THE ECONOMIC BURDEN AND DETERMINANTS OF HEALTHCARE COSTS OF BACK PAIN IN THE UK: AN EMPIRICAL INVESTIGATION USING ELECTRONIC HEALTH RECORDS

By

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ABSTRACT

Back pain is a common health problem globally and it imposes great costs associated with its treatment. In the UK, the healthcare costs associated with back pain were last estimated 20 years ago in a cost-of-illness (COI) study. Given the aging population worldwide, these costs are likely to rise putting further pressure on healthcare services. The use of robust, and more advanced econometric methods to exploit national electronic health records (EHRs) may present up-to-date and more precise estimates for the healthcare costs of back pain. This thesis utilises such data source and methods to estimate the consultations, and prescriptions costs of back pain and to investigate factors associated with these costs.

The systematic review of the literature assessed the methodologies used in COI studies of back pain. The vast majority of studies used a direct method of summing up back pain related costs which underestimated the true cost of back pain compared to an incremental cost approach. The latter approach which is conducted using a matched control or regression-based methods is more accurate, and comprehensive. This thesis further explored potential data sources that could be utilised for estimating healthcare resource use and costs of back pain in the UK. The Health Improvement Network (THIN), one of the two most widely used primary care databases in clinical research, was identified providing complete records of consultations and prescriptions data.

Matched control studies, using propensity score matching, were conducted to estimate annual healthcare costs (2011-2015), and to assess how estimates vary by socio-economic factors, and over time. The incremental costs obtained in comparison with a similar reference population

enabled the risk of confounding effects due to differences in baseline characteristics to be minimised. The thesis further evaluated several alternative econometric methods used in modelling healthcare cost data. A cross-sectional study was then conducted to assess factors associated with healthcare costs of back pain. Regression analysis methods applied included OLS, log transformed OLS, generalised linear models (GLMs), extended estimating equations (EEE) model, and a quantile regression approach. How well the alternative estimators performed in terms of bias, accuracy and goodness-of-fit was compared by examining regression diagnostics, and predictive performance of the models. The findings demonstrate the need for researchers to examine their assumptions about the most appropriate model for analysing healthcare cost data.

DEDICATION

To Elsa D., Mathias D., and Sabela D.

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TABLE OF CONTENTS

LIST OF TABLES i

LIST OF FIGURES iii

LIST OF ABBREVIATIONS v

CHAPTER 1. INTRODUCTION 1

1.1 Background 1

1.2 Cost-of-illness studies 3

1.3 Estimating healthcare resource use and costs 3

1.4 Modelling healthcare expenditure 5

1.5 Aims and objectives of the thesis 7

1.6 Structure of the thesis 8

CHAPTER 2. BACK PAIN: THE CLINICAL AREA AND ITS BURDEN 10

2.1 Introduction 10

2.2 Burden of back pain 10

2.3 Definitions 11

2.4 Classifications of back pain 11

2.5 Risk factors 13

2.6 Prevalence of back pain 13

2.7 Incidence of back pain 15

2.8 Etiology and diagnosis 15

2.9 Prevention and management 16

2.10 Summary 17

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS IN THE ASSESSMENT OF DIRECT AND INDIRECT COSTS OF BACK PAIN: A SYSTEMATIC REVIEW 19

3.1 Introduction 19

3.1.1 Cost of illness studies 20
3.1.2 Overview of COI methodologies 21
3.2 Methods 23
3.2.1 Inclusion and exclusion criteria 23
3.2.2 Literature search strategy 23
3.2.3 Selection of studies for review 26
3.3 Results 29
3.3.1 Study selection 29
3.3.2 Overview of the included studies 32
3.3.3 Methodological characteristics of the studies 39
3.3.4 National estimates of cost of back pain 50
3.4 Discussion 54
3.4.1 Principal findings of the review 54
3.4.1 Key methodological challenges 56
3.4.2 Strengths and limitations 59
3.4.3 Recommendations 61
3.5 Conclusion 62

CHAPTER 4. INTRODUCTION TO ELECTRONIC HEALTH RECORDS AND DATA SOURCE FOR THE THESIS 64
4.1 Introduction 64
4.2 Electronic health records in the UK 65
4.3 The Health Improvement Network (THIN) 69
4.3.1 Structure of the THIN data 70
4.3.2 Proposed use of the database 71
4.3.3 Identification of back pain diagnosis from THIN 72
4.3.4 Identification of prescription drugs from THIN 73
4.3.5 Comorbid conditions and the Charlson Comorbidity Index (CCI) 74
4.3.6 Strength and limitations of THIN in relation to intended analyses 75
4.4 Ethical approval 78

4.5 Summary 78

CHAPTER 5. HEALTHCARE RESOURCE USE AND COSTS OF BACK PAIN IN PRIMARY CARE 80

5.1 Introduction 80

5.2 Aims and objectives 80

5.3 Methods 81

5.3.1 Study population, study design and period 81

5.3.2 Inclusion and exclusion criteria 84

5.3.3 Selection of study sample 85

5.3.4 Extraction of healthcare resource use and other data 87

5.3.5 Assigning costs to healthcare resource utilisation 88

5.3.6 Analysis and costing 89

5.4 Results 91

5.4.1 Study population 91

5.4.2 Healthcare resource use and associated costs 97

5.4.3 Variation of costs by subgroups of population 102

5.4.4 Trends in healthcare costs in recent years 104

5.5 Discussion 108

5.5.1 Principal findings 108

5.5.2 Strengths and limitations of the study 109

5.5.3 Interpretation in relation to other studies 111

5.6 Conclusion 113

CHAPTER 6. ECONOMETRIC METHODS FOR ANALYSING HEALTHCARE COSTS 114

6.1 Introduction 114

6.2 Aims and objectives 116

6.3 Common econometric approaches for healthcare cost 116

6.3.1 Ordinary least squares (OLS) regression 116

6.3.2 Log-transformed OLS regression 118

6.3.3 Generalised linear model (GLM) 119
6.3.4 Extended estimating equations (EEE) 121
6.3.5 Two-part models 122
6.3.6 Quantile regression 123
6.4 Model selection and specification 127
6.5 Assessing model performance 128
6.6 Summary 129

CHAPTER 7. FACTORS ASSOCIATED WITH HEALTHCARE COSTS OF BACK PAIN 132
7.1 Introduction 132
7.2 Aims and objectives 133
7.3 Methods 134
7.3.1 Study population 134
7.3.2 Study design 134
7.3.3 Overview of the data 135
7.3.4 Regression analysis methods 139
7.3.5 Variable selection and specification 142
7.3.6 Model diagnostics and descriptive statistics 144
7.4 Results 146
7.4.1 Study Population 146
7.4.2 Variable selection and specification 151
7.4.3 OLS modelling 155
7.4.4 The log-OLS model 156
7.4.5 GLM modelling 160
7.4.6 Extended Estimating Equations (EEE) modelling 167
7.4.7 Quantile regression (QR) 171
7.4.8 Comparison between alternative models 176
7.5 Discussion 183
7.5.1 Principal findings 183

7.5.2 Strengths and limitations of the study 184
7.5.3 Comparison with other studies and conclusion 185

CHAPTER 8. DISCUSSION 190
8.1 Introduction 190
8.2 Statement of principal findings 191
8.2.1 Systematic review of existing studies 191
8.2.2 Estimating resource utilisation and costs 192
8.2.3 Econometric modelling of healthcare costs 193
8.3 Strengths and limitations of the research 194
8.3.1 Strengths of the research 194
8.3.2 Limitations of the research 196
8.4 Implications of the research 197
8.4.1 Methodological contributions 197
8.4.2 Implications for the NHS and economic evaluation 203
8.5 Conclusions 206

APPENDICES 208
Appendix 3.1: Search strategies used in the systematic review by database type 208
Appendix 4.1: Read codes list developed for identification of back pain diagnosis from the THIN database 211
Appendix 4.2: Pain relief drug list used for identification of prescription drugs from the THIN database 214
Appendix 4.3: List of additional drugs usually prescribed with some pain relief medications 221
Appendix 4.4: Overlap between the Charlson Comorbidity Index (CCI) and the Quality Outcomes Framework (QOF) Conditions 223
Appendix 4.5: Study protocol submitted to Scientific Review Committee for using the THIN database 224
Appendix 4.6: Scientific Review Committee (SRC) approval of protocol 230
Appendix 5.1: Grouping of consultation types for costing 232

Appendix 5.2: Grouping of healthcare professional staff roles for costing 233
Appendix 5.3: Unit cost of prescription drugs used in the analysis for 2015 234
Appendix 5.4: Unit cost per visit for each type of consultation in 2015 242
Appendix 5.5: Back pain prevalence estimates in 2015 calculated from the THIN database 243
Appendix 5.6: Selection of study population in the 2011 study 244
Appendix 5.7: Selection of study population in the 2013 study 245
Appendix 5.8: Estimates of annual healthcare resource use and costs associated with the treatment of back pain in 2011 246
Appendix 5.9: Estimates of annual healthcare resource use and costs associated with the treatment of back pain in 2013 247
Appendix 5.10: Distribution of the study population in THIN vs. the general population 248
Appendix 7.1: A full list of potential variables available for modelling from the THIN database 249
Appendix 7.2: Comparison of the log-transformed cost data vs. a normal distribution curve 251
Appendix 7.3: Output of the GLM model with square root link and gamma variance 252
Appendix 7.4: Output of the GLM model with a log link and gamma variance 253

LIST OF REFERENCES **254**

LIST OF TABLES

Table 3.1: Search strategy for OVID Medline with breakdown of hits obtained 25

Table 3.2: Coding used and further categorisation of studies at stage II 32

Table 3.3: Summary of the main characteristics of the included studies 34

Table 3.4: The contribution of primary care consultations and prescriptions to total healthcare costs of back pain 46

Table 3.5: National estimates of direct, indirect, and total costs of back pain in 2015 USD 51

Table 4.1: Potential EHRs based data sources to measure healthcare resource use and costs 67

Table 5.1: Breakdown of samples in the three studies and their degree of overlap 82

Table 5.2: Description of the statistical tests and diagnostics undertaken 90

Table 5.3: Baseline characteristics of the study population in 2015 96

Table 5.4: Estimates of annual healthcare resource use and costs associated with back pain in 2015 (scenario 1) 98

Table 5.5: Estimates of annual healthcare resource use and costs associated with back pain in 2015 (scenario 2) 102

Table 5.6: Mean healthcare costs (£s 2015) in sub-groups of back pain patients 103

Table 5.7: Comparison of costs and rates of resource use with previous studies 108

Table 6.1: Key methodological issues addressed by commonly used econometric methods 126

Table 7.1: Explanatory variables of patient and clinical characteristics 138

Table 7.2: Summary of the statistical tests and criteria used 145

Table 7.3: Summary statistics of the study population 149

Table 7.4: Forward selection of variables using likelihood ratio test on log-OLS model 151

Table 7.5: Backward elimination of variables using likelihood ratio test on GLM models 152

Table 7.6: Correlation matrix of the independent and dependent variables 153

Table 7.7: Regression estimates of the OLS model 156

Table 7.8: Exponentiated regression estimates of the log-OLS model 159

Table 7.9: Comparison of GLM model selection in order of preference 161

Table 7.10: Regression estimates of the GLM model with identity link and gamma variance .. 162

Table 7.11: Marginal effects of the GLM model with a square root link and gamma variance . 164

Table 7.12: Marginal effects from the GLM model with a log link and gamma variance 166

Table 7.13: Original regression estimates of the EEE model 168

Table 7.14: Estimates of marginal effects and CIs derived from the EEE model 170

Table 7.15: Quantile regression estimates alongside OLS estimates 173

Table 7.16: Comparison of model specification, predictive performance and goodness-of-fit .. 176

Table 7.17: Predicted marginal effects for patients with back pain 180

Table 7.18: Statistical tests of differences in the predictions of the models 181

LIST OF FIGURES

Figure 2.1: Anatomic classification of back pain by regions of the spine. 12

Figure 3.1: Flow chart showing summary of the literature search and study selection 30

Figure 3.2: Allocation of direct costs for back pain 45

Figure 3.3: Allocation of indirect costs for back pain 47

Figure 5.1: Selection of the study population in the 2015 study 92

Figure 5.2: Comparison of the distribution of propensity scores in the two groups before and after matching 93

Figure 5.3: Standardised differences across covariates in the matched sample 94

Figure 5.4: Attribution of resource use to the total consultations in patients with and without back pain. 99

Figure 5.5: Breakdown of the total prescription counts by drug groups. 100

Figure 5.6: Trends in incremental healthcare costs associated with back pain 104

Figure 5.7: Trends in all-cause healthcare costs of patients with back pain 105

Figure 5.8: Trends in incremental healthcare resource use associated with back pain 106

Figure 5.9: Trends in all-cause healthcare resource use of patients with back pain 107

Figure 7.1: Skewed distribution of the total healthcare cost data 135

Figure 7.2: Spread of high expenditure by type of resource use 137

Figure 7.3: Distribution of the total healthcare cost and cost by age showing two outliers 147

Figure 7.4: Distribution of expenditures in the high-cost group versus the rest 150

Figure 7.5: Association between total cost and age showing linear relationship 154

Figure 7.6: Comparison of the transformed total cost using common transformation types 157

Figure 7.7: The log-transformed total healthcare cost versus the raw cost data..... 158

Figure 7.8: Quantile plot of the total healthcare cost data..... 171

Figure 7.9: Graphical representation of the QR vs. OLS estimates..... 175

Figure 7.10: Scatter plot of the residuals against predicted values for the alternative estimators..... 179

Figure 7.11: Plot of the predicted costs across deciles of age for the alternative estimators 182

LIST OF ABBREVIATIONS

AIC	Akaike information criterion
BIC	Bayesian information criterion
BMI	Body mass index
BNF	British National Formulary
CCI	Charlson comorbidity index
CI	Confidence interval
CLBP	Chronic back pain
COI	Cost-of-illness
CPRD	Clinical Practice Research Datalink
EEE	Extended estimating equations
EHR	Electronic health records
FC	Friction cost
GBD	Global Burden of Disease
GLM	Generalised linear model
GP(s)	General practitioner(s)
HC	Human Capital
HES	Hospital Episode Statistics
HRU	Healthcare resource utilisation
ICD	International Classification of Diseases

LBP	Low back pain
MAPE	Mean Absolute Percentage Error
MPE	Mean Percentage Error
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAIDs	Nonsteroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
OLS	Ordinary least squares
ONS	Office for National Statistics
QOF	Quality and Outcomes Framework
QR	Quantile regression
RMSE	Root Mean Squared Error
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
WHO	World Health Organisation

CHAPTER 1. INTRODUCTION

1.1 Background

Back pain, although not life threatening is a major public health problem in developed countries (Deyo, 1998, Duthey, 2013). In the UK, it is estimated that up to 80% of individuals over 16 years of age may experience acute or chronic back pain at some point during their lives (Johnson, 2012). Consequently, back pain imposes great medical and non-medical related costs on patients, employers, and health care providers (Hoy et al., 2014b, Dagenais et al., 2008, Maniadakis and Gray, 2000).

The healthcare costs associated with back pain in the UK was last estimated 20 years ago within a cost of illness (COI) study carried out from a societal perspective (Maniadakis and Gray, 2000). The lack of recent national estimates for the healthcare costs of back pain is a glaring gap in the literature. As society is aging worldwide, these costs are likely to have risen and continue to do so due to increased utilisation of health care resources, putting further pressure on health care services. Manniadakis and Gray (2000) utilised population surveys to estimate many direct cost items such as back pain consultation rates, and prescription rates but the authors argued that other, less widely available data at the time, suggested potentially lower rates than the population surveys they had utilised indicated. In the intervening years, national primary care databases have emerged such as The Health Improvement Network (THIN), and the Clinical Practice Research Datalink (CPRD) which were not available to the authors of the previous published study. These routinely recorded databases or EHRs comprise detailed longitudinal data on primary care consultations, prescriptions, and

potentially referrals, as well as important demographic and clinical factors such as comorbidities.

Therefore, there is now an opportunity to explore through the use of EHRs, a new, and more accurate estimate for the healthcare attributed components of the economic burden of back pain. The only previous study in the UK to have used such data source for back related costs was a study by Hong et al. (2013) which used the CPRD data to assess the costs associated with the treatment of chronic low back pain (CLBP) (Hong et al., 2013). However, by focussing on LBP, and on chronically ill patients only, the estimates were effectively a subset of the broad cost of back pain. Given the substantial costs associated with back pain, assessment of its associated costs ought to be explored more comprehensively and should include both acute, and chronic back pain and over wider anatomical parts including the upper and lower regions of the spine.

Another gap in the literature concerns the relationship between healthcare costs and various patient and clinical characteristics. Although the prognosis and prevalence of back pain has been widely studied, the evidence is lacking on the main determinants of costs. Robust estimates of the healthcare costs of back pain and their predictors may provide important information for clinicians, health care commissioners, and public health policy makers, and will inform economic evaluations of interventions to treat or prevent the consequences of back pain.

This chapter briefly introduces the concept of a COI study, methods used for estimating healthcare resource utilisation and costs in COI studies, and the econometric modelling of healthcare cost data. These topics are expanded further in subsequent chapters. An

explanation of the aims and objectives of the thesis is then provided. Finally, the layout of the thesis is set out.

1.2 Cost-of-illness studies

COI studies aim to identify and measure the economic impact of a disease or illness including the direct and indirect costs. Direct costs comprise healthcare costs and non-healthcare-related costs while indirect costs mainly refer to labour productivity losses and informal care costs (Akobundu et al., 2006, Jo, 2014). COI studies are typically descriptive, and they quantify costs without comparing the possible alternative uses of healthcare resources. These studies are therefore criticised for not providing information on effectiveness, health benefits, or enabling choice of priorities (Drummond, 1992, Wiseman and Mooney, 1998). One accepted use of COI studies is to assist in the allocation of research funding to specific diseases (Rice, 2000, Rosen and Cutler, 2009). COI studies can also serve as a basis for further economic evaluations of interventions by providing cost estimates to populate cost-effectiveness models (Rice, 2000, Clabaugh and Ward, 2008). COI studies have been conducted in numerous disease areas including back pain. There have also been significant improvements in COI methodologies since Dorothy Rice formalised the methodology for costing illnesses in the mid-1960s (Rice, 2000, Cooper and Rice, 1976, Rice, 1967).

1.3 Estimating healthcare resource use and costs

Healthcare costs include costs for consultations, pharmaceuticals, hospitalisation, accident and emergency (A&E), diagnostic tests, and other out-patient services. A healthcare cost estimate is determined by the identification of healthcare resource utilisation and unit cost of each cost component (Cooper et al., 2002, Tan et al., 2010). The total healthcare cost per

patient is then estimated by combining the healthcare resource utilisation data with unit cost of each component using the following general estimation formula which sums up the total expenditure (Cooper et al., 2002):

$$Total\ cost = \sum_{i=1}^{n}.\sum_{j=1}^{m}(frequency)_{ij} * (unit\ cost)_{j}$$

where: i is the i^{th} patient (i = 1, … n) and j is the j^{th} healthcare resource used (j = 1, … m).

Consumption of healthcare resource utilisation is usually estimated using a 'top-down' or a 'bottom-up' approach (Hodgson and Meiners, 1982, Pagano et al., 1999). The top-down approach uses aggregated figures for consultations, hospital admissions and so on, while the bottom-up approach is based on actual consumption of resources by referring to records of each individual's resource utilisation (Pagano et al., 1999). The bottom-up approach which is more detailed, may be conducted either by direct summing of diagnosis specific expenditures, referred to as the 'direct method' or by using the incremental cost approach (Akobundu et al., 2006, Martin et al., 2008). Incremental cost or differential cost refers to the difference in total costs as a result of two alternatives, in this case patients with and without a particular disease. The total costs for patients with the disease are compared against the total costs for those without the disease to provide the incremental cost estimate.

There are usually two methods for estimating the incremental cost: the matched control method and the regression-based method (Akobundu et al., 2006, Coughlan et al., 2014, Martin et al., 2008). In the matching method, patients with the disease are matched with those without the disease based on demographic and clinical characteristics such as age, gender, deprivation, and co-morbidities (Balu and Thomas, 2006, Birnbaum et al., 2004). The method

therefore works under the premise that the matching process accounts for all known underlying differences between the two groups and any cost difference observed has to be attributed to the disease. In contrast, the regression method uses a regression model adjusting for relevant predictor variables to estimate the incremental cost. The choice and specification of the regression models may however hamper accuracy of the estimates and substantial bias could be introduced especially if the underlying distribution of the cost is not accounted for in the model (Akobundu et al., 2006, Lee et al., 2001).

1.4 Modelling healthcare expenditure

Besides estimating the incremental cost of a disease, regression or econometric methods can be used for assessing determinants of the cost or for investigating the relationship between healthcare cost and explanatory variables or predictors. Healthcare cost data are typically characterised by certain attributes that render standard regression methods inappropriate. These attributes are: i) a highly right skewed nature of the distribution, ii) a substantial proportion of zero values for individuals with no resource use, and iii) non-negative values for cost (Deb and Norton, 2018, Mihaylova et al., 2011). These violate the distributional assumption associated with standard modelling techniques that are based on normally distributed outcome data. In the absence of normality of the distribution, the estimated population mean cost which is generally the parameter of interest in economic studies will be drawn to the tail with a non-uniform spread of the data (Jones et al., 2015, Mullahy, 2009). Consequently, there has been much debate about the most appropriate method for modelling healthcare costs for individual patients with suggestions including the use of transformations, the use of non-parametric methods, and separate modelling of zero and non-zero costs in a two-step process (Mullahy, 2009, Manning and Mullahy, 2001, Jones et al., 2015, Basu and

Manning, 2009). A robust modelling approach based on model diagnostics and testing of assumptions is required to address these issues in order to draw valid statistical inference.

Several statistical methods for modelling healthcare cost data have been proposed in the continuously developing health econometrics literature (Mihaylova et al., 2011, Mullahy, 2009). These competing analysis methods vary in their ability to address challenges of the data, and their ease of use. Studies comparing econometric methods for analysing healthcare costs have reported the lack of a single best approach for expenditure modelling (Deb and Norton, 2018, Gregori et al., 2011, Mullahy, 2009). A comprehensive review of methods by Mihaylova et al (2011) recommended the use of simple methods in large samples where near normality of the distribution is assumed, while their usage in smaller samples require checking assumptions and conducting sensitivity analysis. The authors acknowledged the advantages of more complex methods but argued against their use in wider applied work due to being relatively untried and requiring substantial expertise (Mihaylova et al., 2011). Other methodological review work came to broadly similar conclusions about the lack of an optimal or dominant approach which could provide unbiased and efficient estimates for all cost applications (Basu and Manning, 2009, Dunn et al., 2003, Manning and Mullahy, 2001). The results of healthcare cost analyses and interpretation of estimates are usually dependent on the choice of analysis methods with a real risk of arriving at misleading conclusions. Hence there is a need for researchers to examine how robust their methods are to incorrect distributional assumptions. Application of alternative models, and performing tests and validations to find an appropriate model for analysing healthcare costs data is therefore recommended (Buntin and Zaslavsky, 2004).

1.5 Aims and objectives of the thesis

The overarching aim of the thesis is to provide a current up to date estimate for the healthcare costs of back pain focussing on primary care settings. These may be used to inform research studies and help to justify the need for further research and interventions to reduce its impact. There are two main components of this overarching aim. First, it is clear that a range of approaches have been used in the published COI studies of back pain (Dagenais et al., 2008, Deyo et al., 1991, Hong et al., 2013, Maniadakis and Gray, 2000, Martin et al., 2008). It is therefore essential to establish the most appropriate method and apply this to exploit available EHRs in the UK in order to provide the current estimates for the healthcare costs of back pain. It is hypothesised that the national estimate for the healthcare costs of back pain are likely to have increased since it was last estimated almost 20 years ago. Second, the patterns and association of the healthcare costs of back pain with patient, and clinical characteristics are not clear. The skewed nature of the cost data also adds methodological challenges in the analysis of healthcare expenditure. Hence it is important to evaluate alternative econometric techniques used in modelling healthcare cost data applying them in respect of the estimated healthcare cost of back pain.

The specific objectives of the thesis are to:

I - Systematically review the published literature on COI studies of back pain, with particular attention to the range of methodologies used to assess the direct and indirect costs of back pain. This will help in the identification of the most appropriate method for estimating the healthcare costs of back pain from large electronic databases.

II - Identify the components underpinning the healthcare costs of back pain that could be explored and estimated through the use of EHRs. A description and critique of the available data sources and their strengths and weaknesses for this purpose will provide additional merit to this objective.

III - Estimate the annual healthcare resource use and costs associated with the treatment of back pain using patient level data, exploring how the estimates vary in sub-groups of the population and also investigating trends in healthcare cost over time.

IV - Explore appropriate econometric modelling approaches to predict the relationship between patient and clinical characteristics, and the resulting healthcare costs of back pain.

1.6 Structure of the thesis

This thesis comprises seven further chapters, and its structure is organised as follows:

In **Chapter 2**, an overview of the clinical area of back pain is presented. The definitions, classifications, and burden of the condition are explained. The epidemiology, aetiology, diagnosis and management of back pain is also presented.

A systematic review of the methodologies used in COI studies of back pain is presented in **Chapter 3**. A brief overview of COI studies and the methodologies used within them is presented at the outset of the Chapter. A key objective of the review was to explore the approaches used for estimating the direct and indirect costs attributed to back pain with a particular focus on the appropriateness of the methods for EHRs data. Another objective was to identify sources of data that could potentially be utilised in subsequent chapters of this thesis.

Chapter 4 introduces potential databases that could be used for estimating healthcare resource utilisation of back pain in the UK with a particular focus on the principal data source explored in this thesis, The Health Improvement Network (THIN) primary care database. Identification of back pain diagnosis, and prescription drugs from the database is explained. The Chapter also describes sources of unit cost data that could be applied to the resource utilisation to obtain cost estimates for the desired cost components.

