported and accounted for in the statistical analysis.
- **Partially –** Missing data was reported but it is unclear how this has been accounted for or bias considered.
- **No –** Missing data is evident but has not been reported or addressed.
- **NA –** Question not applicable to this study/no missing data evident and it is presumed there is none.

14. Are significant effects identified and the importance of the significance reported? ♠
- **Yes –** The results are expressed statistically, relative to the level of significance set for the null-hypothesis and the p-value is given relative to the significance level (e.g. $p < 0.05$ or $p < 0.01$).
- **Partially –** Vague, inappropriate or confusing reporting, or the importance of the significance omitted for some effects.
- **No –** Significant effects and the importance of the significance are not reported.
- **NA –** Question not applicable to this study e.g. frequencies reported only.

15. Are confidence intervals or measures of variance reported for the statistics (e.g. means, correlation coefficients)? ∗
- **Yes –** Appropriate confidence intervals or measures of variance are reported (e.g., confidence estimates, intervals, standard errors, range, and standard deviations).
- **Partially –** Confidence intervals or variance estimates are reported for some but not all main outcomes.
- **No –** No reporting of confidence intervals or variance estimates.
- **NA –** Question not applicable to this study.

Results

16. Does the study clearly report key results, in sufficient detail, with reference to study objectives? ♣
- **Yes –** Presentation of key results is clear, consistent and easily interpreted with reference to study objectives.
- **Partially –** Vague reporting, insufficient detail or lack of reference to study objectives.
- **No –** Results are not reported clearly therefore, with no reference to study objectives.
- **NA –** Question not applicable to this study.

External validity and practical/clinical significance
17. Do the significant effects provide an idea of the magnitude of the effect?* • **Yes –** Significant effects clearly identified and the magnitude of the effect communicated (e.g. odds ratios, hazard ratios, difference in scores on measures, difference between means, percentage difference, chi-square, r^2, Cohen's d and f, eta^2, proportion of participants) • **Partially –** Vague or confusing reporting, or magnitude omitted for some primary outcomes. • **No –** Magnitude of effect not reported. • **NA –** Question not applicable to this study e.g. frequencies reported only.
18. Does the study discuss the generalisability of the results? ∅ • **Yes –** Clear discussion of the generalisability of the results to the wider population. • **Partially –** Vague description about whether results can be generalised, some acknowledgement of comparison with general population, or sample is highlighted as representative and therefore generalisable. • **No –** No mention of the generalisability of the results. • **NA –** Question not applicable to this study.
Discussion and conclusions
19. Are limitations of the study discussed taking into account potential bias? ♣ • **Yes –** Thorough reporting of limitations and how potential bias/confounding variables may impact upon results. • **Partially –** Some discussion of limitations but reporting of other clear limitations has been omitted. • **No –** Limitations are not reported or considered. • **NA –** Question not applicable to this study.
20. Is caution given to the overall interpretation of the results taking into consideration: aims, limitations, results from similar research, and any other relevant evidence? ♣ • **Yes –** Cautious overall interpretation of results reported, considering all aspects of limitations and other relevant evidence. • **Partially –** Some caution displayed and discussed with reference to limitations or relevant evidence. • **No –** Interpretation of results is not written with caution, no consideration of aims, limitations, results from similar research, and any other relevant evidence. • **NA –** Question not applicable to this study.
21. Is the conclusion clear and reinforced by the results? ⊗ • **Yes –** Yes conclusion is clear and reinforced by the results. • **Partially –** Conclusion is written but is vague or not fully supported by results. • **No –** No conclusion or key findings unaddressed. • **NA –** Question not applicable to this study.
Yes – GREEN (2) **Partially – ORANGE (1)** **No – RED (0)** **NA – Not applicable PURPLE (0)** **Score (%) =** Total sum divided by total possible sum x 100

Appendix VI. Methodological issues

Table 1. Main methodological issues identified in the studies

Methodological issue	Explanation
Selection bias	Participants are less likely to be representative if they are not selected at random from a comprehensive list of individuals who are all in the target population (Thompson et al., 2005). No studies in this review reported random sampling and several were recruited either from a single medical centre/hospital (Larsson et al., 2006) as opposed to national or worldwide multi-site centres (Wetzel et al., 2011; Paulsen et al., 2005 (Dorsey et al., 2013). Some recruited from those who had joined a voluntary register to participate in research (Di Maio, 1993 (Farrer et al., 1986).
Response rate	It is common in research studies that some individuals do not respond to the invitation to participate, some refuse and some do not attend when required; therefore, the response rate is viewed as an indicator of the representativeness of the participants (Fowkes & Fulton, 1991). The response rate and consideration of those who chose not to participate was reported in only two studies (Larsson et al. 2006; Almqvist et al., 1999).
Representativeness of the sample	Studies which received full marks for the representativeness of the sample were those which recruited participants who had decided to undergo predictive testing (Fiedorowicz et al., 2011; Almqvist et al., 2003). Those who undergo genetic testing, however, are a self-selected sample (Almqvist et al., 2003). In other words, individuals who chose to undergo predictive testing may well be more confident and capable to deal with possible 'bad news' which is likely to have contributed significantly to their choice to undergo the testing (Codori, Hanson, & Brandt, 1994; Marteau & Croyle, 1998). People who undergo testing also receive substantial support and counselling (Almqvist et al. 2003).
Reliability and validity of the suicide measure	The use of a validated and reliable outcome measure in research is essential so that the measure consistently measures both a particular outcome and what it claims to (NICE, 2012). No study in this review utilised a whole measure considered both validated and reliable to measure suicidality. In some studies a psychiatrist or psychologist administered the measures (Hubers et al., 2013; Witjes-Ané et al., 2002) which is a strength.
Retrospective cohort studies	Retrospective studies use data which already exists and has been collected for other purposes; heavy reliance on the accuracy of written records means that it is difficult to control for bias and confounding variables (Hess, 2004). The six retrospective cohort studies in this review have utilised: death certificates, medical records, reports from relatives, social work notes, genetic counselling files and a Huntington's disease register (e.g. Baliko et al.,2004; Almqvist et al., 1999; Di Maio et al., 1993; Lipe et al., 1993; Farrer et al., 1986 and Schoenfeld et al., 1984). Some literature has questioned the use of medical records and death certificates as the recording has been proven to be relatively inaccurate (Alderson & Meade, 1967; Glasser, 1981; Haines et al., 1986).
The accuracy of suicide information	In people who have serious physical disease there is a tendency to ignore the possibility of suicide and classify the death as due to the health condition (Stenager & Stenager, 1992). Sainsbury and Jenkins (1982) even suggested that official suicide statistics have been questioned so much due to variation in defining and reporting cases, inaccuracies in reporting information, that some authorities made a decision to dismiss the usefulness of the information for epidemiological research generally.

The accuracy of death certificates	In Britain the reported accuracy rate of death certificates has been found to be as low as 61% (Alderson & Meade, 1967). Haines et al. (1986) suggested that suicides are underestimated because of possible inaccurate recording of death. Studies which have used a combination of sources for each participant for example death certificates, medical records and reports from relatives such as the studies by: Baliko et al. (2004), Farrer et al. (1986) and Schoenfeld et al. (1984) are likely to be more accurate.

Appendix VII. Study origins and authors

The origin of each study and where participants were recruited from is displayed in Table 2 below.

Table 2. Origins and recruitment sites for each study

Origin	Studies	Recruitment sites
The Netherlands	Hubers et al. (2013) in partnership with authors from Germany and the UK	15 European countries (REGISTRY)
	Hubers et al. (2012)	Leiden University Medical Centre and a local nursing home
	Witjes-Ané et al. (2002)	Sites in the Netherlands where genetic testing is available.
USA	Dorsey et al. (2013)	48 sites (HSG) in USA, Australia and Canada
	Wetzel et al. (2011)	43 sites (HSG) in USA, Australia and Europe
	Fiedorowicz et al. (2011)	32 sites in USA, Canada, Europe and Australia (PREDICT-HD)
	Paulsen et al. (2005a)	42 sites (HSG) in USA, Australia and Europe
	Di Maio et al. (1993) in partnership with authors from Italy	National American research roster (NHDRR)
	Lipe et al. (1993)	University of Washington and a local medical centre
	Farrer et al. (1986)	National American research roster (NHDRR)
	Schoenfeld et al. (1984)	New England Huntington's Disease Centre and Massachusetts Chapter of Committee to Combat Huntington's
Sweden	Larsson et al (2006)	Karolinska University of Hospital
	Robins Wahlin et al. (2000)	Huntington's predictive testing programme in Sweden
Canada	Almqvist et al. (2003)	Canadian Study Group (CCSG)
	Almqvist et al. (1999) in partnership with authors in the UK	Sites in Australia, Belgium, Germany, France, Netherlands, Sweeden, UK, USA via an Huntington's association (IHA) and research group (WFN-HD)
Hungary	Baliko et al. (2004)	Via physicians, neurologists and psychiatrists working in Hungary

The above table shows that several of the studies included in this review recruited participants from a large number of European sites which is clearly advantageous. There was potential overlap in the sourcing of participants for Wetzel et al. (2011) and Paulsen et al. (2005a) who used participants from HSG; and Di Maio et al. (1993) and Farrer et al. (1986) who both recruited from the same national research roster (NHDRR).

In seven of the studies there is an overlap in authors; these are displayed in Figure 1 below. The vertical axis is used to identify which studies from the horizontal axis contain one or more of the same authors. For example, the study by Hubers et al. (2013) contains some of the same authors as the studies by Hubers et al. (2012), Almqvist et al. (2003), Witjes-Ané et al. (2002) and Almqvist et al. (1999). Exactly which authors are detailed in Table 3 below.

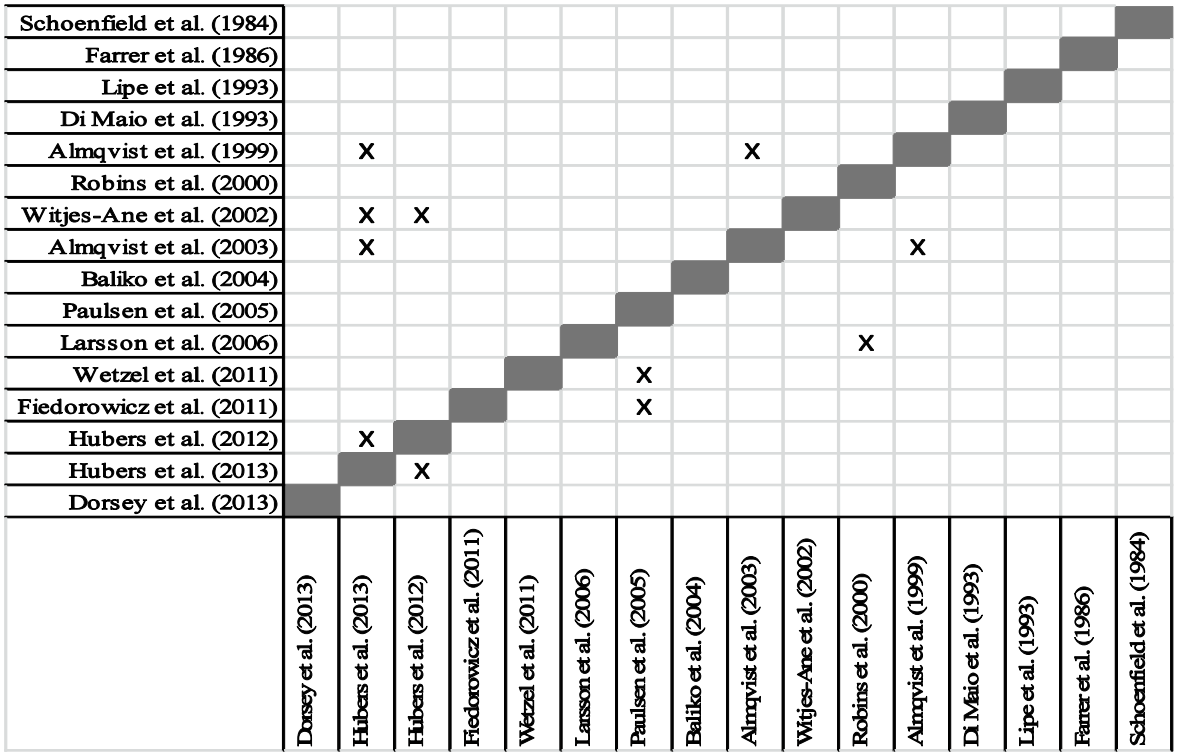


Figure 1. Scatterplot to illustrate the overlap of authors in the studies

Table 3. Authors which have been included in more than one study

Author	Studies
Hubers, A.	Hubers et al. (2013) - first author
	Hubers et al. (2012) - first author
Van Duijn, E.	Hubers et al. (2013)
	Hubers et al. (2012)
Van der Mast, R.	Hubers et al. (2013)
	Hubers et al. (2012)
Roos, R.	Hubers et al., (2013)
	Hubers et al., (2012)
	Witjes-Ané et al. (2002)
Craufurd, D.	Hubers et al. (2013)
	Almqvist et al. (2003)
	Almqvist et al. (1999)
Paulsen, J.	Paulsen et al. (2005) - first author
	Fiedorowicz et al. (2011)
	Wetzel et al. (2011)
Robins Wahlin, T.	Robins Wahlin et al. (2000) - first author
	Larsson et al. (2006)
Almqvist, E.	Almqvist et al. (2003)
	Almqvist et al. (1999)
Hayden, M.	Almqvist et al. (2003)
	Almqvist et al. (1999)

Appendix VIII. Demographics

Table 4. Demographic characteristics of participants

Characteristic	Studies from which data were extracted
Gender:	
59% female, 41% male	Dorsey et al. (2013) Hubers et al. (2013) Hubers et al. (2013) Fiedorowicz et al. (2011) Wetzel et al. (2011) Larsson et al. (2006) Paulsen et al. (2005a) Baliko et al. (2004) Almqvist et al. (2003) Witjes-Ané et al. (2002) Robins Wahlin et al. (2000) Almqvist et al. (1999) Lipe et al. (1993)
Age (mean):	
42.4 years of age	Dorsey et al. (2013) Hubers et al. (2013) Hubers et al. (2013) Fiedorowicz et al. (2011) Wetzel et al. (2011) Larsson et al. (2006) Paulsen et al. (2005a) Almqvist et al. (2003) Witjes-Ané et al. (2002) Robins Wahlin et al. (2000) Almqvist et al. (1999)
Age (range):	
Youngest – 18 years of age Oldest – 90 years of age	Witjes-Ané et al. (2002) Paulsen et al. (2005a) Other studies which recorded range: Almqvist et al. (2003) Robins Wahlin et al. (2000) Lipe et al. (1993)
Race:	
Caucasian made up the largest race	Dorsey et al. (2013) Wetzel et al. (2011) Paulsen et al. (2005a) Farrer et al. (1986)
Marital/partner status:	
59% were married	Dorsey et al. (2014)
67% had a partner	Larsson et al. (2006)
74% had a partner	Almqvist et al. (2003)
Offspring:	
58% had one or more children	Larsson et al. (2006)
60% had one or more children	Almqvist et al. (2003)
Employment status:	
19.8% employed	Dorsey et al. (2013)
79% employed	Almqvist et al. (2003)
47% as ‘unskilled’ workers, 28% as ‘skilled’ and 25% as ‘academic’	Larsson et al. (2006) and Robins Wahlin et al. (2000)
Education status:	
12.9 years – average time spent in education	Fiedorowicz et al. (2011)

72% of participants had completed high school or a greater qualification	Wetzel et al. (2011) Larsson et al. (2006) Paulsen et al. (2005a) Robins Wahlin et al. (2000) Dorsey at al. (2013) Almqvist et al. (2003) Witjes-Ané et al. (2002)

It can be seen from the above table that for some studies information was either omitted or was impossible to extract.

Appendix IX. Descriptions of suicide outcome measures

UHDRS-b (Huntington Study Group, 1996) - specifically designed for Huntington's, a standardised clinical rating scale which assesses four components: motor (e.g. gait oculomotor function, dystonia, gait) cognitive (e.g. symbol digit modalities test, letter fluency, stroop colour) functional (i.e. total functioning, e.g. independence scale, functional checklist) and psychiatric (Wetzel et al., (2011). It assesses the month prior to the interview. 14 psychiatric symptoms are assessed e.g. suicidal thoughts, anger, anxiety, paranoid thinking, low mood, hallucinations (Wetzel et al., 2011). The item 'suicidal thoughts' measures the frequency and severity of suicidal thoughts in the month preceding the interview (Hubers et al., 2013). Suicidal thoughts item = feels life not worth living, has suicidal thoughts, active suicidal intent, preparation for the act. Scoring: the severity and frequency of each item is rated on a 5 point scale. Severity: 0 = absent; 1 = slight/questionable; 2 = mild; 3 = moderate; 4 = severe. Frequency: 0 = almost never; 1 = seldom, 2 = sometimes, 3 = frequently; 4 = almost always.

PBA (Craufurd et al., 2001) - specifically designed for Huntington's, this measure assesses the frequency and severity of 36 common behavioural problems. It rates behaviour in the last month, focussing on three clusters of symptoms: apathy, depression and irritability. The depression subscale consists of five items: 'depressed' mood', 'depressive cognitions', 'anxiety', 'tension' and 'suicide ideation' (Hubers et al., 2015). One question of two parts asks about the severity and frequency of suicide ideation in the last month (Hubers et al., 2012). Scoring: each symptom is rated for severity and frequency on a 5 point scale according to scoring criteria. Severity: 0 = not at all; 1 = trivial; 2 = mild; 3 = moderate (disrupting everyday activities) and 4 = severe/intolerable. Frequency: 0 = symptom absent; 1 = less than once weekly; 2 = at least once a week; 3 = most days (up to and including some part of everyday); and 4 = all day, every day.

BDI –II (Beck et al., 1996) - this measure is used predominantly to measure depression, it is a self-report questionnaire of 21 symptoms and attitudes, rated from 0 to 3 in terms of intensity e.g. mood, sense of failure, feelings of guilt, suicidal wishes, self-dislike (Robins Wahlin et al., 2000).

BHS (Beck & Steer, 1988) - a self-report measure of 20 statements to assess beliefs about the future over the past week, each statement is rated as true or false and the total score reflects negative tendencies of the respondent (Steed, 2001).

SIBS (Fox et al., 1989) - designed specifically for Huntington's, this self-report measure assesses extent of suicidal thoughts and attempts (both previous and current levels, as well as prediction of future possible tendencies) on a scale of 0 never to 4 very often, as well as quality of life and coping resources (Robins Wahlin et al., 2000). It includes a question about the suicidal history of participants and relatives, as well psychiatric history. Questions evaluate previous and current levels of thoughts or attempts and include expected reactions if symptoms develop (Larsson et al., 2006).

Appendix X. Descriptions of other outcome measures

Apathy:

AS (Starkstein et al., 1992) - a semi structured interview consisting of 14 questions to determine level of apathy (Hubers et al., 2012).

Depression:

BDI (Beck et al., 1996) - see Appendix IX.

PBA(Craufurd et al., 2001) - see Appendix IX.

Lipe et al. (1993) – self-designed questionnaire used to review medical records which defined depression as either a diagnosis by a neurologist or psychiatrist, or three of a number of symptoms e.g. weight loss, appetite decrease, sleep difficulties, sadness, worthlessness. The questionnaire also recorded social support and the presence alcohol misuse (Lipe et al., 1993).

Cognitive functioning:

MMSE (Folstein et al., 1975) - used to determine global level of cognitive functioning by assessing memory, language and attention (Hubers et al., 2012).

UHDRS-b (Huntington Study Group, 1996) - see Appendix IX.

Fox et al. (1989) protocol:

SIBS - see Appendix IX.

LSI (Fox et al., 1989) - measured how satisfied participants were with different domains of life experience e.g. leisure time, work, health, social life, family life and total life satisfaction; scores range from 0-7, totally dissatisfied to very satisfied (Robins Wahlin et al., 2000).

LSA (Fox et al., 1989) - acquired information about social and medical background, present circumstances and future plans e.g. no of daily cigarettes smoked, alcohol consumption, sleeping problems, money spent, use of prescription medications (Larsson et al., 2006).

GHQ-30 (Goldberg & Williams, 1988) - measured psychological health and wellbeing as well as: depression, anxiety, somatic complaints and social dysfunction, it is self-report and assesses whether a person has experienced less or more of a different condition than usual (Robins Wahlin et al., 2000).

Wellbeing measure (Robins Wahlin et al., 2000) - a self-report 150 millimetre long line is used, with a cross mark to estimate sense of well-being for the last 3 days; left hand side: very poor wellbeing and right hand side: excellent, range 0-150, participants then were asked to name the problem (Larsson et al., 2006).

One study used one additional measure alongside the Fox protocol:

AttQ (Robins Wahlin et al., 2000) - a self-designed measure assessing attitude to predictive testing e.g. what age participants learned about the risk, the reasons for deciding to have the predictive test, who they would tell results to (Robins Wahlin et al., 2000).

GSI from the SCL90-R (Derogatis, 1983) - a self-report questionnaire used to measure psychiatric distress/ psychopathology. GSI is the overall mean score of the nine subscales (somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism). Described as frequently used in research and well validated (Larsson et al., 2006).

GWB (Dupuy, 1969) - a self-report questionnaire to measure psychological mood. Described as frequently used in research and well validated (Larsson et al., 2006).

Life experiences:

LES (Sarason et al., 1978) - an assessment of life changes in the previous 12 months and whether these are perceived as positive or negative in relation to relationships, work and health (Fiedorowicz et al., 2011).

Motor functioning:

UHDRS-b (Huntington Study Group, 1996) - see Appendix IX.

Psychiatric disorder:

CIDI (World Health Organisation 1997) - a completely standardised interview used to assess presence of psychiatric disorder according to DSM IV (APA, 2000), (Hubers et al., 2012).

MMSE (Folstein et al., 1975) - used to determine global level of cognitive functioning by assessing memory, language and attention (Hubers et al., 2012).

Psychiatric status:

PSS (Spitzer et al., 1970) - a standardised interview used to measure psychopathology including: levels of depression, anxiety, grandiosity, behaviour and misuse of alcohol (Fiedorowicz et al., 2011)

Total functioning:

UHDRS-b (Huntington Study Group, 1996) - see Appendix IX.

Appendix XI. Tables to display the findings of studies in relation to each risk factor

Tables A-H below, detail the findings and quality scores of studies in relation to each risk factor. Information is displayed for suicide ideation and/or attempted and completed suicide.