In **Chapter 5**, the methods of analysis, results, and sensitivity analysis for estimating the annual healthcare resource use and costs of back pain in the UK are presented. How these estimates vary by demographic and clinical factors in sub-groups of back pain patients is described, and the trends in healthcare costs over time are also assessed.

The main focus of **Chapter 6** is a theoretical explanation of the main econometric methods used for modelling healthcare costs. The advantages and disadvantages of each method is explained. The Chapter concludes with theoretical recommendations on the process of model selection, specification, and assessment of model performance.

The results of modelling healthcare costs of back pain to determine factors associated with healthcare costs of back pain is presented in **Chapter 7.** This chapter demonstrates the application of appropriate econometric modelling techniques given the characteristics of the dataset.

Finally, in **Chapter 8**, the main findings of the thesis are summarised, and the strengths and limitations of the research are discussed. The chapter concludes with discussion of implications of the empirical work conducted, and recommendations for future research.

CHAPTER 2. BACK PAIN: THE CLINICAL AREA AND ITS BURDEN

2.1 Introduction

This chapter presents a brief description of the clinical area of back pain. An overview of the burden, definition and classifications of back pain as a medical condition is presented. The risk factors, epidemiology, aetiology, diagnosis and management of back pain are also briefly explained in this chapter.

2.2 Burden of back pain

Back pain is an extremely common health problem globally affecting people from all walks of life, and it is often recurrent (Hoy et al., 2010a, Macfarlane et al., 1999, Duthey, 2013, Buchbinder et al., 2013). Anyone may develop back pain, but it is more common in adults aged 35 – 55 years (Wong et al., 2017). Around 80% of the population will experience back pain at some point during their life (Freburger et al., 2009, Norris, 2004, Rubin, 2007). Back pain can have a high impact on patients' quality of life and their daily activities including work, leisure and sleep. The Global Burden of Diseases (GBD) study in 2010 listed low back pain (LBP) among the top 10 ten high burden diseases and injuries worldwide, with GBD 2015 reaffirming that LBP was also the leading cause of years lived with disability in most countries and age groups (Murray et al., ET AL. (GBD 2010 Collaborators) 2012, Vos et al., ET AL. (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators) 2016, Hurwitz et al., 2018). The pain may resolve quickly in 75% - 90% of acute LBP patients, but others experience long-term or recurring problems leading to disability, work loss, and costly treatment options such as surgery (Atlas and Deyo, 2001). Although back pain has low impact

in terms of mortality, it imposes great costs on patients, employers, health care providers and society as a whole (Dagenais et al., 2008, Hoy et al., 2014b, Maniadakis and Gray, 2000, Pai and Sundaram, 2004).

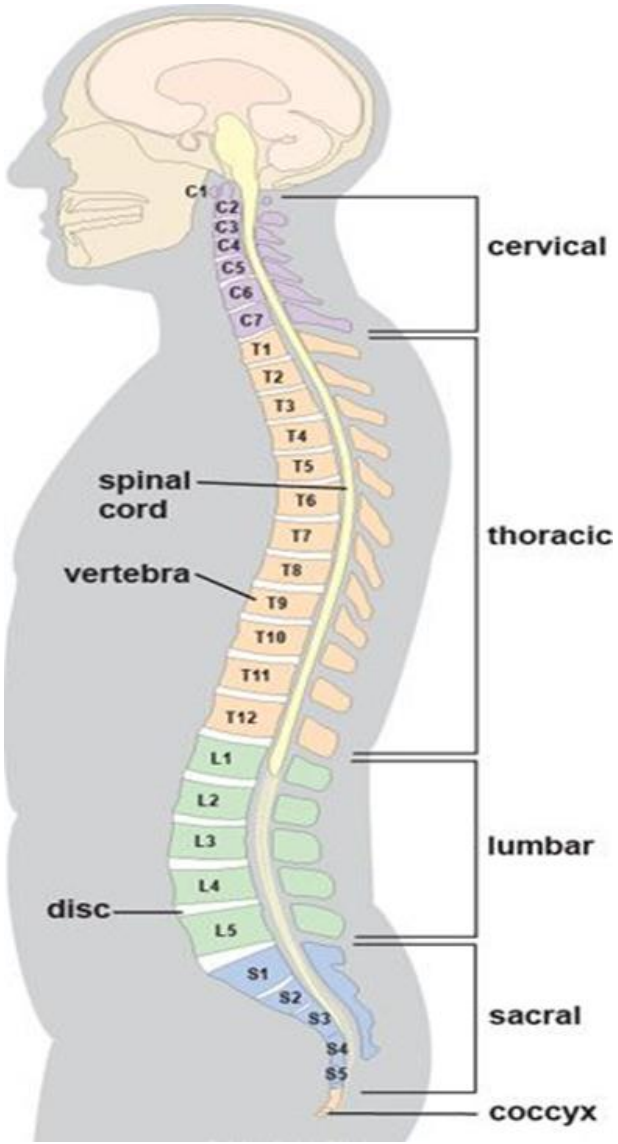
2.3 Definitions

Back pain is a general term used to express pain felt in the lower or upper back. The majority of the literature on back pain focuses on low back pain (LBP), and there is a paucity of definition and specific information on the broader terminology of 'back pain'. LBP is defined as pain, stiffness or soreness in the lumbosacral area of the back, between the bottom of the rib cage and the legs (NICE, 2016, Dionne et al., 2008). The pain can range from a dull ache to sudden piercing pain or to a burning sensation, and the pain may start in the body parts and structures in the spine, and this could propagate into the arms and legs (Farlex-M.D, 2009). In the literature, researchers have not been consistent with the terminology, and LBP has often been referred to as back pain. This mixed use of terminologies may cause confusion and uncertainties for clinical research with regard to the definition and classification of the problem. Back pain in this thesis is defined as pain originating from the area between the base of the neck (vertebrae prominens) and the tail bone (coccyx) as described in a previous published UK studies (Maniadakis and Gray, 2000, Hollingworth et al., 2002).

2.4 Classifications of back pain

Back pain covers a wide range of conditions resulting in great diversity in the classification and diagnosis of back pain. The classification of back pain by anatomy of the body follows sections of the spine (Figure 2.1), and these are neck pain (cervical), middle back pain (thoracic), low back pain (lumbar) and coccydynia (sacral) (Mayfield-Clinic, 2018). Of these,

pain in the lumbar area is most common (Church and Odle, 2007), and the term ‘low back pain’ is very often used in the literature sometimes interchangeably with the general term ‘back pain’. Back pain may also be classified into three categories by duration: acute (lasting up to 12 weeks), sub-chronic/sub-acute which overlaps with acute period (6 to 12 weeks) and chronic pain (lasting beyond 12 weeks) (King, 2013).



(Source: Mayfield Brain and Spine)

Figure 2.1: Anatomic classification of back pain by regions of the spine.

LBP may in turn be classified in different ways with little consensus that any one method is best (Manusov, 2012). It can be classified by cause as mechanical back pain (musculoskeletal related), systemic or non-mechanical back pain and referred pain from internal organs (Manusov, 2012). Around 90% of the LBP cases belong to the mechanical pain category, and the specific causes are not known in most of these (Hall, 2014). Another classification of LBP is by signs and symptoms of the problem. Non-specific LBP refers to pain that is not due to any specific or underlying condition, while specific LBP is resulting from known medical conditions such as cancer or trauma and requires more urgent attention (Manusov, 2012, O'Sullivan, 2005).

2.5 Risk factors

Back pain often arises without a specific cause, but some factors might contribute to increased risk of back pain. Obesity, sedentary lifestyle, and poor posture may increase a person's risk of back pain (Church and Odle, 2007, Shiri et al., 2010). Other factors including aging (Dionne et al., 2006, Hoy et al., 2010a), presence of co-morbid conditions (Hestbaek et al., 2003, Nordin et al., 2002), occupational hazards (Coenen et al., 2014), smoking (Shiri et al., 2018), and psychological factors (Burton et al., 1995, Dionne, 2005) have also been associated with increased risk of back pain. However, patients with back pain have variable outcome, and the association of back pain with these socio-demographic, lifestyle, psychological, and occupational factors is still a subject of debate (Dunn and Croft, 2004).

2.6 Prevalence of back pain

The prevalence of back pain is a measure of the number of people in a population who have back pain during a certain period or at a particular point in time. Back pain is an extremely

common health problem globally and not confined to Western industrialised countries as previously thought (Manchikanti, 2000). In the UK, it is estimated that up to 80% of people over 16 years of age experience back pain at some point during their life time (Johnson, 2012). Versus Arthritis, formerly Arthritis Research UK estimates that 9.1 million people (17%) in England have back pain (ARUK, 2015). The prevalence estimate for Scotland was similar with 910,000 (19%) of adults over 18 years of age living with pain (ARUK, 2015).

The lifetime prevalence of LBP in industrialised countries is in the range of 60-70% while one-year prevalence is estimated at 15-45% (Duthey, 2013). The lifetime prevalence is slightly lower than the 80% reported for the UK which was for the broader category of back pain rather than LBP. Comparison of country specific prevalence of back pain is problematic due to the substantial methodological heterogeneity among epidemiological studies. The Global Burden of Disease (GBD) 2015 study reported that there was an increase of 17.3% in the global point prevalence of LBP between 2005 and 2015 (Vos et al., ET AL. (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators) 2016). Back pain most commonly affects people in their 40s and 50s with the prevalence declining in older age groups (Buckley, 2015, Mody and Brooks, 2012). In terms of gender differences, women have higher prevalence of back pain (Schneider et al., 2006, Wang et al., 2016), and they are more likely to consult their general practitioners than men in general (Hunt et al., 2011, Wang et al., 2013). A possible explanation for the higher prevalence and consultation rates among women is that their experience of back pain may be connected with physiological processes associated with the menses and hormonal changes (Wang et al., 2016).

2.7 Incidence of back pain

The incidence of back pain measures the rate at which healthy individuals develop a new symptom of back pain over a specified period. However, measuring the true incidence of back pain is challenging since symptoms of back pain tend to be episodic and usually recur over time, and can consequently become chronic (Hoy et al., 2010a). Incidence of back pain may hence refer to 'first ever episode' or 'new episodes' of back pain during a specific period. Therefore, there is much less evidence in the literature on the incidence of back pain in contrast to the abundance of information available for prevalence of back pain. According to the World Health Organisation (WHO), the adult incidence rate of LBP is about 5% per year (Duthey, 2013). Hillman et al (1996) indicated a higher annual incidence rate of 5.4% in women compared 4.1% in men. Lifetime incidence of back pain on the other hand is estimated to vary between 58% to 84% (Dionne, 1999).

2.8 Etiology and diagnosis

Back pain occurs as result of a broad array of possible causes and consequently, it can be difficult to make a specific diagnosis. There are a number of anatomical structures in the spine including bones, muscles, joints, ligaments, and nerves, and any one of these structures may become a source of pain. For specific back pain resulting from other medical conditions, identification of the etiology is important for providing appropriate treatment. The proportion of back pain attributed to specific causes such as infection, trauma, or tumours however, is very low (5 – 15%) while the reasons for the remaining high proportion of non-specific back pain are multifactorial and not well understood (Deyo and Weinstein, 2001, Hollingworth et al., 2002).

The diagnosis of back pain is also complex due to the variety of symptoms and pain experienced, the complicated nature of the etiology and non-standardised approach taken by physicians for clinical decision making (Duthey, 2013). Information about the location and duration of pain, frequency of symptoms, previous history of symptoms and treatment are essential for making an appropriate diagnosis (Chou et al., 2007). However, there has been little consensus on the appropriate clinical evaluation and diagnostic tests used for assessing back pain (Chou et al., 2007).

2.9 Prevention and management

There is no clear evidence on the best approach for individuals to prevent developing back pain, but regular low-impact aerobic exercises may reduce the frequency of recurrence of back pain by increasing strength and endurance of the back (Deyo and Weinstein, 2001). There appears to be a mixed evidence regarding whether exercise alone or exercise combined with education has a better effect in reducing risk of developing back pain. A systematic review and meta-analysis reported by Steffens et al 2015 found moderate-quality evidence that suggests exercise combined with education may reduce the risk of LBP, while the evidence in support of exercise alone was low to very low quality (Steffens et al., 2016). Shiri et al 2017 report another more recent systematic review and meta-analysis which showed that exercise alone reduced the risk of developing an episode of LBP by 33% (risk ratio = 0.67, 95% CI 0.53-0.85) compared with exercise combined with education that showed 27% (risk ratio = 0.73, 95% CI 0.59-0.91) risk reduction (Shiri et al., 2017).

The symptoms of back pain in most cases resolve naturally after a few weeks, and there is no evidence that individuals who seek diagnosis via imaging for example are likely to have better outcome than those waiting for the problem to resolve naturally in a few weeks (Chou et al.,

2007). Currently, the main treatment for the management of back pain is the use of analgesics such as paracetamol, NSAIDs or opioids (Duthey, 2013). The latest NICE guidelines on the management of LBP and sciatica provides several recommendations on the use of both non-invasive and invasive options for the management of individuals with LBP. This includes self-management (advice and information), exercise, orthotics, therapies, acupuncture, pharmacological interventions, spinal injections, epidurals, surgical interventions and return to work programs (NICE, 2016). The guideline also suggests the use of risk stratification using methods such as the STarT Back risk assessment tool for assisting in selection of specific treatment (NICE, 2016).

2.10 Summary

Back pain is a major public health problem in Western industrialised societies. Its impact on disability and adverse quality of life is substantial. Back pain often develops without specific cause, but several factors might put people at greater risk of developing back pain including their working conditions, lifestyle factors, and psychological conditions. Various options exist for the assessment and treatment patients with back pain, but with little consensus on the best approach. Moreover, not all treatment options work for all patients, and individuals may need to try different treatments before finding what works best for them. The healthcare costs associated with back pain are consequently very high.

Previous research has investigated the occurrence, causes, treatment, and patient outcomes of back pain, but we know little about the economic burden of back pain, and the factors driving these costs. The details of the healthcare resource use and cost estimation carried out will be presented in more detail in Chapter 5. Prior to embarking on assessing the costs, a systematic

review of previously published COI studies and the underlying methodologies was carried out. This is presented in greater detail the next chapter.

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS IN THE ASSESSMENT OF DIRECT AND INDIRECT COSTS OF BACK PAIN: A SYSTEMATIC REVIEW

3.1 Introduction

Chapter two presented an overview of the clinical area of back pain. It also summarised back pain prevalence estimates in the UK and other high-income countries providing a basis for extrapolation of cost estimates to a national level in the empirical work. This chapter aims to identify and examine the existing literature on the direct and indirect costs of back pain in the UK and other high-income countries. Due to differences in health systems, it was desired to focus the systematic review on high-income countries for making suitable comparison with the UK. A high-income country in this review refers to a member country of the high-income status as defined by the Organisation for Economic Co-operation and Development (OECD) (OECD, 2016). This chapter provides an overview of the approaches used in a cost of illness (COI) study in general before presenting the methodologies and findings of a systematic review of studies assessing the direct and indirect costs of back pain. Intangible costs (eg, the cost of pain, grief, and suffering on individuals and their families) whilst important, are beyond the scope of this review since they are particularly difficult to quantify in monetary terms and are often not included in COI studies (Jo, 2014).

The significance of the review was threefold. First, COI studies may employ several approaches in terms of epidemiological design, study perspective, type of costs included and cost estimation methods. It was, therefore, essential to assess the various approaches to establish the most appropriate method for estimating the economic burden of back pain.

Second, it was important to provide informative data and present the state of knowledge with respect to the economic burden of back pain identifying where the major burden of cost might lie in the treatment and care of these patients. Third, some of the data input for estimating the healthcare costs of back pain in the empirical part of this thesis may not be available. The review may therefore, shed light on potential sources of data used in the UK context.

The specific objectives of the review are to:

I - Explore methodologies for estimating the direct and indirect costs attributed to back pain in the UK and other high-income countries.

II - Synthesise results of relevant studies that have used quantitative methods to estimate direct or indirect costs resulting from back pain.

III - Identify and assess potential sources of data for exploring and presenting an updated account of the healthcare costs of back pain in the UK.

Before presenting a detailed account of the findings of the systematic review, a brief explanation of cost of illness studies and an overview of the methodologies used in such studies is provided to ensure that different terminologies used in the review are clearly defined and explained.

3.1.1 Cost of illness studies

Cost of illness (COI) studies are descriptive studies conducted to identify and measure costs associated with a particular disease or illness including direct and indirect costs. Such studies are generally used to prioritise specific disease areas for allocation of scarce resources such as research funding (Rice, 2000, Rosen and Cutler, 2009) and they are thus important for health

policy decision making (Durand-Zaleski, 2008, Rice, 2000). Although different in their purpose from economic evaluations, cost of illness studies can serve as a basis for conducting economic evaluations of interventions based on cost drivers identified (Jo, 2014, Rice, 2000). However, they offer no information on effectiveness or health benefits, and this is the main concern in using the reports of COI studies in informing health policy decision-making. COI studies have been conducted in numerous disease areas including back pain. There have also been significant improvements in COI methodologies since Dorothy Rice formalised the methodology for costing illnesses in the mid-1960s (Rice, 2000).

3.1.2 Overview of COI methodologies

The costs of an illness can typically be classified into three categories: direct costs, indirect costs, and intangible costs (Yousefi et al., 2014, Jo, 2014). Direct costs are costs that are due to resource use directly attributed to the illness, and these are divided into medical and non-medical costs (Tarricone, 2006, Jo, 2014). Medical costs include costs for hospitalisation, pharmaceuticals, laboratory tests, out-patient services and so on, while direct non-medical costs refer to expenditures not due to direct purchasing of medical services. Examples of direct non-medical costs include transportation, home modifications and child-care costs. A 'top-down' or a 'bottom-up' approach is usually adopted for estimating consumption of resources. The top-down approach is based on aggregate figures for consultations, hospital admissions etc, while the bottom-up approach is based on the actual consumption of resources for a particular illness (Pagano et al., 1999, Olsson, 2011, Tarricone, 2006).

Indirect costs on the other hand refer to costs due to loss or reduction of productivity, and informal care costs caused by morbidity or mortality related to the illness. However, informal care is often not included in COI studies or economic evaluations due to the complexity of

valuation of time spent on informal caregiving (Goodrich et al., 2012, Hoefman et al., 2019, Krol et al., 2015). The two commonly used approaches of evaluating indirect costs are the human capital (HC) approach and the friction cost (FC) method (van den Hout, 2010, Tarricone, 2006, Koopmanschap and Rutten, 1996). From the HC perspective, the productivity losses associated with morbidity and mortality is approximated by the market value of the individual's future earnings assuming that the person would have continued to work in full health (Jo, 2014). The FC method on the other hand uses what is known as the friction period which is an initial adaptation period until another individual from the unemployment pool takes over the patient's work (Koopmanschap et al., 1995, van den Hout, 2010). The value of productivity losses is then estimated over the friction period until production levels are restored (Koopmanschap et al., 1995, van den Hout, 2010). Based on the purpose of the study and availability of data, different approaches and methods are adopted for valuing health care resource use as well as productivity costs.

It is also necessary to specify the epidemiological approach and the perspective of the study when conducting a COI study. The prevalence-based epidemiological approach is more commonly used, and it involves the estimation of the costs in a given period usually reported as one year (Byford et al., 2000, Tarricone, 2006). Incidence refers to the number of new cases in a predefined period, and this approach estimates the lifetime costs expected to occur from diagnosis until its cure or death (Segel, 2006a, Tarricone, 2006). The perspective of the analysis (societal, healthcare provider, industry or insurer perspective) describes the point of view taken and indicates who bears the costs (Asche et al., 2007). The viewpoint taken dictates which costs are to be included in the analysis, and eventually may lead to different results for the same condition (Jo, 2014). The broader societal perspective is usually preferred because it considers all costs regardless of who pays them (Bovolenta et al., 2017, Jo, 2014).

3.2 Methods

3.2.1 Inclusion and exclusion criteria

A scoping search of the available literature was conducted prior to the commencement of the systematic review. The result informed the development of the selection criteria and search strategy. The systematic review was designed to be exploratory, focusing on evaluating methodologies used to estimate the direct and indirect costs of back pain. Back pain in this review refers to both lower (lumbar) back pain and upper (thoracic) back pain, but not including neck pain. To be included in this review, studies had to meet the following criteria:

1 - Conducted in UK and other developed countries (OECD members).

2 - Concerned with economic burden of back pain including LBP.

3 - Cost provided as monetary estimate of direct or indirect costs.

4 - Studies investigating adult patients.

5 - Reports written in English.

The exclusion criteria used in the current review were as follows:

1 - Neck pain only.

2 - Economic evaluations of interventions.

3 - Review papers or conference abstracts.

4 - Non-English language

3.2.2 Literature search strategy

The literature searches were conducted using a combination of keyword searching and medical subject headings (MeSH). The following keywords combining both ‘illness’ and

‘cost’ terms were used in the search strategy: back Pain or low back pain or spinal pain or lumbar pain or vertebral pain or backache or lumbago or back disorder and costs or economics or health care use or financial impact or health expenditures or resources use or utilisation or economic burden or productivity loss or loss of earning or sickness expense or absence expenditure. The searches were made robust by making use of wildcards, phrase searching and truncation of the search terms as appropriate. In addition, MeSH terms containing the words ‘back pain’, ‘backache', ‘costs and cost analysis’, ‘economics’ and ‘cost of illness’ were exploded where necessary.

The search strategy was initially developed in Ovid MEDLINE (Table 3.1), and it was designed to be as inclusive as possible. This search strategy was later translated to suit the other databases. The MEDLINE, Embase, CINAHL Plus, Web of Science and EconLit databases were searched in November 2016. Additional searches were conducted in Centre for Reviews and Dissemination (CRD) database which includes DARE (Database of Abstracts of Reviews of Effects), NHS EED (NHS Economic Evaluation Database) and HTA (Health Technology Assessment Database). In order to supplement the list of studies and avoid overlooking important studies, reference lists of key studies identified were manually searched. The full outline of search strategies used in the different databases is shown in Appendix 3.1. The initial search was conducted in November 2016, and this was subsequently updated in March 2019.

Table 3.1: Search strategy for OVID Medline with breakdown of hits obtained

MEDLINE (1946 to November 2016), **Date of search:** 23 Nov 2016, **Total hits:** 1,610
1. exp Back Pain/ (34,476)
2. ((lumb* or spin* or vertebra*) adj5 pain).ti,ab. (13,336)
3. (backache or lumbago).ti,ab. (3,261)
4. (back adj5 (disorder* or ach*)).ti,ab. (1,742)
5. (back adj5 pain).ti,ab. (35,387)
6. or/1-5 (58,838)
7. exp "Costs and Cost Analysis"/ (217,015)
8. economic*.ti. (35,418)
9. cost*.ti. (93,479)
10. (health care adj5 (us* or utili* or expen*)).ti,ab. (33,098)
11. (financ* adj5 (burden or impact)).ti,ab. (5,222)
12. (resource* adj5 (us* or utili*)).ti,ab. (41,041)
13. (los* adj5 (product* or earn*)).ti,ab. (10,899)
14. ((sick* or absen*) adj5 expen*).ti,ab. (267)
15. or/7-14 (333,380)
16. 6 and 15 (1,733)
17. limit 16 to (english language and humans) (1,610)

A preliminary scoping search revealed an abundance of potential studies published in English and from high-income countries. It was considered sufficient to restrict the search to English language and within the OECD countries for comparability to the UK context. It was however, deemed undesirable to put restriction on the year of publication. Studies that were not published in peer reviewed journals were not included in this review as they may not have been reviewed thoroughly compared to published studies. Moreover, as the primary aim of this systematic review was to assess approaches for estimating direct and indirect costs attributed to back pain rather than arriving at pooled estimates, there was little risk of biasing

the review results. In order to ensure that studies with sufficient methodological detail were identified, only full transcript articles were included.

3.2.3 Selection of studies for review

First, duplicate studies were removed from the search results. The remaining studies went through an eligibility criteria that included successive screening process outlined as follows. Due to a high number of potential studies identified by the search, studies were initially screened on the basis of their title. This was aimed at identifying additional duplicates and studies that were clearly not relevant for the systematic review. A two-stage categorisation approach was then applied to assess eligibility of the remaining studies. The method is described in detail in previous systematic reviews (Jackson et al., 2014, Jackson and Roberts, 2016, Roberts et al., 2002).

Stage I — Initial categorisation of studies:

The initial categorisation of studies was conducted based on title and abstract screening. Each study was assigned to one of the six pre-defined initial criteria groups in order to assess its relevance to the systematic review. The categories used for the initial criteria were as follows:

> A. The study reports primary or secondary research on the economic burden of back pain and provides substantial cost data.
>
> B. The study discusses the cost of back pain and provides estimates of some aspects of COI or components of direct or indirect costs.
>
> C. The study provides useful information on assessing the economic burden of back pain but does not entirely fall into either A or B. (eg. methodological studies on COI without reporting direct or indirect costs estimates).

D. The study discusses general aspects of the economic impact of back pain but provides little or no data on direct or indirect costs (eg. economic evaluations).

E. Full text of the study is not available (abstracts, conference proceedings and published studies where the full articles could not be obtained).

F. The study does not have any relevance to the economic burden of back pain.

Studies in category (A), (B) or (C) met the inclusion criteria and were deemed relevant for the current systematic review while those in category (D), (E) or (F) were excluded at this stage.

Stage II – Further categorisation of studies

The full transcripts of all papers deemed potentially relevant (categories A, B or C) were obtained and reviewed for further examination of their suitability. Based on type of study they represented, and the type of cost reported, the studies were further classified into the following categories:

1. COI analysis studies (direct or indirect cost)
2. Other cost studies
3. Description of methods used in assessing cost of back pain
4. Private out of pocket expenditure
5. Economic evaluations
6. Review articles without new data
7. Not relevant for economic burden of back pain.

After reviewing the full transcripts, studies classified as A(1), A(2), B(1) and B(2) met the inclusion criteria and were determined to be suitable for the final stage of data extraction. Studies coded as C(3) and ABC(6) were excluded but were retained for background literature

and discussion purposes. All other studies and articles not classified into one of the above categories were excluded. A second reviewer (Dr Jesse Kigozi) retrieved and reviewed a random sample of 10% of the studies at each stage of the selection process. Any discrepancies were resolved by discussion until a consensus was reached by the team of supervisors and the student. As the main aim of this review was to assess the methodological approaches used for estimating the direct and indirect costs of back pain, studies were not excluded subject to formal quality appraisal criteria. This enabled as many relevant studies as possible to be included in the current review. It is also important to note that unlike economic evaluations, formal guidelines to define the necessary elements for cost of illness studies have not yet been established.

In order to examine the studies and present them systematically, a wide range of characteristics were extracted from the included studies including: country, study population, source and year of data, cost perspective, study design, sample size, types of costs, analysis methods, case definition of back pain, and reported cost estimates. Cost estimates must be put in a common currency by applying price indices and currency converters when comparing expenditures between countries (Cooper, 2019, Young et al., 2015). Since many of the studies in this review were from the USA, the US dollar was chosen as a common currency. This is also consistent with OECD statistics that are generally presented in US dollars (Cooper, 2019). Hence, all national cost estimates have been converted to 2015 US dollars using a web-based tool: http://eppi.ioe.ac.uk/costconversion/default.aspx developed jointly by The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) (Shemilt et al., 2010). The tool adjusted estimates of costs for currency and cost-year using a two-stage computation. Stage one extrapolated the costs from the original cost-year to 2015 using a country-specific

gross domestic product inflator index. Stage two converted the cost-year adjusted estimates from the original currency into US dollars using purchasing power parities (PPP). The full detail of the underlying methodology and data behind this conversion tool is described in Shemilt et al. (2010).

3.3 Results

3.3.1 Study selection

The search (Figure 3.1) identified a total of 8009 potential citations (MEDLINE: 1610, Embase: 2,114, Web of Science: 1,837, CINAHL Plus: 2,192, EconLit: 13 and CRD: 243). The reference manager software identified 2,424 duplicates and these were removed leaving 5,585 studies for processing. The title screening phase identified a further 798 citations as duplicates, and these were subsequently removed. In addition, 3,200 studies were deemed not relevant for the systematic review (category F). These studies were excluded on the basis of title leaving 1,587 studies for initial categorisation (stage I).

One additional paper was retrieved as a result of screening the bibliographies of key papers identified. The initial categorisation of titles and abstracts led to 1,535 studies to be excluded. Of these, 736 studies discussed some aspects of the economic burden of back pain but had little or no extractable data on direct or indirect costs of back pain (category D). A further 22 studies did not have full text available for review (category E) and therefore, their suitability for inclusion could not be determined due to lack of sufficient relevant information. These were abstracts and conference proceedings while the remaining were category F studies. This left 53 studies for further categorisation using their full text (stage II). These articles were read in full to determine their suitability for inclusion. A total of 13 studies were excluded; and the reasons for exclusion were: not providing relevant information (2 studies), they were

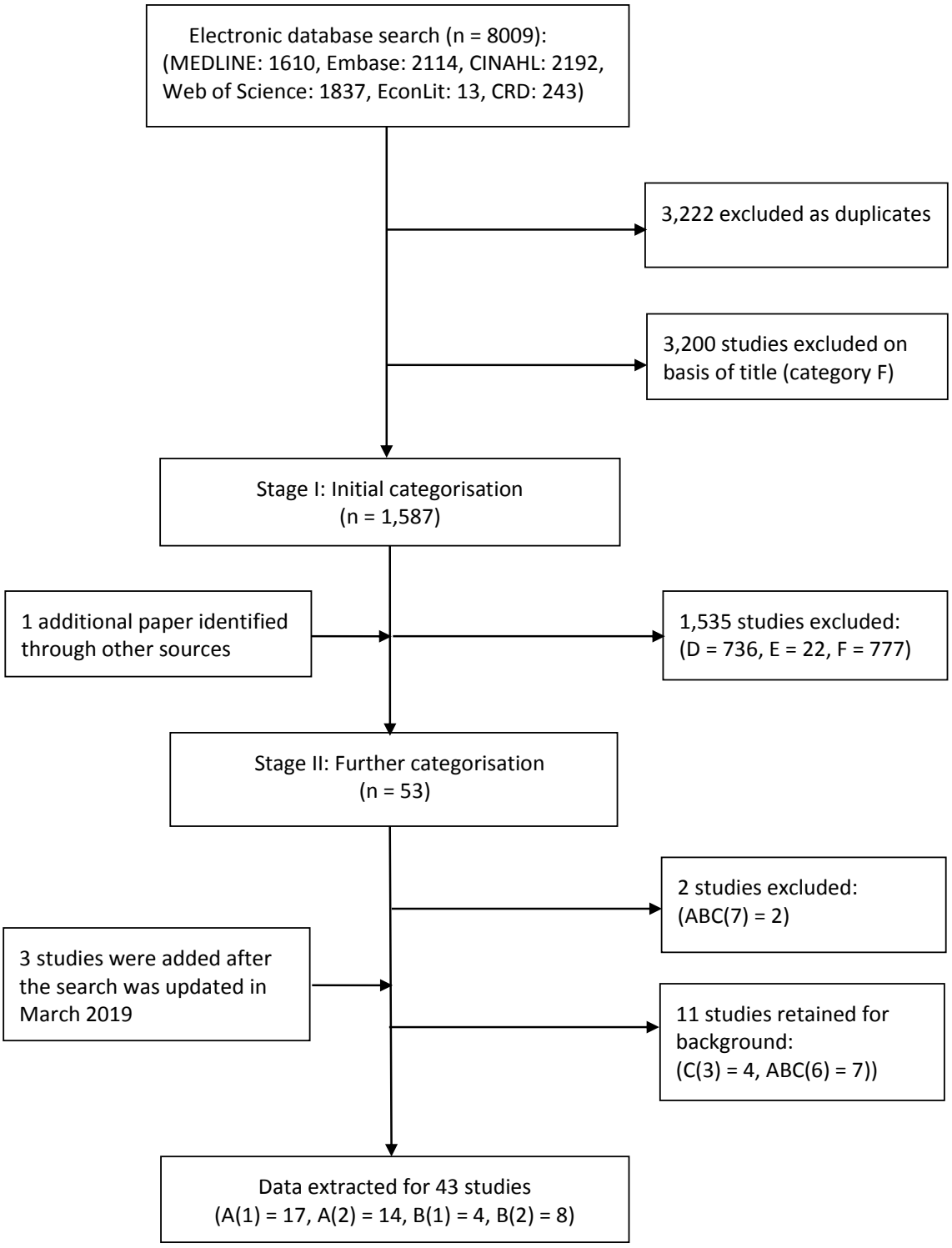


Figure 3.1: Flow chart showing summary of the literature search and study selection

reviews and did not contain primary data (7 studies) and they were concerned with knowledge and description of methods (4 studies). Studies in the last two categories were retained for background information. No discrepancy was found by the second reviewer (Dr Jesse Kigozi) who retrieved and reviewed a random sample of 10% of the studies at each stage of the selection process. The literature search was updated in March 2019 and three new studies were subsequently added resulting in 43 studies for final data extraction.

Description of the coding and categorisation of studies at stage II is shown in Table 3.2. Of the 43 studies included for data extraction, 17 studies were COI studies with substantial cost data, coded A(1), and 14 studies were other types of cost studies but with substantial cost data, coded A(2). The remaining studies with slightly less substantial cost data comprised COI studies, coded B(1) (n = 4) and other cost studies, coded B(2) (n = 8). In the following sections, the important aspects of the review overall are presented first followed by the key methodological characteristics of the studies.

Table 3.2: Coding used and further categorisation of studies at stage II

Code	Description	N	Study reference
A(1)	COI study with substantial cost data	17	(Boonen et al., 2005, Depont et al., 2010, Ekman et al., 2005 (a), Ekman et al., 2005 (b), Hansson and Hansson, 2005, Hutubessy et al., 1999, Icatasiotlu et al., 2013, Itoh et al., 2013, Lambeek et al., 2011, Maniadakis and Gray, 2000, van Tulder et al., 1995, Walker et al., 2003, Wenig et al., 2009, Wieser, 2011, Montgomery et al., 2017, Olafsson et al., 2018)
A(2)	Other cost study with substantial cost data	14	(Gore et al., 2012, Hemmilä, 2002, Hong et al., 2013, Jonsson and Husberg, 2000, Kim et al., 2005, Lind et al., 2005, Luo et al., 2004, Mapel et al., 2004, Mehra et al., 2012, Ritzwoller et al., 2006, Shinohara et al., 1998, Vogt et al., 2005, Watson et al., 1998, Williams et al., 1998, Yumusakhuylu et al., 2018)
B(1)	COI study, less substantial cost data	4	(Becker et al., 2010, Gustafson et al., 1995, van Zundert and van Kleef, 2005, Martin et al., 2008)
B(2)	Other cost study, less substantial cost data	8	(Coyte et al., 1998, Guo et al., 1999, Hashemi et al., 1998, Müller-Schwefe et al., 2011, Ricci et al., 2006, Rizzo et al., 1998, Smith et al., 2013, Stewart et al., 2003)
C(3)	Description of methods	4	(Hoy et al., 2014b, Reville et al., 2001, Sleed et al., 2005, Weiner and Notturno, 2007)
ABC(6)	Review articles	7	(Asche et al., 2007, Baumeister et al., 2012, Dagenais et al., 2008, Deyo et al., 1991, Maetzel and Li, 2002, Parthan et al., 2006, Tymecka-Woszczerowicz et al., 2015)
ABC(7)	Not relevant or the review	2	(Engel et al., 1996, Lawrence et al., 1992)

3.3.2 Overview of the included studies

The main characteristics of the included studies are summarized in Table 3.3. Of the 43 studies included in this review, 16 (37%) are from the United States (Gore et al., 2012, Guo et al., 1999, Gustafson et al., 1995, Hashemi et al., 1998, Lind et al., 2005, Luo et al., 2004,

Mapel et al., 2004, Mehra et al., 2012, Ricci et al., 2006, Ritzwoller et al., 2006, Rizzo et al., 1998, Smith et al., 2013, Stewart et al., 2003, Vogt et al., 2005, Williams et al., 1998, Martin et al., 2008), five (12%) from Sweden (Ekman et al., 2005 (a), Ekman et al., 2005 (b), Hansson and Hansson, 2005, Jonsson and Husberg, 2000, Olafsson et al., 2018), four (9%) from The Netherlands (Boonen et al., 2005, Hutubessy et al., 1999, Lambeek et al., 2011, van Tulder et al., 1995), three (7%) each from the UK (including one from the Isle of Jersey) (Hong et al., 2013, Maniadakis and Gray, 2000, Watson et al., 1998), Germany (Becker et al., 2010, Müller-Schwefe et al., 2011, Wenig et al., 2009), and Japan (Itoh et al., 2013, Shinohara et al., 1998, Montgomery et al., 2017), and two studies from Turkey (Icatasiotlu et al., 2013, Yumusakhuylu et al., 2018). The remaining eight studies (Coyte et al., 1998, Depont et al., 2010, Hemmilä, 2002, Kim et al., 2005, van Zundert and van Kleef, 2005, Walker et al., 2003, Watson et al., 1998, Wieser, 2011) were single studies conducted in the respective countries.

Table 3.3: Summary of the main characteristics of the included studies

Lead author, Year of cost	Country/ perspective	Population	Study Design	Data sources	Back pain case definition	Direct cost estimation	Indirect cost approach
Walker, 2001	Australia /Societal	National	R, PB	Australian adult LBP prevalence survey	Diagnostic code	Top-down	Human capital & friction cost
van Zundert, 1999	Belgium /Societal	National	R, PB	IDEWE (workers welfare body)	Other/non-specific	Top-down	n/s
Coyte, 1994	Canada /Societal	National	R, PB	Ontario Health Survey	Diagnostic code	Top-down	Human capital
Hemmila, 1994	Finland /Societal	Regional	R, PB	Social Insurance Institution files, and patient records	Self-reported	Bottom-up	Human capital
Depont, 2007	France /Societal	National	R, PB	Surveys/ questionnaires	Self-reported	Bottom-up	n/a
Muller-Schwefe, 2006	Germany /Insurer	Health insurer with 5.2 million members	R, IB	German statutory health insurance fund (DAK) claims data	Diagnostic code	Bottom-up	n/a
Becker, 2004	Germany /Societal	Regional	P, PB	Cross sectional sample from an RCT	Self-reported	Bottom-up	Human capital
Wenig, 2005	Germany /Societal	National	R, PB	Postal survey by German Back Pain Research Network (GBPRN)	Self-reported	Bottom-up	Human capital
Watson, 1994	Isle of Jersey /Societal	National	P, PB	Social Security database	Other/non-specific	n/a	n/s
Itoh, 2011	Japan /Societal	National	R, PB	Survey of Medical Care Activities in Public Health Insurance	Diagnostic code	Bottom-up	n/a

Shinohara, 1994	Japan /Insurer	National	R, PB	Labour Standards Inspection Office claims database	Other/non-specific	Bottom-up	n/s
Montgomery, 2017	Japan/ Societal	National	R, PB	Japan National Health & Wellbeing Survey (NHWS)	Self-reported & diagnosed	Bottom-up	Human capital
Kim, 1997	Korea /Insurer	National	R, IB	Korea Labour Welfare Corporation	Other/non-specific	n/s	n/a
Ekman, 2001 (a)	Sweden /Societal	National	R, PB	Survey and registry data	Diagnostic code	Top-down	human capital
Hansson, 1995	Sweden /Societal	Regional	P, PB	Prospectively entered diaries and questionnaires	Diagnostic code	Bottom-up	Human capital
Ekman, 2002 (b)	Sweden /Societal	Regional	R, PB	Surveys/ questionnaires	Self-reported	Bottom-up	Human capital
Jonsson, 1994	Sweden /Societal	National	R, PB, IB	National Board of Health and Welfare's register	Diagnostic code	Top-down	Human capital
Olafsson, 2018	Sweden /Societal	Regional	R, PB	Administrative database VEGA	Diagnostic code	Bottom-up	Human capital
Wieser, 2005	Switzerland /Societal	Regional	R, PB	Large population-based survey	Self-reported	Bottom-up	Human capital & friction cost
van Tulder, 1991	Netherlands /Societal	National	R, PB	Survey and registry data	Diagnostic code	Top-down	human capital
Boonen, 2002	Netherlands /Societal	National	P, IB	Cost diaries from three cohorts	Self-reported	Bottom-up	Friction cost
Hutubessy, 1991	Netherlands /Societal	National	R, PB	Social Insurance Council data	Diagnostic code	n/a	Human capital & friction cost
Lambeek, 2007	Netherlands /Societal	National	R, PB	National registries and authorities	Diagnostic code	Top-down	Human capital
Icatasiotlu, 2013	Turkey /Societal	National	R, PB	Surveys/ questionnaires	Self-reported	Bottom-up	Human capital

Yumusakhuylu, 2018	Turkey /Societal	National	R, n/s	Surveys/questionnaires	Other/non-specific	Bottom-up	Human capital
Maniadakis, 1998	UK /Societal	National	R, PB	Office of Population Censuses and Surveys (OPCS)	Diagnostic code	Top-down	Human capital & Friction cost
Hong, 2009	UK /NHS	National	CC, PB	UK General Practice Research Database (GPRD)	Diagnostic code	Bottom-up	n/a
Martin, 2008	USA /Societal	National	CC, PB	Medical Expenditure Panel Survey (MEPS)	Diagnostic code	Bottom-up	n/a
Hashemi, 1996	USA /Insurer	Insurer with 10% of WC market	R, IB	Claims data from a large insurer	Self-reported	n/a	n/s
Gustafson, 1992	USA /Employer	Four participating hospitals	P, n/s	Employer records	Self-reported	Bottom-up	n/s
Guo, 1995	USA /Employer	US industries	R, PB	National Health Interview Survey (NHIS)	Self-reported	n/a	n/s
Lind, 2002	USA /Insurer	Two Washington State companies	R, PB	Health insurance claims data from insurance companies	Diagnostic code	Bottom-up	n/a
Mapel, 2001	USA /Insurer	Health insurer with 240,000 members	CC, PB	Lovelace Health Plan (LHP) administrative databases	Diagnostic code	Bottom-up	n/a
Mehra, 2008	USA /Insurer	Large regional health insurer	CC, PB	PharMetrics IMS LifeLink claims database	Diagnostic code	Bottom-up	n/a
Luo, 1998	USA /Societal	National	CC, PB	Medical Expenditure Panel Survey (MEPS)	Diagnostic code	Bottom-up	n/a
Gore, 2008	USA /Insurer	Health insurer with > 62 million members	CC, IB	LifeLink Health Plan Claims Database	Diagnostic code	Bottom-up	n/a
Williams, 1992	USA /Insurer	Regional WC insurer	R, n/s	Detailed Claim Information (DCI) database	Diagnostic code	Bottom-up	n/s
Ricci, 2004	USA /Societal	National	R, PB	Caremark American Productivity Audit (telephone survey)	Self-reported	n/a	Human capital

Ritzwoller, 1999	USA /Insurer	Health insurer with > 410,000 members	R, IB	Keiser Permanente Colorado (KPCO) claims database	Diagnostic code	Bottom-up	n/a
Rizzo, 1996	USA /Societal	National	R, PB	National Medical Care Expenditure Survey (NMES)	self-reported	n/a	Human capital
Smith, 2010	USA /Societal	National	R, PB	Medical Expenditure Panel Survey (MEPS)	Diagnostic code	Bottom-up	n/a
Stewart, 2002	USA /Societal	National	R, PB	American Productivity Audit (telephone survey)	Other/non-specific	n/a	Human capital
Vogt, 2001	USA /Insurer	Health insurer with 255,958 members	R, PB	UPMC Health Plan claims database	Diagnostic code	Bottom-up	n/a

n/a = not applicable, n/s = non-specific, P = prospective, R = retrospective, PB = prevalence based, IB = incidence based, CC = matched case-control
LBP = low back pain, RCT = randomised controlled trial, WC = workers compensation, UPMC = University of Pittsburgh Medical Centre

The focus of the studies from the USA was largely on health insurer or compensation claims and employers compared to studies from Europe and other international studies. Of the 16 US studies included in this review, only six were of societal perspective (Luo et al., 2004, Ricci et al., 2006, Rizzo et al., 1998, Smith et al., 2013, Stewart et al., 2003, Martin et al., 2008) while eight were insurer perspective (Gore et al., 2012, Hashemi et al., 1998, Lind et al., 2005, Mapel et al., 2004, Mehra et al., 2012, Ritzwoller et al., 2006, Vogt et al., 2005, Williams et al., 1998) and two were employer perspective (Guo et al., 1999, Gustafson et al., 1995) studies. Moreover, none of the societal perspective studies assessed both direct and indirect costs of back pain. In contrast, all except one (Müller-Schwefe et al., 2011) of the European studies adopted societal perspective, and most of the studies (72%) included both direct and indirect costs of back pain in their assessment.

In terms of publication period, the majority of studies (68%) selected for this review were conducted after 2000 with many of them being fairly recent since they were published after 2010. Surprisingly, no study was found from the pre-1990s period. This review found no significant differences by publication period both in terms of cost components included and other methodologies used to estimate the economic burden of back pain. However, there were discrepancies between the year of data and the year of publication which should be carefully considered in order to avoid drawing conclusions from outdated data. There were significant such delays in publication period among the reviewed studies ranging from one year (Stewart et al., 2003) to as large as 11 years (Guo et al., 1999, Rizzo et al., 1998). Quantitative estimates reported should therefore be interpreted with caution taking into consideration any changes that may have taken place in the time period between pricing and publication. It is worth noting that the number of publications concerned with the economic burden of back

pain appears to have declined recently, with only three studies (Montgomery et al., 2017, Olafsson et al., 2018, Yumusakhuylu et al., 2018) being published in the last five years.

3.3.3 Methodological characteristics of the studies

There was high heterogeneity among the included studies both in terms of the countries of study as well as study methodologies used including the diagnostic criteria, data sources, study populations, study design and analysis methods. Direct comparisons of costs between the included studies were therefore deemed not appropriate. The main methodological characteristics of the studies included in this review are presented as follows:

Back pain diagnostic criteria: Case definitions of back pain used in the studies varied by both number and type of conditions included. International Classification of Diseases codes (ICD-9 or ICD-10 codes) or a variant of these were typically used to define back pain by over half of the studies, while self-reported back pain assessment was reported in 14 studies (Becker et al., 2010, Boonen et al., 2005, Depont et al., 2010, Ekman et al., 2005 (b), Guo et al., 1999, Gustafson et al., 1995, Hashemi et al., 1998, Hemmilä, 2002, Icatasiotlu et al., 2013, Montgomery et al., 2017, Ricci et al., 2006, Rizzo et al., 1998, Wenig et al., 2009, Wieser, 2011). The diagnostic criteria used was not explicitly specified in some of the studies (Gustafson et al., 1995, Kim et al., 2005, Shinohara et al., 1998, Stewart et al., 2003, van Zundert and van Kleef, 2005). Variation of costs by type of diagnostic criteria used was heterogeneous. However, studies with diagnostic codes were often used to produce national cost estimates compared to studies with self-reported or non-specific back pain definition types that mainly provided either average costs per patient or indirect cost estimates.

Classification of the included studies by duration or severity of back pain was not possible due to the diverse range of diagnostic criteria used. Only four studies (Ekman et al., 2005 (b), Hong et al., 2013, van Zundert and van Kleef, 2005) explicitly specified chronic back pain/LBP in their case definition while some other studies reported duration of back pain ranging from four weeks to 180 days. Disease severity was otherwise not generally measured in the studies. A direct comparison of studies looking at different subtypes of back pain was not possible, but some studies provided comparison of costs for different diagnosis types that they identified. Becker et al. (2010) grouped patients into acute LBP (<= 90 days duration/6 months) and chronic LBP (continuous or episodic LBP >= 90 consecutive days/6 months) and found that mean direct and indirect costs for LBP were about twice as high for individuals with chronic LBP compared to acutely ill individuals. A Japanese study, Shinohara et al. (1998) grouped accidental/traumatic low back pain at workplace into organic and non-specific low back pain types based on the diagnosed diseases and estimated the difference in costs between these two broader classifications of LBP. The mean value reported for the amount of compensation for both medical cost and leave were significantly higher in the organic LBP patients than the non-specific group.

Source of data: A diverse range of data sources was used including surveys, national databases, compensation claims and cost diaries. Multiple sources of data were typically used in many of the studies, and the reported direct or indirect costs were the result of combining and summing an array of data sources. Based on the single main source of data used for each study, secondary data sources were typically used by most of the studies (n=33) while primary data utilisation was less common (Boonen et al., 2005, Depont et al., 2010, Ekman et al., 2005 (b), Gustafson et al., 1995, Hansson and Hansson, 2005, Icatasiotlu et al., 2013, Müller-Schwefe et al., 2011, Ricci et al., 2006, Wieser, 2011, Yumusakhuylu et al., 2018).

Large-scale surveys (national and special surveys) comprised the largest (37%) source of healthcare resource utilisation data among the included studies. Patients were asked retrospectively about their resource utilisation, and this source of data was mainly used in societal perspective studies. Private insurance or compensation claims databases was the second largest (28%) source of utilisation and cost information; and these were largely used in insurer perspective US studies. Only one European study, Muller-Schwefe et al. (2011) used this type of claims data and assessed the average direct cost of back pain in Germany in 1996.

The use of electronic health records (EHRs) and registry data was limited (Ekman et al., 2005 (a), Hong et al., 2013, Jonsson and Husberg, 2000, Lambeek et al., 2011, Olafsson et al., 2018), with most of them coming from Sweden (Ekman et al., 2005 (a), Jonsson and Husberg, 2000, Olafsson et al., 2018). The UK study, Hong et. al (2013) used the General Practice Research Database (GPRD) to estimate the direct costs of chronic LBP in 2009. The other study conducted in the UK, Maniadakis and Gray (2000) utilised the Office of Population Censuses and Surveys (OPCS) as the main source data to estimate the direct and indirect costs of back pain in the UK in 1998. Direct cost comparison between the two studies was not possible due to inherent methodological heterogeneity. The differences between the two studies were not limited to the sources of data utilised, but also includes the case definition of back pain used, the cost components included in the analysis, and analysis methods employed in the two studies. In the US, the Medical Expenditure Panel Survey (MEPS) database was the single most common source of data for analysing COI for back pain (Luo et al., 2004, Rizzo et al., 1998, Smith et al., 2013, Martin et al., 2008). The MEPS is a set of large-scale surveys of families and individuals, their medical providers, and employers across the United States; and it is the most complete source of data on the cost and use of health care and health insurance coverage (AHRQ, 2015).

Study design: Two-thirds of the included studies selected their study cohort from pre-existing data using a retrospective study design. This study design was used across different cost perspectives, epidemiological approaches and analysis methods, and there was no particular pattern found. The use of a prospective study design was limited (Becker et al., 2010, Boonen et al., 2005, Gustafson et al., 1995, Hansson and Hansson, 2005, Watson et al., 1998). Of the retrospective studies, only few studies (Gore et al., 2012, Hong et al., 2013, Luo et al., 2004, Mehra et al., 2012, Martin et al., 2008) adopted a comparative method using a case-control study design. This enabled the differences in the costs incurred between the study groups, known as incremental or attributable costs to be calculated as illustrated in the following two examples. Hong et al. (2013) compared resource use between patients with and without chronic low back pain (CLBP) and uncovered that the total direct cost for patients with CLBP was about twice as high as that of the matched controls not affected by the illness. Similarly, a US study Gore et al. (2012) examined total health care costs of patients with CLBP and a control group without CLBP and found that patients with CLBP were characterised by significantly higher economic burdens compared with those without CLBP.