Table A: Psychiatric symptoms and history

Table B: Suicidality in the past

Table C: Proximity to genetic testing

Table D: Genetic testing result

Table E: Age at onset and proximity to 'formal' diagnosis

Table F: Results of neurological examination, stage of disease and symptom severity

Table G: Estimated disease duration

Table H: Medication

Table I: Other

Table A. Psychiatric symptoms and history

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Psychiatric symptoms and history						**Psychiatric symptoms and history**					
Depressed mood	Hubers et al. (2013) baseline & longitudinal	83.3	UHDRS-b	UHDRS-b	Sig	Depressed mood	Almqvist et al. (2003) attempted suicide	85.7	Medical records	BDI	Yes
	Hubers et al. (2012) baseline & longitudinal	90.5	PBA	PBA	Sig		Lipe et al. (1993) completed suicide	35.3	Medical records	Medical records (3 symptoms)	Yes
	Fiedorowicz et al. (2011) longitudinal	85.7	UHDRS-b & BDI & BHS	BDI	Sig						
	Wetzel et al. (2011) Cross-sectional	85.0	UHDRS-b	BDI	Sig						
Anxiety	Hubers et al. (2013) baseline	83.3	UHDRS-b	UHDRS-b	Sig	Psychiatric distress (inc. anxiety)	Almqvist et al. (2003) attempted suicide	85.7	Medical records	GSI	Yes
	Wetzel et al. (2011)	85.0	UHDRS-b	UHDRS-b	Sig	In psychiatric hospital at time of death	Schoenfeld et al. (1984) completed suicide	79.4	Death certificates	Medical records	Yes
	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	PSS	Non sig						

Apathy	Hubers et al. (2013) Baseline	83.3	UHDRS-b	UHDRS-b	Sig						
Irritability	Hubers et al. (2013) baseline	83.3	UHDRS-b	UHDRS-b	Sig						
Aggression	Hubers et al. (2013) baseline	83.3	UHDRS-b	UHDRS-b	Sig						
	Wetzel et al. (2011)	85.0	UHDRS-b	UHDRS-b	Sig						
Psychiatric history	Larsson et al. (2006)	78.6	SIBS	SIBS	Sig	Psychiatric history	Almqvist et al. (2003) attempted suicide	85.7	Medical records	Medical records	Yes
Alcohol misuse	Wetzel et al. (2011)	85.0	UHDRS-b	A question	Sig	Alcohol misuse	Lipe et al. (1993) completed suicide	35.3	Medical records	Medical records	No
	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	PSS	Non sig						
Grandiosity	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	PSS	Non sig						
Tobacco/drug use	Wetzel et al. (2011)	85.0	UHDRS-b	A question	Non sig						

Table B. Suicidality in the past

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Suicidality in the past						**Suicidality in the past**					
Previous suicide attempt(s)	Hubers et al. (2013)	83.3	UHDRS-b	A question	Sig	Previous suicide attempt(s)	Fiedorowicz et al. (2011) completed suicide	85.7	UHDRS-b & BDI & BHS	Previous attempts recorded in an event log	Yes
	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	Previous attempts recorded in an event log	Sig		Farrer et al. (1986) completed suicide	36.8	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	Yes
Previous attempted or completed suicide in family members	Robins Wahlin et al. (2000)	85.0	SIBS	A question	Yes	Previous attempted or completed suicide in family members	Baliko et al. (2004) completed suicide	46.7	Death certificates, medical records, relative reports	Death certificates, medical records, relative reports	Yes
							Almqvist et al. (2003) attempted suicide	85.7	Medical records	BDI	Yes
							Di Maio et al. (1993) completed suicide	44.1	HD register information	HD register information	Yes
							Lipe et al.	35.3	Medical	Medical	No

							(1993) completed suicide		records	records	
							Schoenfeld et al. (1984) completed suicide	79.4	Death certificates	Medical records	Yes

Table C. Proximity to genetic testing

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Proximity to genetic testing						**Proximity to genetic testing**					
Testing result received 1 year before study or longer	Hubers et al. (2012) baseline & longitudinal	90.5	PBA	A question	Non sig	Day of result, waiting, and 4 years after.	Almqvist et al. (2003) attempted suicide	85.7	Medical records	Medical records	Yes
						Shorter time period following result	Almqvist et al. (1999) completed suicide	85.0	Medical records	Medical records	Yes

Table D. Genetic testing result

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Genetic testing result						**Genetic testing result**					
Number of CAG repeats	Hubers et al. (2013)	83.3	UHDRS-b	Electronic case report forms	Non sig						
	Hubers et al. (2012)	90.5	PBA	Electronic case report forms	Non sig						
	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	Medical records	Non sig						
‘Mutation’ carrier status	Robins Wahlin et al. (2000)	85.0	SIBS	A question	Sig	‘Decreased risk’ result	Almqvist et al. (2003) attempted suicide	85.7	Medical records	Medical records	Yes
	Hubers et al. (2012)	90.5	PBA	A question	Sig	‘Possibly at risk’	Di Maio et al. (1993) completed suicide	44.1	HD register information	HD register information	Yes
	Larsson et al. (2006)	78.6	SIBS & a question about possible future suicidal thoughts	A question	Sig	‘At risk’	Lipe et al. (1993) completed suicide	35.3	Medical records	Medical records	Yes
	Witjes-Ané et al. (2002)	87.5	UHDRS-b	A question	Non sig						

Table E. Age at onset and proximity to ‘formal’ diagnosis

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Age at onset						**Age at onset**					
						Younger age at onset	Baliko et al. (2004) completed suicide	46.7	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	Yes
							Di Maio et al. (1993) completed suicide	44.1	HD register information	HD register information	No
							Farrer et al. (1986) completed suicide	36.7	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	No
Proximity to ‘formal’ diagnosis						**Proximity to ‘formal’ diagnosis**					
>15 years <9 years	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	A question	Non sig						

Table F. Results of neurological examination, disease stage and symptom severity

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Results of diagnosis and symptom severity						**Results of diagnosis and symptom severity**					
'Non-specific motor abnormalities'	Paulsen et al. (2005a)	86.8%	UHDRS-b	UHDRS-b	Sig	Symptomatic, 'suspected' & recently diagnosed	Almqvist et al. (1999) completed suicide	85.0	Medical records	Medical records	Yes
'Motor abnormalities indicating possible HD'	Paulsen et al. (2005a)	86.8%	UHDRS-b	UHDRS-b	Sig	'Suspected'	Schoenfeld et al. (1984) completed suicide	79.4	Death certificates	Medical records	Yes
Cognitive functioning	Hubers et al. (2012)	90.5	PBA	UHDRS-b	Non sig	'Possibly affected'	Di Maio et al. (1993) completed suicide	44.1	HD register information	HD register information	Yes
	Wetzel et al. (2011)	85.0	UHDRS-b	MMSE	Non sig	Affected	Lipe et al. (1993) completed suicide	35.3	Medical records	Medical records	Yes
Total functioning	Hubers et al. (2012)	90.5	PBA	UHDRS-b	Non sig	Symptomatic ('formally' diagnosed)	Schoenfeld et al. (1984) completed suicide	79.4	Death certificates	Medical records	Yes
	Wetzel et al. (2011)	85.0	UHDRS-b	MMSE	Non sig						
	Hubers et al. (2013)	83.3	UHDRS-b	UHDRS-b	Non sig						
Motor functioning	Hubers et al. (2012)	90.5	PBA	UHDRS-b	Non sig						
	Wetzel et al. (2011)	85.0	UHDRS-b	MMSE	Non sig						

	Hubers et al. (2013)	83.3	UHDRS-b	UHDRS-b	Non sig						
	Fiedorowicz et al. (2011)	85.7	UHDRS-b & BDI & BHS	UHDRS-b	Non sig						
Earlier stages of the disease	Paulsen et al. (2005a)	86.8	UHDRS-b	UHDRS-b	Sig	Early or late stage of the disease	Baliko et al. (2004) completed suicide	46.7	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	Yes
Later stages of the disease	Larsson et al. (2006)	78.6	SIBS & a question about possible future suicidal thoughts	A question	Yes	Early to middle stages	Farrer et al. (1986) completed suicide	36.7	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	Yes
						Within one year of onset	Lipe et al. (1993) completed suicide	35.3	Medical records	Medical records	Yes
						Early stages	Schoenfeld et al. (1984) completed suicide	79.4	Death certificates	Medical records	Yes

Table G. Estimated disease duration

Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Estimated disease duration						**Estimated disease duration**					
Shorter	Hubers et al. (2013)	83.3	UHDRS-b	UHDRS-b	Sig	Shorter	Di Maio et al. (1993) completed suicide	44.1	HD register information	HD register information	Yes
	Hubers et al. (2012)	90.5	PBA	UHDRS-b	Non sig		Farrer et al. (1986) completed suicide	36.7	Death certificates, medical records, reports from relatives	Death certificates, medical records, reports from relatives	Yes

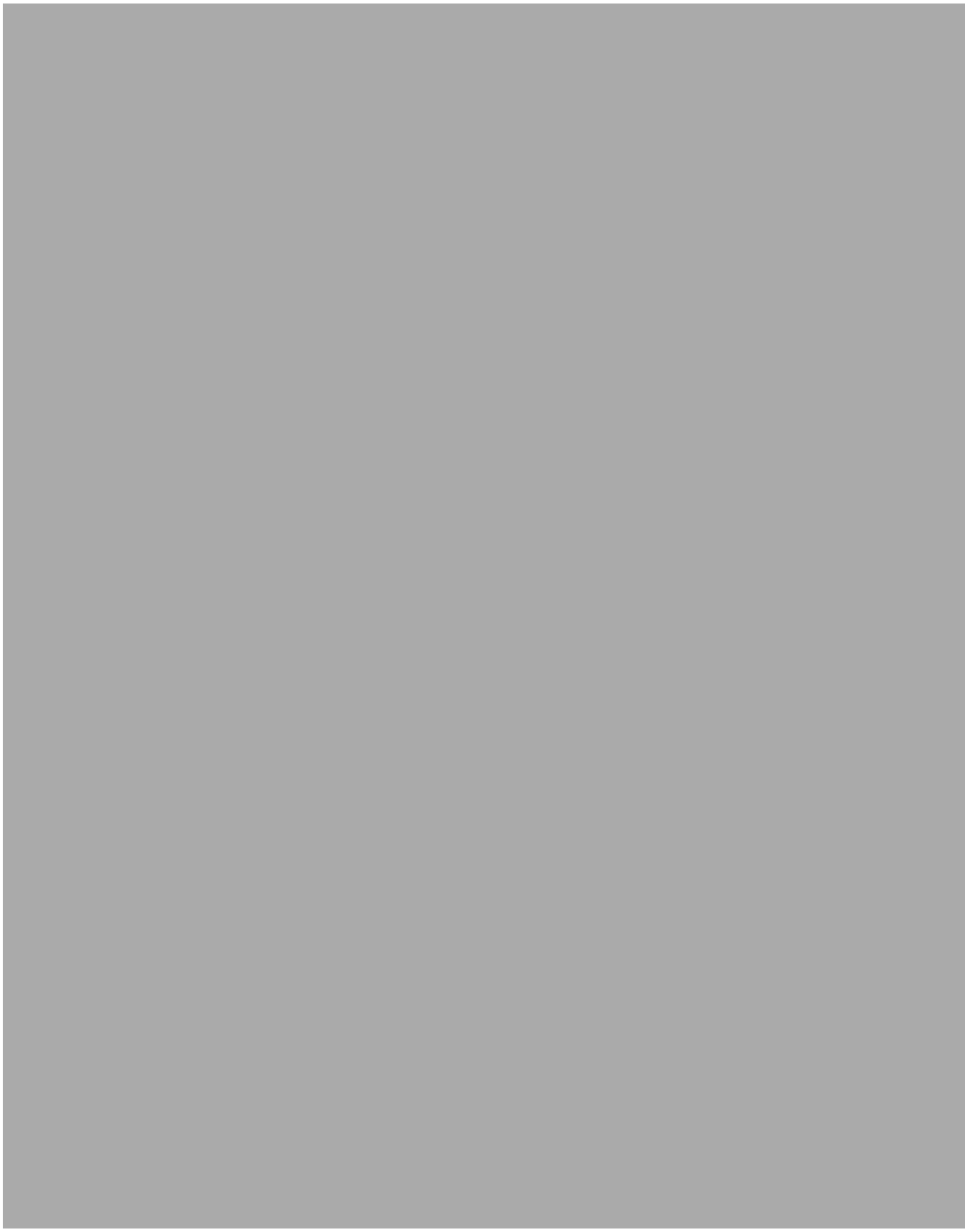
Table H. Medication

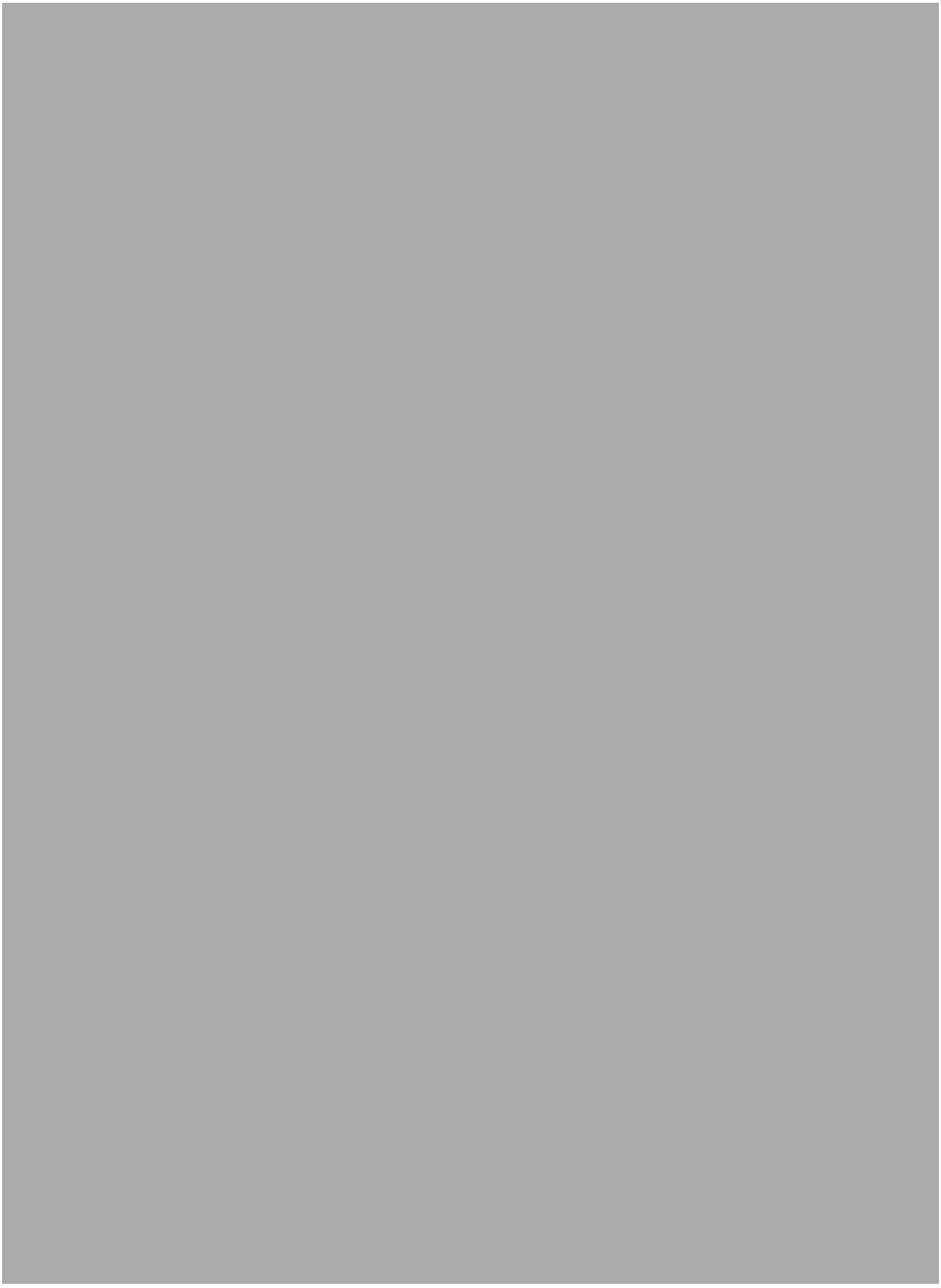
Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Medication						**Medication**					
Tetrabenazine	Dorsey et al. (2013)	82.5	UHDRS-b	The drug was administered	Non sig						
Psychotropics	Hubers et al. (2013)	83.3	UHDRS-b	A question	Sig						

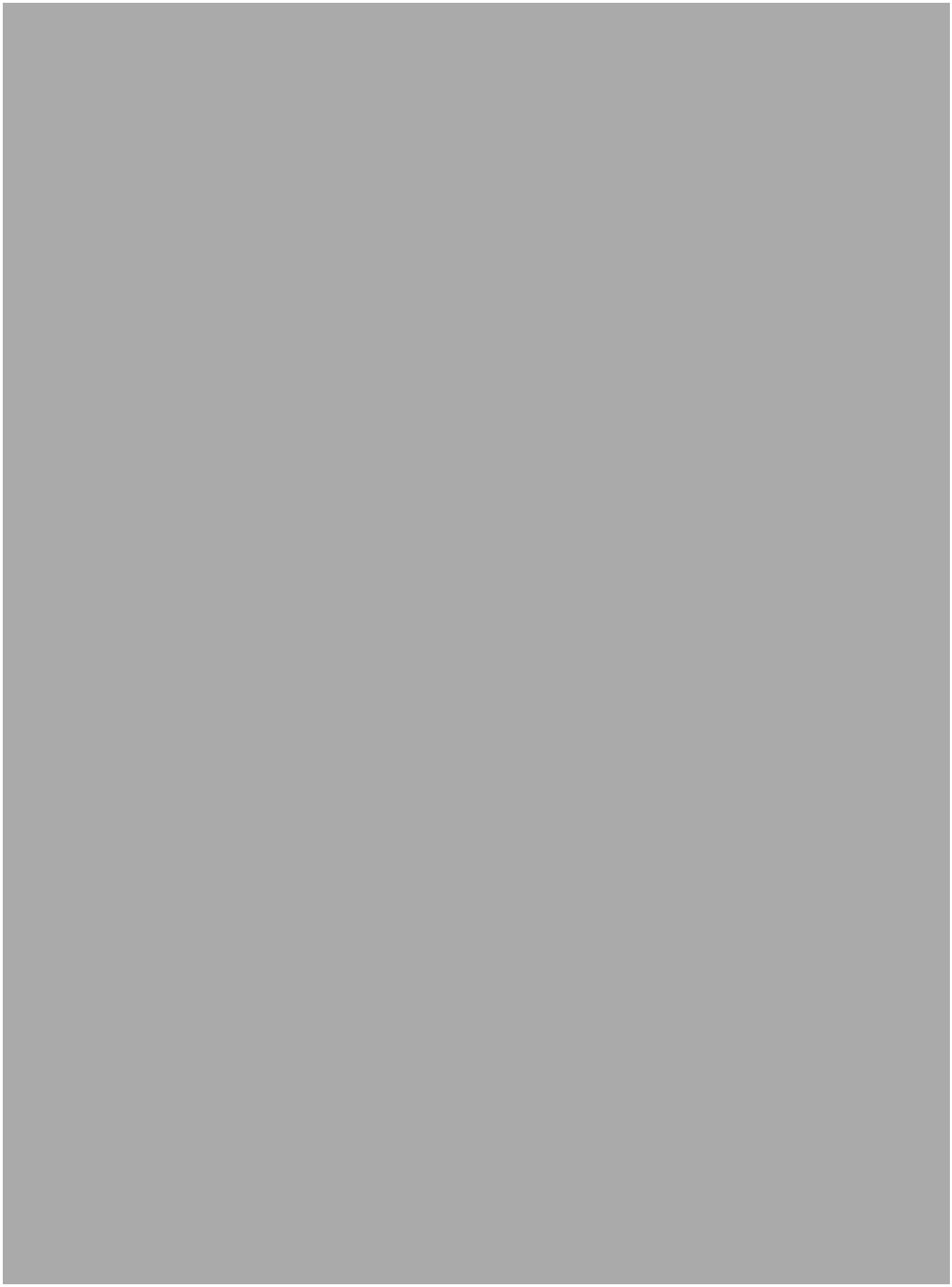
Table I. Other

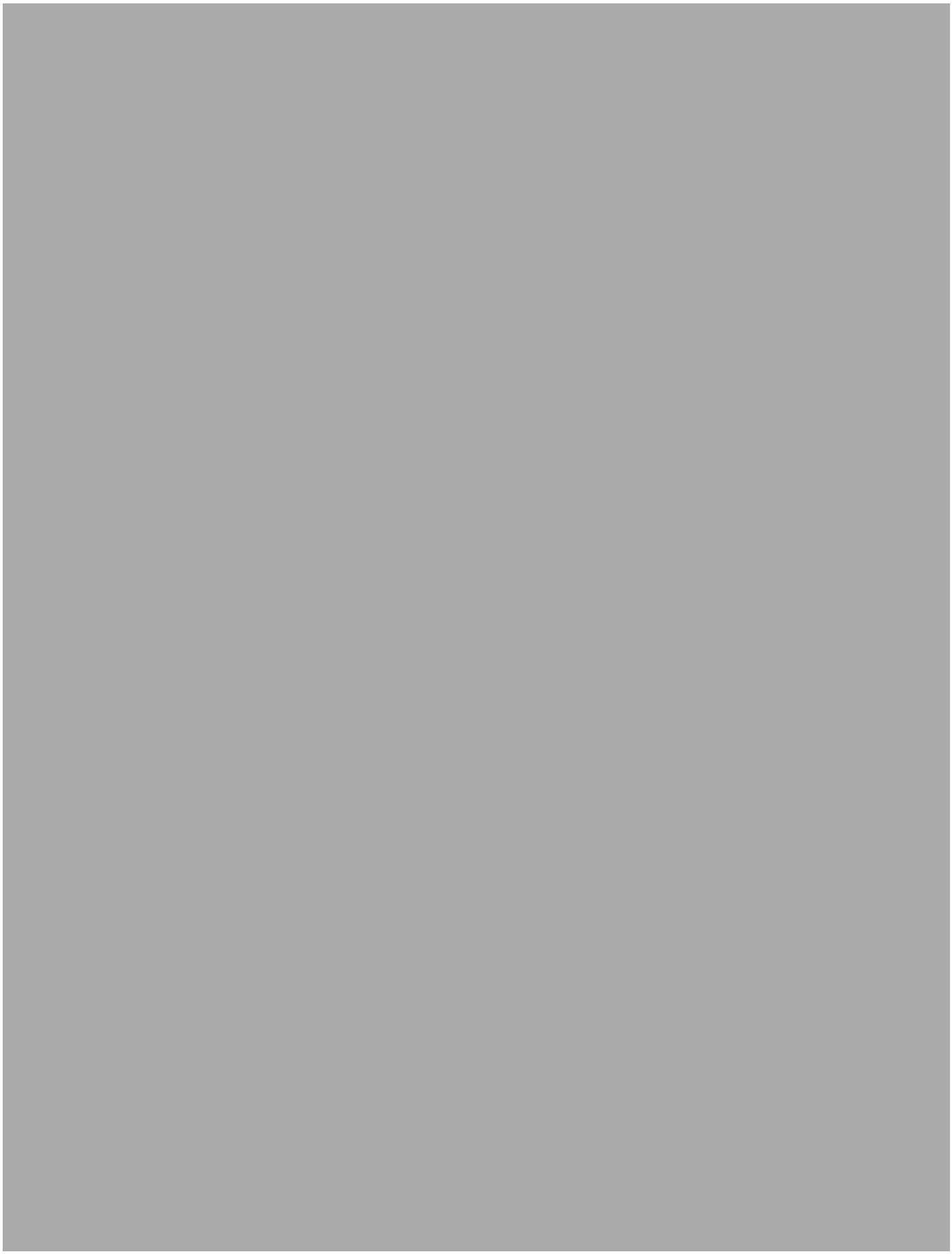
Suicide ideation						Attempted or completed suicide					
Risk factor	**Paper**	**Quality score (%)**	**Suicide measure**	**Other measure**	**Risk factor?**	**Risk factor**	**Paper**	**Quality score**	**Suicide measure**	**Other measure**	**Risk factor?**
Other						**Other**					
Living in residential institution	Hubers et al. (2012)	82.5	PBA	A question	Non sig						
Recent lifestyle changes	Fiedorowicz et al. (2011)	85.7	UHDRS-b	LES	Non sig						
Incarceration in the past 2 years	Fiedorowicz et al. (2011)	85.7	UHDRS-b	A question	Sig						

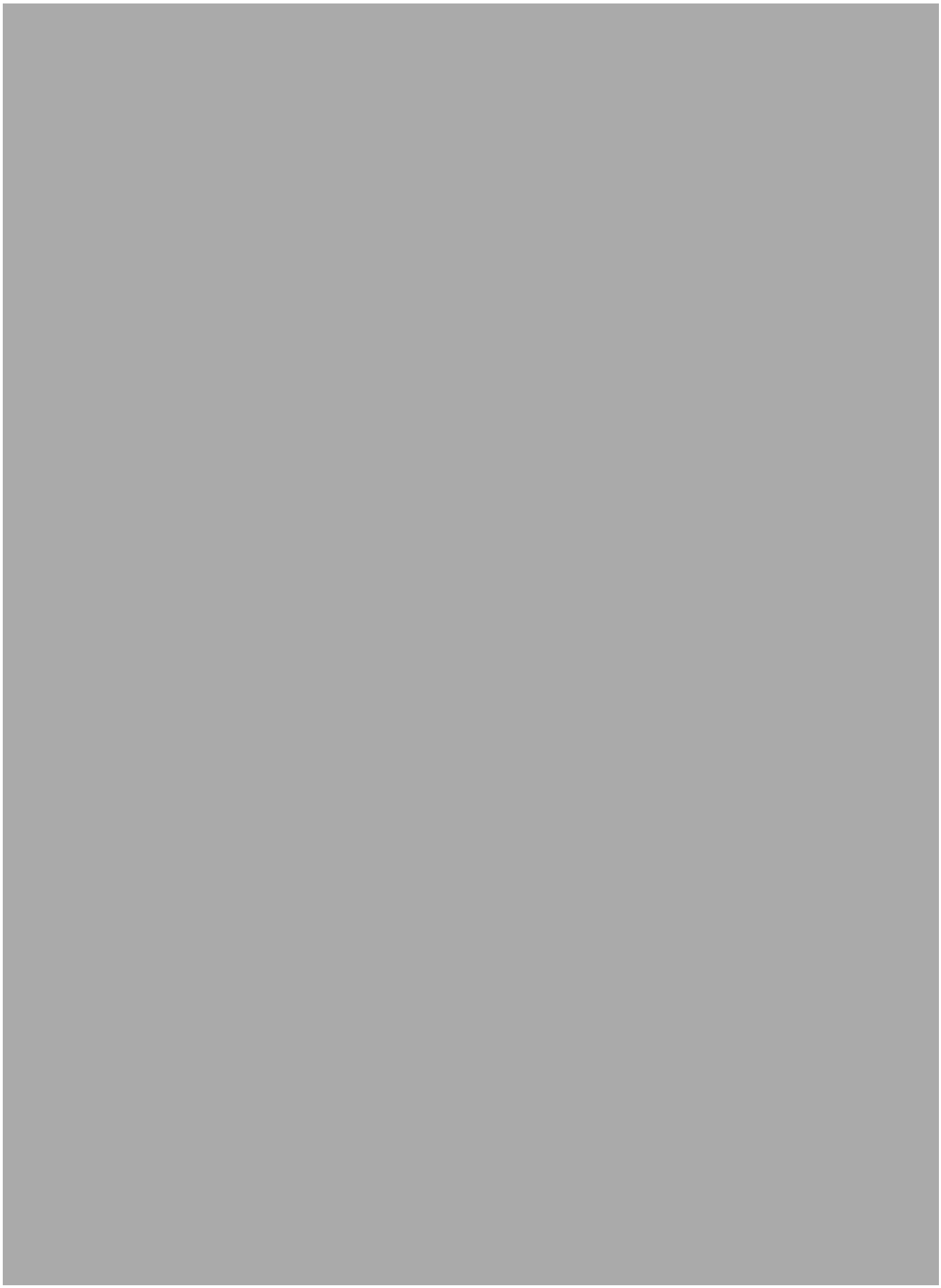
Appendix XII. Instructions for authors – Acta Neurologica Scandanivica