Cost perspectives: The perspective of the studies was not typically made explicit and was deduced in this review from the types of utilisation and cost data represented in the analysis. The societal perspective which is preferred since it is the most comprehensive perspective was adopted by the majority of the studies (n=28). Taking the viewpoint of insurance-based health care, the insurer perspective was the second most popular (Gore et al., 2012, Hashemi et al., 1998, Kim et al., 2005, Lind et al., 2005, Mapel et al., 2004, Mehra et al., 2012, Müller-Schwefe et al., 2011, Ritzwoller et al., 2006, Shinohara et al., 1998, Vogt et al., 2005, Williams et al., 1998) perspective. It was apparent that most of the insurer perspective studies (8 out of 11) were US studies (Gore et al., 2012, Hashemi et al., 1998, Lind et al., 2005,

Mapel et al., 2004, Mehra et al., 2012, Ritzwoller et al., 2006, Vogt et al., 2005, Williams et al., 1998) conducted using claims databases. The insurer perspective studies generally focussed on either the direct or indirect costs of back pain, while the societal perspective studies were mostly inclusive of both cost components. Cost analysis from industry or employer perspective is limited in its scope and was less common (Guo et al., 1999, Gustafson et al., 1995). It was however surprising that a healthcare provider perspective was only adopted by two studies (Hong et al., 2013, Depont et al., 2010), one UK and one French.

Epidemiological approach: On the basis of how the epidemiological data were utilised, the included studies were categorised as prevalence-based or incidence-based studies. Prevalence-based approach involves the estimation of the costs of back pain in a given period usually reported as one year; whereas Incidence refers to the number of new cases in a predefined period, and this approach estimates the excess costs expected to occur from the onset of the back pain until its cure or death (Hashemi et al., 1998). A prevalence-based approach was most commonly adopted (n=33) in the included studies. Studies that used an incidence-based approach (Boonen et al., 2005, Gore et al., 2012, Hashemi et al., 1998, Kim et al., 2005, Müller-Schwefe et al., 2011, Ritzwoller et al., 2006) were all claims-based studies except Boonen et al. (Boonen et al., 2005) which utilised cost diaries and questionnaires to estimate the costs. As incidence-based studies assigned costs to the year in which back pain first occurred, the methodologies employed in these studies were relatively more complex than studies using prevalence-based approach.

Costs were linked to both prevalence and incidence in one study (Jonsson and Husberg, 2000) while the epidemiological approach could not be determined in some of the included studies (Gustafson et al., 1995, Williams et al., 1998, Yumusakhuylu et al., 2018). Many of the

included studies did not explicitly specify the epidemiological approach adopted, but they were implied in some of the studies. These data were therefore deduced from the study population and types of utilization used in the analysis. The prevalence-based studies used a variety of cross-sectional survey and administrative data, while incidence-based studies largely utilised employer/industry or insurance claims databases. Moreover, the databases used in incidence-based studies tend to be linked to one another allowing for new cases of back pain to be identified and followed over the course of illness or multiple years.

Cost categories and components of care: Reported cost components used in calculating the direct and indirect costs of back pain were highly heterogeneous, varying both in number and type. No significant methodological differences were observed between studies that assessed both direct, and indirect costs (n=22) and those that reported on direct costs only (Depont et al., 2010, Gore et al., 2012, Hong et al., 2013, Itoh et al., 2013, Kim et al., 2005, Lind et al., 2005, Luo et al., 2004, Mapel et al., 2004, Mehra et al., 2012, Müller-Schwefe et al., 2011, Ritzwoller et al., 2006, Smith et al., 2013, Vogt et al., 2005) or indirect costs only (Guo et al., 1999, Hashemi et al., 1998, Hutubessy et al., 1999, Ricci et al., 2006, Rizzo et al., 1998, Stewart et al., 2003, Watson et al., 1998).

This review examined the cost components reported with the aim of identifying the most important cost drivers. For direct costs, studies reporting all three major categories of inpatient, outpatient, and pharmaceutical costs were summarised for comparison (Figure 3.2). All other directs cost components reported such as complementary and alternative medicine (CAM), mental healthcare costs, and direct non-medical costs were put under the rubric of ‘other costs’. This review did not make distinction between specialist and non-specialist outpatient visits allowing the outpatient category to represent all visits to GPs, and other

primary care services as well as visits to specialists and hospital departments. The reason for this was to enable making comparison between the studies as there was significant heterogeneity in the cost components included in the studies. Figure 3.2 shows the proportion of each cost category where the combination of these categories was set at 100%. Outpatient costs were the most important cost driver in the majority of the studies, followed by inpatient costs. Not many studies took into account direct non-medical costs in their analysis; with costs for social services that include counselling and retraining being the main cost components analysed.

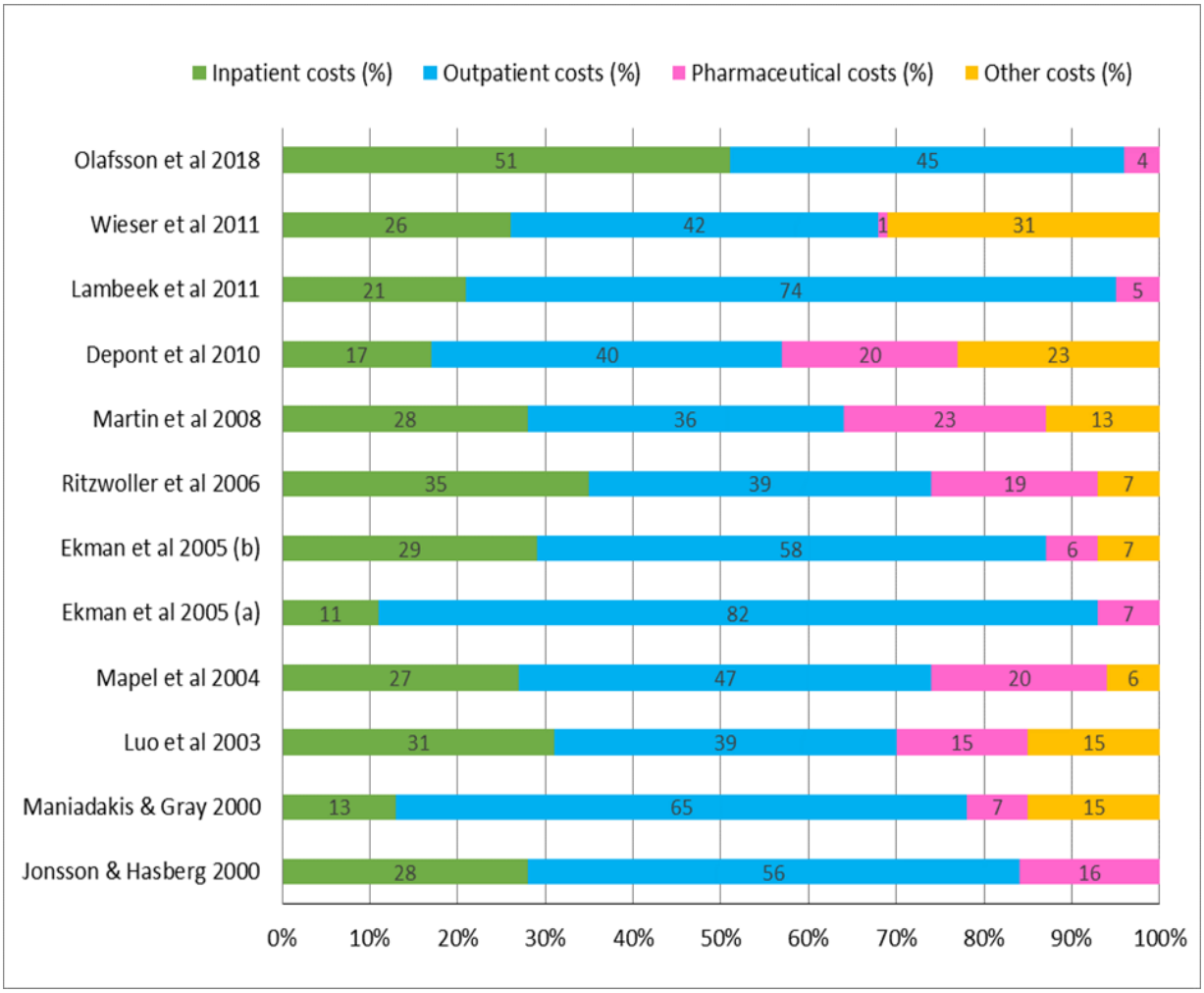


Figure 3.2: Allocation of direct costs for back pain

Since outpatient costs represented both specialist and non-specialist visits (GP consultations), the review also attempted to separate consultation costs from the specialist services. The five EHRs based studies in this review were selected for this in order to inform healthcare cost estimation from primary care databases (focussing on consultations and prescriptions). Of the five studies, Ekman et al., 2005 (a) did not explicitly report cost of consultations or non-specialist visits and it was therefore not included. Comparison of the proportion of primary care costs from the four studies is shown in Table3.4. While the proportion of prescription costs were small (average of 11%, and range: 4% to 19%), the proportion of consultation costs on the other hand were substantial (average of 35.5%, and range: 22% to 59%).

Table 3.4: The contribution of primary care consultations and prescriptions to total healthcare costs of back pain

	Primary care			
Study	**Consultation**	**Prescription**	**Sum**	**Other costs**
Hong et al 2013	58.9%	18.9%	77.8%	22.2%
Jonsson & Hasburg 2000	21.8%	16.5%	38.3%	61.7%
Lambeek et al 2011	23.8%	4.4%	28.2%	71.8%
Olafsson et al 2018	37.3%	4.0%	41.3%	58.7%
Average	35.5%	11.0%	46.4%	53.6%
Range	21.8% - 58.9%	4% - 18.9%	28.2% - 77.8%	22.2% - 71.8%

Indirect costs analysed in the included studies were typically those for morbidity with the exception of Coyte et al. (Coyte et al., 1998) which assessed mortality related costs of back pain by estimating the cost of premature mortality in a Canadian population. In order to identify the most important indirect cost drivers, this review compared studies reporting at

least two of the three major cost components of absenteeism, presenteeism and early retirement (Figure 3.3). Absenteeism which was assessed in all the studies compared was the most relevant cost driver in most studies, and this was followed by early retirement or disablement costs. However, the comparison maybe curtailed by the fact that only two studies analysed all three cost components.

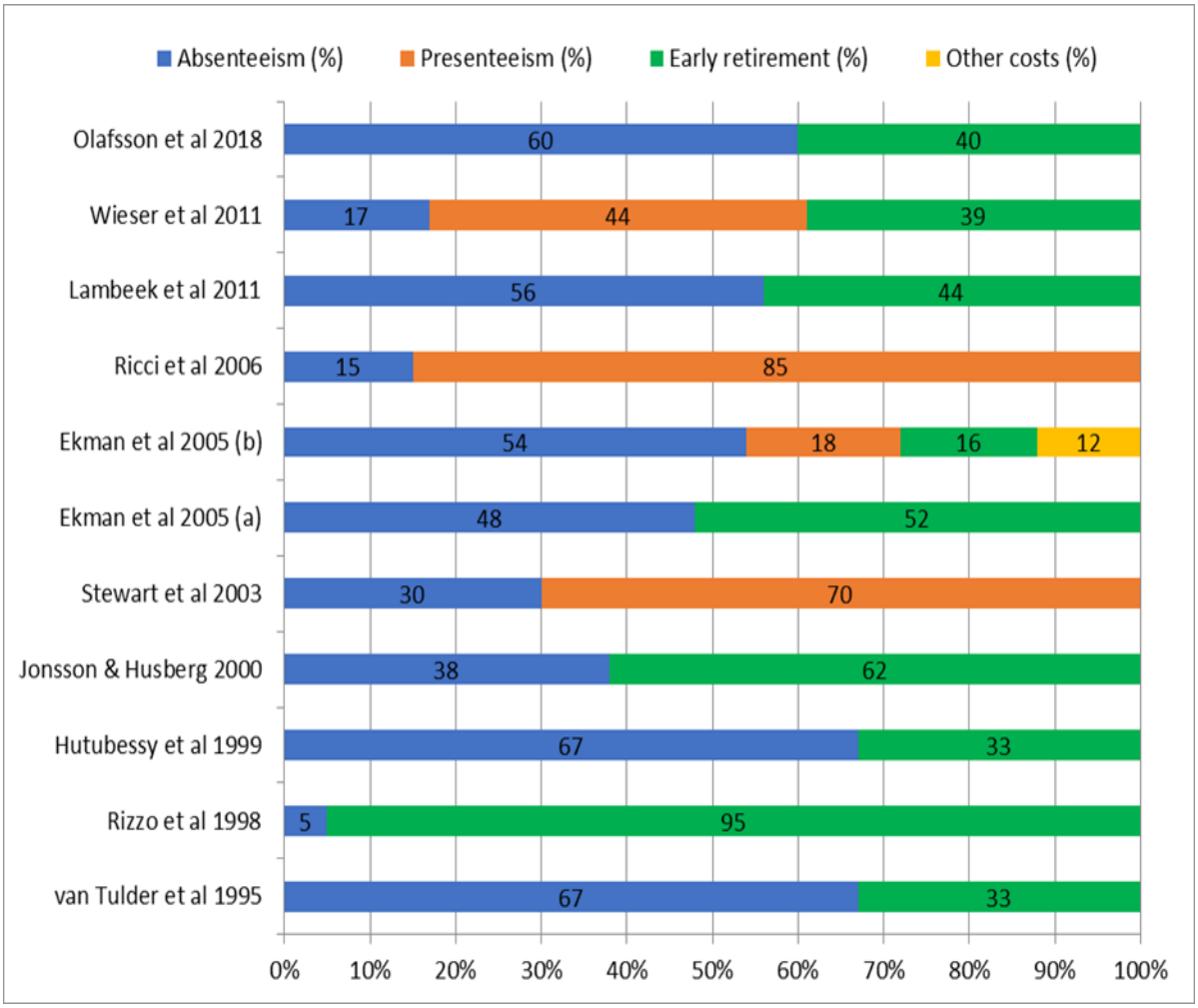


Figure 3.3: Allocation of indirect costs for back pain

Although presenteeism was only assessed in four of the studies, it was found to be the most significant cost component in three of them representing 44%, 70% and 85% of the total indirect costs. This indicates that presenteeism is often underexplored but represents a significant proportion of the indirect costs of an illness. Cost categories included for indirect costs were much fewer compared to direct costs, with only one of the 11 studies (Figure 3.3) reporting a fourth category of indirect costs. In the remaining 10 studies, indirect costs were entirely made up of either two or three of the major cost categories identified.

Estimating direct costs: Estimation of healthcare resource utilisation and costs in the included studies were generally carried out using one of the two common analysis methods: the top-down or the bottom-up approaches. The bottom-up approach was a commonly adopted method (n=27) compared to the top-down approach (Coyte et al., 1998, Ekman et al., 2005 (a), Jonsson and Husberg, 2000, Lambeek et al., 2011, Maniadakis and Gray, 2000, van Tulder et al., 1995, van Zundert and van Kleef, 2005, Walker et al., 2003). The top-down approach was preferred in studies where cost data were widely available from national health statistics. Cost estimations were more detailed in bottom-up studies since individual-level data were aggregated to get the population-level estimates. However, the application of an incremental cost method using a matched-control or econometric methods was limited (Gore et al., 2012, Hong et al., 2013, Luo et al., 2004, Mapel et al., 2004, Martin et al., 2008, Mehra et al., 2012). This method enabled isolation of the costs attributed to back pain by estimating the cost difference between patients with back pain and those without. Martin et al (Martin et al., 2008) was the only study that employed both incremental and conventional approaches allowing for comparison of costs directly attributed to the analysis method. The study revealed that the conventional direct summing of expenditures related to back pain resulted in

a significant underestimation of costs compared to the incremental approach ($32.7 billion vs. $85.9 billion in 2005).

The analysis method used could not be determined in some of the studies (Ekman et al., 2005 (b), Hansson and Hansson, 2005, Hemmilä, 2002, Kim et al., 2005, Müller-Schwefe et al., 2011, Smith et al., 2013). The direct costs reported in the included studies varied widely, and these differences could not be explained by the different cost analysis approaches adopted. This is because monetary valuation of the direct costs was dependent on average costs obtained from national health statistics as well as market prices and fees that differed greatly in international studies. This was in addition to other inherent methodological differences among the studies.

Indirect cost estimation approaches: The human capital (HC) approach was typically applied (n=17) in studies that estimated the indirect costs of back pain. The use of both HC and FC approaches was limited (Hutubessy et al., 1999, Maniadakis and Gray, 2000, Walker et al., 2003, Wieser, 2011) while Boonen et al. (2005) reported the use of FC approach alone. In studies that applied both methods, the HC approach resulted in significantly higher estimates of indirect costs of back pain. Hutubessy et al. (1999) reported the indirect costs of back pain in The Netherlands in 1991 to be $1.5 billion using the FC method; but this increased by three-fold to $4.6 billion under the HC approach. Similarly, the HC approach in Maniadakis and Gray (2000) resulted in an indirect cost of £10.7 billion in the UK in 1998, which was more than double the estimate they obtained using the FC approach of £5 billion.

The approach used in some of the studies (Guo et al., 1999, Gustafson et al., 1995, Hashemi et al., 1998, Shinohara et al., 1998, van Zundert and van Kleef, 2005, Watson et al., 1998, Williams et al., 1998) was unclear and could not be determined explicitly. Two Dutch studies

conducted at different time points, van Tulder et al. (1995) and Hutubessy et al. (1999) arrived at the same estimate for indirect cost of back pain in 1991 using the human capital approach. Despite slight differences in the data sources used, both studies reported a total indirect of cost of $4.6 billion.

3.3.4 National estimates of cost of back pain

The annual national cost estimates of back pain from 25 studies that reported national estimates are summarised in Table 3.5. The results are sorted by the total cost per capita except where a study only provided either direct or indirect cost, or where a second, alternative cost estimate using a different approach was reported. For the purposes of consistency and standardisation, all costs were converted to 2015 US dollars using a web-based tool developed jointly by The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre) (Shemilt et al., 2010). The cost year of 2015 was chosen in order to make comparison with results of the empirical work in this thesis which is based on a 2015 data. However, direct comparison of costs between the studies was not deemed appropriate due to significant differences in case definition of back pain used, cost components included, and other methodologies adopted among the studies. This review also calculated per-capita costs for these studies based on the countries' population obtained from OECD Population Data 2016 and World Bank 2017 data in the year of costs. The studies were conducted in different countries and geographical locations with considerable differences in health care, social and other environmental factors.

Table 3.5: National estimates of direct, indirect, and total costs of back pain in 2015 USD

			Direct costs			Indirect costs			Total costs	
Ref	Country	Population (million)	National (million $)	%	Per capita	National (million $)	%	Per capita	National (million $)	Per capita
1	Sweden	8.9	42	16	4.7	217	84	24.4	259	29.1
2	Sweden	8.9	61	15	6.9	346	85	38.9	407	45.7
3	Sweden	9.4	261	33	27.7	527	67	56.1	788	83.7
4	Belgium	10.2	302	16	29.5	1,603	84	156.7	1,905	186.2
5	Netherlands	16.4	622	13	38	4,014	87	245.1	4,636	283
6	Japan	127.8	26,699	69	208.9	11,866	31	92.8	38,565	301.8
7	Canada	29.1	832	8.3	28.6	9,209	92	316.4	10,041	344.9
8	UK	58.5	3,363	13	57.5	22,015	87	86.7	25,378	433.9
		58.5	3,363	25	57.5	*10,358	75	177.1	13,721	234.6
9	Sweden	8.8	130	3.3	14.8	3,799	97	432.7	3,929	447.5
10	Australia	19.4	1,058	11	54.5	8,400	89	432.8	9,458	487.3
		19.4	1,058	17	54.5	*5,220	83	268.9	6,278	323.4
11	Netherlands	15.01	586	7.4	38.9	7,319	93	485.7	7,905	524.6
12	Holland	16.2	6,101	66	377.8	3,206	34	198.5	9,307	576.3
13	Switzerland	7.4	2,109	39	283.5	3,326	61	449.5	5,435	730.5
		7.4	2,109	54	283.5	*1,785	46	239.9	3,894	523.4
14	Germany	82.5	33,176	46	402.3	38,438	54	466.1	71,614	868.4
15	Japan	127.8	791	na	6.2	na	na	na	na	na
16	Korea	45.9	564	na	12.3	na	na	na	na	na
17	UK	62.3	4,457	na	71.6	na	na	na	na	na
18	USA	295.5	39,000	na	132.5	na	na	na	na	na

		295.5	~102,000	na	346.9	na	na	na	na	na
19	USA	275.9	126,258	na	457.6	na	na	na	na	na
20	USA	292.8	na	na	na	9,115	na	31.1	na	na
21	Jersey	0.1	na	na	na	3	na	36.6	na	na
22	USA	266.3	na	na	na	20,287	na	76.2	na	na
23	USA	287.6	na	na	na	25,559	na	88.9	na	na
24	USA	269.4	na	na	na	40,318	na	149.7	na	na
25	Holland	15.1	na	na	na	7,339	na	487	na	na
		15.1	na	na	na	*2,387	na	158	na	na

All costs are presented in 2015 USD
***** *Estimated with alternative friction cost (fc) approach for the study above*
~ *Estimated with alternative incremental cost method for the study above*
Ref to studies:
1 - Ekman et al (2005), 2 - Hansson et al (2005), 3 - Olafsson et al (2018), 4 - van Zundert et al (2005) , 5 - Lambeek et al (2011), 6 - Montgomery et al (2017), 7 - Coyte et al (1998), 8 - Maniadakis & Gray (2000), 9 - Jonsson & Husberg (2000), 10 - Walker et al (2003), 11- van Tulder et al (1995), 12 - Boonen et al (2005), 13 - Wieser et al (2011),14 - Wenig et al (2009), 15 - Itoh et al (2013), 16 - Kim et al (2005), 17 - Hong et al (2013), 18 - Martin et al (2008), 19 - Luo et al (2004), 20 - Ricci et al (2006),21 - Watson et al (1998), 22 - Guo et al (1999), 23 - Stewart et al (2003), 24 - Rizzo et al (1998), 25 - Hutubessy et al (1999)

In studies that provided both direct and indirect cost estimates (n=14), indirect costs generally far outweighed the direct costs. This review also uncovered that sensitivity analysis is often not conducted in COI studies with only a minority of studies (Boonen et al., 2005, Coyte et al., 1998, Hong et al., 2013, Maniadakis and Gray, 2000, Martin et al., 2008, Walker et al., 2003, Wenig et al., 2009, Wieser, 2011) performing any sensitivity analysis. The use of an alternative cost estimation method as a sensitivity analysis resulted in the greatest impact on reported cost although other approaches such as changing underlying assumptions on cost components (Boonen et al., 2005, Wieser, 2011), unit costs (Wenig et al., 2009, Walker et al., 2003), and case definition of back pain (Hong et al., 2013) were also considered.

The trend in COI for back pain over a given period was only assessed in two of the included studies. Lambeek et al. (2011) conducted a COI study for the years 2002 to 2007 and found that the total cost of back pain to the Dutch society decreased in successive years from €4.3 billion in 2002 to €3.5 billion in 2007. On the other hand, a US study Smith et al. (2013) conducted a longitudinal study (2000 to 2007) to estimate the treatment costs for patients who used only ambulatory services (direct costs). They uncovered that, inflation-adjusted (to 2010 dollars) biennial expenditures on ambulatory services for back pain doubled over the time period, from $26.9 billion in 2000/01 to $52.8 billion in 2006/07.

Some studies reported national cost estimates relative to the country's gross domestic product (GDP) or gross national product (GNP) (Coyte et al., 1998, Hansson and Hansson, 2005, Hutubessy et al., 1999, Lambeek et al., 2011, van Tulder et al., 1995, Wenig et al., 2009, Wieser, 2011). These studies reported indirect costs or total costs as a proportion of either GDP or GNP ranging from 0.28% to 2.3%. The findings were even more consistent (range: 1.1% - 2.3%) in the studies that presented total cost of back pain as GDP proportions (Coyte

et al., 1998, Wenig et al., 2009, Wieser, 2011). Irrespective of which national economic measures were used, these results represent significant economic burden on healthcare systems and society as a whole.

3.4 Discussion

3.4.1 Principal findings of the review

This review examined 43 COI studies with the aim of assessing the methodologies used to estimate direct and indirect costs associated with back pain. The studies were conducted in various countries and settings with different socio-economic factors and health systems which inevitably contributed to the significant differences observed in both the methodologies and cost estimates of the direct and indirect costs of back pain. The main findings of the review in relation to the objectives set out earlier in this chapter are summarised as follows:

Methodologies used in COI studies of back pain: One of the most notable findings of this review was that the methodologies used to derive cost estimates for back pain varied significantly which meant that there was little comparability across the studies in terms of the cost estimates reported. The discrepancies in reported costs and methodologies did not appear to be attributed to the epidemiological approach and cost perspective taken since most studies were prevalence-based and the cost perspective was largely societal. The main sources of variations in the methodologies used in COI studies of back pain were the sources of data used, the way in which back pain was defined, and how healthcare resource utilisation and costs were subsequently estimated across the included studies. The estimation step was in turn influenced by other factors such as the cost components included, and the approaches used to estimate both direct and indirect costs (eg. Top-down vs. bottom-up or human capital vs. friction cost methods).

Reported costs estimates: Findings from the included studies confirm that back pain is a costly problem worldwide. The national cost estimates in 2015 USD ranged from $259 million ($29.1 per capita) in Sweden to $71.6 billion ($868.4 per capita) in Germany. It was clear from the studies reviewed that indirect costs were the main cost drivers for back pain and consequently, major cost savings could be obtained from interventions that bring about early return to work and reduce productivity losses. Outpatient costs were the main cost drivers of direct costs, while absenteeism represented the largest share of indirect costs. The cost categories included in the studies (such as inpatient, outpatient, absenteeism etc.) and the type and number of cost components (such as physiotherapy, surgery, primary care etc.) in each category were likely to have influenced the magnitude and accuracy of the estimates reported. In addition, almost all studies that assessed direct costs reported costs relating to inpatient, outpatient and pharmaceutical costs; however, few studies included costs relating to emergency department, occupational therapy or allied health care. Hence, a wide range of estimates were found across the included studies both nationally and internationally.

Available data sources: One of the objectives of this review was to identify and assess potential sources of data for use in the empirical sections of this thesis. However, unlike the US studies, the European studies did not yield any particular, commonly used sources of data. The Medical Expenditure Panel Survey (MEPS) database in the US proved to be the most comprehensive and well utilised data source for COI studies. Most of the estimates from the first UK study, Maniadakis and Gray (2000), were derived from a survey conducted by the Office of Population Censuses and Surveys (OPCS). Hong et al. (2013) on the other hand utilised routinely collected health records to estimate the healthcare costs of CLBP from CPRD (formerly GPRD) database. Although other large primary care databases available in

the UK have been widely used for clinical research, these have not been utilised to date for estimating the costs of back pain.

3.4.1 Key methodological challenges

The main methodological challenges with respect to the homogeneity of COI studies of back pain were related to the case definition of back pain, the source of data and bias, the included cost components, and the method of estimation used in the analysis.

Case definition of back pain: The definition of back pain can have considerable influence on the magnitude and accuracy of the cost estimates reported. For example, back pain assessment in the included studies was mainly conducted using either diagnostic codes that varied extensively, or via data derived from self-report. Such case definitions result in variations in the prevalence or incidence of the illness which will have a direct consequence on cost estimates. Diagnosis of back pain should ideally be on clearly defined criteria such as the International Classification of Diseases (ICD) codes or the Read codes (NHS, 2000) so that studies might be comparable and replicated as necessary. Consensus on criteria and assessment of the reported cases may be a practical solution for addressing the discrepancies in case definitions (Coggon et al., 2005). Ambiguous and non-specific terms such as backache or back disorder should also be avoided.

Source of data and bias: The main data sources reported for direct cost estimates were large surveys and insurance claims databases. Self-reported measures for healthcare resource utilisation are known to have limitations with validity of the data due to recall bias (Franklin and Thorn, 2019, Leggett et al., 2016) and some resources may be over or under-reported compared to others. Since many episodes of back pain are recurrent and short lived (Hoy et

al., 2010a), resource utilisation may crucially be under-reported in survey-based data thereby underestimating the derived costs. Studies that were based on insurance claims data used this source of data to identify resource utilisation as well as capture the costs. Using charges to value resource use in this way may be fraught with biases inherent in the structure of the claims data. For example, the claims might be subject to co-pays, and deductibles or the insurance coverage may vary from plan to plan or from employer to employer. Hence, services that fell within the remits of other sources of payment or funders were not considered leading to an underestimation of the true cost of back pain. Moreover, since cost estimations are conducted in relation to insured individuals, generalisation of the findings to the wider population may not be appropriate.

On the other hand, patient-level data from EHRs may permit detailed estimates of the direct costs of back pain. However, this source of data was hardly used in the reviewed studies owing to potential complexity of the analysis, and possibly costliness and access restrictions of the databases. Hence, the predictor of costs, and the costs associated with co-morbidities remained largely unanswered. By accounting for potentially confounding variables in the model, econometric methods using EHRs data would have enabled factors associated with increased economic burden of back pain to be identified. It is important to identify these associated factors or predictors of costs as they could potentially alter treatment patterns and their associated costs (Ritzwoller et al., 2006).

Included cost components: The cost components included in the analysis are likely to be major determinants of the magnitude and accuracy of the estimates reported. The number and type of cost components reported in the studies reviewed varied widely for both the direct and indirect cost categories, but particularly the direct cost. Some studies focussed only on major cost components of consultations, prescriptions, and hospitalisations, whereas others also

considered services such as diagnostic imaging, physiotherapy, and accident and emergency. This meant that significant discrepancies existed in reported costs, and studies with partial estimates of healthcare costs could not be compared with those reporting full COI estimates. Furthermore, costs due to secondary care services were estimated in some studies based on referrals made rather than actual episodes in secondary care. An audit by NHS England found that one in 50 patients who missed one appointment in secondary care went on to miss three or more appointments within three months (ONS, 2015). Hence by not considering unattended referrals in secondary care, studies based on secondary referrals are likely to have overestimated healthcare costs.

Method of estimation: The way in which healthcare resource utilisation is valued could also impact significantly on the reported costs. Most studies used a direct method of summing up back pain related costs which mis-estimated the true cost of back pain usually leading to a lower estimate compared to an incremental cost approach. The incremental approach was more comprehensive and accounted for costs that would otherwise have been missed such as costs due to recording error, and mental health costs as a result of back pain. A systematic review in COI studies of osteoarthritis revealed that comprehensive estimates from incremental healthcare costs showed less variability in the results between countries, as well as within country (Puig-Junoy and Ruiz Zamora, 2015). Valuation of indirect costs using the human capital and friction cost approaches also resulted in widely different estimates with the HC method consistently producing significantly higher costs than the FC method. However, unlike the direct cost estimation methods, the justification for the choice of one method over the other is not clear and there is ongoing debate as to the best method (Brouwer et al., 1997, Koopmanschap et al., 1995, van den Hout, 2010). A review and assessment of the evidence

suggests that a pragmatic approach is to use both the HC and FC approaches as sensitivity analyses (Hanly et al., 2014).

3.4.2 Strengths and limitations

Despite the methodological challenges and discrepancies in cost estimates, the results reported in this review represent an impressively large cost of back pain, with indirect costs accounting for the largest share of the total costs. This is the first systematic review aimed at assessing the methodologies used in COI studies of back pain. The previous review (Dagenais et al., 2008), which focussed on synthesising results rather than methodologies, was from 2008 and the findings were limited by having searched only one database for studies published in the previous 10 years. A major strength of this review was that a large number of studies were included that varied greatly by country and methodology. The search was conducted using multiple databases, and with no restriction on publication date making this review a comprehensive one. Methodological differences that may not always be apparent but result in significant influence on COI estimates of back pain were revealed by this review. A potential limitation was that this review only considered studies conducted in high income countries and published in English. Nevertheless, the findings of this review can be considered robust given that such a large number of studies were examined.

It was noteworthy that several studies did not explicitly describe their methodologies posing several challenges to assess them. This lack of clarity is also confirmed by other systematic reviews (Bovolenta et al., 2017, Dagenais et al., 2008, Molinier et al., 2008, Pagano et al., 1999), and appears to be a common feature of COI studies. The transparency and replicability of COI studies could therefore be improved by including sufficient explanation of the methodologies subject to word limits by the journals which could be restrictive. Another

marked feature uncovered by this review was the lack of consensus and guideline on the use of methodologies for COI analysis. Consequently, these analyses were prone to underestimation or overestimation of the true costs of the illness. Methodological inconsistencies may therefore have considerable impact on the credibility of reports of COI studies. This finding is consistent with that of other systematic reviews of COI analyses, and was not restricted to back pain (Costa et al., 2012, Luppa et al., 2007, Verhaeghe et al., 2016, Cooper, 2000). For example, a systematic review by Cooper et al. (2000) found vast discrepancies in the cost of rheumatoid arthritis among the included studies; nevertheless, these could not be explained by socio-demographic or clinical differences present in the samples (Cooper, 2000).

Furthermore, sensitivity analysis does not appear to be a standard practice in current COI studies with only a minority of studies conforming to the norm. A methodological review by Molinier et al. (2008) found no sensitivity analysis in a review of 15 COI studies on cost of prostate cancer (Molinier et al., 2008). Similar findings were reported in another systematic review by Costa et al. (2012) where only three studies had performed sensitivity analysis out of 17 COI studies on Alzheimer disease (Costa et al., 2012). This is unlike other quantitative studies (eg. economic evaluations, epidemiological research) and may cast doubts on the reliability of the estimates. It was also notable that although some studies in this review assessed cost differences by duration of the illness (for example, chronic vs. non-chronic back pain), sub-group analyses were generally not conducted in most of the included studies. How the economic impact of back pain varied by patient characteristics such as age, gender or ethnicity as well as by disease characteristics such as pain levels or presence of co-morbidities remained largely unanswered.

3.4.3 Recommendations

Based on the findings of this review, some important recommendations for good practice can be drawn which may help produce more reliable estimates for the costs of back pain with implications for COI studies in general:

- As back pain imposes an enormous economic burden, costs must be estimated more accurately and inclusively, and a bottom-up approach using an incremental cost method is recommended as base case analysis.
- The case definition of back pain will have direct impact on the magnitude of cost estimates. Hence, identification of cases should be based on a broad consensus on case definition of back pain, and the use of diagnostic codes is preferred.
- Resource utilisation may be better estimated by following up a large sample of patients, and valuation of unit costs should be carefully assessed. Although a growing number of large healthcare databases or EHRs are available, these remain underutilised and COI studies should aim to exploit these.
- Patient characteristics, such as comorbidities, should be clearly reported. Where appropriate, separate cost estimates need to be reported for subgroups of patients as these may reveal patterns and variations in costs not assuming that the costs are the same across the study population.
- Researcher should test the sensitivity of the analysis by varying important parameters and keys assumptions made in the analysis. They should also give detailed descriptions and discuss limitations of the methodological choices.

- Finally, development of formal guideline and standardisation of the methodologies used for COI studies may not only enhance the reliability and interpretation of the estimates, but also enables comparability of the results across studies.

3.5 Conclusion

COI studies may provide important information and serve as a basis for further economic evaluations and allocation of resources. This review assessed 43 studies on the economic burden of back pain in high income countries with the aim of evaluating the various methodologies used. The included studies varied greatly by country, methodologies used, and the direct or indirect cost estimates they reported. Insufficient description of methodologies may lead to misunderstanding of resulting estimates. In the absence widely accepted standards and consensus on methodology, conducting a COI study capable of identifying and measuring the true cost of an illness remains a challenge. Detailed methodological considerations in the assessment of the direct and indirect costs of back pain were provided by this study with important recommendations for good practice. The guidance can be used for COI studies across a range of illnesses. Methodological variations and the discrepancies that arise within them have direct impact on the comparability and credibility of the studies. This review has reported a widespread heterogeneity in the methodologies used, and the direct or indirect cost estimates produced for back pain. Despite these issues and other limitations discussed, the economic burden of back pain reported by the studies reviewed was significant. By informing the relative importance of this health problem, the information obtained here has important implications on the allocation of scarce resources and other health policy decision making.

This review also highlighted some factors that might have substantial impact on the reported cost estimates. Recommendations about good practice for COI studies of back pain have been

suggested based on the findings of this review. These recommendations may help obtain reliable estimates of the true cost of the illness, improve the quality and reporting of the analysis, and provide validity to COI studies. Given that an incremental cost approach has great advantage in exploiting large patient level data such as EHRs to obtain reliable estimates of the economic burden of back pain, this is the approach that will be adopted in this thesis. However, it is acknowledged that primary care databases only capture data from patients who choose to consult their GPs. Therefore, healthcare resource utilisation in the private sector, out-of-pocket costs and productivity related costs of patients are generally not captured in such databases. An exploration of EHRs and research databases derived from them is the focus of the next chapter.

CHAPTER 4. INTRODUCTION TO ELECTRONIC HEALTH RECORDS AND DATA SOURCE FOR THE THESIS

4.1 Introduction

The previous chapter presented a systematic review of studies that assessed the direct and indirect costs of back pain. The objective of this chapter is to introduce electronic health records (EHRs) and to explore potential data sources that could be utilised for quantifying, and modelling healthcare costs of back pain in the UK. It focuses on The Health Improvement Network (THIN) primary care database which is one of the most respected and reliable data sources in the world for primary care records (THIN, 2018). The database is nationally representative of the UK population and contains anonymised patient data for about 6% of the population (THIN, 2018). The longitudinal patient level data in THIN have been collected since 1990, and they include extensive information on patient's demographic, clinical, medications, consultations, and other event history data (Adjah et al., 2017, Quintiles-IMS, 2017b).

The chapter starts by presenting routinely collected data sources both in primary and secondary care services comparing them on some of the attributes necessary for the studies in this thesis. Next, an overview of the THIN database and the structure of data recorded in it is presented. The proposed use of the data is then explained focussing on two important steps, the identification of recorded back pain, and prescription drugs from the database. These are conducted using diagnostic codes and drug codes respectively, and they are essential steps

before any analysis is conducted. Finally, the strengths and limitations of using the THIN database for the intended analyses are discussed.

4.2 Electronic health records in the UK

EHRs are a system of computerised medical records that collect, store, and display information on patient's health and care (Ajami and Bagheri-Tadi, 2013). GP surgeries, hospitals, and other community-based healthcare providers hold these EHRs which may vary in structure, content, software system, access and usage (Warren-Gash, 2017). The electronic records consist of coded data and some free-text notes recorded by the healthcare professionals. These include information on clinical diagnosis, consultations, prescriptions, investigations, referrals, demographics, lifestyle factors, and engagement with health services. Hence, electronic record keeping of routine data may aid in making patients' records paperless and enable the collection of data for various purposes. In the UK, there are three major EHR systems used for GP recording and these three hold the majority of the market share for clinical computer systems (Kontopantelis et al., 2018). They are the Egton Medical Information Systems (EMIS), Vision, and SystemOne (Kontopantelis et al., 2018). Although the primary purpose of EHRs is clinical, they are a rich source of information for research with ability to link patient data with other EHR sources across primary and secondary care services (Casey et al., 2016). However, research using routine data poses several challenges including data linkage capability, missing or sporadic data entries, and barriers to access and sharing of data including the high cost of licenses with data providers, which limit the utilisation of these data sources for research (Warren-Gash, 2017).

Several data providers in the UK produce and maintain research databases that are derived from existing EHRs. These include the different health authorities in the UK, Quintiles-IMS,

EMIS Health for primary care databases, NHS Digital (secondary care data), and the Office for National Statistics (vital registration data) (Warren-Gash, 2017, Vezyridis and Timmons, 2016). Table 4.1 compares the main routinely collected data sources that may be used for quantifying and modelling healthcare resource utilisation and costs. The three major primary care databases used for research in the UK are the Clinical Practice Research Datalink (CPRD) which was previously called the General Practice Research Database (GPRD), The Health Improvement Network (THIN) and QResearch (Chaudhry et al., 2017, Shephard et al., 2011, Vezyridis and Timmons, 2016).

These routine, population-based databases contain coded data from patients who registered at contributing general practices. Clinical events in these databases are recorded using the Read clinical code system (Benson, 2011). As of April 2018, the Read code system is being replaced by Systematised Nomenclature of Medicine - Clinical Terms (SNOMED CT) in a phased approach across all GP practices (NHS-Digital, 2019). SNOMED CT or SNOMED for short is a systematically structured clinical terminology and it was intended to be more comprehensive and precise than the existing Read codes (NHS-Digital, 2019). Drugs and prescribing information are recorded using drug codes, and data dictionaries for both clinical and drug information are generally available with these databases.

Table 4.1: Potential EHRs based data sources to measure healthcare resource use and costs

Sources: (Gnani and Majeed, 2006, Kneale et al., 2016, McDonnell et al., 2017, Quintiles-IMS, 2017a, Raftery et al., 2005, NHS-England, 2013, Kontopantelis et al., 2018)

Data source	Type of data/ Coverage	Strengths	Weaknesses
Clinical Practice Research Datalink (CPRD)	Primary care, UK wide	693 contributuing Gp practices (14.2 millon patients), linkage with HES data, widely used for research	Complexity of data requiring expertise, indirect link b/n diagnosis & prescribing (no direct link)
The Health Improvement Network (THIN)	Primary care, UK wide	760 contributing GP practices with 400 active practices (16 million patients), linkage with HES data, widely used for research	Complexity of data requiring expertise, indirect link b/n diagnosis & prescribing, relatievly new database (started in 2003)
QResearch	Primary care, UK wide	Approximately 1,200 GP practices (over 18 million patients), linkage to several data sources.	Only coded data (no free text), indirect link b/n diagnosis & prescribing, less widely used for research, relatively new database (started in 2003)
Hospital Episode Statistics (HES)	Secondary care, England only	Around 19 million inpatient records, 90 million outpatient records, & 18 million A&E records per year, high accuracy, linkage to several data sources	Stringent data access process, no patient-level hospital prescribing data, data requires high level of expertise to use
Research One	Primary care, England only	28 million (primary and secondary care) records and 423 practices, linkage with other data sources	New database (started in 2013), less widely used for research
Primary Care Clinical Informatics Unit (PCCIU)	Primary care, Scotland only	Covers approx. 15% of the Scottish population, Read codes based data, started in 1999	No linkage to any other data, less widely used for research
SAIL (Secure Anonymised Information Linkage) Databank	Primary care, Wales only	Over 170 practices or 2.25 million patients (75 % of total Welsh population), linkage with several data sources	Mainly Read codes but local codes also used, less widely used for research
Consultations in Primary Care Archive CiPCA)	Primary care, Regional	Primary care data from 9 GP practices, quality of data compareable to large national databases	No linkage to any other data, regional data (North Staffordshire only)

Over a ten-year period (2004 – 2013), research outputs using the three major primary care databases (CPRD, THIN and QResearch) collectively resulted in about 1,300 publications (Chaudhry et al., 2017). These included 825 studies using CPRD, 394 using THIN, and 77 studies coming from QResearch, and publications have been increasing substantially (Chaudhry et al., 2017). As of July 2018, research output using the THIN database alone has risen to over 600 medical research publications (THIN, 2018). The growth in outputs may be driven by the continuously increasing population coverage of the databases and improvements in data quality although it is acknowledged that considerable variations still exist in quality of data recorded in EHRs (Chaudhry et al., 2017, van der Bij et al., 2017, Vezyridis and Timmons, 2016). The other routinely collected primary care databases were not UK-wide representing either England (Research One), Wales (SAIL), or more regionally focussed such as the North Staffordshire's CiPCA database (Salcher et al., 2018, Shephard et al., 2011). These may restrict the generalisability of cost estimates to a UK level. While primary care databases are curated by multiple data providers, HES database remained the principal source of secondary care data which is provided by NHS Digital (NHS-England, 2013). Although HES is England based rather than UK-wide, it is considered an invaluable source of hospital data worldwide and is subjected to strict data access and controls (NHS-England, 2013).

The national primary care databases may also provide secondary care data such as investigations and hospital admissions through data linkage mechanisms with HES data (Chaudhry et al., 2017). Anonymised hospital data may be made available for researchers through data licences held by academic institutions. The CPRD and THIN databases are largely equivalent in structure and content of data they contain with about half of the general practices contributing data to CPRD also contributing to THIN (Matcho et al., 2014, Petherick et al., 2015). Previous validation studies have shown that comparable estimates of burden of

disease can be obtained using these two competing primary care databases independently (Lewis et al., 2007, Petherick et al., 2015). The THIN database is considered one of the most comprehensive and reliable databases for patient level data, and it has been used extensively for research worldwide (Adjah et al., 2017). The accuracy and completeness of THIN for research have also been validated previously (Blak et al., 2011, Denburg et al., 2011). Therefore, the THIN database was chosen for this thesis to explore and estimate the healthcare costs of back pain in the UK. Despite being a rich source of patient-level data, the THIN database has been underutilised in health economic research, and this was another motivation for making use of this important data source. Access to THIN data was also available through the sub-licence held at the University of Birmingham, and the version used in this thesis was Version 1705 from May 2017.

4.3 The Health Improvement Network (THIN)

The THIN database was set up in 2002 by a collaboration between In Practice Systems (INPS), who developed and provide the Vision medical recording software for general practices in the UK, and Epidemiology and Pharmacology Information Core (EPIC) as an alternative to the GPRD database (Quintiles-IMS, 2017a). Both companies were later acquired by Cegedim, a global technology and services company specialising in healthcare, and is the owner of THIN (Quintiles-IMS, 2017a). The THIN database is currently managed by Quntiles-IMS, who make anonymised data available to researchers, under licence from Cedegim (Quintiles-IMS, 2017a, Vezyridis and Timmons, 2016). Collection of electronic medical records started in 2003 and over 780 Vision practices have joined the scheme since then, with about 400 of them (equivalent to over 3 million patients) being currently active (Quintiles-IMS, 2017a).

4.3.1 Structure of the THIN data

The data collected in THIN are routine clinical care information that general practices record using the Vision software. They are therefore not particularly collected for research purposes. However, since the database contain comprehensive prescribing, consultation, and other clinical information, it allows for healthcare research in many areas. The collected data are entered into four separate main files (1 – 4) and three additional linked files (5 – 7) as follows (Quintiles-IMS, 2017b):

1 **Patient file:** Demographic information such as age, gender and registration information such as practice entry and exit dates.
2 **Medical file:** Medical diagnosis including date and geographical location, and additional information on secondary care referrals.
3 **Therapy file:** Prescriptions information including date, formulation, quantity, dosage and advisory information
4 **Additional health data (AHD) file:** Miscellaneous information such as vaccinations, laboratory results, and lifestyle factors including smoking and pregnancy.
5 **Consultation file:** Information on consultation duration, time and date. These can be linked to the four major files by patient ID.
6 **Staff file:** Information on general practice staff who entered the data. These can be linked to the therapy, medical and AHD files by staff ID.
7 **Postcode variable indicators (PVI) file:** Postcode linked socio-economic and environmental data. These can be linked to the patient file by patient ID.

Although there are options for free text recording or scanned information in the medical and AHD files, data collected in THIN are generally recorded in the form of coded information.

Medical diagnoses and other clinical data are recorded using a seven-character Read code scheme, while prescriptions data are recorded using drug codes which can be linked to the British National Formulary (BNF) codes (Quintiles-IMS, 2017b). Patients can enter and exit the database at various times and therefore patients' records are continuously collected and updated making the database dynamic. Patients may also opt out from consenting to contribute to the THIN data.

4.3.2 Proposed use of the database

It is intended that THIN data will be used to estimate healthcare resource use and costs of back pain in primary care settings. This will be done by comparing the costs of patients with back pain (cases) against those without back pain (controls). The incremental costs obtained from the sample will then be extrapolated to a national level using UK prevalence estimates. Variation of these costs by patient characteristics such as age-group, gender, socio-economic status (SES) as well as trends over time will be explored. This is achievable with THIN, since patients included in the database are representative of the UK in relation to patients demographics and prevalence of medical conditions (Blak et al., 2011). The THIN version used in this thesis collected data from over 760 practices and contained the electronic medical records of about 16 million patients (3.7 million active patients, covering about 6% of the UK population) (Quintiles-IMS, 2017a, Vezyridis and Timmons, 2016). Prior to data extraction for analysis, two important steps needed to be completed using the database, which defined the study population and outcomes. These were the identification of Read clinical codes for back pain, and the identification of drug codes for analysing prescription drugs associated with back pain.

4.3.3 Identification of back pain diagnosis from THIN

The included Read codes that define the study population determine the magnitude of the results and generalisability of the study. Hence it was essential that the searches were conducted as thoroughly as possible, and that transparency was maintained in the reporting of the codes. This study was not restricted in scope with regard to a specific type of back pain to be included, therefore, a comprehensive list of commonly reported and studied diagnoses of back pain were sought. The following strategies were used to identify all relevant codes for the study:

I - Reviewing the literature for previously used back pain code lists.

II - Exploring and reviewing back pain definitions and Read code lists developed at Keele University, and another code list by an online clinical codes repository (ClinicalCodes.org).

III - Searching for key words using the Clinical Terminology Browser (downloaded from NHS Digital) and using the Read code dictionary from THIN.

IV - Seeking clinical expertise from a clinician (Dr Majid Artus) via personal communication.

After exploring and examining these resources, the ICD-9 based back pain definition (described below) used by the previous UK study (Maniadakis and Gray, 2000) was adopted for the following reasons. First, one of the aims of the thesis is to compare the current estimates of the costs of back pain with that of previously available estimates, therefore, a closely similar and comparable definition of diagnosis was essential. Second, this definition of back pain has been used internationally by other studies on the economic burden of back pain (Luo et al., 2004, Martin et al., 2008), thus, providing consistency and validity for this

study. Another US study (Gore et al., 2012) also used a closely similar set of codes to define diagnosis of back pain.

The definition of back pain used in this thesis consisted of those conditions that relate to ICD-9 codes 720-724 (dorsopathies), 846 (sprains and strains of sacroiliac region), and 847 (sprains and strains of other and unspecified parts of back). The ICD-9 codes for these conditions were first mapped to the equivalent Read classification system using the Read code dictionary in THIN and the Clinical Terminology Browser. A final code list (Appendix 4.1) with 101 Read codes was developed for use in this thesis. This covered a broad range of pain diagnoses experienced in the spine including upper (thoracic) pain, lower back pain, and pain related to the sacroiliac region. The code list was reviewed independently by a clinician (Dr Majid Artus) for completeness and relevance.

4.3.4 Identification of prescription drugs from THIN

It was important to develop a comprehensive list of drug codes to assess healthcare resource use and costs of prescription drugs for back pain. Therefore, the following strategies were used in line with the approaches used for defining the morbidity:

I - Reviewing the literature for previously used drug code lists.

II - Searching the drug code dictionary of THIN using relevant BNF chapters.

III - Seeking clinical expertise from clinicians (Dr Majid Artus and Professor Tom Marshall).

As it was not possible to utilise and cost all medications prescribed for both the case and control cohorts in such a large sample, this thesis focussed on the broad definition of drug categories that are likely to be related to back pain. Definition and categorisation of pain

medications or analgesia were adopted from previously published studies (Bedson et al., 2013, Ndlovu et al., 2014) conducted at Keele University. The drugs spanned four BNF chapters: opioids/opioids-like agents (BNF section 4.7.2), non-opioids (BNF section 4.7.1), nonsteroidal anti-inflammatory drugs or NSAIDs (BNF section 10.1.1), and rubefacients, topical NSAIDs, capsaicin, and poultices (BNF section 10.3.2). These were further classified into six pain therapy categories (drug groups) based on potency: basic analgesics, weak analgesics, moderate analgesics, strong analgesics, very strong analgesics, and NSAIDs. The drug codes corresponding to these drugs were identified using the THIN drug dictionary. The final pain relief drug list consisted of 255 unique drugs (Appendix 4.2) with 1,490 drug codes (many drugs had multiple drug codes representing different formulations and brands).