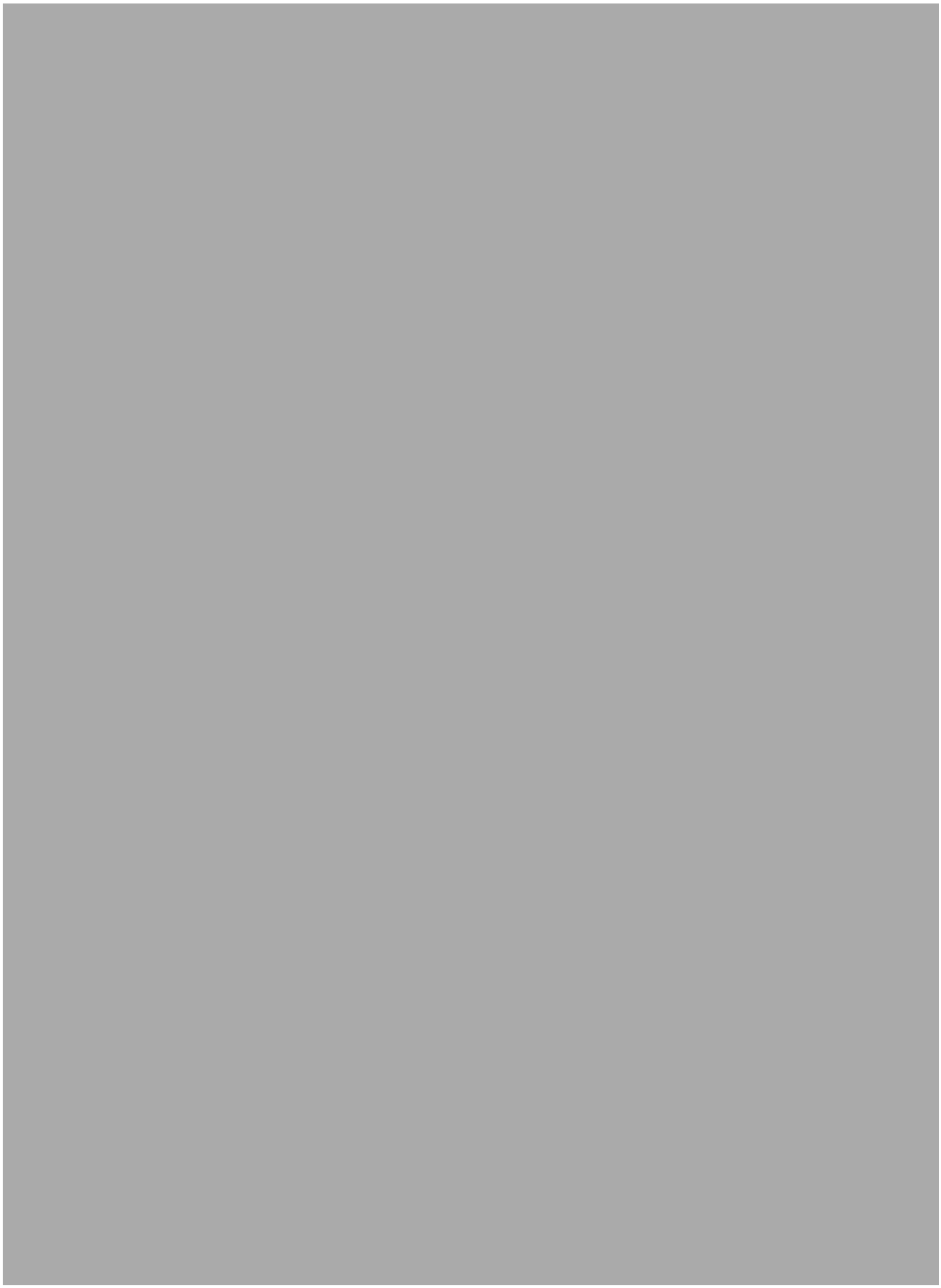


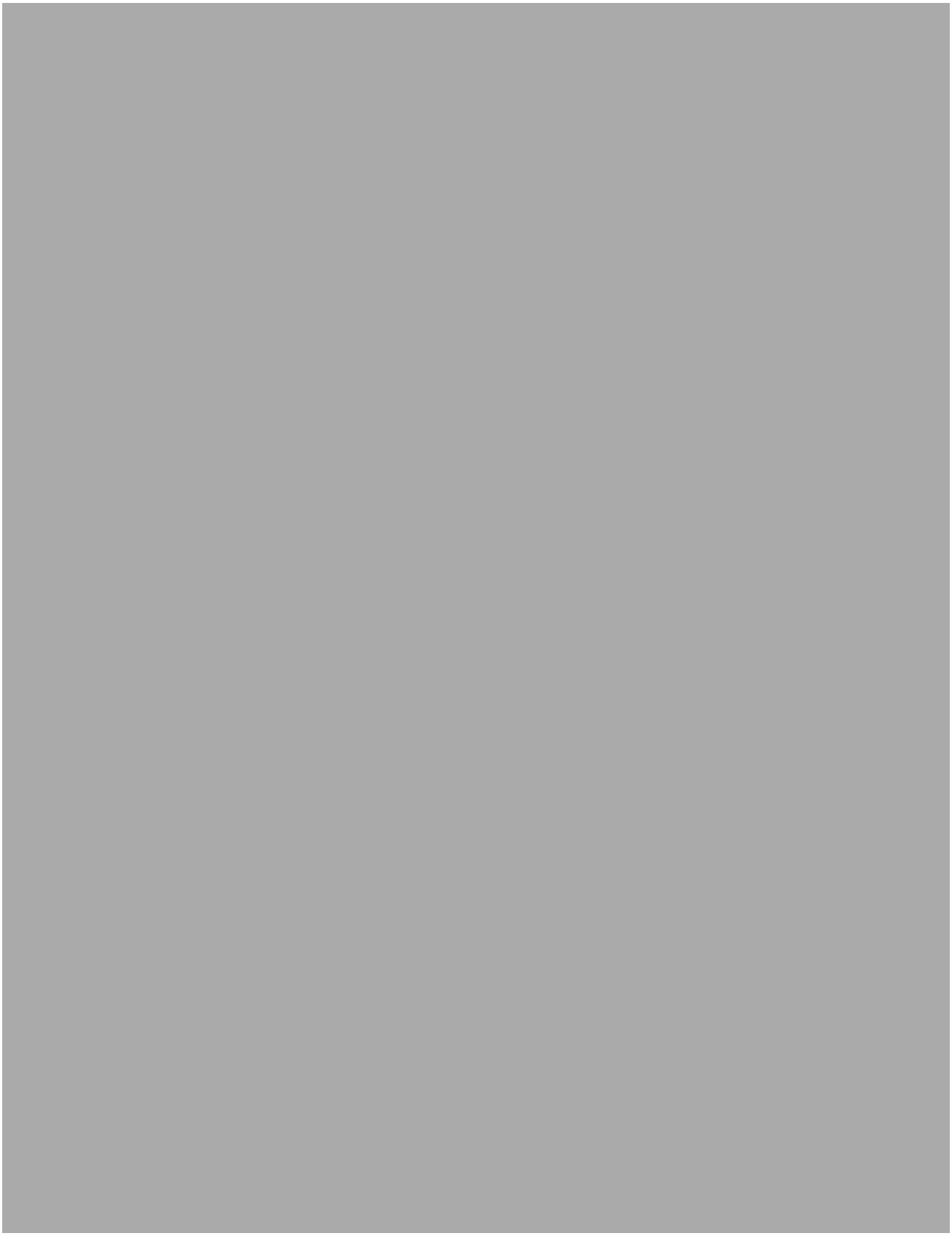






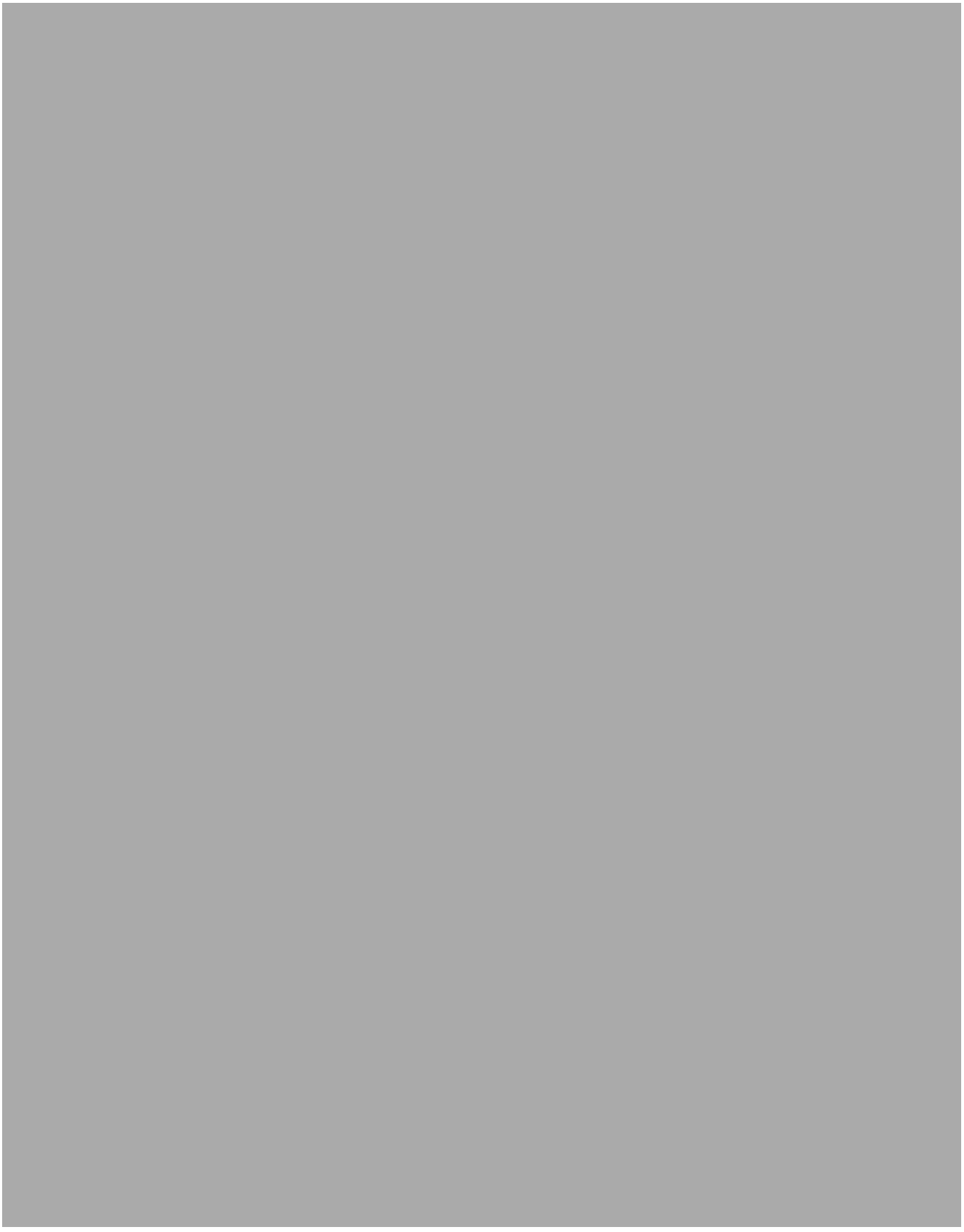


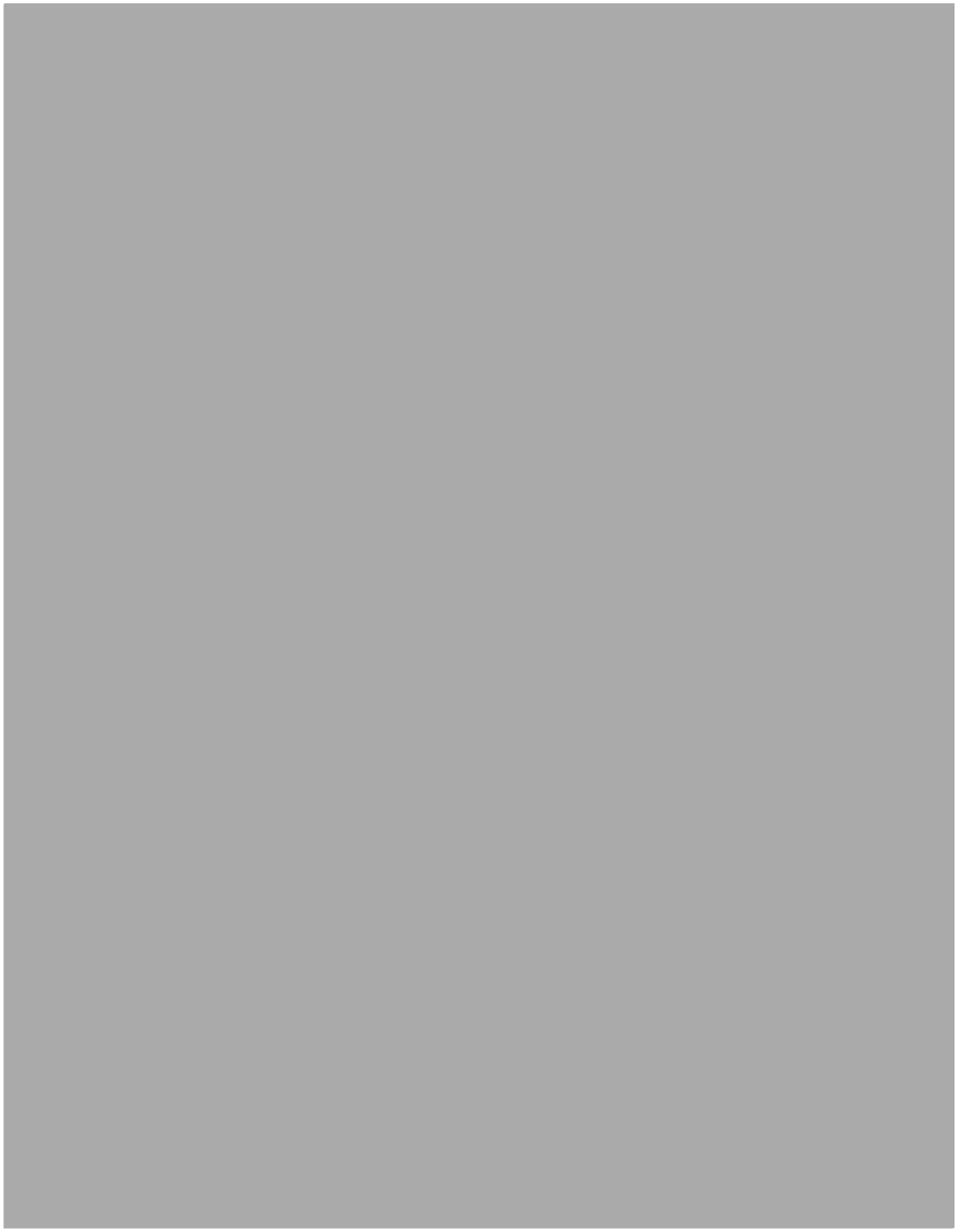


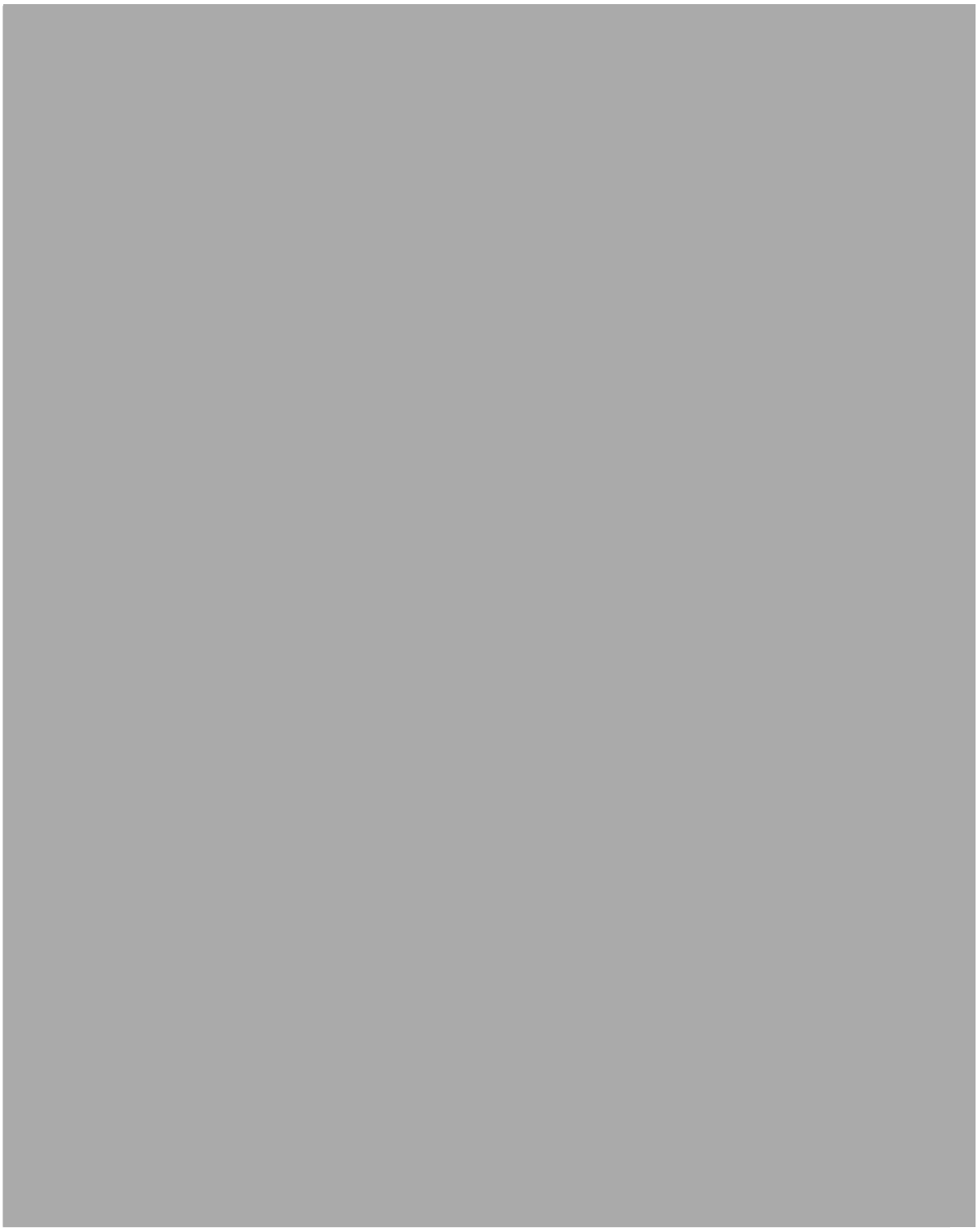


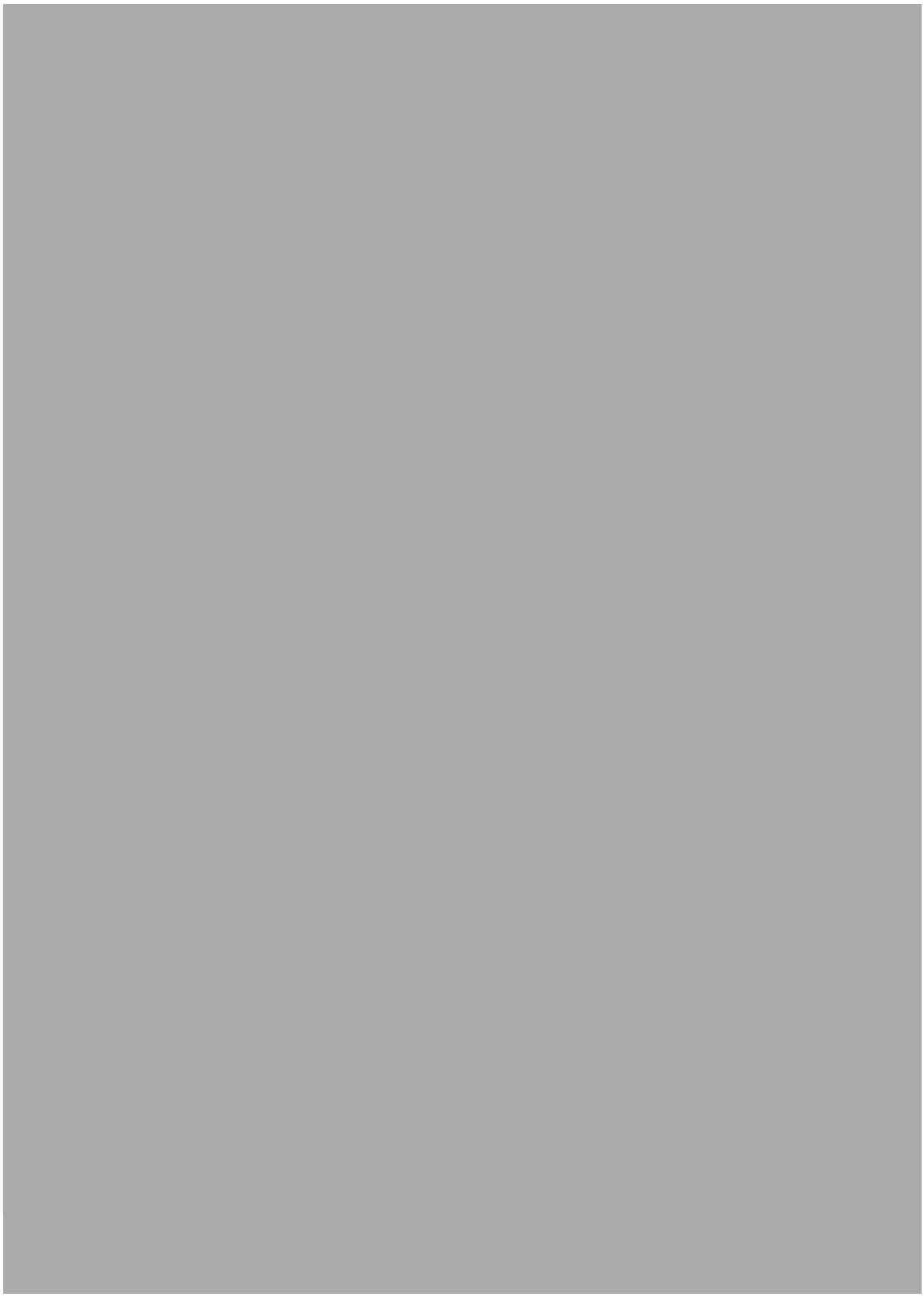
Empirical Paper Appendices

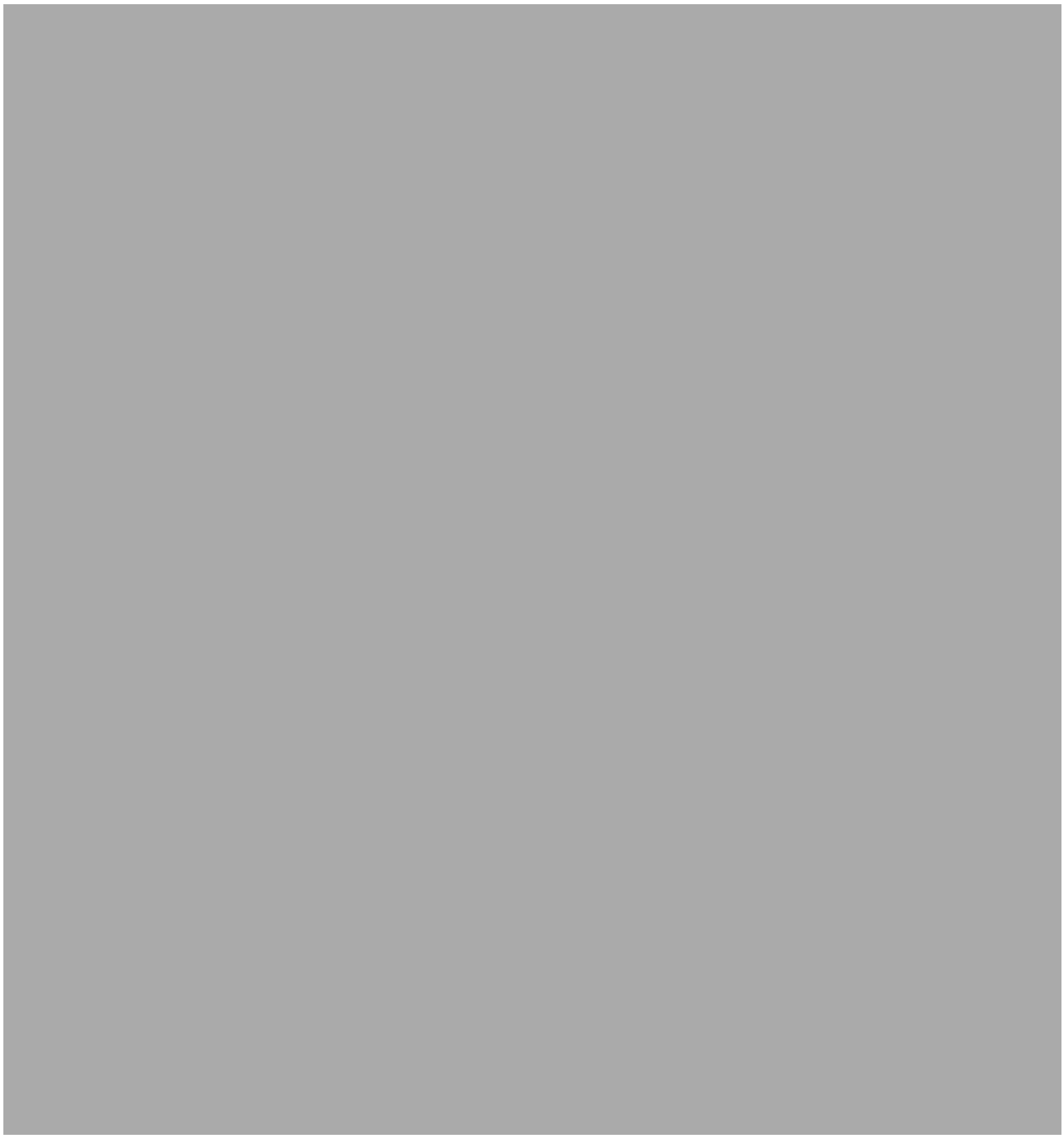
Appendix I. NRES Ethical approval letters (original and three amendments)

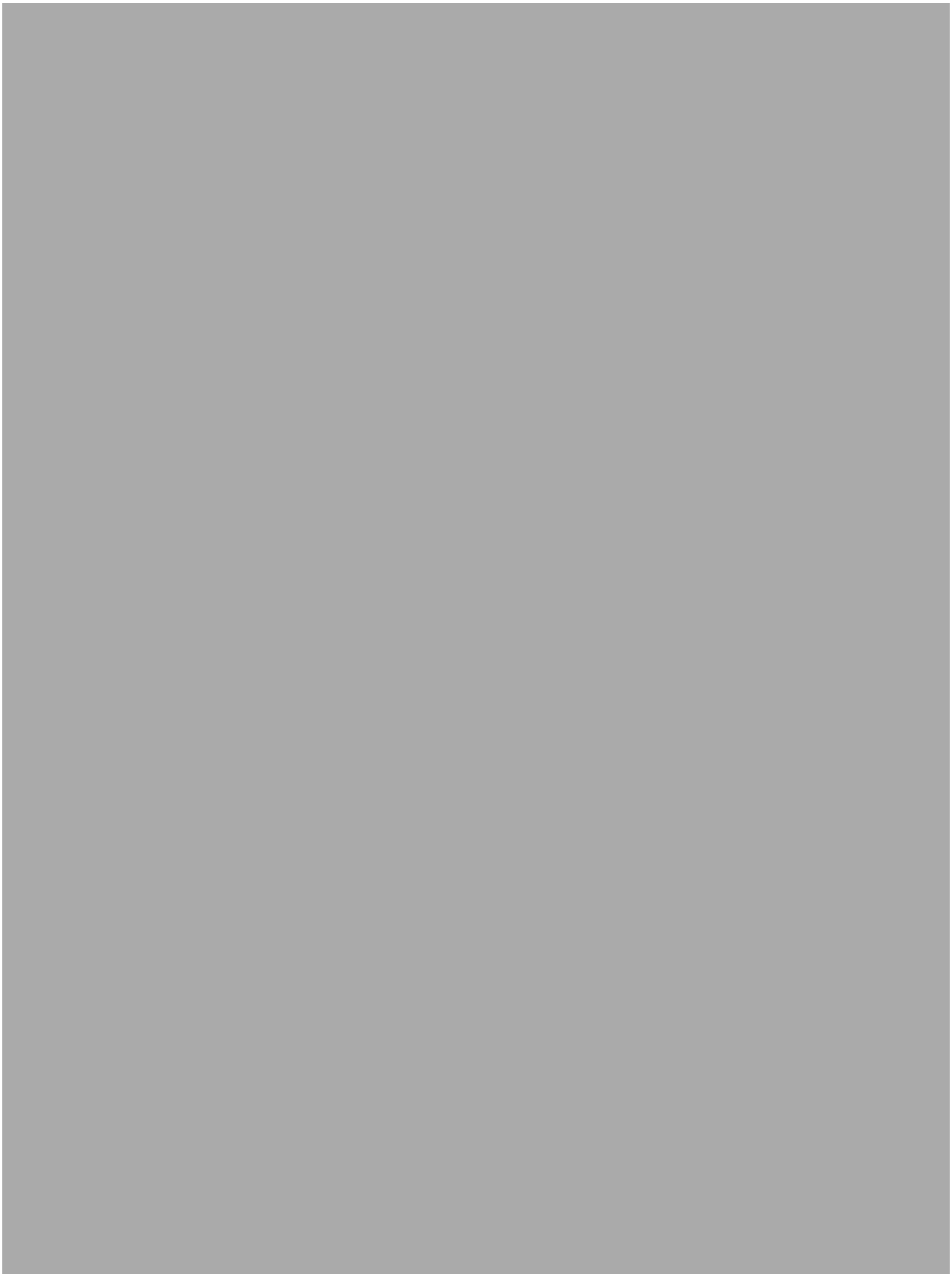


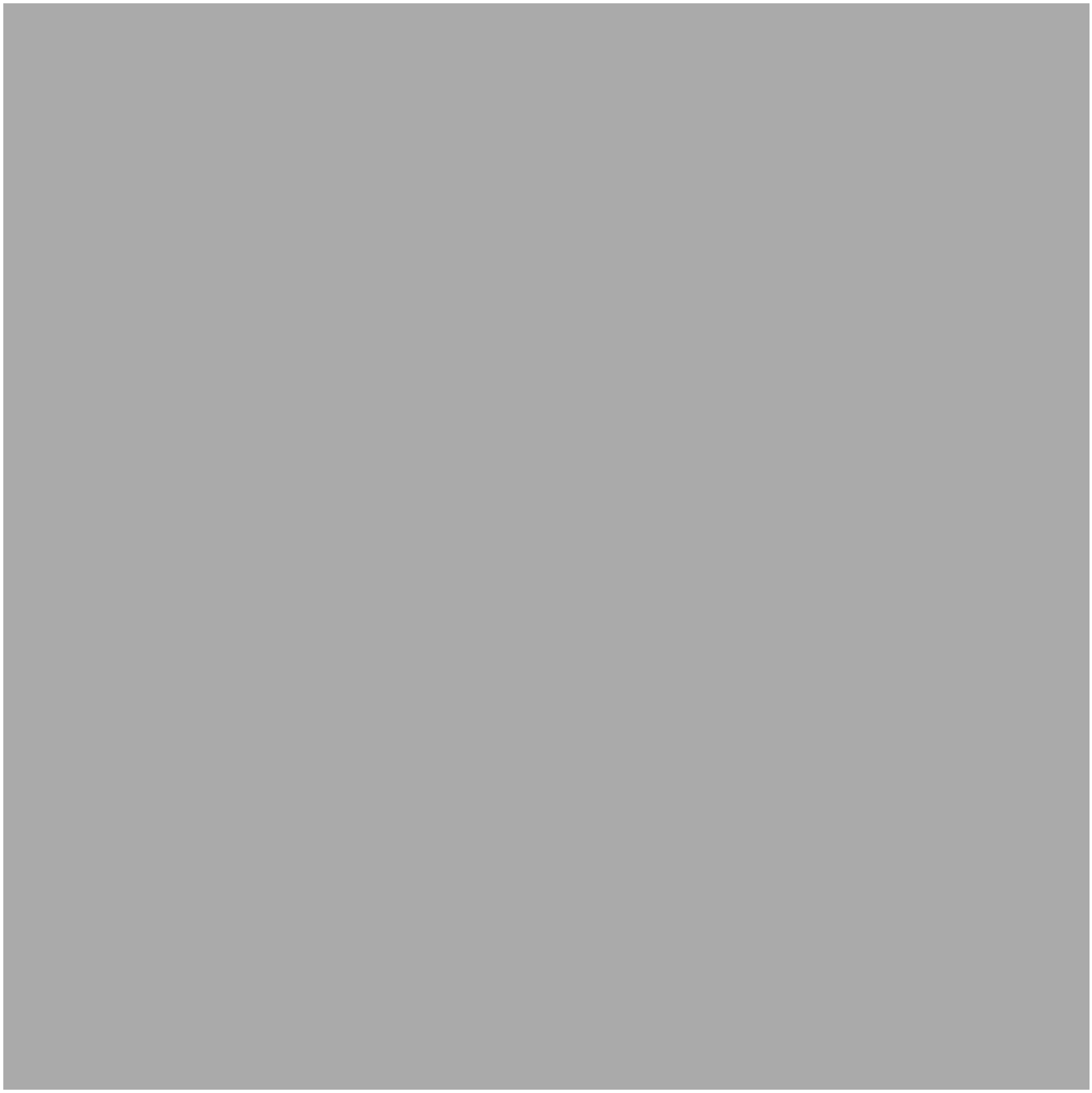


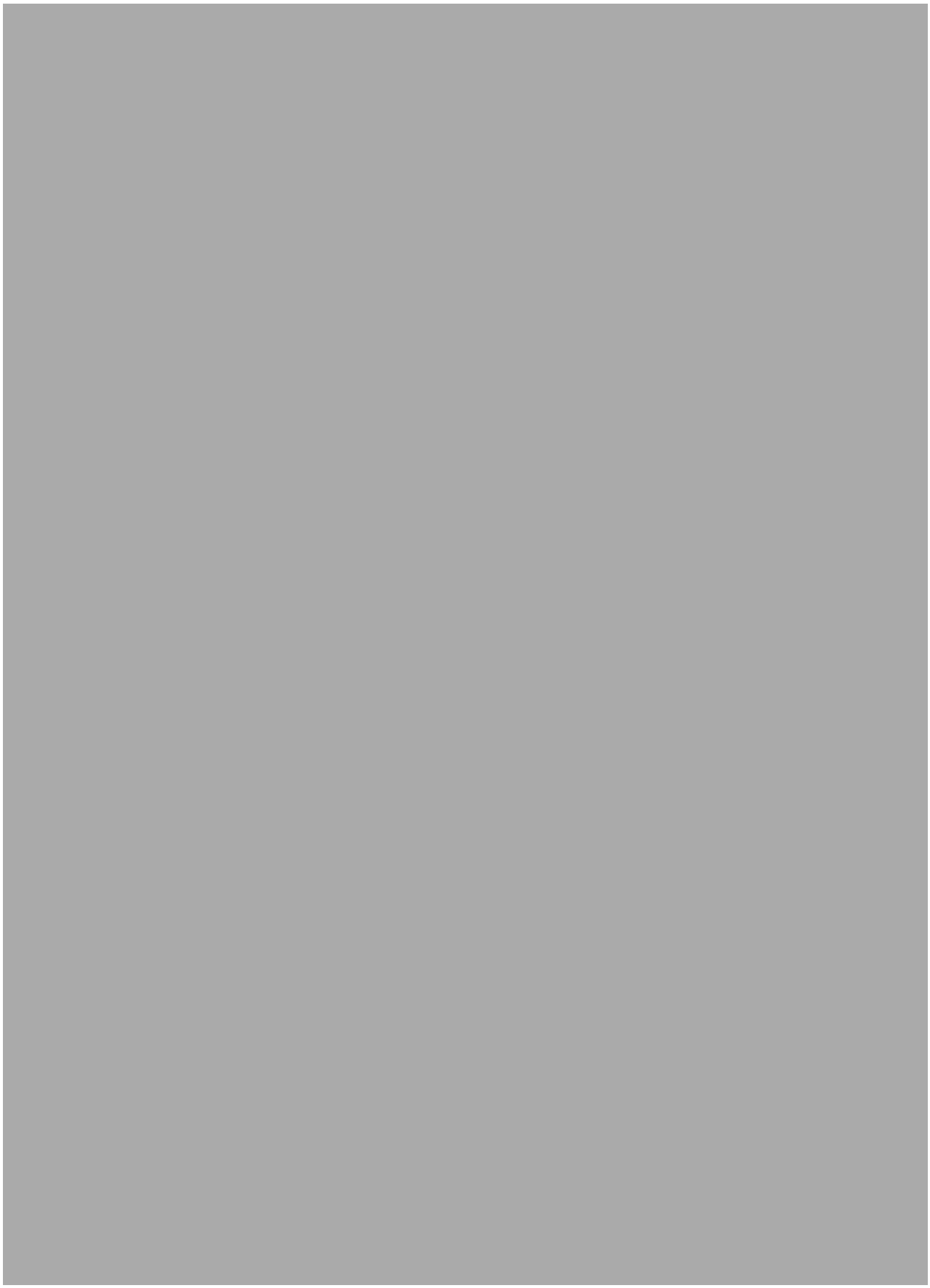


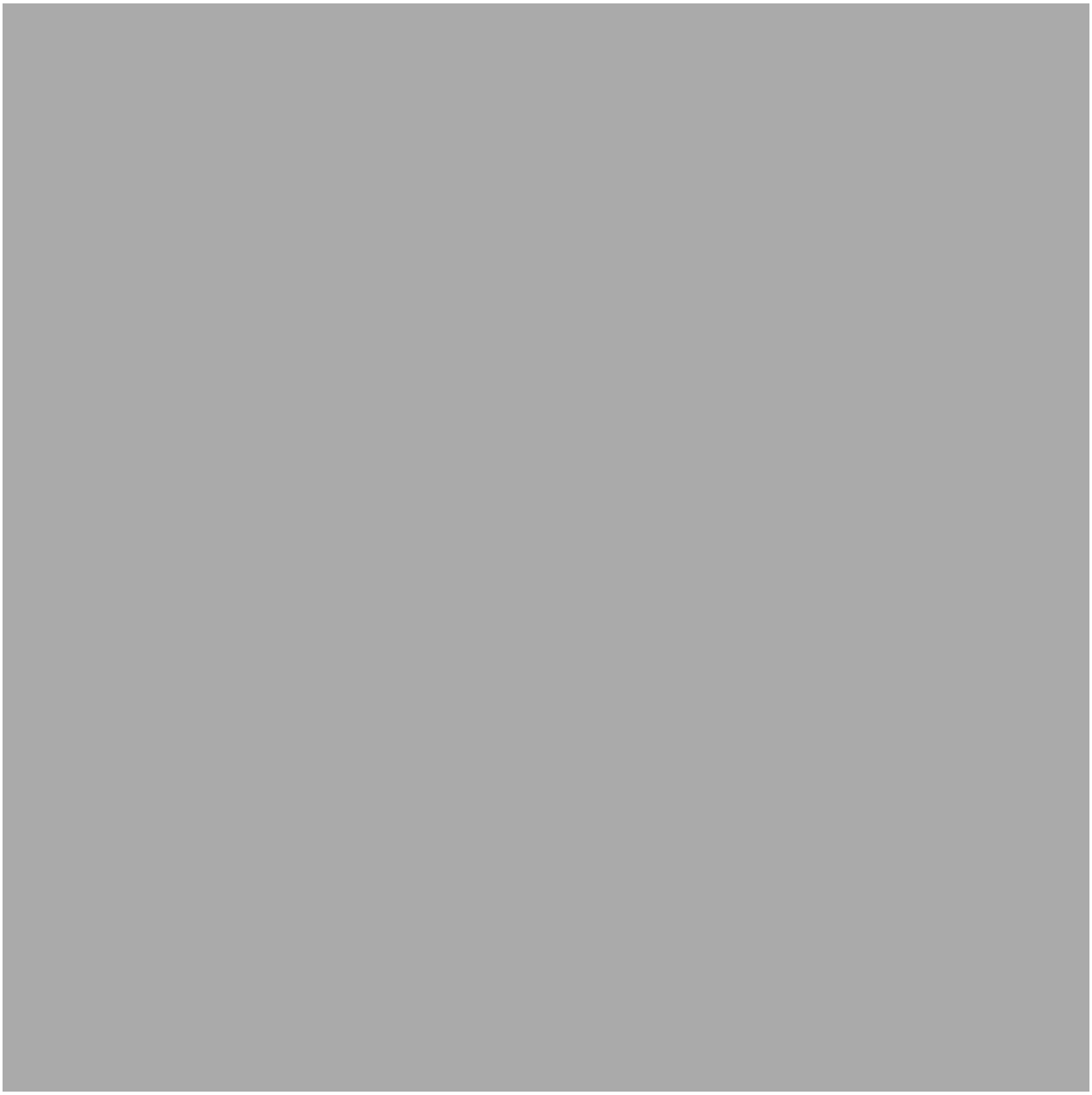




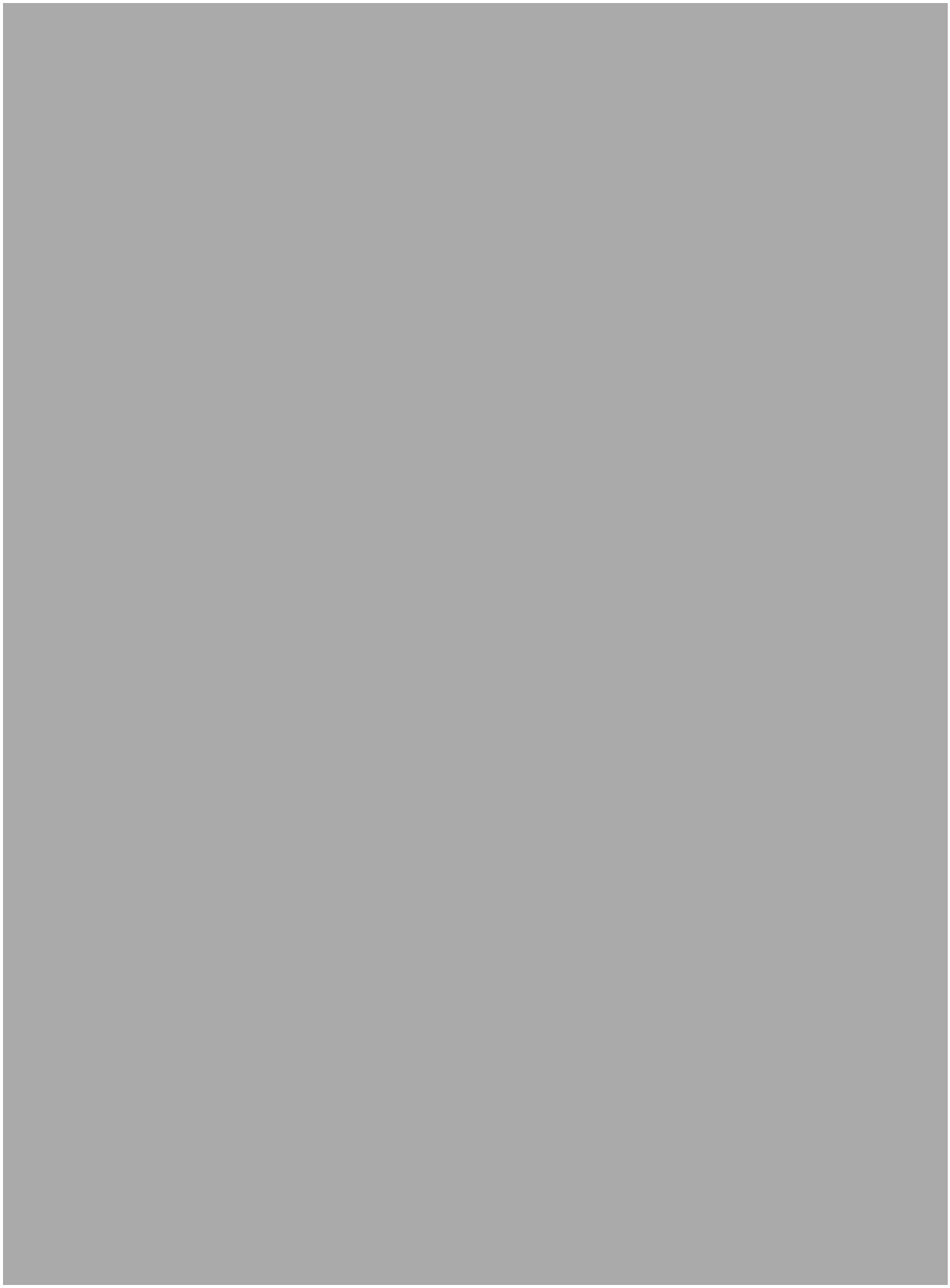




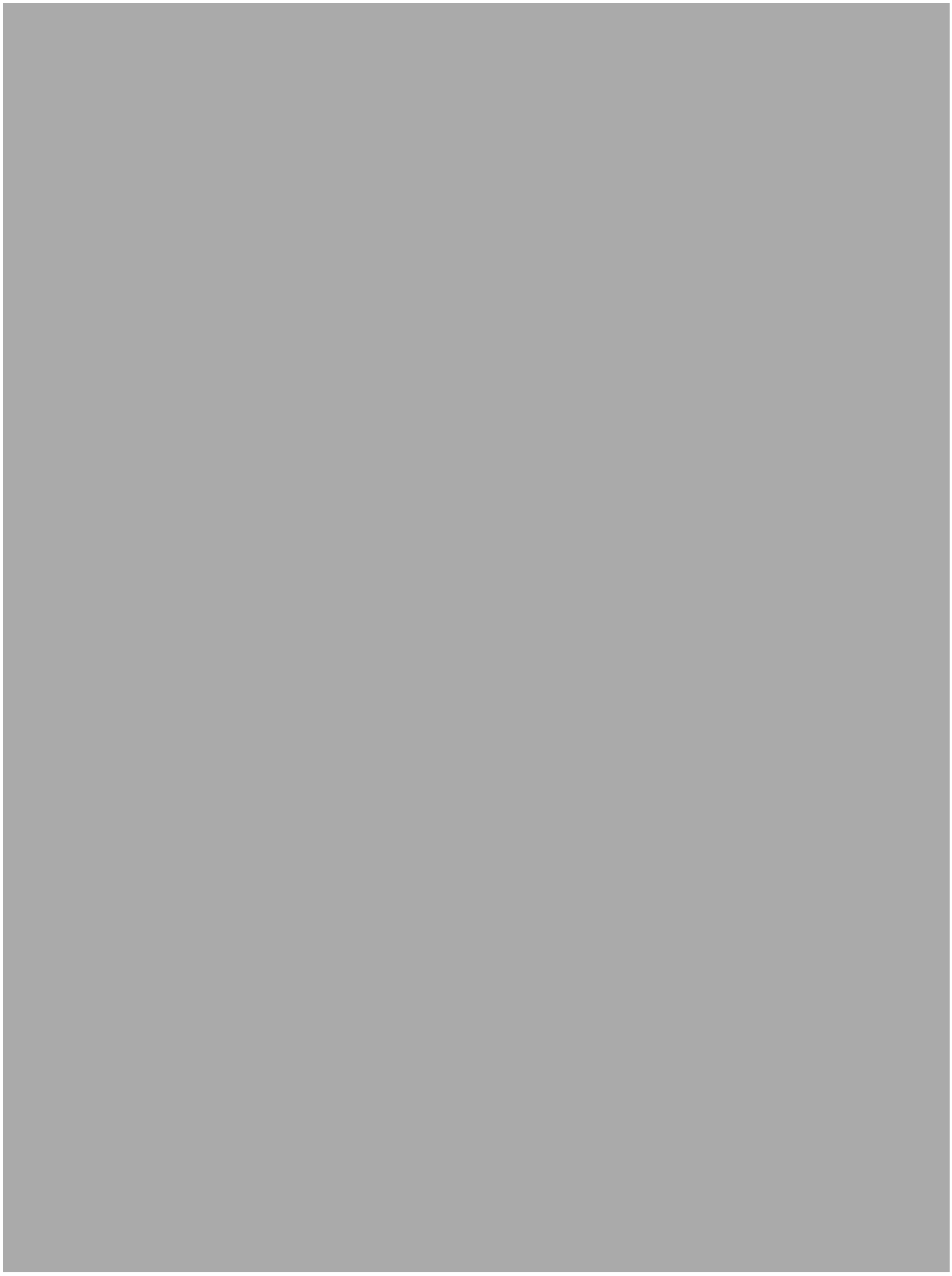


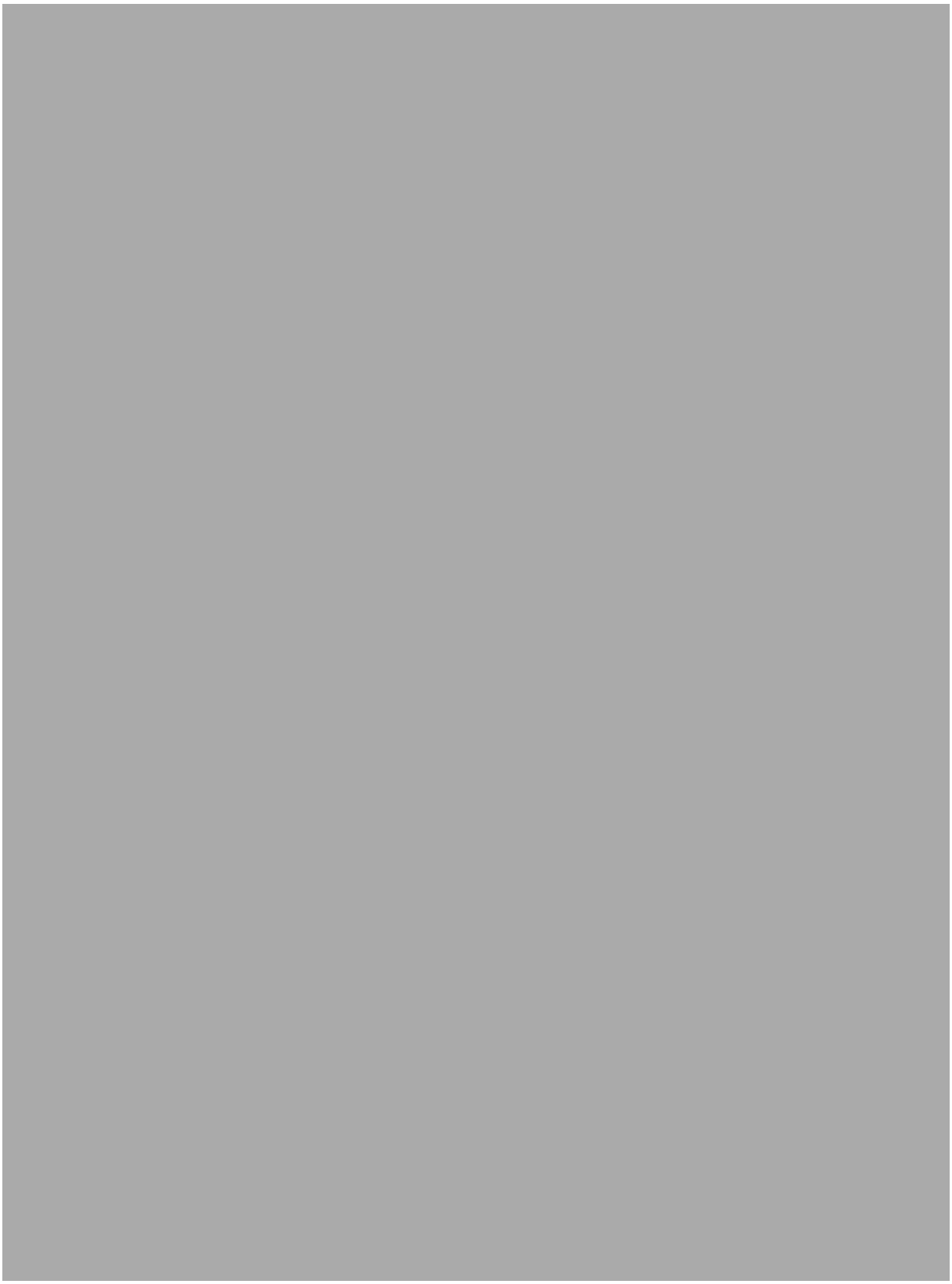


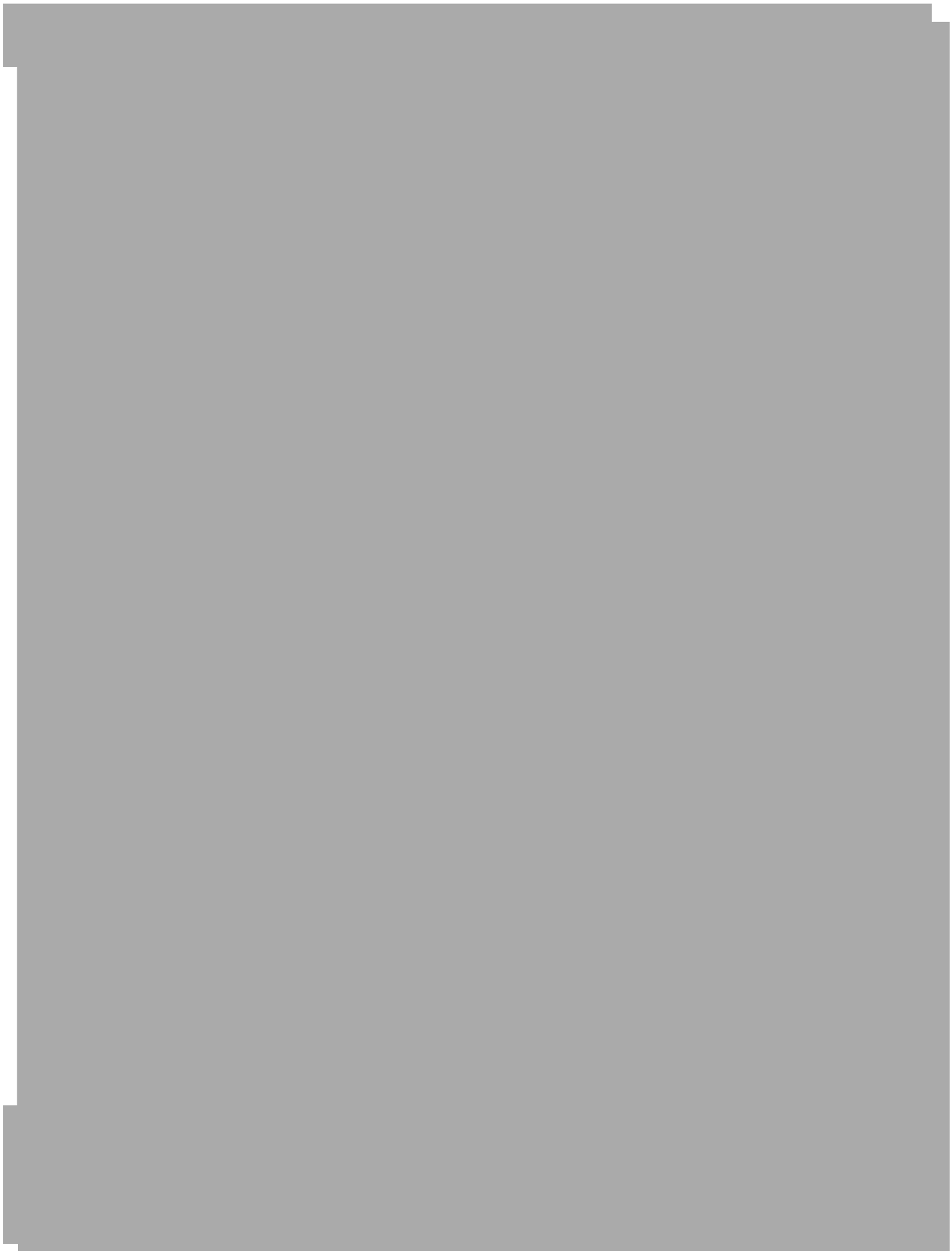
Appendix II. R&D Ethical approval letters

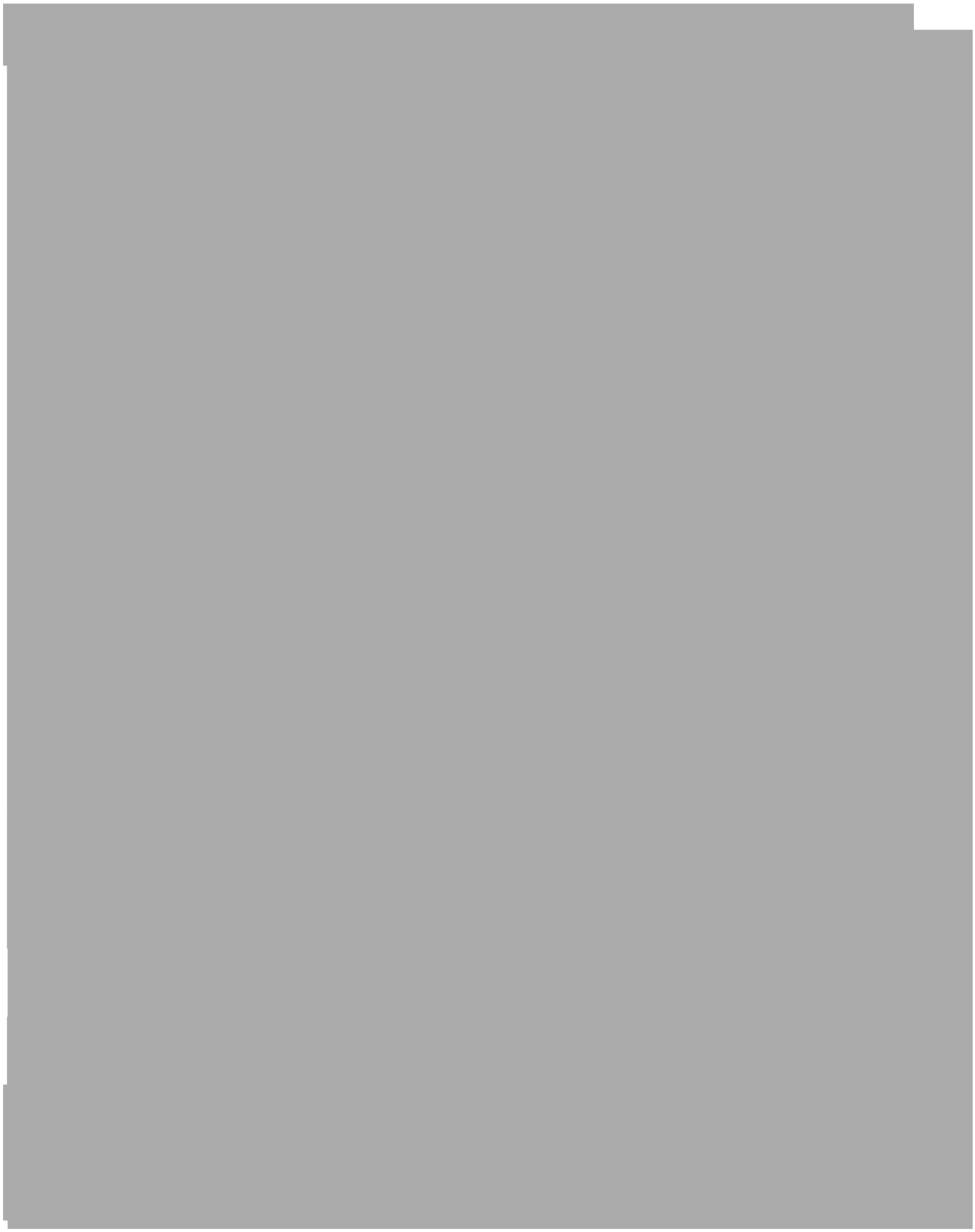












Appendix III. Participant information sheets



UNIVERSITY OF BIRMINGHAM

Negative thoughts and feelings and disability in Multiple Sclerosis

Participant Information Sheet

We are inviting you to take part in a research study. Before you agree to participate, it is important that you understand the purpose and nature of the study.

What is the purpose of this study?

The purpose of this study is to examine whether the extent of impairment and disability in Multiple Sclerosis is related to feelings of depression and thoughts about harming oneself.

Why have I been chosen?

You have been asked to participate in this study as you have Progressive Multiple Sclerosis which is the group of people we are interested in and you are a patient at the West Midlands Rehabilitation Centre.

Do I have to take part?

No. Participation is completely voluntary so you are under no obligation to take part. If you decide to participate, then you may keep this information and you will be asked to sign a consent form. If you do change your mind at any time during the study, you are able to withdraw your participation by contacting the researcher (see below). You can also withdraw from the study at any time within two weeks of completing the questionnaires. If for any reason you do choose to withdraw, any identifiable data will be destroyed and will not be used in the study.

What will happen to me if I take part?

If you are interested in taking part or finding out more about this study please:

1. Return the expression of interest letter to a member of the MS clinic team. Or

2. Post (in the stamped addressed envelope) the expression of interest letter enclosed within this letter. Or

3. Email the researcher Vicky Lewis who is a Trainee Clinical Psychologist studying at the University of Birmingham – [redacted]

Vicky will telephone you to answer your questions, and if you are happy to take part, will arrange a time to meet with you for 45-60 minutes at West Midlands Rehabilitation Centre or at your home. When you meet with Vicky, you will be given the opportunity to ask any further questions and will then be asked to sign a consent form (to say that you agree to take part in the study). You will be given four questionnaires to fill in. Vicky will be there to help you if you need anything.

What are the possible disadvantages and risks of taking part?

As the study is looking at feelings of depression and negative thoughts, you will be asked to fill in a questionnaire that asks you about thoughts you may have or had about harming yourself which you may find upsetting. If your questionnaires suggest that you are having thoughts like this, then Vicky will let the clinic team know about this so that you can talk to them. If Vicky has met with you at your home and is concerned that you are having thoughts about harming yourself, then she will need to telephone Dr Koko to let him know and then arrange for you to speak with your GP.

If you feel in any way distressed by the study after participating, then we suggest you call your MS nurse or the MS Society helpline on 0808 800 8000 (available 9am to 9pm, Monday to Friday) or the Samaritans on 08457 90 90 90 (available 24hrs a day 365 days a year).

What are the possible benefits of taking part?

There is no direct benefit to you in taking part. However, you will be assisting in furthering research into suicide and depression in Multiple Sclerosis, which could help to shape services in the future and raise awareness about this.

Will my taking part/performance in the study be kept confidential?

You will be allocated a participant reference number at the start of the study. From the point of completing the study your questionnaires will be kept anonymous and identified by a participant reference number only. All data collected will be kept in a locked cabinet in a secure office. Once the raw data has been analysed, it will be deleted.

What will happen to the results of this study?

The results will be written up in a report within the University of Birmingham. If the study is found to be significant and add to the current research, it may be selected for publication in an academic journal. If this is the case, then the results will be available to be viewed by the general public.

Who is organising and funding the research?

This is a joint study which is being conducted by the University of Birmingham and the West Midlands Rehabilitation Centre.

Who has reviewed this study?

This study has been reviewed and approved by IRAS.

If you wish to seek advice about taking part in research in the NHS generally, please contact our patient advice and liaison service on 0800 917 2855.

Contact details

For further details on this study, or to withdraw from the study, please e-mail Vicky Lewis [redacted] Alternatively, if you have any concerns that you feel the researcher may not be able to address please contact Dr Theresa Powell on [redacted] who is supervising the research.

UNIVERSITY OF BIRMINGHAM

[redacted]

[redacted]

Negative thoughts and feelings and disability in Multiple Sclerosis

Participant Information Sheet

We are inviting you to take part in a research study. Before you agree to participate, it is important that you understand the purpose and nature of the study.

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Why have I been chosen?

You have been asked to participate in this study as you have Progressive Multiple Sclerosis which is the group of people we are interested in and you are a patient at University Hospitals Birmingham, Neurology Department.

Do I have to take part?

No. Participation is completely voluntary you are under no obligation to take part. If you decide to participate, then you may keep this information sheet and you will be asked to sign a consent form. If you do change your mind at any time during the study, you are able to withdraw your participation by contacting the researcher (see below). You can also withdraw from the study up to two weeks after participating. If for any reason you do choose to withdraw, your data will be destroyed and will not be used.

What if I want to take part or find out more information?

If you are interested in taking part or finding out more about this study please complete an expression of interest letter and:

1. Hand it to a member of the MS clinic team. Or

2. Post it (in the stamped addressed envelope) enclosed within this letter. Or

3. Email the researcher Vicky Lewis who is a Trainee Clinical Psychologist studying at the University of Birmingham – [redacted]

Vicky will telephone you ask whether you have any questions and then if you are happy to take part, she will arrange a time to meet with you for 45-60 minutes either at Queen Elizabeth Hospital Birmingham or at your home. When you meet with Vicky, you will be given the opportunity to ask any further questions and will then be asked to sign a consent form (to say that you agree to take part in the study). You will be given four questionnaires to fill in. Vicky will be there to help you if you need anything.

What are the possible disadvantages and risks of taking part?

As the study is looking at feelings of depression and negative thoughts, you will be asked to fill in a questionnaire that asks you about thoughts you may have or had about harming yourself which you may find upsetting. If your questionnaire responses suggest that you are having thoughts like this then Vicky will talk to you in more detail about this. If necessary Vicky will telephone Dr Woolmore to let him know and arrange for you to speak with your GP or another support agency.

If you feel in any way distressed by the study after participating, then we suggest you call your GP, MS nurse or the MS Society helpline on 0808 800 8000 (available 9am to 9pm, Monday to Friday); or the Samaritans on 08457 90 90 90 (available 24hrs a day 365 days a year).

What are the possible benefits of taking part?

There is no direct benefit to you in taking part. However, you will be assisting in furthering research into suicide and depression in Multiple Sclerosis, which could help to shape services in the future and raise awareness about this.

Will my taking part/performance in the study be kept confidential?

You will be allocated a participant reference number at the start of the study. From the point of completing the study your questionnaires will be kept anonymous and identified by a participant reference number only. All data collected will be kept in a locked cabinet in a secure office. Once the raw data has been analysed, it will be deleted.

What will happen to the results of this study?

The results will be written up in a report within the University of Birmingham. If the study is found to be significant and add to the current research, it may be selected for publication in an academic journal. If this is the case, then the results will be available to be viewed by the general public.

Who is organising and funding the research?

This is a joint study which is being conducted by the University of Birmingham, West Midlands Rehabilitation Centre and University Hospitals Birmingham, Neurology Department.

Who has reviewed this study?

This study has been reviewed and approved by Solihull Research Ethics Committee.

If you wish to seek advice about taking part in research in the NHS generally, please contact our patient advice and liaison service on 0800 917 2855.