Additional drugs that are usually prescribed along with pain relief medication were also identified. These are drugs that are prescribed for various reasons in relation to the pain such as to counteract the side effects of pain killers (eg. laxatives) or to deal with anxiety and depression associated with back pain (eg. hypnotics and anxiolytics). This group of drugs constituted eight BNF chapters: proton pump inhibitors (BNF 1.3.5), bulk-forming laxatives (BNF section 1.6.1), stimulant laxatives (BNF section 1.6.2), faecal softeners (BNF section 1.6.3), osmotic laxatives (BNF section 1.6.4), corticosteroids (BNF section 10.1.2), hypnotics (BNF section 4.1.1), and anxiolytics (BNF section 4.1.2). In total, 504 drug codes were extracted from the THIN database representing 79 unique drugs in this group of additional drugs (Appendix 4.3).

4.3.5 Comorbid conditions and the Charlson Comorbidity Index (CCI)

A comorbid condition in this thesis is defined as a chronic medical condition that coexists with the index condition or the primary condition of interest which is back pain. Comorbidity

therefore describes the effect of other medical conditions a patient might have other than back pain. Comorbidities are highly prevalent among older adults, and an increased burden of comorbidity is associated with poorer health outcomes including survival (Fraser et al., 2015, Kaur et al., 2018). In addition, comorbid conditions may require treatment with multiple medications, potentially increasing the patient's healthcare resource utilisation. It was therefore important to include comorbidity during the matching of case and control groups as well as adjust for the effect of comorbidities when modelling the healthcare cost data in this thesis. While a number of measures of comorbidity have been suggested including a simple count of diseases, the Charlson comorbidity index (CCI) is one of the most commonly used method to adjust for patient casemix (Hall et al., 2004, Khan et al., 2010).

The CCI is calculated for all patients who may have a range of chronic conditions such as diabetes, HIV, cancer, rheumatoid arthritis and so on, a total of 22 conditions (Charlson et al., 2014, Charlson et al., 1987). Each condition is assigned a weight from 1 to 6 based on the risk of dying associated with each one, and these weights are summed to produce the final CCI score for each patient (Charlson et al., 1987, Khan et al., 2010). Guided by the conditions in the Quality Outcome Framework (QOF), this thesis included 18 chronic conditions in the development of the CCI variable. The scores were then categorised for the purpose of matching case and control groups, as well as to assess healthcare costs by CCI categories. The included conditions and how they compare with the QOF clinical domains are shown in Appendix 4.4.

4.3.6 Strength and limitations of THIN in relation to intended analyses

Since data contained in primary care databases represent the care patients have actually received, the key advantage of using the THIN database for this research is that it provides

more accurate and detailed healthcare resource use data compared to survey based data. A very large number of GP practices and patients contribute data to THIN allowing more precise estimation of healthcare costs and investigation of factors associated with the costs. Another strength is the nationwide spread of the THIN database including men and women of all ages and regardless of other socio-demographic and clinical factors. The patient-level data comprised within THIN are derived from a representative subset of the UK population, hence the findings are generalisable to the wider population (Denburg et al., 2011, Kneale et al., 2016). The large size and representation also enable analyses of healthcare resource use and costs of back pain by sub-groups of the population such as by demographics and clinical characteristics.

The THIN database is updated regularly and data quality checks are also conducted by Quintiles-IMS (Quintiles-IMS, 2017c). At extraction of data for research, better quality of data can also be ensured by applying a number of alternative dates as a restriction on the start date of a patient follow-up. These include date of computerisation for the practice, Vision date which is the date the practice started to use the Vision data recording software, registration date of patients with the general practice, and the acceptable mortality recording (AMR) date (Horsfall et al., 2013). The AMR date is assigned by THIN and is the date at which the practice's reporting of mortality data is deemed to have reached the UK general population level (Quintiles-IMS, 2017c). It is recommended that application of restrictions on the start date of patient follow-up using one or more of these dates before the selection of study population could reduce potential biases surrounding the definition of active patients (Maguire et al., 2009, Horsfall et al., 2013). For the studies in this thesis, patients were eligible for selection only after 12 months (as per the general guideline for THIN data extraction) of AMR date, Vision date and patient registration dates to ensure better quality

data. The 12 months period may allow sufficient time to build up the quality of recording while practices adapt to new systems. It also helps to avoid the flurry of activities that might take place immediately after a patient registered with a new practice which could otherwise result in exaggerated healthcare resource utilisation in the first 12 months.

Although the THIN database has several advantages, there are also limitations for the intended research. As a primary care database, a major limitation of THIN is that it has limited information recorded on activities that occur outside of GP surgeries. While complete information on consultations and prescriptions can be obtained, they only constitute a proportion (averaging about 46% from the review) of the total healthcare costs of back pain. Important outpatient services for back pain such as physiotherapy and diagnostic imaging, and inpatient resource utilisation such as surgeries are generally not recorded in THIN apart some from referral information. There is also a paucity of data on risk factors and patient characteristics that are important for back pain such as occupation type, physical activity/sedentary behaviour, pregnancy, and education level. As EHRs data are routinely collected for clinical management purposes and not for research, these types of information are not necessarily recorded by GPs. Ethnicity data are also poorly recorded. Moreover, although comprehensive prescription data are available in THIN, these reflect the prescribing behaviour of the GPs and does not guarantee that the drugs have been dispensed or taken by the patients. Finally, a key aspect of EHRs data such as THIN is that the available information represents those who chose to consult, and hence there is a lack of information on patients who do not consult their GPs.

4.4 Ethical approval

All research in the UK involving NHS patients must have ethical approval from a Research Ethics Committee (REC), and THIN data collection was approved by REC in 2003 (Quintiles-IMS, 2017e). Data recorded in THIN are anonymised so that individual patient identifiers like name, address, date of birth, and NHS number cannot be identified by users of the data. Hence if researchers are using only the pre-collected THIN data, REC approval is not required (Quintiles-IMS, 2017e). However, the protocols must be reviewed for scientific merit and feasibility and get approval from Quintiles-IMS through a Scientific Review Committee (SRC) (Quintiles-IMS, 2017e). The protocol (Appendix 4.5) for the studies within this thesis that utilised THIN database received SRC approval (Appendix 4.6) in May 2018 (SRC ref: 18THIN041).

4.5 Summary

A reliable source of patient-level data is needed for meeting the objectives of the studies in this thesis. Routinely collected EHRs data are not commonly used for COI analysis despite being a rich source of patient-level data. This chapter explored EHRs and large databases derived from them which have potential to provide data for estimating healthcare resource utilisation and costs of back pain. The guidance in the use of EHRs in general, and the THIN database in particular presented in this chapter can be used by other researchers intending to use EHRs for medical research. Coded electronic patient records are made available to researchers through these databases informing population health research. A summary of the structure of the THIN database and the identification of coded back pain diagnosis and prescription drugs is also presented. In the rest of the thesis, the term ‘healthcare costs of back pain’ used in connection with THIN database refers to the consultation and prescription costs

in primary care that are estimated from the THIN database. It is acknowledged that these costs only account for a proportion (averaging about 46%) of the total healthcare costs associated with back pain. However, the two cost components are used as exemplars for estimating the wider healthcare costs of back pain. A matched control cohort will be extracted from THIN which will serve as a reference group for comparison with the cases. This is the basis upon which incremental healthcare resource utilisation and costs of back pain in primary care settings are estimated in the next chapter.

CHAPTER 5. HEALTHCARE RESOURCE USE AND COSTS OF BACK PAIN IN PRIMARY CARE

5.1 Introduction

The previous chapter explored the availability of primary care databases and other sources of data that could potentially be used for this study. It also presented the process of identifying back pain diagnoses, co-morbid conditions and prescription drugs from THIN database. This chapter presents the methods of analysis, results, and sensitivity analysis for estimating the costs of back pain in UK primary care. Comparisons are made with the previous cost-of-illness (COI) study that is available in the published literature which was published nearly two decades ago (Maniadakis and Gray, 2000). The authors argued at the time that the economic burden of back pain was expected to rise in the future due to a combination of changing methods of healthcare provision, and changing health seeking behaviour (Maniadakis and Gray, 2000). The global burden of low back pain has also been rising rapidly thereby increasing the healthcare resource utilisation and costs associated with it (Hoy et al., 2014a, Hoy et al., 2010b). It is therefore appropriate to hypothesise that the consumption of resources and medical costs incurred by back pain patients have increased since their last estimate in 1998.

5.2 Aims and objectives

The aim of this chapter is to assess healthcare resource utilisation and associated direct medical costs for patients with back pain, and to compare these with previous estimates available. The perspective adopted is that of the UK healthcare provider, the National Health

Service (NHS). Patient-level data on consultations and prescriptions from the THIN database are used for this purpose. The specific objectives of the chapter are to:

I - Estimate annual healthcare resource utilisation and costs associated with the treatment of back pain.

II - Explore the variations, if any, in the estimated costs by demographic, socio-economic, and clinical factors.

III - Investigate trends in healthcare costs over a five-year period (2011-2015).

5.3 Methods

5.3.1 Study population, study design and period

Data for the study were obtained from the THIN primary care database. A retrospective, matched case-control study design was used to isolate resource use and costs associated with back pain. This method, also referred to as 'the incremental cost' approach was explained in chapter 3, and has been used in previous back-related cost studies (Hong et al., 2013, Luo et al., 2004, Martin et al., 2008). In order to control for confounding factors, patients with back pain (cases) were matched with those without back pain (controls) based on demographic and disease characteristics. All such characteristics or variables available in the dataset except ethnicity were used for matching. These were: age, gender, GP practice (practice ID), Townsend deprivation quintiles, body mass index (BMI) categories, smoking status, and Charlson comorbidity index (CCI). Ethnicity is poorly recorded in the THIN database (only available for about 53% of patients) and therefore not included in this analysis. Townsend index or score is a measure of material deprivation within a population (Jarman et al., 1991, Townsend, 1991). The scores derived from the 2001 UK census data were available in the THIN database in the form of quintiles or five equal-sized groups (Quintiles-IMS, 2017d).

The comorbidities included and the development of CCI was reported in Chapter 4. Further detail on selection of the study sample and the rationale for matching is given in section 5.3.3.

It was intended that trends in cost would be assessed over a five-year period of 2011-2015. However, this would require separate data extraction for each of the five years to ensure that the eligibility criteria were met consistently across the years. For example, a patient who did not have diagnosis of back pain in 2011 may develop a diagnosis in subsequent years and become eligible for inclusion. In order to mitigate this complexity, three studies were conducted instead of five for the cost years 2011, 2013 and 2015 to show trend over a five-year period. The justification for this approach was because conducting several data extractions and undertaking an enormous amount of data manipulation including identifying unit costs for the relevant years was anticipated to be time consuming and deemed impractical for the thesis. A breakdown the population in the three studies, their observation periods, and the number of patients overlapping across the studies is shown in Table 5.1. A total of 41,921 patients (11% of the 2011 sample) had longitudinal data for the full five years period.

Table 5.1: Breakdown of samples in the three studies and their degree of overlap

	Study year			
	2011	**2013**	**2015**	**Overlap 2011-15**
Total study sample (n)	385,452	358,528	266,682	
Observation period	01/01/02 to 31/12/11	01/01/04 to 31/12/13	01/01/06 to 31/12/15	
Overlap b/n samples (n)	115,873	88,182		41,921

For each of the three studies conducted, a 10-year observation period including the study year was used for identifying patients with a diagnosis of back pain. A long observation period was chosen in order to allow sufficiently for any fluctuations in the incidence of back pain. A sensitivity analyses was conducted using a shorter observation period of two years enabling investigation of patients with more recent diagnoses.

Patients who had the first diagnosis of back pain in the 10-year observation period were identified using their diagnosis date recorded in THIN. For the 2015 study for example, the observation period was from 01 January 2006 until 31 December 2015. The index date for patients was defined as the start date of the study follow-up and the same index date was assigned to matched controls at the initial data extraction stage. The time period before the index date is referred to as baseline period in this study, and the time period following the index date is the follow-up period where diagnoses of back pain were identified, and costs estimated accordingly in the study year. For prevalent cases, who are patients that were diagnosed before the study year, the index date was the first day of the study year (eg. 01 Jan 2015). Incident cases in this study refer to patients with a first diagnosis of back pain during the study year for whom there was no diagnosis code for back pain in the previous nine years. For incident cases, the date of diagnosis for back pain remained as their index date.

Healthcare resource use and costs were estimated and reported for each of the three years, with the main cost year for the purpose of updating the COI for back pain in the UK being 2015, the most recent of the three studies. The total healthcare costs (consultations and prescription drugs) between the cases and controls were compared to obtain the incremental costs associated with back pain. The incremental cost method was chosen because it provides mechanisms for isolating the costs specifically due to back pain by using appropriately

matched controls. When the matching is applied properly, the resulting estimates are more accurate estimates of the true cost of the illness, because the only systematic difference between the two groups is that one of the them was diagnosed with the disease of interest (Akobundu et al., 2006, Martin et al., 2008).

Due to recent changes in data access requirements from Quintiles-IMS/IQVIA, the linked secondary care data from the Hospital Episode Statistics (HES) were not available with the THIN data used in this thesis (IQVIA, 2019). Although THIN data alone contained some indicators of secondary care resource utilisation in the form of GP referrals, these were deemed inappropriate to use for the purpose of estimating resource utilisation and costs. This is because referrals do not necessarily equate to attendance of appointments or completed episodes in secondary care leading to incorrect estimation. The studies in this thesis therefore focussed on the THIN database without using HES data for reasons of time, data access delays and cost. GP consultations and prescription drugs data, which are well documented in THIN, will be extracted to estimate the costs associated with back pain.

5.3.2 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied for all eligible patients:

Inclusion criteria:

1 - All patients must be aged 18 years or older at the index date.

2 - Both the case and control cohorts were required to have continuous registration with the GP practices for the duration of the study unless they died.

3 - Cases were required to have at least one diagnostic Read code for back pain from the code list (Appendix 4.1) in the nine years prior to the study (prevalent cases) or

during the study year (incident cases). They must also have had at least one prescription drug for pain (Appendix 4.2) during the study year.

4 - Control cohorts were required to be without a diagnosis of back pain recorded in THIN to be eligible for inclusion. However, they may or may not have had prescription drugs for pain during the study year. In the 2015 study, a second scenario was considered where controls were also required to have prescription drugs for pain to be included in the study and comparisons were made with the first scenario.

Exclusion criteria:

1 - Patients with under 12 months of AMR, Vision and patient registration dates recorded in THIN as described in the previous chapter.

2 - Patients under 18 years old were excluded since the study intended to investigate adult patients.

3 - In order to capture the full history of resource use and expenditure, patients not registered for the full study period were excluded unless they died during the study year. Inclusion of patients who died during the study year did not cause censoring issue or affect the analysis since the outcome is known and these patients were not able to continue using resources elsewhere in contrast to patients who joined or dropped out during the study year.

5.3.3 Selection of study sample

The case and control cohorts were initially extracted from the eligible population in the THIN database using a 4:1 (4 controls for each case) matching by GP practice, age (+/- 1 year), gender, and Townsend index category. After applying the inclusion and exclusion criteria, the

remaining population were matched again even more closely by including additional matching variables, and using a propensity score matching method.

Propensity score matching is an advanced matching technique providing a means to balance variables across case(treatment) and control groups using the individual's propensity scores (Garrido et al., 2014, Austin, 2009). The propensity score is defined as the probability of receiving treatment conditional on the observed baseline characteristics (Becker and Ichino, 2002, Austin, 2009). The matching method adjusted for any differences in average outcomes for differences in patients' characteristics (confounding variables), and cases and controls were matched using their propensity scores. The balancing hypothesis was that observations with the same propensity score must have the same distribution of observable (and unobservable) characteristics independently of treatment status (Becker and Ichino, 2002). Therefore, for a given propensity score, exposure to back pain is random and case and control groups should be on average observationally identical.

The propensity score matching in this study was implemented using diagnosis of back pain as a treatment and number of consultations at exit date as outcome variable. Cases and controls were matched on the following variables: age, gender, GP practice (practice ID), deprivation index (Townsend categories), BMI categories, smoking status, and Charlson comorbidity index (CCI) categories. The quality of matching for both cohorts was checked with density plots using their propensity scores before and after matching. Further inspection was conducted to assess balance between matched samples using the percentage bias and variance ratio for each of the seven matching characteristics.

5.3.4 Extraction of healthcare resource use and other data

The following components of healthcare resource utilisation data were extracted for all patients in the study:

Prescription drugs: The identification of prescription drugs and development of drugs list was explained in chapter 4. Information on all identified pain medications and additional drugs that may be prescribed along with the analgesics were extracted from the therapy file of THIN database using their drug codes. The data included date of prescription, quantity prescribed, formulation and dosage, and prescription type (acute or repeat prescription).

Consultations: Consultation is in this study was defined as direct contact with healthcare professionals. Three major groups of consultations (Appendix 5.1) were constructed from the consultation types extracted from the consult file in THIN. These were surgery consultations, home visits, and telephone consultations. The healthcare professionals who conducted the consultations were obtained from the staff file in THIN, and two staff groups (GP and nurse) were created (Appendix 5.2). Each consultation was then attached to a staff group for assessing resource use and costs associated with it. Other data extracted included consultation date and duration of consultation.

Data were also extracted from the THIN database on several patient and disease characteristics including:

Socio-demographic: Country, year of birth, gender, ethnicity, Townsend index, and smoking status.

Health service related: Practice ID, practice-patient ID (unique identifier), registration date, transfer date, death date and exit date.

Medical history: Exposure (back pain clinical codes), date of diagnosis (recording of clinical codes), BMI, and comorbid conditions.

5.3.5 Assigning costs to healthcare resource utilisation

Healthcare resource use and costs for each cost component and the total for each patient were calculated for the calendar years 2011, 2013, and 2015. All costs were valued in £ Sterling using unit costs for the respective years. The costs of prescription drugs were obtained primarily from NHS Electronic Drug Tariff (NHS, 2011-15a). BNF and Prescription Cost Analysis (NHS, 2011-15b) were additionally used when drug prices could not be found from the Drug Tariff. If unit cost was not available in any of the three sources, a group cost by BNF sub-paragraph was obtained from Prescription Cost Analysis to approximate the individual drug's cost. For example, for a drug belonging to opioid analgesics (BNF sub-paragraph 4.7.2.0), the net ingredient cost (NIC) for this group of drugs was used which reflected the average unit cost of drugs in this group. This approximation method has been used in previous study estimating healthcare cost (Vaz et al., 2018). Each prescribed drug in the patient's record was matched to the unit costs using drug name and formulation. Multiple drug codes representing a single prescription drug were assigned the same unit cost. The unit costs of prescription drugs used in this study are shown in Appendix 5.3. The estimated total costs of drugs for each patient reflected the quantities specified in the prescriptions.

Unit cost per visit for each type of consultation for the relevant year (Appendix 5.4) was derived from the Unit Costs of Health and Social Care (PSSRU, 2011-15). The unit cost of each consultation was based on a combination of consultation type and the primary staff role that conducted the consultation and/or entered the record in the patient's file. The same cost

was assumed for the different staff roles grouped as GP, and similar assumption was made for the practice nurse.

5.3.6 Analysis and costing

Descriptive statistical methods were used to evaluate the different variables as appropriate for both groups (numbers and percentages for categorical variables, means with standard deviations for continuous variables). Overall differences in cost between the case and control groups (incremental cost) due to consultations, prescriptions, and total cost were tested using the Wilcoxon signed-rank test. This non-parametric test was used due to the skewed nature of the cost data, and the test assessed whether the distributions of costs between the matched groups were systematically different from one another (Doshi et al., 2006, Metfessel and Greene, 2012). Mean healthcare costs were estimated in sub-groups of back pain patients stratified by gender, age-groups, deprivation quintiles and CCI categories. Variations in mean costs within the groups were tested using t-test (for groups of two) and ANOVA (for more than two groups) on bootstrapped samples of the same size as the original data obtained through repeated sampling (5000 replications). Bootstrap simulation is effective for comparison of the arithmetic means without making distributional assumptions, and this method has been widely used for analysis of cost data (Barber and Thompson, 2000, Doshi et al., 2006, Walters and Campbell, 2004). A summary of the statistical tests and diagnostic checks used in this chapter is described in Table 5.2.

Table 5.2: Description of the statistical tests and diagnostics undertaken

Type of test /Diagnostics	Description and usage	Assumptions
T-test	A t-test is used to compare the means of two independent groups (eg. Cost difference in bootstrapped samples by gender)	Residuals should be normally distributed
ANOVA (One-way)	It is used to detect the difference in means of three or more independent groups.	Residuals should be normally distributed
Wilcoxon signed-rank Test	A non-parametric equivalent to the paired t-test. It is used with the raw data rather than the bootstrapped samples.	No distributional assumptions
Standardised % bias	It is a measure used to assess the balance of the covariate distributions between the case and control groups. The % bias is desired to be closer to zero.	N/A
Variance ratio	Is another measure for covariate balance between case and control groups during matching. A score of 1 or closer in matched sample indicates a good matching.	N/A

A bottom-up costing method was applied by identifying and enumerating healthcare resources used and assigning a unit to each component. The annual cost of the individual healthcare resource for each patient was estimated as a product of the quantities of the resource per year and the attached unit costs. The total cost of all healthcare resource utilisation for each patient

was then aggregated to make up the total direct cost of healthcare resource use for the sample. The annual incremental costs associated with the treatment of back pain were then calculated as the difference between the total direct costs for the cases and the controls. Trends over time were assessed using the incremental and all-cause total direct costs for 2011, 2013 and 2015. The mean incremental cost for a back-pain patient in 2015 was derived as the most recent estimate, and this was used to extrapolate the cost of consultations and prescriptions to the UK population using national prevalence estimates. The prevalence of back pain was also calculated from the THIN database for comparison with prevalence estimates in the published literature. The mid-year point prevalence of back pain for 2015 was calculated from a cross-sectional data extracted for 01 July 2015. This was the full extract of THIN data which included all patients registered at that time point. The point prevalence was then obtained by dividing the number of patients with the identified Read codes by the total population size extracted. Similarly, prevalence estimates stratified by gender and age-groups were also calculated (Appendix 5.5).

5.4 Results

5.4.1 Study population

A flow chart showing the study selection process for the 2015 study is shown in Figure 5.1. The initial eligible population for this study included 914,461 cases and 1,862,230 controls matched on a 4:1 basis. Of these, 674,043 cases (74%) and 1,402,197 controls (75%) were continuously registered for the full study year in 2015. Successive application of the inclusion and exclusion criteria left a final number of 133,341 cases that were then matched 1:1 with controls using propensity score matching. The study selection process in the 2011 and 2013 studies are shown in Appendix 5.6 and Appendix 5.7 respectively.

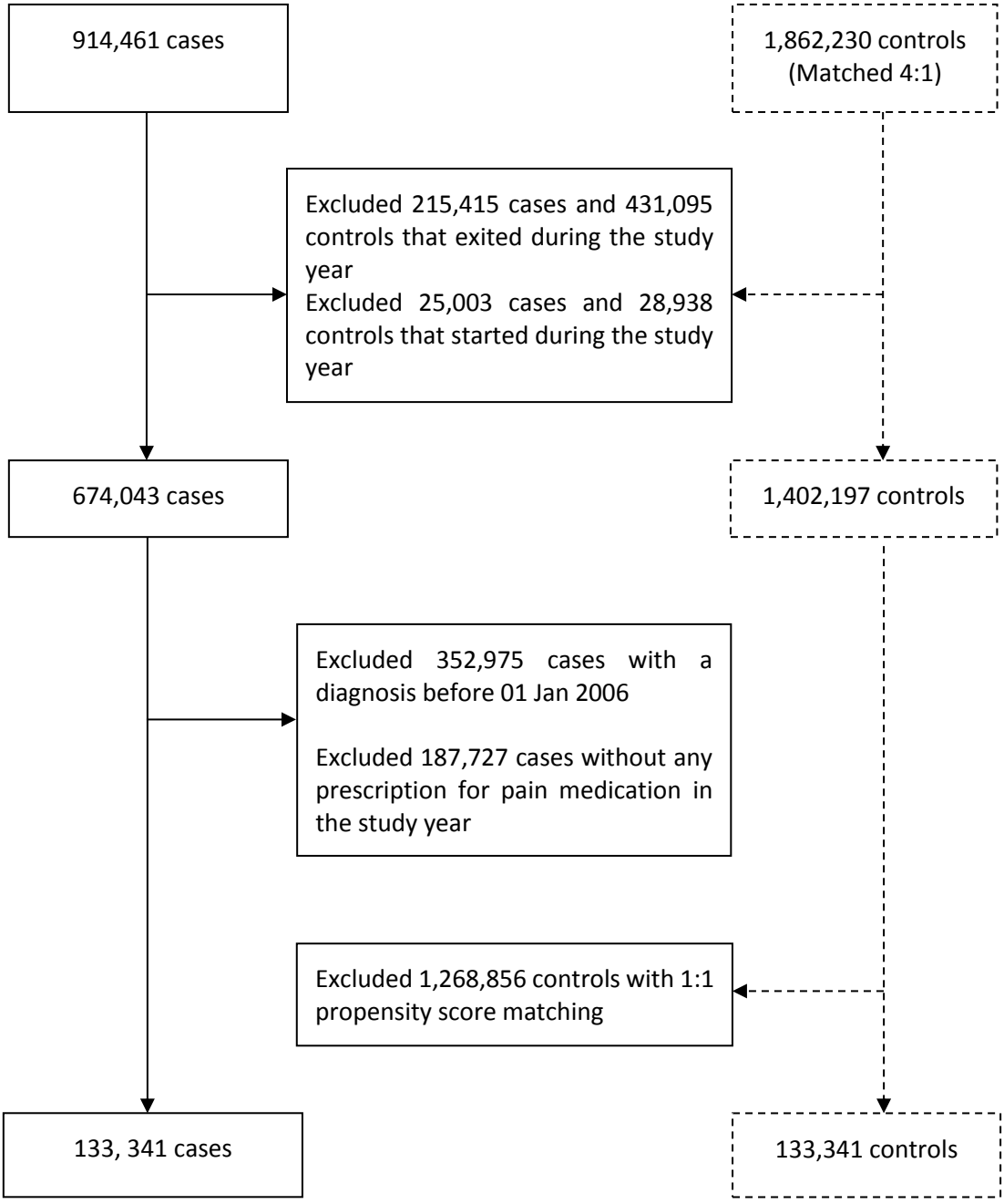


Figure 5.1: Selection of the study population in the 2015 study

The propensity scores matching method used a regression model to estimate the average treatment effect of back pain (treatment) on total number consultations on exit date (outcome) based on seven potential confounding variables or covariates in the dataset. These were GP practice, gender, age, Townend quintiles, BMI category, CCI category and smoking status. In estimating the treatments effects, the given characteristics of each patient were summarised into a single index variable (the propensity score), and case and control groups with similar propensity scores were matched and selected for the study.