Contact details

For further details on this study please e-mail Vicky Lewis [redacted]

Alternatively, if you have any concerns that you feel the researcher may not be able to address please contact Dr Theresa Powell on [redacted] who is supervising the research.

Appendix IV. Expression of interest forms

[redacted]

UNIVERSITY OF BIRMINGHAM

Negative thoughts and feelings and disability in Multiple Sclerosis

Expression of Interest Form

This is a study examining whether the extent of impairment and disability in Multiple Sclerosis is related to feelings of depression and thoughts about harming oneself. Participation in this study will involve meeting with a researcher and completing four questionnaires which will take approximately 45 - 60 minutes. Information provided will be kept confidential.

The researcher carrying out this study is Vicky Lewis [redacted] who is a Trainee Clinical Psychologist studying at the University of Birmingham. The research is being supervised by Dr Koko at the West Midlands Rehabilitation Centre and Dr Theresa Powell [redacted] at the University of Birmingham. You may contact Dr Koko through his secretary, Lynn Humphreys on [redacted].

Please initial each box which applies

☐ I am unsure whether I would like to participate in this study and would like a researcher to telephone me with further information.

☐ I would like to participate in this study (Vicky will telephone you to arrange a time to meet with you).

☐ I do not wish to take part - my name is _____.

Please provide your name and telephone number so that Vicky can contact you:

Name: _____ Phone number: _____.

Please return this form to West Midlands Rehabilitation Centre or email [redacted]

Thank you for your consideration.

UNIVERSITY OF BIRMINGHAM

[redacted]

[redacted]

Negative thoughts and feelings and disability in Multiple Sclerosis

Expression of Interest Form

This is a study examining whether the extent of impairment and disability in Multiple Sclerosis is related to feelings of depression and thoughts about harming oneself. Participation in this study will involve meeting with a researcher and completing four questionnaires which will take approximately 45 - 60 minutes. Information provided will be kept confidential.

The researcher carrying out this study is Vicky Lewis [redacted] who is a Trainee Clinical Psychologist studying at the University of Birmingham. The research is being supervised by Dr Woolmore at the Queen Elizabeth Hospital Birmingham and Dr Theresa Powel [redacted] at the University of Birmingham.

Please initial each box which applies

☐ I am unsure whether I would like to participate in this study and would like a researcher to telephone me with further information.

☐ I would like to participate in this study (Vicky will telephone you to arrange a time to meet with you)

☐ I do not wish to take part - my name is _____.

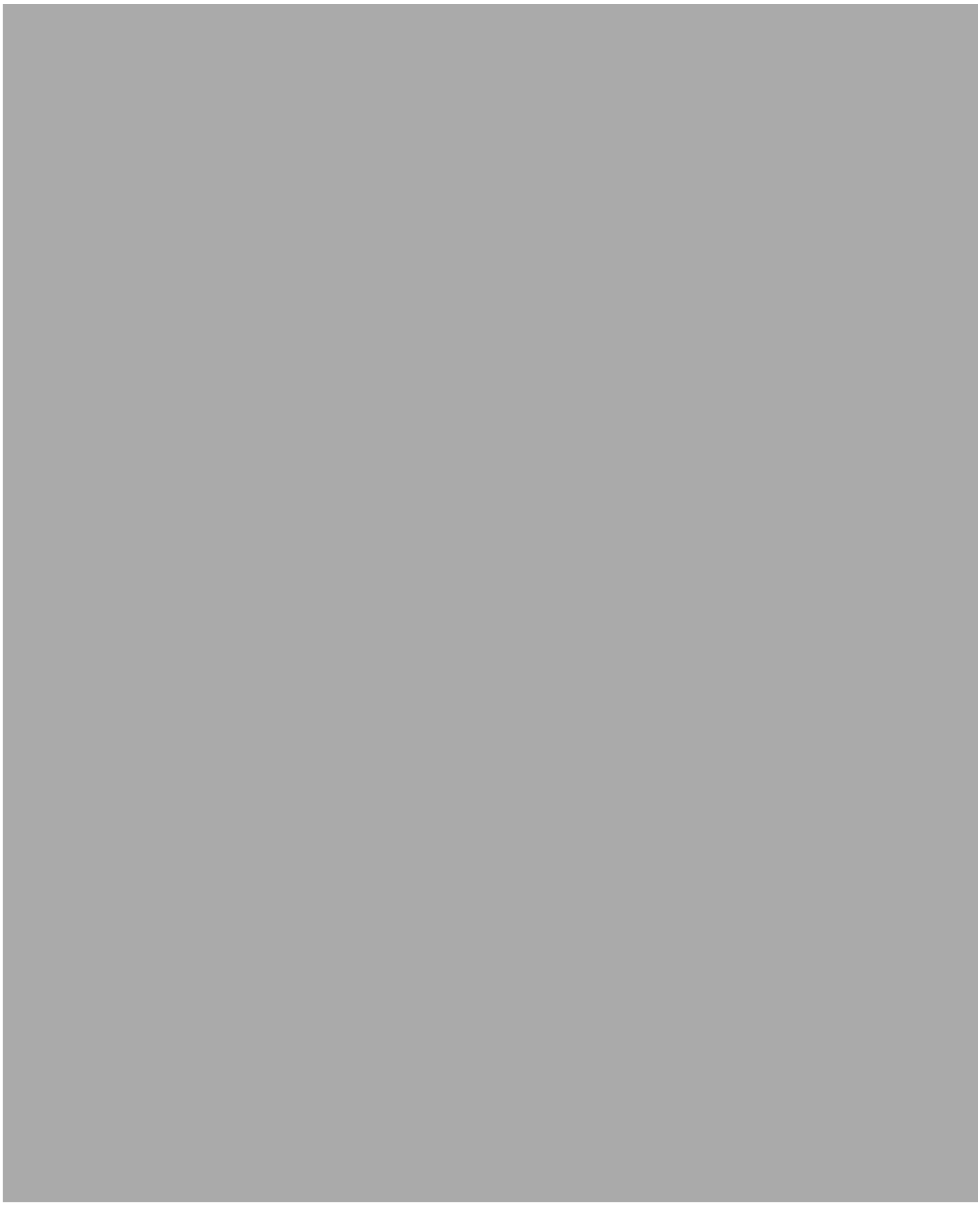
Please provide your name and telephone number so that Vicky can contact you:

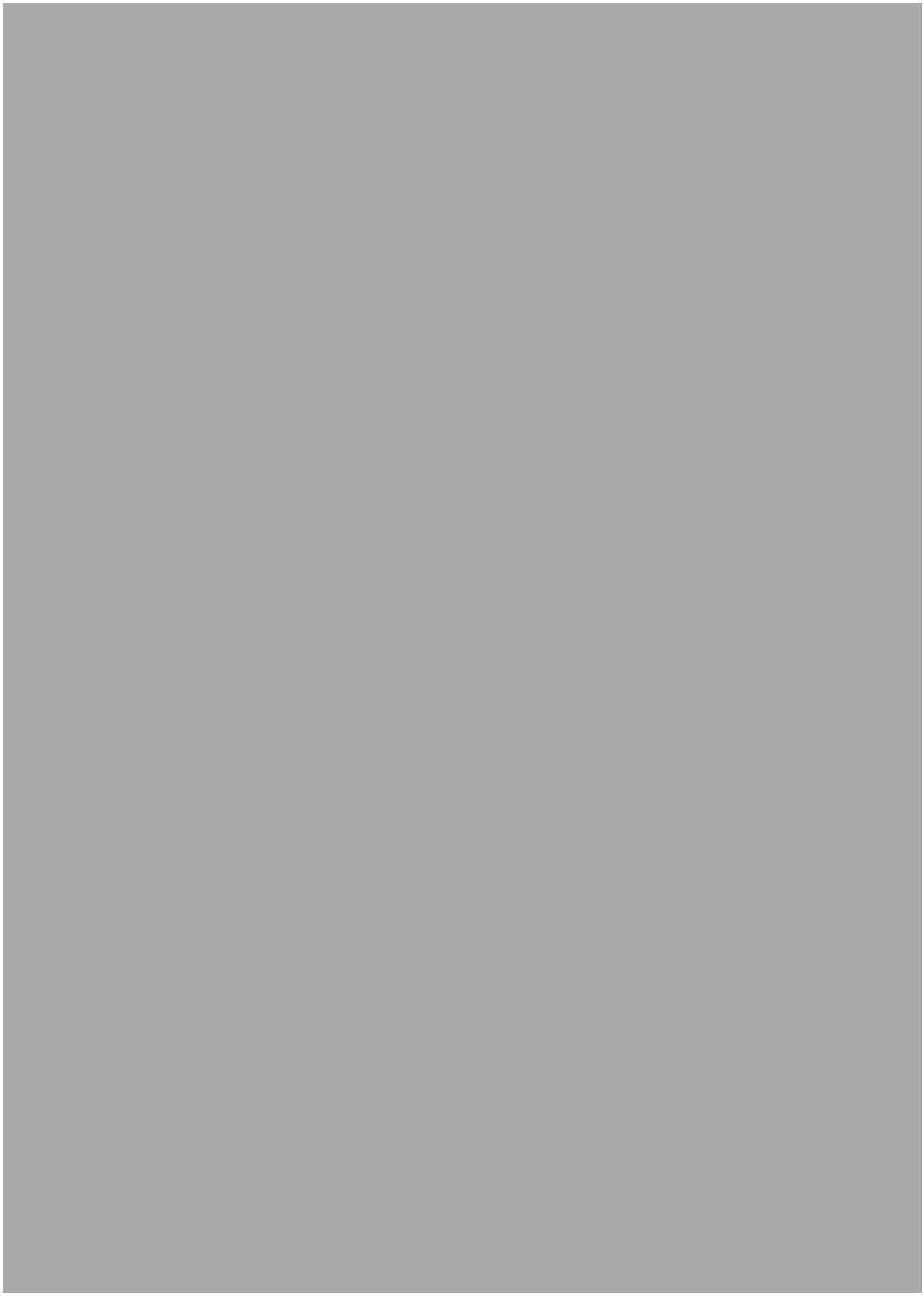
_____.

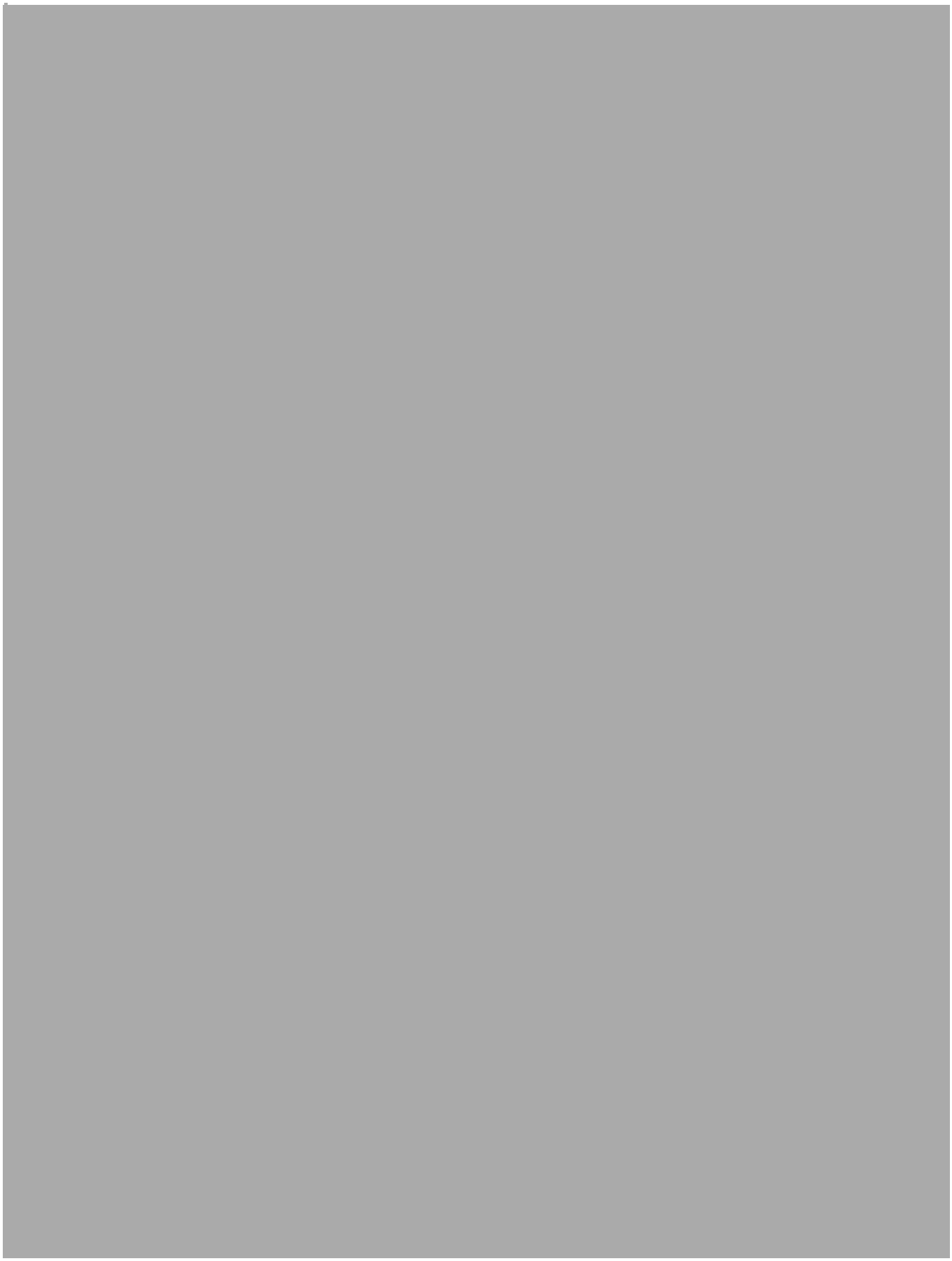
Please return this form by post or email [redacted]

Thank you for your consideration.

Appendix V. Beck Suicide Scale (Beck and Steer, 1993)





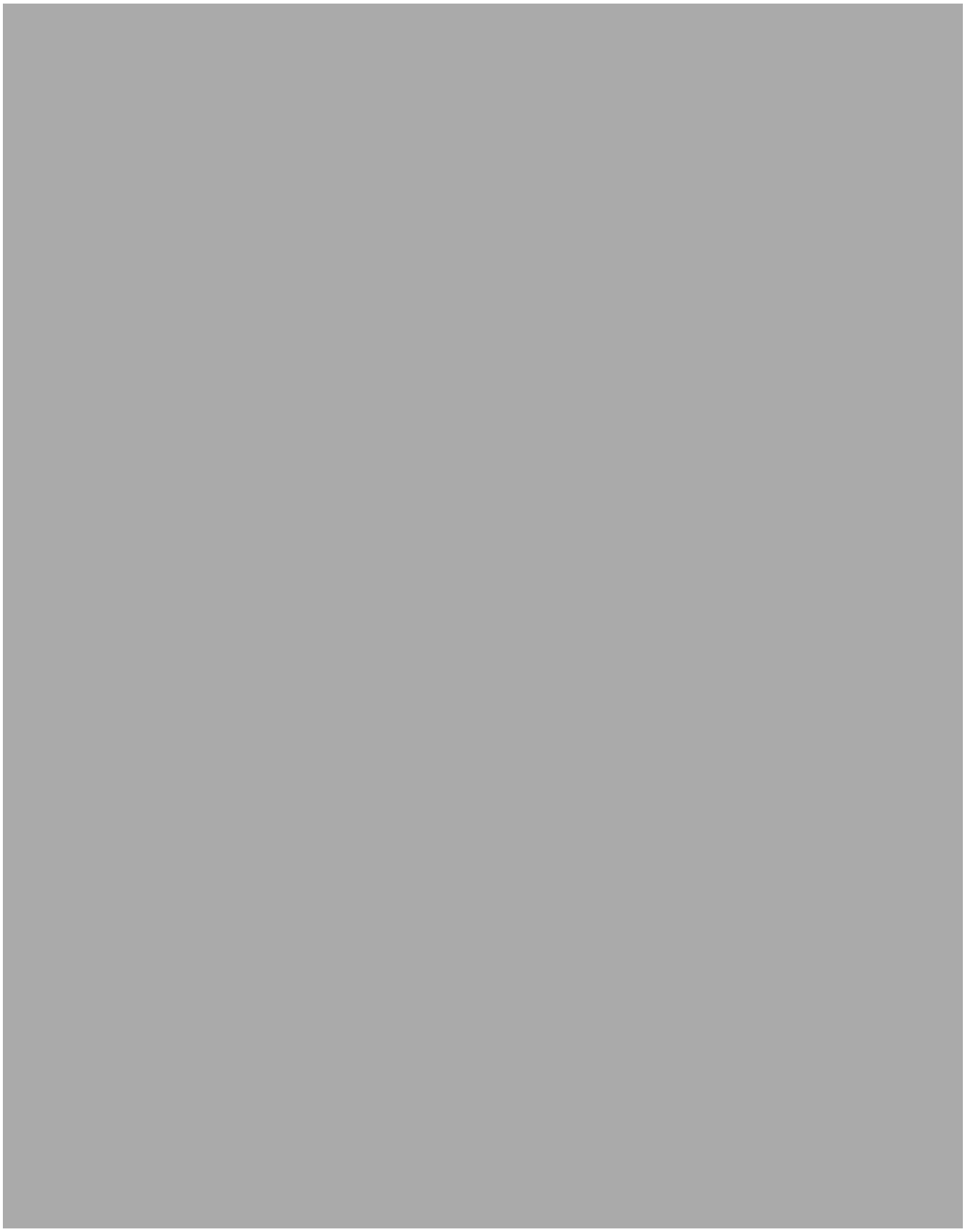


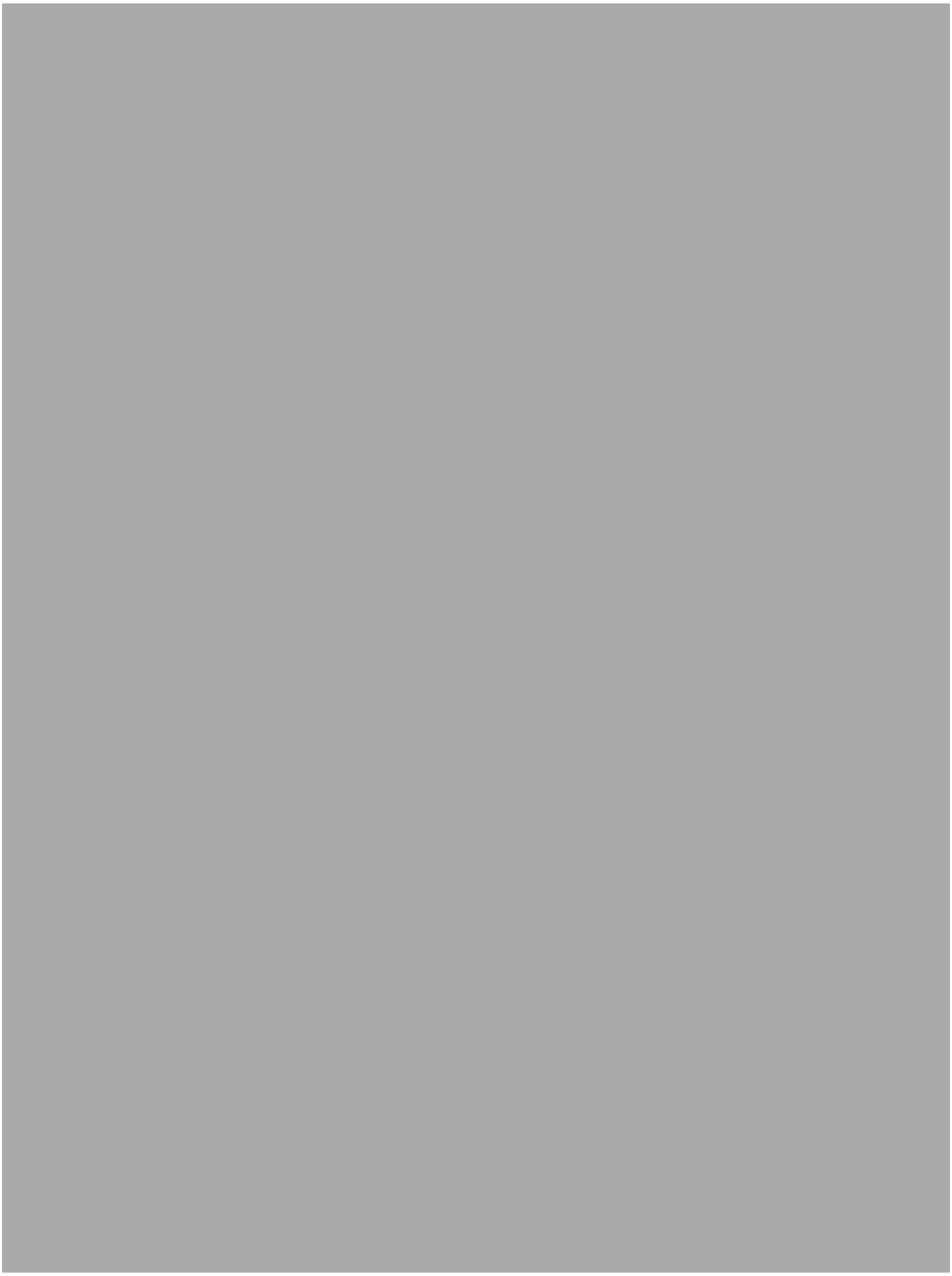
Total score___

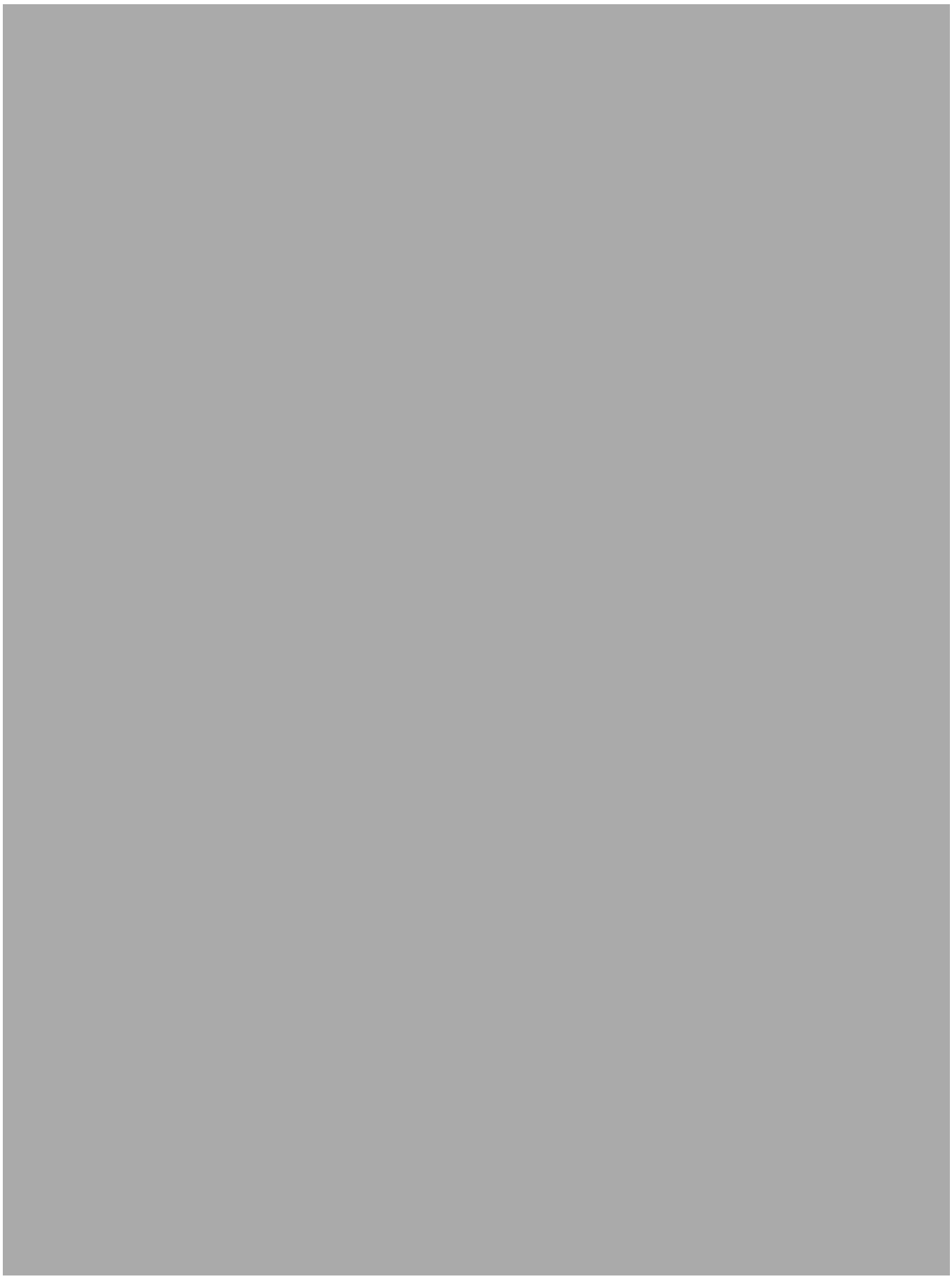
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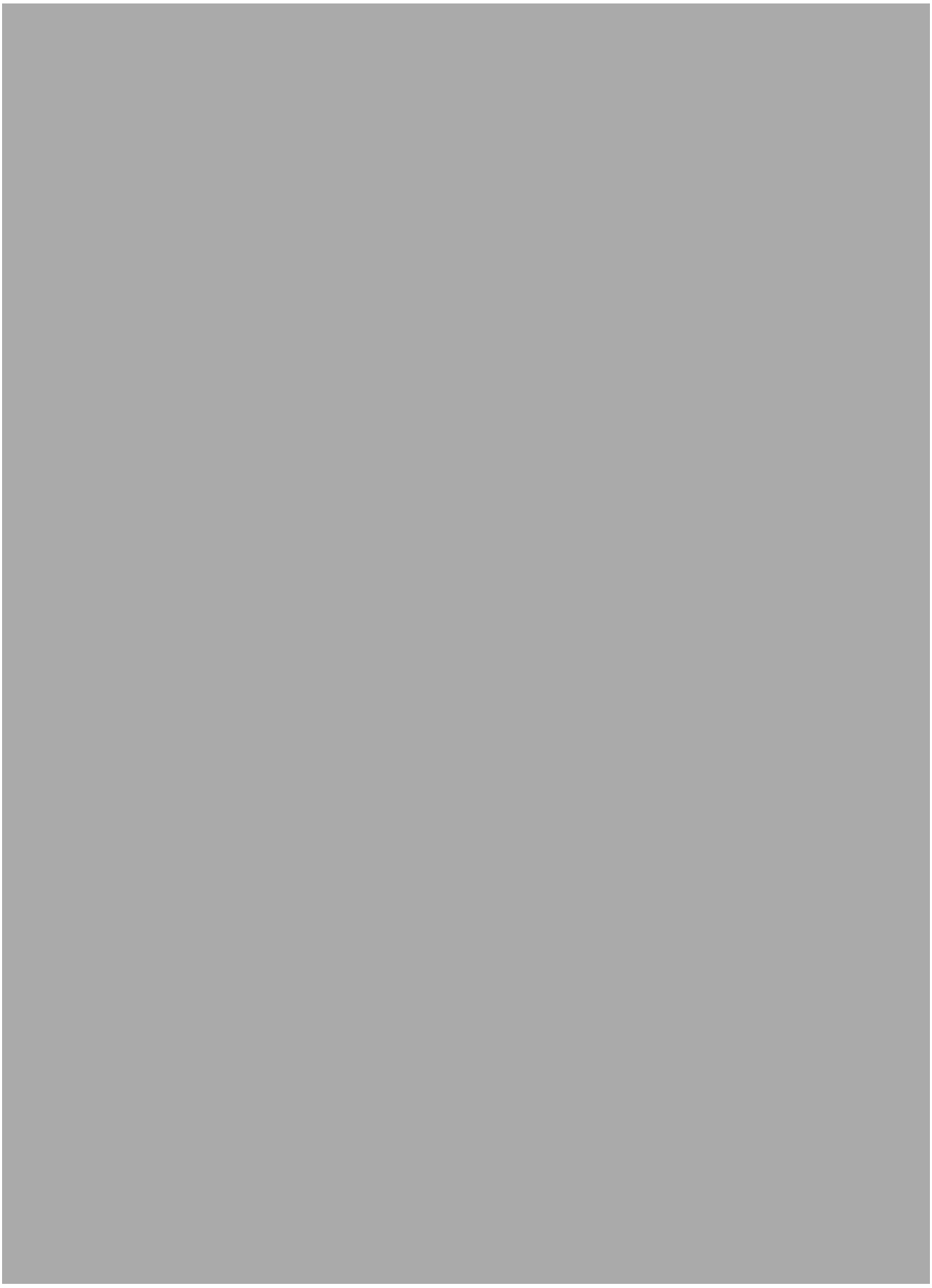
© Copyright 1991 Aaron.T.Beck.

Appendix VI. Beck Depression Inventory (Beck, Steer and Brown, 1996)







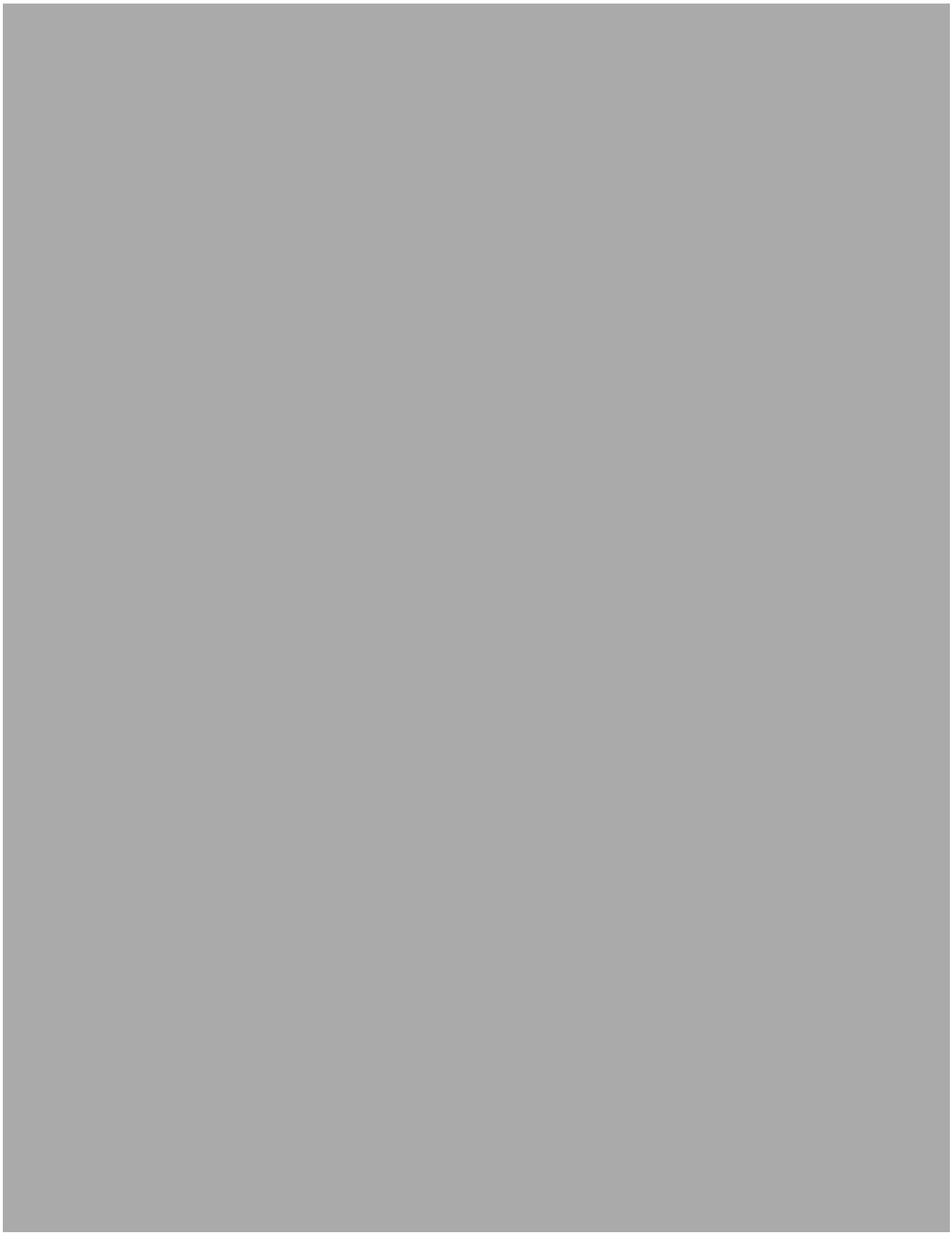




Beck, A. T., Steer, R.A., & Brown, G.K. (1996). *Beck Depression Inventory-II* (2nd ed.). United States of America: Pearson.

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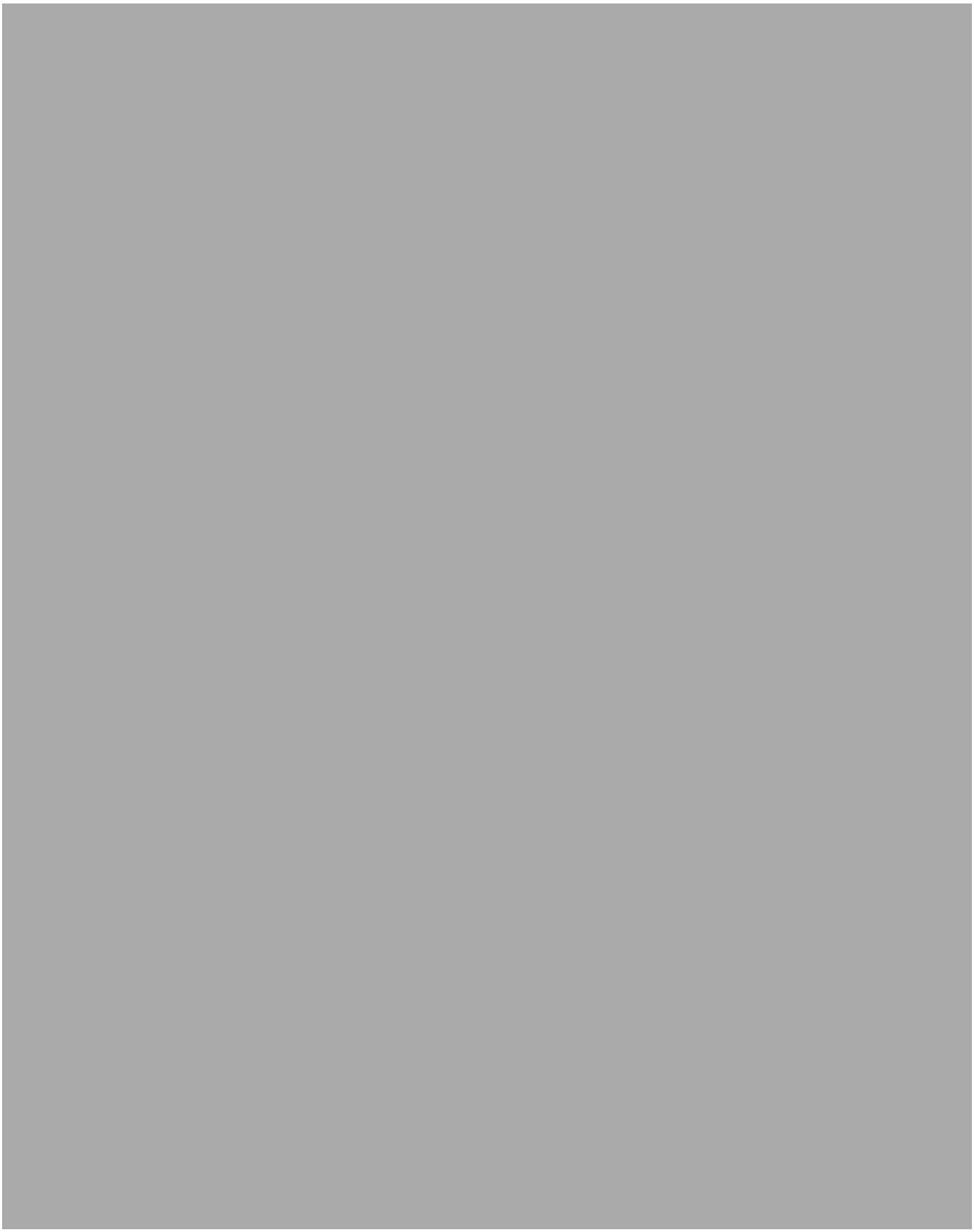
Appendix VII. Multiple Sclerosis Impact Scale MSIS-29 (Hobart et al., 2001)

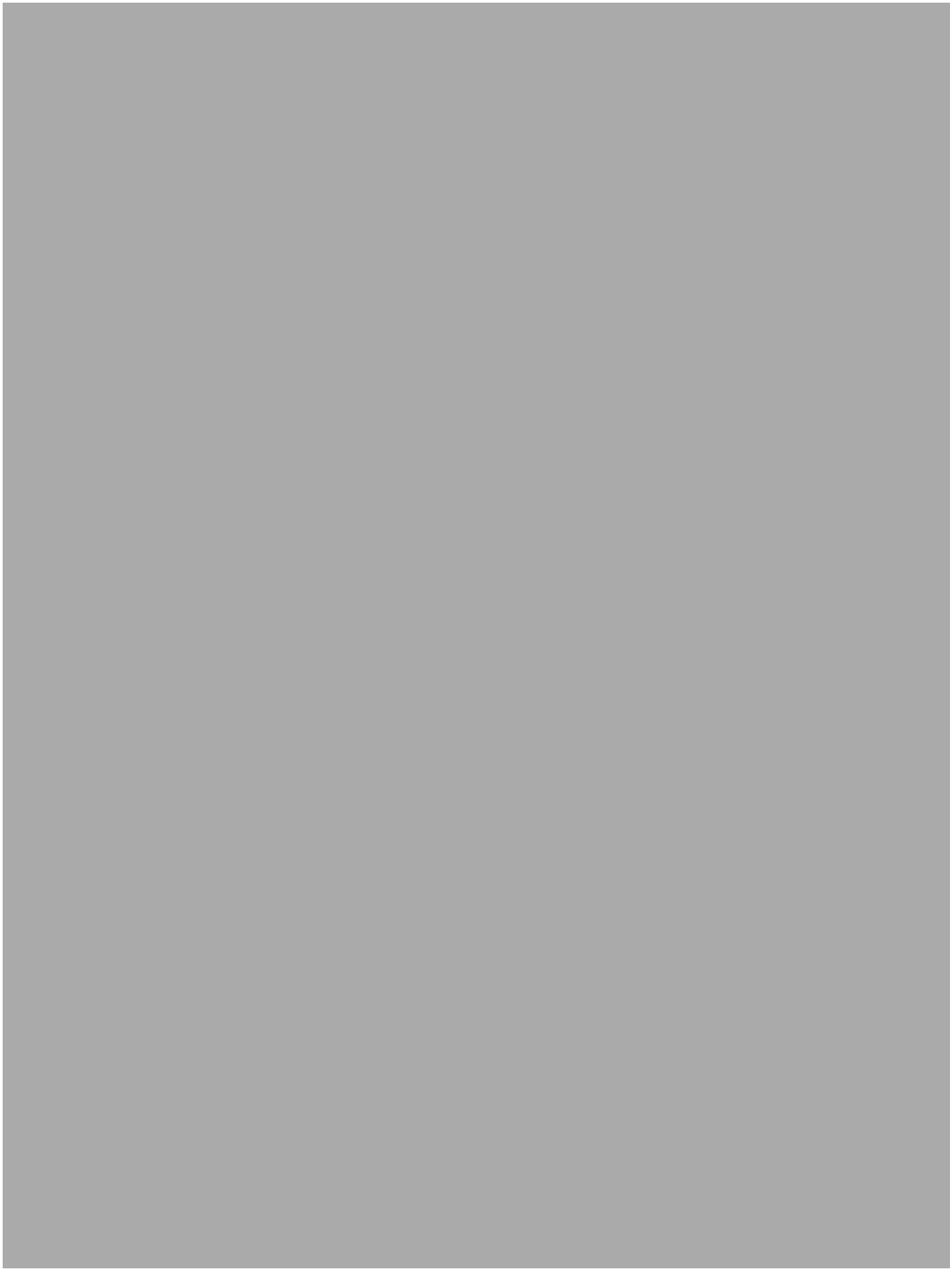


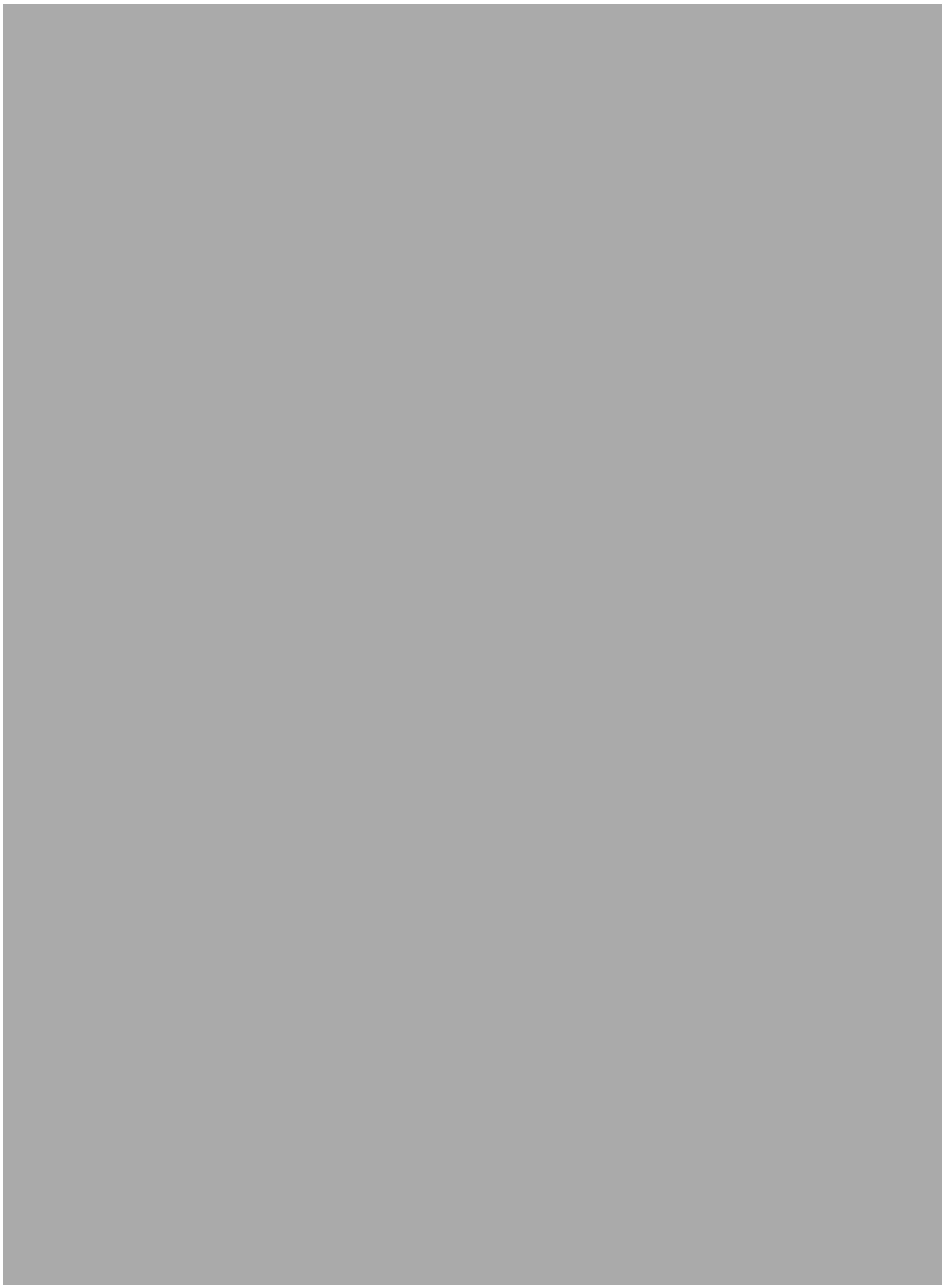


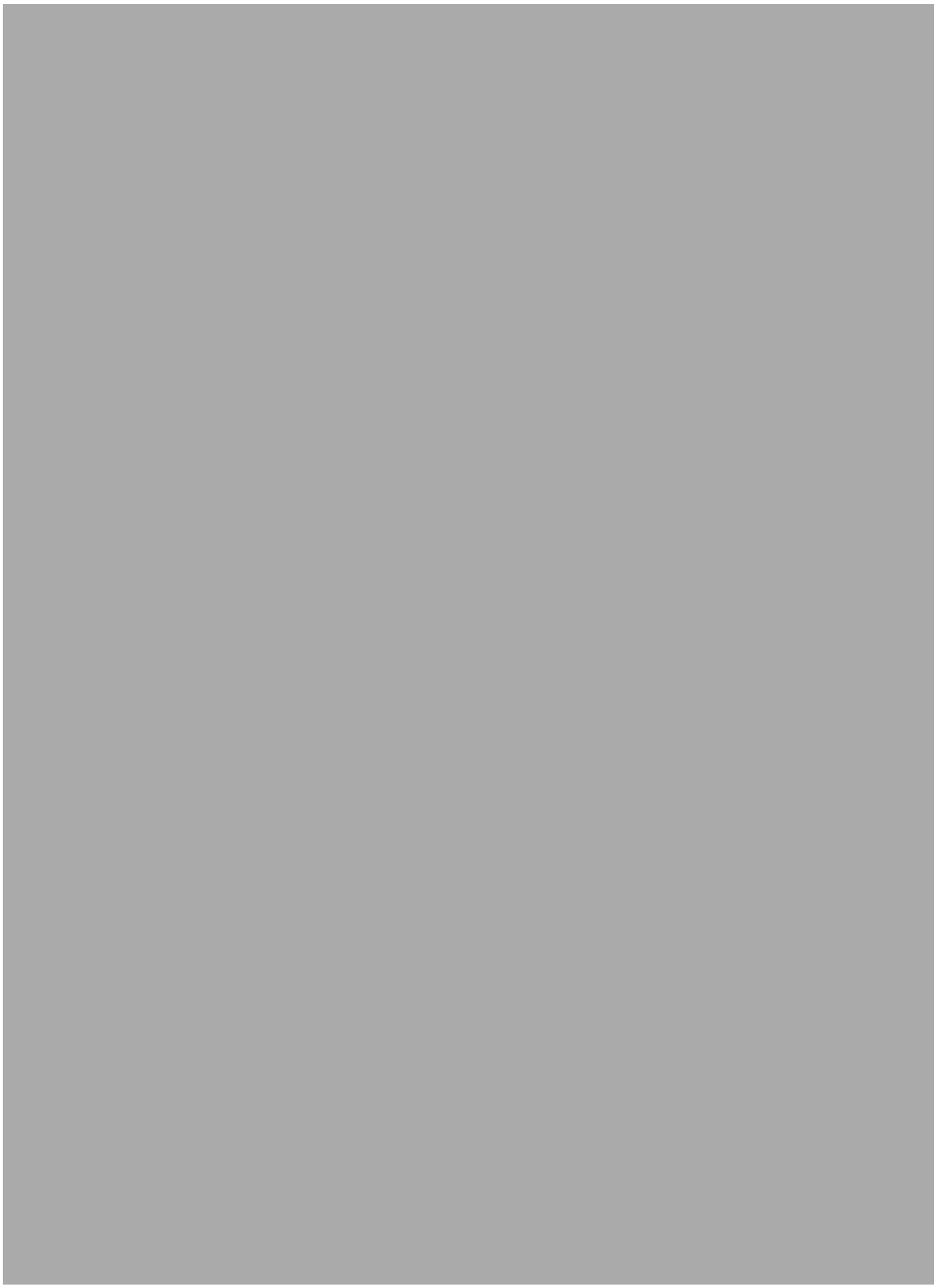
© 2000 Neurological Outcome Measures Unit, 4th Floor Queen Mary Wing, NHNN, Queen Square London, WC1N 3BG, UK.