To check the quality of matching between the case and control groups graphically, density estimate graphs were used by plotting their propensity scores before and after matching (Figure 5.2). When the two groups are perfectly matched, the density estimate line for the

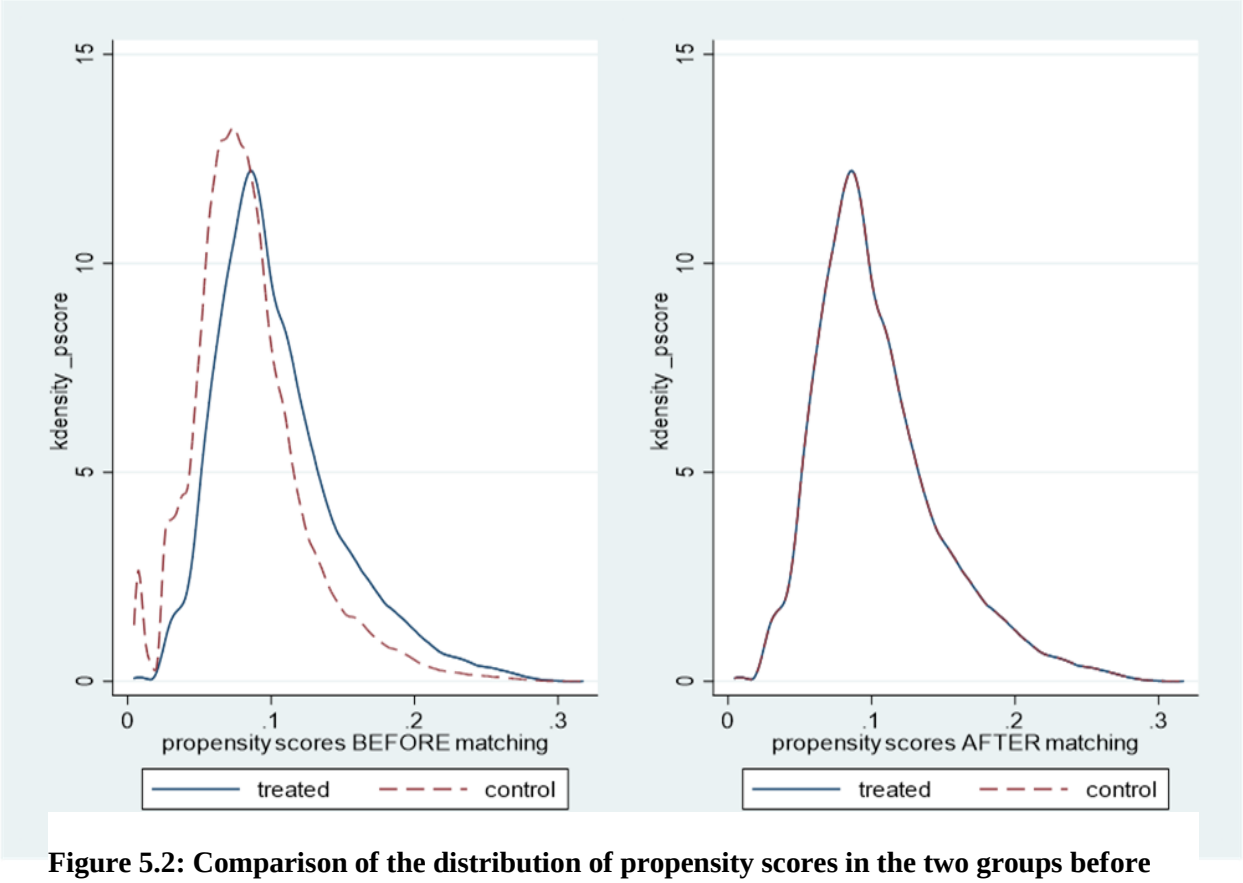
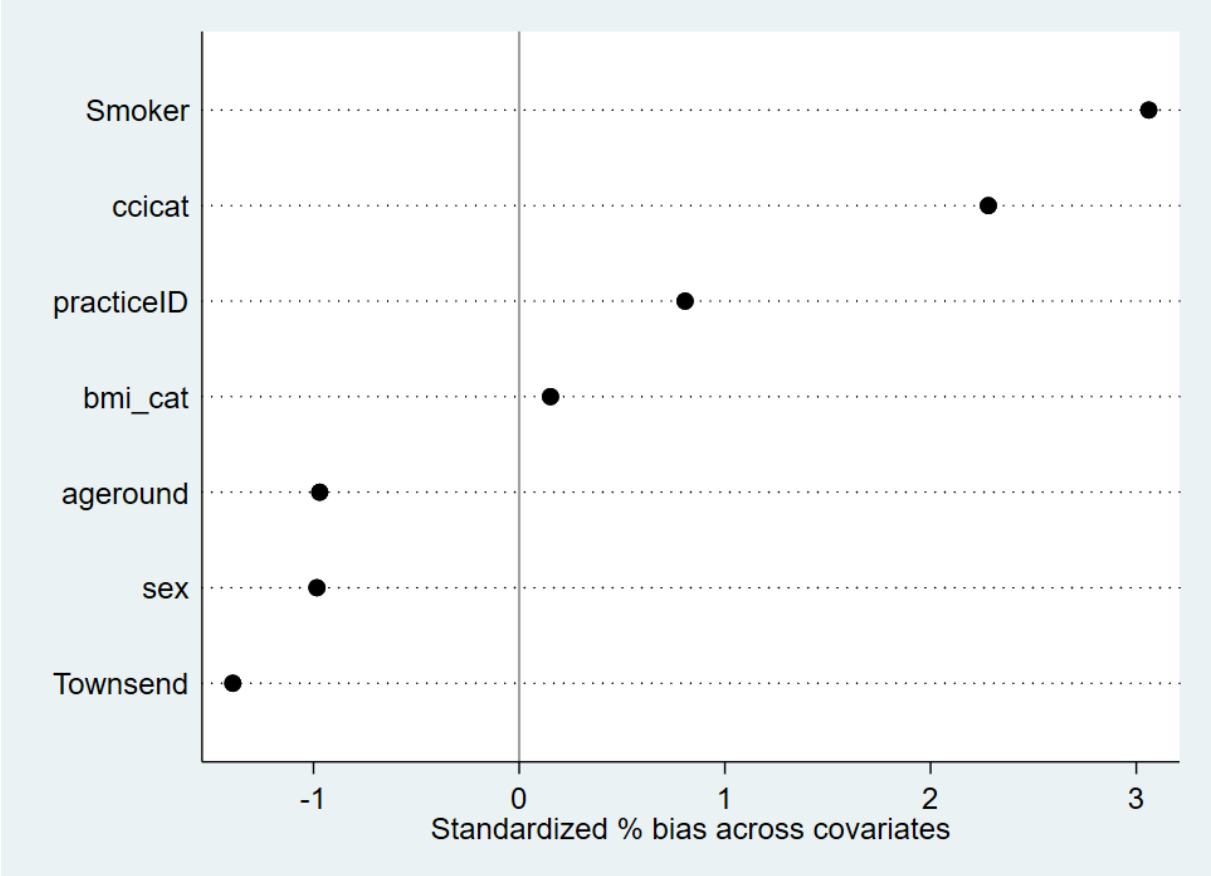


Figure 5.2: Comparison of the distribution of propensity scores in the two groups before and after matching

cases (solid line) should coincide with the density estimate line for the controls (broken lines). Although the two groups were initially matched (4:1) upon extraction, some imbalance was visible between the groups before they were re-matched (Figure 5.2). After the propensity score matching, almost identical distribution of the scores were observed indicating that the matching was effective in reducing the differences between the case and control groups.

Further checks were conducted to assess balance between matched samples using the percentage bias and variance ratio between the case and control groups for each of the seven characteristics. Inspection of the standardised differences (Figure 5.3) showed that the



The standardised % bias is distributed around zero indicating a good balance of the covariate distributions between the case and controls groups.

Figure 5.3: Standardised differences across covariates in the matched sample

percentage of bias remained well below 5% for all seven characteristics after matching. The standardised % bias is the % difference of the sample means in the case and control groups as a percentage of the square root of the average of the sample variances in the case and control groups (Rosenbaum and Rubin, 1985). The mean bias was 1.4% with a range of -1.4 to 3.1. Similarly, the variance ratio which compared the variance in the cases to that of the controls for each of the characteristics ranged from 0.95 to 1.01, and these were close to one which was desired. Given that many covariates were used, making exact matching more difficult, potential differences between the case and control groups were minimised making the groups as comparable as possible.

The baseline characteristics of the case and control groups in the 2015 study is shown in Table 5.3. The two groups were closely similar in all the characteristics considered including baseline comorbidities. The mean age was 56.5 years (SD 16.9) and 56.7 years (SD 16.8) for the cases and controls respectively. In both the case and control groups, the proportion of females was about 24% higher than the males. Over half of the population in both groups were older adults over the age of 55, and nearly half of the population also presented with at least one co-morbidity.

Table 5.3: Baseline characteristics of the study population in 2015

Variables	Case (n=133,341) n (%)	Control (n=133,341) n (%)
Gender		
Male	50,798 (38.1)	50,162 (37.6)
Female	82,543 (61.9)	83,179 (62.4)
Age (mean, SD)	56.5 (16.9)	56.7 (16.8)
Age group		
18 - 24	3,167 (2.4)	3,210(2.4)
25 - 34	11,633 (8.7)	11,590 (8.7)
35 - 44	19,831 (14.9)	19,151 (14.4)
45 - 54	27,431 (20.6)	26,991 (20.2)
55 - 64	24,958 (18.7)	25,022 (18.8)
65 - 74	23,823 (17.9)	25,280 (18.9)
75 & overs	22,498 (16.9)	22,097 (16.6)
Townsend quintiles		
Least deprived 1	22,233 (16.7)	26,046 (19.5)
2	23,244 (17.4)	26,341 (19.7)
3	25,543 (19.2)	25,275 (19)
4	24,503 (18.4)	21,528 (16.2)
Most deprived 5	20,180 (15.1)	15,607 (11.7)
Missing	17,638 (13.2)	18,544 (13.9)
BMI category		
< 25	35,949 (27)	43,798 (32.9)
25 - 30	44,901 (33.7)	44,187 (33.1)
> 30	43,655 (32.7)	36,395 (27.3)
Missing or implausible	8,836 (6.6)	8,961 (6.7)
CCI category		
0	71,853 (53.9)	75,961 (56.9)
1	33,076 (24.8)	28,479 (21.4)
2	16,163 (12.1)	16,648 (12.5)
3	7,253 (5.4)	7,156 (5.4)
4	2,905 (2.2)	2,969 (2.2)
5 and above	2,091 (1.6)	2,128 (1.6)

5.4.2 Healthcare resource use and associated costs

The healthcare resource use (HRU) and the costs associated with consultations and prescriptions in 2015 is shown in Table 5.4. This was the main analysis where cases were defined by presence of a Read code for back pain, and at least one prescription drug for pain during the study year. However, since controls may or may not have received pain medication prescriptions for other conditions, it was possible that this may have resulted in the control population being healthier than the cases in general terms. Therefore, a second scenario was considered where controls were also required to have prescription drugs for pain during the study year. The estimated HRU and costs from the second scenario (Table 5.5) were compared with that of the first scenario in order to assess the underlying assumptions in the control group selection.

Scenario 1: No requirement for controls to have prescription for pain medications:

The recorded counts of consultations and/or rates of consultations in the back-pain group were nearly double that of the control group in both the main analysis and sensitivity analysis. The annual incremental costs of consultations associated with back pain were £25.3 million in 2015, with the cost per patient amounting to £189.7. In the sensitivity analysis, the incremental cost per patient was slightly higher at £223.45 compared to the main analysis. Counts of prescriptions and/or rates of prescriptions showed a three-fold increase in the back-pain group compared to the control group. The annual incremental costs of prescriptions associated with back pain were £7.2 million or £54.4 per patient. The incremental cost per patient in the sensitivity analysis was £57 which was consistent with the findings of the main study.

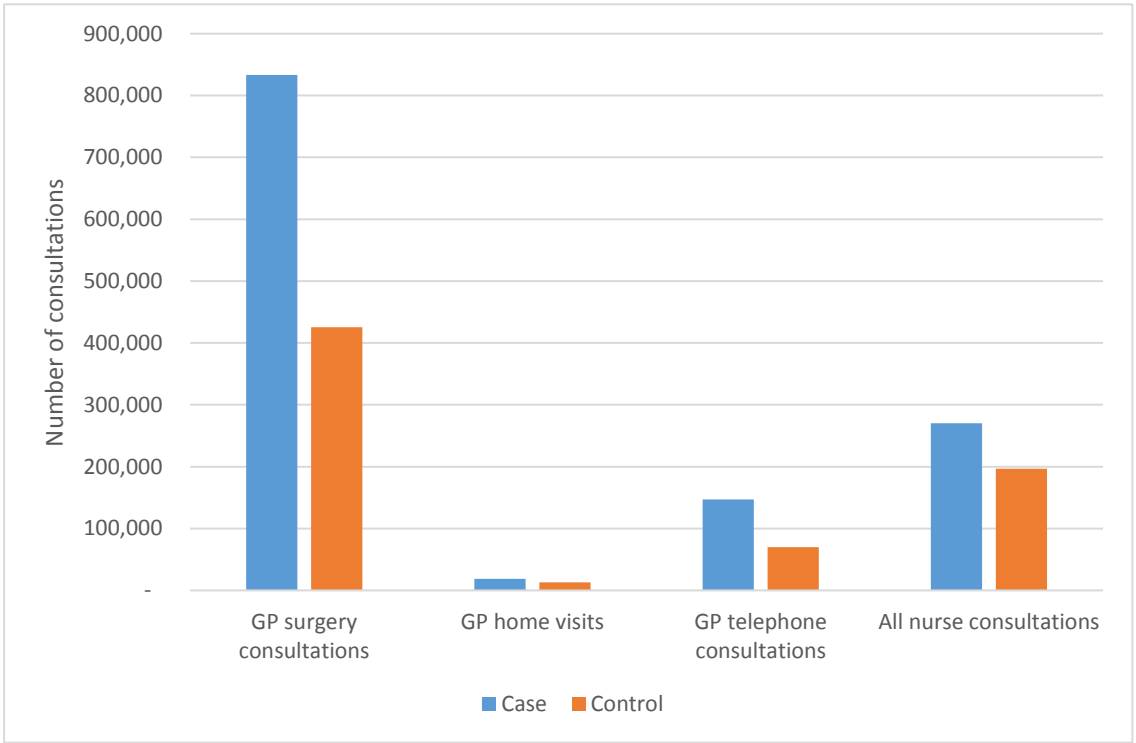
Table 5.4: Estimates of annual healthcare resource use and costs associated with back pain in 2015 (scenario 1)

	Main analysis		Sensitivity analysis*	
Cost component	**Back pain** (n=133,341)	**No back pain** (n=133,341)	**Back pain** (n=24,607)	**No back pain** (n=24,607)
Consultations				
Count	1,269,228	705,234	244,069	124,011
Rate	9.52	5.29	9.92	5.04
Total costs	£52,700,000	£27,400,000	£10,300,000	£4,801,599
Per patient	£395.23	£205.49	£418.58	£195.13
Prescriptions				
Count	1,601,863	550,969	282,742	89,942
Rate	12.01	4.13	11.49	3.66
Total costs	£10,300,000	£3,051,975	£1,654,807	£498,190
Per patient	£77.25	£22.89	£67.25	£20.25
Sum				
Total costs	£63,000,000	£30,451,975	£11,954,807	£5,299,789
Per patient	£472.47	£228.38	£485.83	£215.38

** The sensitivity analysis was conducted by including only patients with most recent (2 years) back pain diagnoses and their matched controls*

The total incremental costs of back pain reported in this study amounted to about £32.5 million, with the per-patient cost being £244 per year. The sensitivity analysis also corroborated this with a reported incremental cost of about £270 per patient per year. Around 78% of the total cost difference between the case and control groups in the main study was attributed to consultations, and the remaining 22% to prescriptions. The equivalent figures to Table 5.4 for the 2011 and 2013 studies are shown in Appendix 5.8 and Appendix 5.9 respectively.

This study also assessed details of healthcare resource utilisation in the case and control groups in 2015. Descriptive details of resource utilisation by consultation types and drug groups is shown in Figure 5.4 and Figure 5.5 respectively. Surgery consultations with a GP make up the largest proportion of consultations in primary care for both patients with back pain and those without (65.7% and 60.3% respectively). The largest difference in consultations between the cases and controls was also in the GP surgery consultation category where the cases showed twice the number of consultations compared to the controls. Home visits by GPs had the least attribution to the total consultations with 1.5% and 1.9% of the share for the case and control groups respectively.



GP indicates general practitioner

Figure 5.4: Attribution of resource use to the total consultations in patients with and without back pain.

In terms of prescription drugs resource use in primary care, the largest attribution came from the category of 'other drugs' which included anxiolytics/hypnotics, laxatives, corticosteroids and proton pump inhibitors. These were additional drugs prescribed for anxiety/depression or to counteract the side effects of pain killers. The attribution of the main drug groups to the incremental resource use associated with back pain was 29.5%, 27.2%, and 21.7% for the other drugs, strong analgesics, and the basic/weak analgesics groups respectively.

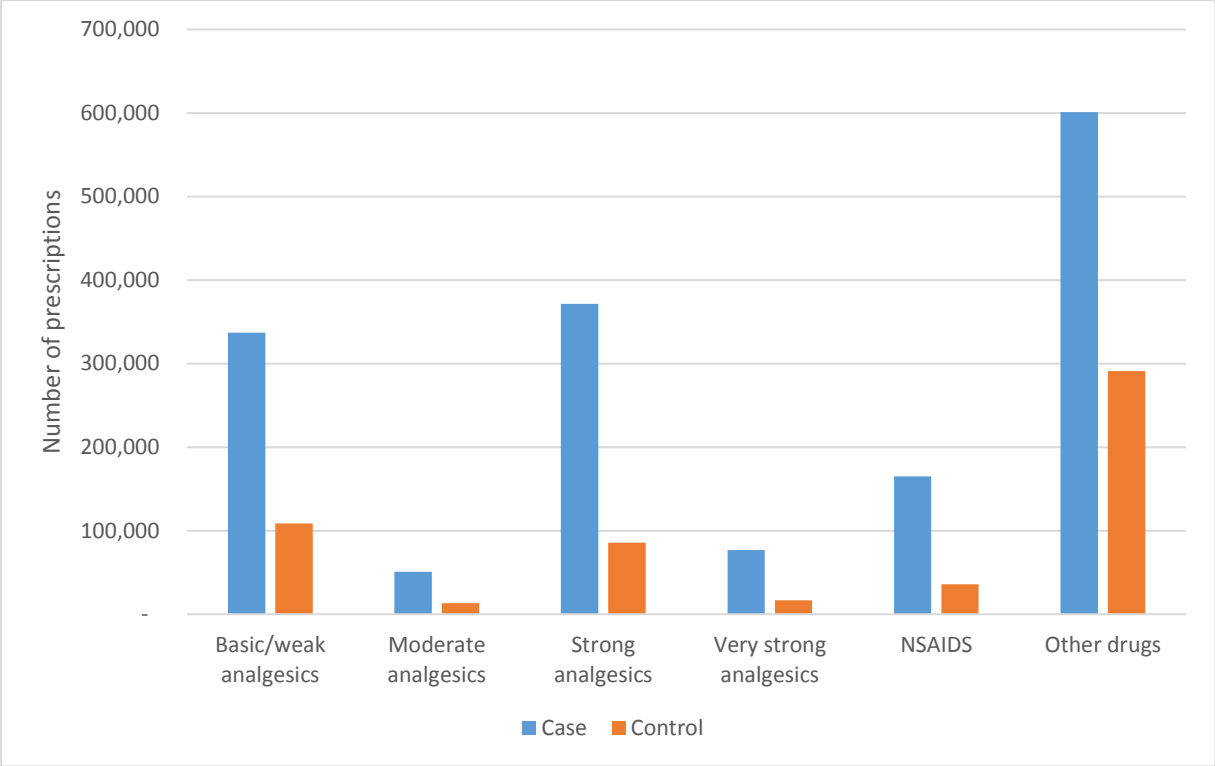


Figure 5.5: Breakdown of the total prescription counts by drug groups.

The total incremental cost from the 2015 study was extrapolated to a national level based on the prevalence estimate for back pain calculated from the 2015 eligible population in the THIN database. Detailed data on the overall point prevalence (25.7%) and the prevalence stratified by gender and age-groups are described in Appendix 5.5. The prevalence of back

pain obtained from THIN was within the range of prevalence estimates reported in the literature (Chapter 2) and is comparable to the general population. The mid-year UK population estimates were obtained from the Office for National Statistics (ONS). The figure for the adult population (18 years or above) in 2015 was 51.3 million (ONS, 2016). Applying the prevalence estimate to this adult population yields an estimated 13.2 million people affected by back pain in 2015. This generated an incremental cost associated with back pain costing the healthcare system an estimated £3.2 billion (£244*13.2 million) in 2015.

Scenario 2: Controls required to have prescription for pain medication:

The estimation of the HRU and costs reported in Table 5.5 was conducted in an identical manner to the results reported in scenario 1 (Table 5.4). The only difference here was that the controls selected had at least one prescription for pain medication during the study year in line with the cases. The results showed that difference in resource use and costs between the back-pain group and those without back pain had reduced considerably in comparison to the first scenario. The incremental costs per patient were now £65.3, £15.1 and £80.4 for consultations, prescriptions and total costs respectively. However, these observed cost differences were still statistically significant for all three categories (Wilcoxon sign-rank test $p < 0.0001$). The extrapolated incremental cost of back pain nationally was estimated at £1.1 billion (£80.4*13.2 million) in 2015.

Table 5.5: Estimates of annual healthcare resource use and costs associated with back pain in 2015 (scenario 2)

	Main analysis		Sensitivity analysis*	
Cost component	**Back pain** (n=133,341)	**No back pain** (n=133,341)	**Back pain** (n=24,607)	**No back pain** (n=24,607)
Consultations				
Count	1,269,228	1,085,206	244,069	201,548
Rate	9.52	8.14	9.92	8.19
Total costs	£52,700,000	£44,000,000	£10,300,000	£8,170,876
Per patient	£395.23	£329.98	£418.58	£332.05
Prescriptions				
Count	1,601,863	1,327,984	282,742	242,394
Rate	12.01	9.96	11.49	9.85
Total costs	£10,300,000	£8,292,034	£1,654,807	£1,450,413
Per patient	£77.25	£62.19	£67.25	£58.94
Sum				
Total costs	£63,000,000	£52,292,034	£11,954,807	£9,621,289
Per patient	£472.47	£392.17	£485.83	£391.00

** The sensitivity analysis was conducted by including only patients with most recent (2 years) back pain diagnoses and their matched controls*

5.4.3 Variation of costs by subgroups of population

Variation of all-cause mean healthcare costs by sociodemographic factors in patients with back pain is shown in Table 5.6. Except for nurse consultations, the mean healthcare costs per patient was higher for females than males. The mean healthcare costs increased by age groups across all cost components. The exception to this was the second age group (25-34 years) who had higher mean costs than the third age group (35 - 44 years) for GP consultations, nurse consultations and total cost components. The mean healthcare costs per patient also varied by

Table 5.6: Mean healthcare costs (£s 2015) in sub-groups of back pain patients

	Consultations mean(SD)		Prescriptions mean(SD)		Total cost	
Characteristics	GP	Nurse	Analgesics	Other drugs	mean (SD)	p-value*
Gender						
Male	338.6(306.7)	51.3(71.5)	60.7(215)	24.3(60.6)	421.5(424.4)	< 0.001
Female	408.1(348.8)	50.1(64.4)	64.9(213.4)	26.4(81.3)	503.4(464.7)	
Age-group						
18 - 24	362(348.2)	46.5(79.4)	20.1(53.3)	9.8(41.5)	397.6(385.5)	<0.001
25 - 34	366.3(325.1)	41.3(44.2)	41.8(208.9)	14.4(62.4)	421.3(438.1)	
35 - 44	347(310.7)	40.9(48.1)	57.2(250.6)	18.9(130.3)	418.2(469.6)	
45 - 54	349.1(303.9)	43.5(53.2)	66.4(253.7)	21.1(55.6)	433.4(445.7)	
55 - 64	358.2(308.5)	48(62.6)	71.6(230.7)	25.1(61.3)	454.5(435.1)	
65 - 74	389.3(335.1)	54.6(72.4)	65.7(165.1)	28(58.3)	491.4(421.5)	
75 & overs	481.1(398.2)	64.6(86)	70.6(160.5)	37.8(71.1)	603.2(478.7)	
Townsend quintiles						
Least deprived 1	367.3(318.2)	48.9(66.4)	54.4(206.2)	22.5(47.8)	448(425)	<0.001
2	374.7(325.6)	51.2(69.7)	56.2(182.7)	23.5(57.7)	456.6(422.2)	
3	379.6(337.5)	52.9(72)	62.4(185)	24.8(58.1)	468.4(436.7)	
4	391.7(344.5)	52.5(69.7)	71.7(285.1)	26.8(61.6)	492.9(499)	
Most deprived 5	404.4(351.5)	50.6(63.6)	73.6(208.9)	31.5(133.7)	510.9(484.5)	
Missing	373.2(331.4)	44.7(52.5)	61.9(189.2)	25.3(60.9)	455.7(429.5)	
CCI category						
0	329.3(287.3)	40.2(51.3)	50.6(183.6)	19.1(47.3)	392.4(378.7)	<0.001
1	409.2(350.4)	52.3(65)	70.5(222.3)	27.6(68.1)	514.9(465.8)	
2	442.4(366.6)	61(80)	81.1(264.4)	32.1(69.4)	569.7(504.3)	
3	494.3(396.2)	67.2(83.5)	88.8(234.7)	38(75)	645.1(518.8)	
4	562.6(442.3)	79.1(100.3)	101.1(301.3)	48.9(269.2)	744.4(704.2)	
5 and above	611.8(485.4)	84(113)	109.2(329)	42.5(79.2)	806.4(643.6)	

* *Bootstrap t-test and anova on total cost*

Townsend deprivation quintiles across all cost components, however, the variations did not show any patterns. Variation of the mean costs by CCI categories showed clear patterns with costs increasing with comorbidities across all cost components with no exception. T-test and ANOVA tests on bootstrapped samples showed significant evidence of variation of the mean total healthcare costs per patient by sociodemographic factors.