Appendix VIII. Guys Neurological Disability Scale GNDS (Sharrack & Hughes, 1999a)











Appendix IX. A description of the four measures utilised and their clinical relevance

Beck Suicide Scale - BSS (Beck & Steer, 1993) is a measure of presence and severity of suicide ideation assessing thoughts, plan and intent occurring during the week leading up to and including the day of completion (see Appendix V). It is a 21 item self-report measure, each item consisting of graded options according to suicidal intensity on a three point scale (from 0-2: 0 = no suicide ideation, 2 = highest level of suicide ideation). There are no clinical cut off points. For those who have previously attempted suicide, two additional items record incidence, frequency and a subjective estimate of the seriousness of the attempt(s) which provides an additional indication of risk which could result in a total score of up to 42. The BSS has previously been used to assess suicide ideation in the MS population e.g. Feinstein (2002), Korostil and Feinstein (2007).

Beck Depression Inventory – BDI-II (Beck et al., 1996) provides a measure of presence and severity of depressive symptoms over the previous two weeks including the day of completion (see Appendix VI). It is a 21 item self-report measure, each item consisting of graded options according to intensity of depressive symptoms on a four point scale (from 0-3: 0 = no depressive symptoms, 4 = highest level of depressive symptoms), with a maximum score of 63. There are clinical cut off points to categorise the level of depression: mild = 14-19, moderate = 20-28. Severe = 29-63 (Beck et al., 1996). The BDI has previously been used to assess depressive symptoms in the MS population e.g. Mohr et al. (1997), Pujol et al. (2000).

Multiple Sclerosis Impact Scale – MSIS-29* (Hobart et al., 2001) is a measure of *perceived* level of disability over the previous two weeks (see AppendixVII). Specifically designed for

use with MS, it is becoming increasingly widely used and has been translated into 20 different languages (Hobart & Cano, 2009). It is a 29 item self-report measure which uses a five point scale (from 1-5) to gauge how much different aspects of living with MS impact upon the respondent. Responses can range from "not at all" = 1 to "extremely" = 5, a higher score indicating a greater the level of perceived disability. The maximum total score is 145; perceived physical impact is assessed in 20 questions (highest possible score: 100) and perceived psychological impact is assessed in 9 questions (highest possible score: 45). The MSIS-29 has been previously used to assess perceived disability in MS e.g. Forbes et al. (2006), McCullagh, Fitzgerald, Murphy, and Cooke (2008).

Guys Neurological Disability Scale for Multiple Sclerosis – GNDS* (Sharrack & Hughes, 1999a) is a self-report measure of *actual* physical disability, regularly used in clinical practice and consisting of 12 functional domains (e.g. cognition, speech, bowel function, sexual function) which uses a six point scale (from 0-5), ranging from: 0 = normal status to 5 = total loss of function (see AppendixVIII). The overall maximum score for this measure is 60. As advised by Sharrack & Hughes (1999a), for respondents who did not wish to disclose information about sexual function, a mean score of bladder, bowel and lower limb function was calculated instead. The GNDS has been previously used to assess actual disability in MS e.g. (Nicholl et al., 2001), Kileff and Ashburn (2005).

*NB. The Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) has been referred to as the most widely used scale for assessing physical limitation in MS (Cheng et al., 2001). However, a requirement of the scale is that it is administered by a physician which includes neurological examination. It has also been criticised because it doesn't include a self-report section. Self-report measures allow for the encapsulation of additional information, such as

the full impact of the disease on the patient's life (Hawton, Green, Telford, Zajicek, & Wright, 2012) and patient's perceptions of change were found to differ from the opinions of the physician when compared (Hoogervorst, Eikelenboom, & Polman, 2003). The EDSS is not patient lead and it is thought to be biased towards mobility rather than the whole spectrum of disability types (Whitaker, McFarland, Rudge, & Reingold, 1995). The MSIS provides an assessment of the impact of the disease on quality of life (Hawton et al., 2012) and the GNDS has been referred to as a measure which is, user friendly, practical and capable of assessing patient's views across the whole range of possible disabilities in MS (Sharrack & Hughes, 1999a; Sharrack & Hughes, 1999b).

Appendix X. Psychometric properties of the four measures

The psychometric properties of each measure are detailed in Table 1, below.

Table 1. Psychometric properties of each measure

<table>
<tr><th>Measure</th><th>Reliability</th><th>Validity</th></tr>
<tr><td>BSS</td><td>High internal consistency was found, including in outpatient settings.
Scores ranged from α=0.87 to α=0.97 (Beck & Steer, 1991; Beck, Steer, & Ranieri, 1988; Steer, Rissmiller, Ranieri, & Beck, 1993).</td><td>Beck et al. (1988): the measure correlated highly (r = 0.94) with the Scale for Suicide Ideation: SSI (Beck, Kovacs, & Weissman, 1979).
It also correlates moderately (r=0.64 to 0.75) with the Beck Depression Inventory (Beck et al., 1996) according to Beck and Steer (1993).</td></tr>
<tr><td>BDI-II</td><td>High internal consistency was found when used with physical health populations, in outpatient settings
Scores were α=0.90 (Williams et al., 2012) and α=0.94 (Turner et al., 2012).</td><td>Prinz et al. (2013): the measure correlated highly (r=0.80) with the Symptoms Checklist 90 Revised: SCL90-R (Derogatis, 1983).
Lipps et al. (2010): it also correlated moderately (r=0.74) with the Centre for Epidemiological Scales: Depression measure: CES-D (Radloff, 1977).</td></tr>
<tr><td>MSIS-29</td><td>High internal consistency was found by Hobart et al. (2001) α=0.91 and by Hobart (2011) α=0.96, both in outpatient settings.</td><td>Measure found to correlate with three physical health scales (Riazi, Hobart, Lamping, Fitzpatrick, & Thompson, 2002) were: Short Form 36: SF36 (Stewart, Hays, & Ware, 1988), Functional Assessment of Multiple Sclerosis: FAMS (Cella et al., 1996), General Health Questionnaire: GHQ (Goldberg & Hillier, 1979).
<table>
<tr><th>Measure</th><th>MSIS-29 Physical</th><th>MSIS-29 Psychological</th></tr>
<tr><td>SF36</td><td>Physical functioning r=-0.79
Mental health r=-0.41</td><td>Physical functioning r=-0.41
Mental health r=-0.76</td></tr>
<tr><td>FAMS</td><td>Mobility r=-0.88
Emotional wellbeing r=-0.68</td><td>Mobility r=-0.50
Emotional wellbeing r=-0.68</td></tr>
<tr><td>GHQ</td><td>r=0.46</td><td>r=0.68</td></tr>
</table>
</td></tr>
<tr><td>GNDS</td><td>Moderate internal consistency was found in outpatient settings by Sharrack and Hughes (1999a) α= 0.79.
Fraser and McGurl (2007): moderate internal consistency was found by recording α each time the measure was administered: time one α=0.79, time two α=0.78 and time three α=0.80.</td><td>Rossier and Wade (2002): the measure correlates highly with the Expanded Disability Status Scale (Kurtzke, 1983): EDSS r=0.64 and the Barthel Index of Activities of Daily Living: BI (Wade & Collin, 1988) r=0.76.
Sharrack and Hughes (1999a): the measure also correlates highly with the functional functioning domain of the SF36, r=-0.81.
Measuring the validity of the 12 domains of the GNDS with corresponding indices, correlations were found ranging from r=-0.557 to 0.910 (Rossier & Wade, 2002).</td></tr>
</table>

Appendix XI. Consent forms



UNIVERSITY OF BIRMINGHAM

Negative thoughts and feelings and disability in Multiple Sclerosis

Consent Form

Please initial box:

1. I, ..., confirm that I have read and understood the participant information sheet for this study. I have had the opportunity to ask any questions, and these questions have been answered satisfactorily. ☐

2. I give consent for the researcher to contact Dr Koko (or a member of the MS clinic team) and my GP should they have concerns that I am having thoughts of harming myself. ☐

3. I understand that any information I provide will be kept confidential. ☐

4. I understand that the data will be treated according to the British Psychological Society Code of Ethics. ☐

5. I understand that the information I provide will be used and analysed for research purposes. I also understand that these findings may be published in an academic journal. ☐

6. I understand that I can withdraw from the study up to two weeks after participating, without giving reason, by contacting the researcher with my unique participant reference code. I have made a note of my participant reference code. I understand that if I do withdraw from this study, my data will be destroyed and will not be used in this study. ☐

7. I understand that relevant sections of my data collected during the study, may be looked at by individuals from the University of Birmingham, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

8. By signing this consent form, I agree to participate in this study. ☐

_____	_____	_____
Name of participant	Signature	Date
_____	_____	_____
Name of researcher	Researcher's signature	Date

UNIVERSITY OF BIRMINGHAM

[redacted]

[redacted]

Negative thoughts and feelings and disability in Multiple Sclerosis

Consent Form

Please initial box:

1. I, ..., confirm that I have read and understood the participant information sheet for this study. I have had the opportunity to ask any questions, and these questions have been answered satisfactorily. ☐

2. I give consent for my GP to be sent a standard letting informing him/her that I am participating in this research. ☐

3. I give consent for the researcher to contact Dr Woolmore (or a member of the MS clinic team) and my GP should they have concerns that I am having thoughts of harming myself. ☐

4. I understand that any information I provide will be kept confidential. ☐

5. I understand that the data will be treated according to the British Psychological Society Code of Ethics. ☐

6. I understand that the information I provide will be used and analysed for research purposes. I also understand that these findings may be published in an academic journal. ☐

7. I understand that I can withdraw from the study up to two weeks after participating, without giving reason, by contacting the researcher with my unique participant reference code. I have made a note of my participant reference code. I understand that if I do withdraw from this study, my data will be destroyed and will not be used in this study. ☐

8. I understand that relevant sections of my data collected during the study, may be looked at by individuals from the University of Birmingham, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

9. By signing this consent form, I agree to participate in this study. ☐

_____	_____	_____
Name of participant	Signature	Date

_____	_____	_____
Name of researcher	Researcher's signature	Date

Appendix XII. SPSS output for K-S tests

Total sample:

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BSS	.347	75	.000	.499	75	.000
BDI	.132	75	.002	.952	75	.006
MSIS29	.079	75	.200*	.985	75	.549
GNDS	.066	75	.200*	.990	75	.830

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.077	75	.200*	.978	75	.217
Age at onset	.092	75	.182	.971	75	.081
Age at diagnosis	.073	75	.200*	.986	75	.573

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

PPMS sample:

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BSS	.391	26	.000	.345	26	.000
BDI	.122	26	.200*	.961	26	.408
MSIS29	.132	26	.200*	.972	26	.666
GNDS	.119	26	.200*	.981	26	.903

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.095	26	.200*	.975	26	.747
Age at onset	.095	26	.200*	.985	26	.956
Age at diagnosis	.103	26	.200*	.980	26	.866

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

SPMS sample:

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BSS	.328	49	.000	.568	49	.000
BDI	.137	49	.023	.947	49	.029
MSIS29	.107	49	.200*	.965	49	.146

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Age	.103	49	.200*	.973	49	.310
Age at onset	.075	49	.200*	.972	49	.289
Age at diagnosis	.097	49	.200*	.982	49	.645

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Appendix XIII. SPSS output for *perceived* disability mediation analysis

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Release 2.11 ***************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2013). www.guilford.com/p/hayes3

****
Model = 4
Y = ZBSS
X = ZMSIS29
M = ZBDI

Sample size
75

****
Outcome: ZBDI

Model Summary

R	R-sq	F	df1	df2	p
.6630	.4396	42.7621	1.0000	73.0000	.0000

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.0886	.0000	1.0000	-.1765	.1765
ZMSIS29	.6630	.1014	6.5393	.0000	.4610	.8651

****
Outcome: ZBSS

Model Summary

R	R-sq	F	df1	df2	p
.5495	.3019	3.7010	2.0000	72.0000	.0295

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.1035	.0000	1.0000	-.2063	.2063
ZBDI	.4801	.2161	2.2217	.0294	.0493	.9109
ZMSIS29	.0973	.1146	.8490	.3987	-.1311	.3257

************************** TOTAL EFFECT MODEL **************************

Outcome: ZBSS

Model Summary

R	R-sq	F	df1	df2	p
.4156	.1727	6.3806	1.0000	73.0000	.0137

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.1090	.0000	1.0000	-.2173	.2173
ZMSIS29	.4156	.1645	2.5260	.0137	.0877	.7435

********** TOTAL, DIRECT, AND INDIRECT EFFECTS **********

Total effect of X on Y

Effect	SE	t	p	LLCI	ULCI
.4156	.1645	2.5260	.0137	.0877	.7435

Direct effect of X on Y

Effect	SE	t	p	LLCI	ULCI
.0973	.1146	.8490	.3987	-.1311	.3257

Indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3183	.1491	.1197	.7259

Partially standardized indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3183	.0943	.1450	.5183

Completely standardized indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3183	.0960	.1480	.5342

Ratio of indirect to total effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.7659	.3667	.3054	1.3877

Ratio of indirect to direct effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	3.2719	1214.8854	-4.5040	341.3568

R-squared mediation effect size (R-sq_med)

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.1674	.0604	.0650	.3109

Preacher and Kelley (2011) Kappa-squared

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.2649	.0746	.1275	.4182

********** ANALYSIS NOTES AND WARNINGS **********

Number of bootstrap samples for bias corrected bootstrap confidence intervals:
    1000
Level of confidence for all confidence intervals in output:
   95.00

NOTE: All standard errors for continuous outcome models are based on the HC3 estimator

------ END MATRIX -----

Appendix XIV. SPSS output for *actual* physical disability mediation analysis

Run MATRIX procedure:

***************** PROCESS Procedure for SPSS Release 2.11 ****************

Written by Andrew F. Hayes, Ph.D. www.afhayes.com
Documentation available in Hayes (2013). www.guilford.com/p/hayes3

****
Model = 4
Y = ZBSS
X = ZGNDS
M = ZBDI

Sample size
75

****
Outcome: ZBDI

Model Summary

R	R-sq	F	df1	df2	p
.6031	.3637	39.7386	1.0000	73.0000	.0000

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.0940	.0000	1.0000	-.1874	.1874
ZGNDS	.6031	.0957	6.3039	.0000	.4124	.7938

****
Outcome: ZBSS

Model Summary

R	R-sq	F	df1	df2	p
.5463	.2984	3.7071	2.0000	72.0000	.0294

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.1038	.0000	1.0000	-.2070	.2070
ZBDI	.5123	.1884	2.7187	.0082	.1367	.8880
ZGNDS	.0536	.1113	.4813	.6318	-.1683	.2754

********** TOTAL EFFECT MODEL **********
Outcome: ZBSS

Model Summary

R	R-sq	F	df1	df2	p
.3625	.1314	4.0532	1.0000	73.0000	.0478

Model

	coeff	se	t	p	LLCI	ULCI
constant	.0000	.1122	.0000	1.0000	-.2235	.2235
ZGNDS	.3625	.1801	2.0132	.0478	.0036	.7214

********** TOTAL, DIRECT, AND INDIRECT EFFECTS **********

Total effect of X on Y

Effect	SE	t	p	LLCI	ULCI
.3625	.1801	2.0132	.0478	.0036	.7214

Direct effect of X on Y

Effect	SE	t	p	LLCI	ULCI
.0536	.1113	.4813	.6318	-.1683	.2754

Indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3090	.1197	.1292	.6145

Partially standardized indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3090	.0680	.1651	.4369

Completely standardized indirect effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.3090	.0724	.1710	.4638

Ratio of indirect to total effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.8523	1.1434	.4168	1.9654

Ratio of indirect to direct effect of X on Y

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	5.7695	1965.9762	1.4727	849.5738

R-squared mediation effect size (R-sq_med)

	Effect	Boot SE	BootLLCI	BootULCI
ZBDI	.1296	.0667	.0200	.2894

Preacher and Kelley (2011) Kappa-squared

	Effect	Boot SE	BootLLCI	BootULCI

ZBDI .2701 .0608 .1480 .3875

********** ANALYSIS NOTES AND WARNINGS **********

Number of bootstrap samples for bias corrected bootstrap confidence intervals:
1000
Level of confidence for all confidence intervals in output:
95.00

NOTE: All standard errors for continuous outcome models are based on the HC3 estimator

------ END MATRIX -----

Appendix XV. Post hoc power analysis information

Table 2. Empirical estimates of sample size requirements (Fritz & MacKinnon, 2007)

Empirical Estimates of Sample Sizes Needed for .8 Power

	Condition															
Test	SS	SH	SM	SL	HS	HH	HM	HL	MS	MH	MM	ML	LS	LH	LM	LL
BK ($\tau' = 0$)	20,886	6,323	3,039	1,561	6,070	1,830	883	445	2,682	820	397	204	1,184	364	175	92
BK ($\tau' = .14$)	562	445	427	414	444	224	179	153	425	178	118	88	411	147	84	53
BK ($\tau' = .39$)	531	403	402	403	405	158	124	119	405	125	75	59	405	122	60	38
BK ($\tau' = .59$)	530	404	402	403	406	158	124	120	405	125	74	58	404	122	59	36
Joint significance	530	402	403	403	407	159	124	120	405	125	74	58	405	122	59	36
Sobel	667	450	422	412	450	196	144	127	421	145	90	66	410	129	67	42
PRODCLIN	539	402	401	402	402	161	125	120	404	124	74	57	404	121	58	35
Percentile bootstrap	558	412	406	398	414	162	126	122	404	124	78	59	401	123	59	36
Bias-corrected bootstrap	462	377	400	385	368	148	115	118	391	116	71	53	396	115	54	34

Note. All sample sizes have been rounded up to the next whole number. In the condition labels, the first letter refers to the size of the α path, and the second letter refers to the size of the β path; S = 0.14, H = 0.26, M = 0.39, and L = 0.59 (e.g., condition SM is the condition with $\alpha = 0.14$ and $\beta = 0.39$). All results, except for those for Baron and Kenny's (1986) test (BK), have been collapsed across τ' conditions.

Appendix XVI. Non-significant differences for *actual* physical disability

Table 3. Comparing no suicide ideation and suicide ideation for area of *actual* disability

Area of disability	*M*	*SD*	*t*(73)	*p*
Memory				
No suicide ideation	1.55	1.61	-1.94	0.57
Suicide ideation	2.31	1.62		
Mood				
No suicide ideation	1.14	1.31	-2.36	0.06
Suicide ideation	1.96	1.64		
Vision				
No suicide ideation	0.73	0.93	-1.76	0.95
Suicide ideation	1.12	0.82		
Speech				
No suicide ideation	0.98	1.22	0.63	0.09
Suicide ideation	0.81	0.94		
Swallowing				
No suicide ideation	1.24	1.39	0.04	0.67
Suicide ideation	1.23	1.53		
Arms				
No suicide ideation	2.75	1.53	-1.21	0.54
Suicide ideation	3.19	1.41		
Mobility				
No suicide ideation	4.06	1.06	0.54	0.82
Suicide ideation	3.92	1.90		
Bladder				
No suicide ideation	2.83	1.90	-0.63	0.19
Suicide ideation	3.12	1.66		
Bowel				
No suicide ideation	1.49	1.84	-1.71	0.98
Suicide ideation	2.23	1.73		
Fatigue				
No suicide ideation	1.86	1.73	-2.38	0.07
Suicide ideation	2.81	1.47		
Sexual				
No suicide ideation	3.12	2.03	-0.53	0.95
Suicide ideation	3.38	2.02		
Other				
No suicide ideation	1.51	1.36	0.39	0.10
Suicide ideation	1.38	1.29		

Appendix XVII. Visual inspection of participants with suicide ideation and minimal or mild depressive symptoms

Table 4. Participants showing suicide ideation and minimal or mild depressive symptoms

Participant	BDI score	BSS score
Participant 19	0	1
Participant 25	3	1
Participant 37	7	6
Participant 5	8	1
Participant 11	9	1
Participant 74	9	1
Participant 7	10	3
Participant 18	13	3
Participant 14	14	2
Participant 16	14	1
Participant 6	15	1
Participant 72	15	3
Participant 46	17	9
Participant 66	19	3

Appendix XVIII. SPSS outputs for K-S tests

For rational suicide ideation group sample:

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BDI	.142	14	.200*	.961	14	.732
MSIS29	.142	14	.200*	.954	14	.631
GNDS	.238	14	.031	.913	14	.176
Age	.214	14	.081	.940	14	.418
Age at onset	.146	14	.200*	.950	14	.554
Time since onset	.089	14	.200*	.955	14	.643

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

For the remainder of the total sample with suicide ideation:

Tests of Normality

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
BDI	.259	11	.037	.920	11	.318
MSIS29	.185	11	.200*	.954	11	.692
GNDS	.247	11	.059	.881	11	.106
Age	.161	11	.200*	.946	11	.595
Age at onset	.134	11	.200*	.961	11	.789
Time since onset	.167	11	.200*	.952	11	.664

*. This is a lower bound of the true significance.

a. Lilliefors Significance Correction

Appendix XIX. Comparison of the MSIS-29 and GNDS

Table 5. Variables which are measured in both the MSIS-29 and the GNDS

Variables	MSIS-29	GNDS
Physically demanding tasks	✓	✓
Gripping things tightly	✓	✓
Carrying things	✓	✓
Problems with balance	✓	✓
Difficulties moving about indoors*	✓	
Bring clumsy	✓	
Stiffness	✓	
Heavy limbs	✓	
Tremors*	✓	
Spasms	✓	✓
Body not doing what you want	✓	
Having to depend on others	✓	
Limitations in social/leisure activities	✓	
Being stuck at home	✓	
Difficulties using hands	✓	✓
Having to cut down on work/leisure	✓	✓
Problems using transport	✓	
Taking longer to do things*	✓	
Difficulty doing things spontaneously*	✓	
Toilet urgency	✓	✓
Feeling unwell	✓	
Problems sleeping*	✓	
Feeling mentally fatigued	✓	✓
Worries related to MS	✓	
Feeling anxious or tense*	✓	✓
Feeling irritable	✓	✓
Problems concentrating	✓	✓
Lack of confidence	✓	
Feeling depressed*	✓	✓
Memory/concentration	✓	✓
Mood/emotions	✓	✓
Vision		✓
Speech and communication		✓
Swallowing		✓
Use of arms and hands	✓	✓
Mobility	✓	✓
Bladder function	✓	✓
Bowel function	✓	✓
Fatigue	✓	✓
Sexual function		✓
Any other problem e.g. spasms, balance	✓	✓

*Significant differences found when comparing suicide ideation with no suicide ideation.

Appendix XX. Instructions for authors – Clinical Psychology Review