5.4.4 Trends in healthcare costs in recent years

Trends in healthcare costs in primary care over a five-year period were assessed in the study population and presented by type of resource utilization (Figure 5.6 and Figure 5.7). Fluctuations in costs were observed in both the incremental costs (Figure 5.6) and the all-

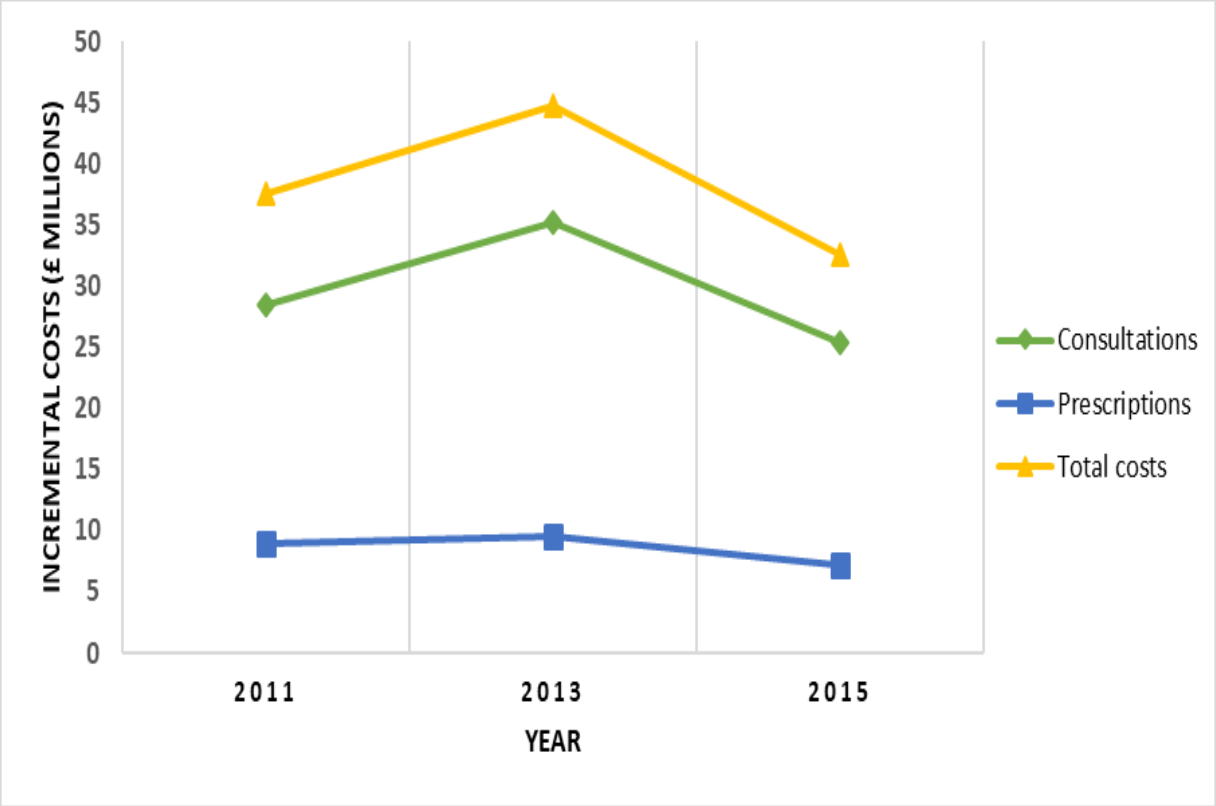


Figure 5.6: Trends in incremental healthcare costs associated with back pain

cause total healthcare costs (Figure 5.7) associated with back pain patients. A 24% increase in annual incremental costs of consultations were observed between 2011 and 2013, followed by a 28% decline between 2013 and 2015. However, the increase in the incremental costs of prescriptions for the same period was only about 6%, followed by a 24% decline in the second period. Closely similar patterns were observed for all-cause healthcare costs (Figure 5.7) of patients with back pain. The figure shows that there was a slight peak in 2013 for both consultation and prescription costs followed by a decline to about the 2011 level. In both the incremental and all-cause healthcare cost scenarios, the total costs were largely influenced by consultation costs.

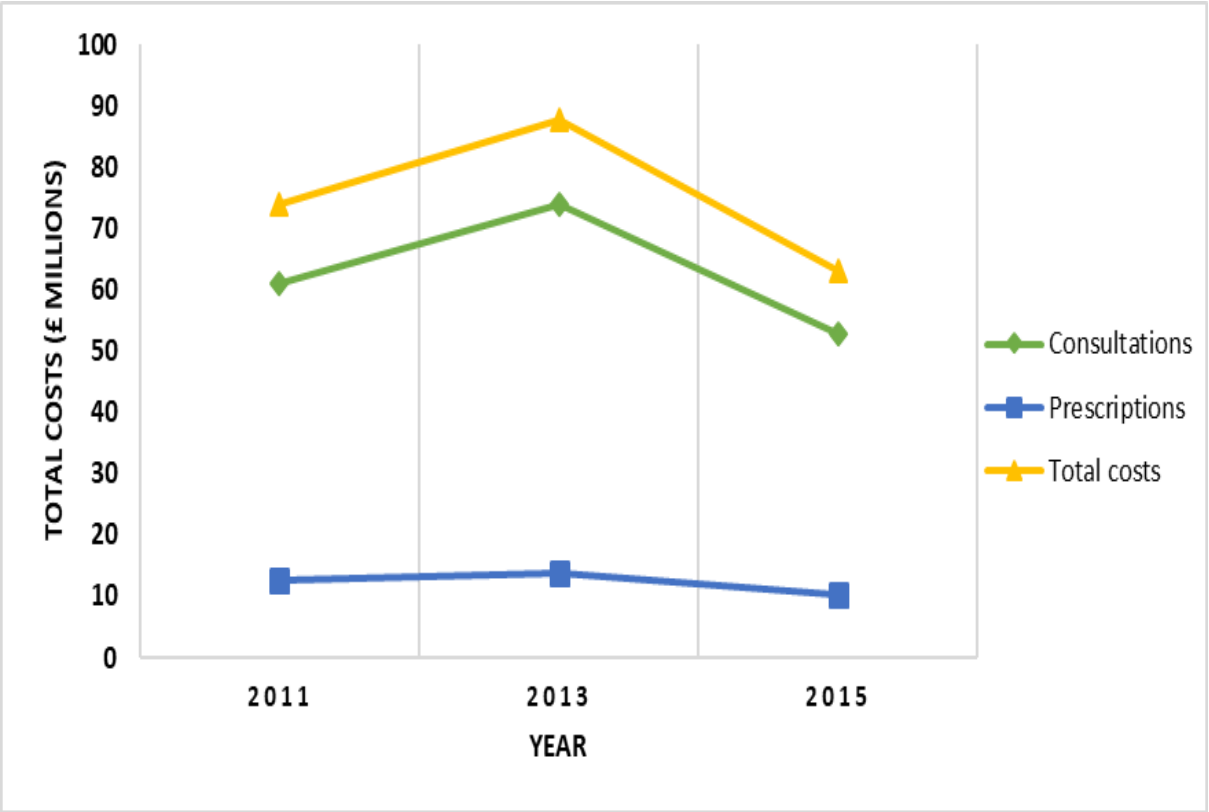


Figure 5.7: Trends in all-cause healthcare costs of patients with back pain

In order to separate out the effects of changes in unit costs over time, trends in actual healthcare resource utilisation were also assessed. The five-year trends by type of resource use for the incremental volume (counts) of resources associated with back pain and the all-cause volume of resources for patients with back pain are shown in Figure 5.8 and 5.9 respectively. These paint a slightly different picture to the trends in costs shown earlier (Figure 5.6 and 5.7). There was no longer a peak in 2013, but instead a slight decline in incremental resource use from 2011 to 2013 (4.1% for consultations and 0.3% for prescriptions) followed by a considerable decline from 2013 to 2015 (26.3% for consultations and 21.3 for prescriptions).

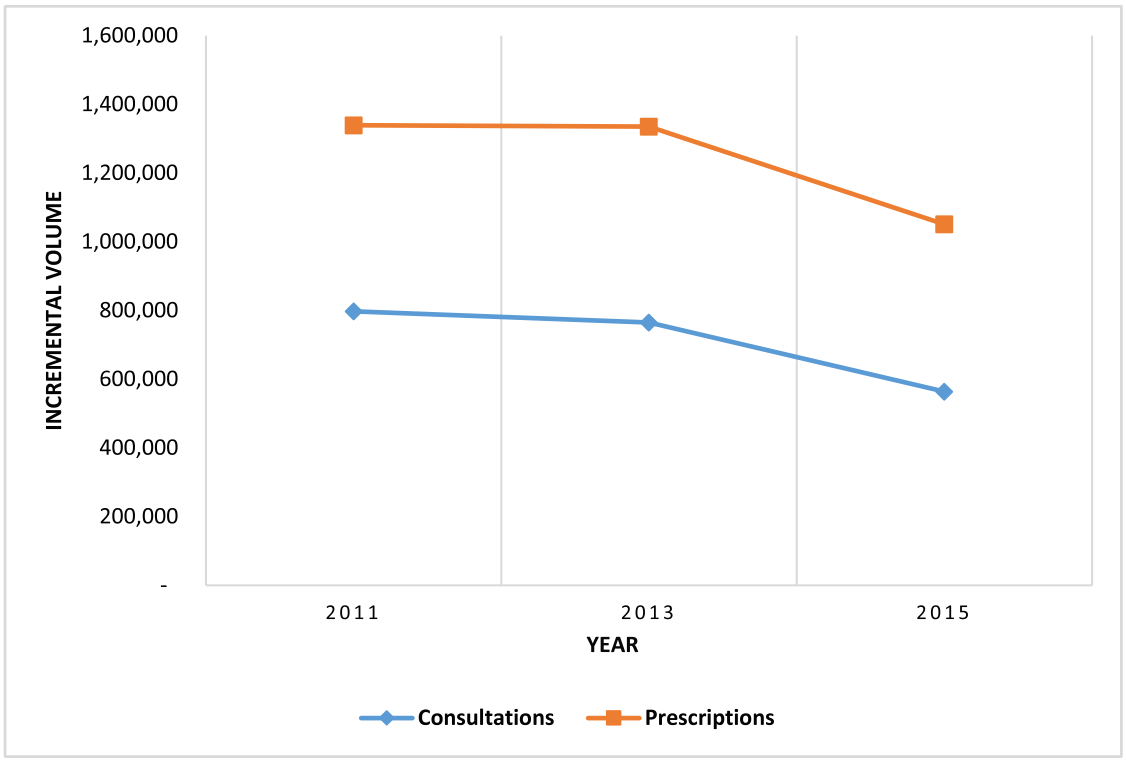


Figure 5.8: Trends in incremental healthcare resource use associated with back pain

Similar trends were observed for the all-cause healthcare resource utilisation of patients with back pain. Figure 5.9 shows that there was a slight decline in resource use from 2011 to 2013 (5.5% for consultations and 0.9% for prescriptions). The was followed by a considerable decline in resource use from 2013 to 2015 (26.8% for consultations and 21.2% for prescriptions). The analyses showed the importance of separating out the effects of changes in unit costs of resource utilisation when presenting trends in healthcare costs of an illness.

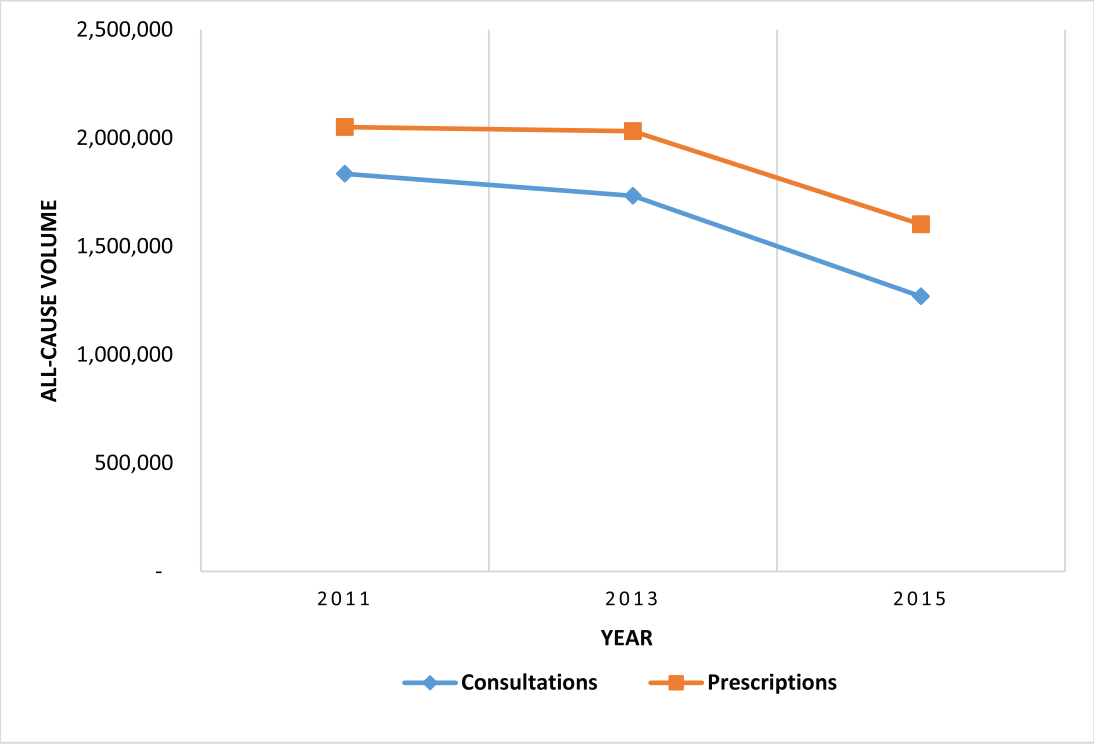


Figure 5.9: Trends in all-cause healthcare resource use of patients with back pain

Comparisons were also made with estimates from the previous two studies (Table 5.7) to provide an indication of how the individual level costs and rates of healthcare resource use changed over the last 20 years. The current estimates (2011-15) showed only small changes in average costs per patient and rates of resource utilisation. Compared to the earliest estimates

(1998), however, there were significant increase in both average costs (5 to 7-fold increase for consultation and 2.5 to 3-fold increase for prescriptions) and rates of utilisation (around 2.5 and 7-fold increase in consultation and prescription rates respectively). The 2009 estimates are, not surprisingly, the highest since they represent patients with chronic low back pain.

Table 5.7: Comparison of costs and rates of resource use with previous studies

	Cost per patient per year				
	2011	**2013**	**2015**	**2009***	**1998****
Consultation	£147.88	£196.36	£189.74	£328	£28.10
Prescription	£46.68	£52.99	£54.36	£105	£18.74
	Consultation & prescription rates				
Consultation	4.14	4.27	4.23	10.2	1.72
Prescription	6.95	7.45	7.88	14.7	1.06

* Hong et al 2013, incremental costs of CLBP estimated

** Maniadakis & Gray 2000, non-incremental costs (direct method) of back pain

5.5 Discussion

5.5.1 Principal findings

The aim of this chapter was to estimate healthcare resource use and costs of back pain in UK primary care and also to investigate trends and variations in these estimates. The analyses utilised data from a large routinely collected EHR to report annual resource utilisation and costs of prescriptions and consultations associated with back pain. The estimates are based on a case-control study design where the two groups were matched on a range of commonly

reported baseline characteristics. The study considered two different scenarios for selection of controls. In the main analysis, patients in the control group were not required to have prescription drugs for pain to be included in the study, whereas in the second scenario, this restriction was applied to the controls in line with the cases. HRU and costs of patients with back pain were nevertheless significantly higher than those without back pain in both cases.

The results also provided evidence that the reported healthcare costs of back pain varied greatly depending on the underlying assumptions taken in a case-control design as presented earlier in scenario 1 and scenario 2. The main findings (scenario 1) estimated the annual incremental costs of back pain due to consultations and prescriptions to be £32.5 million for the sample which equated to an average cost per patient of £244. The cost to the healthcare system amounted to £3.2 billion in 2015. The mean total healthcare costs per patient varied significantly by gender, age-group, Townsend quintiles and CCI categories, with female gender, increasing age, higher Townsend index and higher CCI categories all being associated with increasing costs. A five-year trend in healthcare costs revealed that costs of consultations were slightly higher in 2013 compared to 2011 and 2015. However, the full fluctuations in costs for the period 2011-15 could not be captured in the current study as the analyses were based on three years of data.

5.5.2 Strengths and limitations of the study

This retrospective study provided the first estimates of HRU and costs associated with a broad range of back pain diagnoses using one of the largest primary care databases in the UK. A very large sample of patients from a population-based database was included in the study, and the distribution of the sample stratified by age and gender were comparable with the general population obtained from ONS (Appendix 5.10). Hence the findings of this study can be

considered generalisable to the UK population. The case-control design of the study enabled the costs associated with back pain to be isolated using an incremental cost approach rather than presenting all-cause costs of patients with back pain. It was also a strength of the study that the advanced matching technique used was effective in balancing the observed baseline covariates between the case and control groups. However, it is acknowledged that the matching could not balance unobserved characteristics and hence unmeasured confounding could still exist. This study also analysed and presented details of variations of the costs in subgroups of back pain patients. These variations might be a reflection of the heterogeneous nature of back pain in relation to its diagnosis, duration and severity of illness.

This study however had some limitations. First, healthcare resource use in this study comprised of consultations and prescription drugs only as these were the components primarily recorded and could directly be extracted from the consultation file and drugs file respectively of the primary care database. Data on the other cost components were limited in the database, and these were recorded in the form of referrals and other indictors rather than actual completed episodes. Second, cases were identified based on the first recorded diagnosis of back pain during the 10-year study period. Since many back-pain conditions recover within a certain period of time, the diagnostic picture may have been blurred by subsequent diagnoses of other pain conditions. However, the incremental cost approach has isolated the back pain specific costs and the findings remained robust. Another limitation was in the use of Read codes to identify back pain where there might have been considerable miscoding or misclassification and variation among practices and clinicians in the usage of specific codes due to lack of standardisation of diagnostic codes (Reed et al., 2013). However, this study included a high number of Read codes covering a broad range of back pain diagnoses with a large sample size in both comparison groups increasing the validity of the findings.

5.5.3 Interpretation in relation to other studies

This study has some similarities and important differences with other studies estimating the costs associated with back pain. Manniadakis and Gray estimated the costs of consultations and prescriptions in 1998 to be £140.4 million and £93.7 million respectively for the UK (Maniadakis and Gray, 2000). Although this was the first study estimating the costs of back pain in the UK, the estimates were based on survey data and other aggregated sources of data. Using patient level data, our study estimated the incremental costs of consultations and prescriptions in 2015 to be £189.74 million and £54.36 million respectively for the sample which corresponds to £2.5 billion and £718 million respectively on a national level. This was in agreement with Manniadakis and Gray who argued at the time that costs of back pain were expected to rise considerably in the future (Maniadakis and Gray, 2000).

Comparison was also made with estimates from 2009 obtained from a study (Hong et al., 2013) that was similar in relation to the study design to the current study. Hong et al. investigated the costs associated with the treatment of CLBP in the UK using CPRD data. They reported a much higher marginal costs of consultations (£328) and prescriptions (£105) compared to our study (Hong et al., 2013). However, their study compared CLBP patients with patients without CLBP which explained the greater cost difference between the two groups. Moreover, Hong et al. matched the case and control groups on the basis of three variables: year of birth, gender, and practice ID, which may have limited the comparability of the groups. This was in contrast to seven matching characteristics used in the study in this thesis providing better basis for comparison and validity of the findings. However, limitations of the matching with regard to not accounting for unmeasured characteristics and confounders is acknowledged.

Consultations accounted for a greater proportion (78%) of the cost difference between the case and control groups in this study. Similarly, higher proportions of consultation costs compared to prescription costs were reported in other COI studies of back or spine conditions adopting the incremental costs approach (Martin et al., 2008, Hong et al., 2013). On the other hand, a US study by Gore et al. found that consultations and prescriptions contributed almost equally to the marginal cost of CLBP (Gore et al., 2012), hence there was no consistency due to methodological differences among the studies. For example, Martin et al. had combined consultations and other ambulatory services into a single outpatient service category making direct comparison of the findings problematic.

Analysis of trends in healthcare costs of back pain for the period 2011-2015 in this study showed a slight peak in 2013 for consultation costs. This was consistent with the findings of the most recent data from the Personal Social Services Research Unit (PSSRU) which reports data on the unit costs of health and social care annually (Curtis and Burns, 2018). Their findings on how GP prescription costs have changed in England over a 10-year period between 2007 and 2017 showed that the average number of prescriptions per GP consultation increased gradually since 2007 reaching a peak in 2013 and gradually declining until 2017 (Curtis and Burns, 2018). It is plausible that the rise and fall of the number of prescriptions per consultation is reflected in the consultation rates for patients with back pain. The changes in prescription costs during 2011-2015 on the other hand were marginal in the current study and this was also consistent with the reports of PSSRU. The data reported by Curtis and Burns (2018) showed that prescription costs per GP consultation only showed a slight decline from 2011 to 2015, and these changes were mainly attributable to a small decline in the unit cost (net ingredient cost) of prescriptions (Curtis and Burns, 2018). This finding was also supported by a 2018 report by The King's Fund which analysed prescribing costs by care

setting (Ewbank et al., 2018). The report found that the cost of primary care prescribing only showed a 0.6% change per year on average between 2010/11 and 2016/17 while the cost of hospital prescribing represented an average growth of 12.1% per year (Ewbank et al., 2018).

5.6 Conclusion

The findings of this study confirm the substantial direct medical costs associated with back pain to the NHS. A comprehensive list of Read clinical codes back pain was created and utilised for the study. The list can be added to the online clinical codes repository (www.clinicalcodes.org) and be used to extract back pain related data from databases that are based on the Read medical codes such as THIN and CPRD databases. Two comprehensive lists of prescription drugs were also created that can be used for prescription drugs analysis in relation to back pain. The first, based on previous work at Keele University, was a pain relief/analgesics drug list categorised by drug strength. The second was a list of additional drugs that are usually prescribed along with some analgesics.

The use of routinely collected health data allows identification of resource utilisation types and enables more accurate analysis of expenditure. However, the limited record in primary care databases of resource utilisations outside of consultations and prescriptions may affect ability to directly estimate the full medical costs of an illness. It is also important to identify through econometric methods, the factors contributing to higher health expenditure in order to better understand the economic burden of back pain. The next chapter presents an exploration of the main regression-based models used for analysing healthcare cost data.

CHAPTER 6. ECONOMETRIC METHODS FOR ANALYSING HEALTHCARE COSTS

6.1 Introduction

The previous chapter estimated healthcare costs of back pain in the UK primary care setting using patient level consultations and prescriptions data from the THIN database. It also presented variations in cost by patient characteristics and trends over time. It was shown that the mean total healthcare costs in 2015 varied by gender, age-groups, deprivation quintiles and comorbidity categories. However, the importance of these characteristics as predictors of cost may not be known without explicitly investigating the association between these factors and the reported healthcare costs using regression based statistical or econometric methods. Before running regression models to analyse the healthcare cost data, it was considered necessary to review the commonly used econometric methods comparing the advantages and disadvantages of each method. The aim of this chapter was to assess alternative econometric methods in an attempt to identify the models which are most appropriate to represent the characteristics and features of the healthcare costs data for back pain.

The distribution of healthcare costs at patient level is generally characterised by a long positive skew with a high proportion of the data concentrated near zero reflecting little or no resource use. This violates the classical normal or "bell-shaped" distribution assumption associated with some of the modelling techniques. The estimated population mean cost which is generally the parameter of interest in economic studies will be drawn to the tail with a non-uniform spread (variance) of the data. These characteristics of healthcare cost data impose challenges in using standard regression analysis methods such as linear regression models

using ordinary least squares (OLS) (Deb and Norton, 2018, Gregori et al., 2011, Mihaylova et al., 2011). This is because implementing linear regression relies on an assumption that the cost data being modelled resemble a particular distribution ignoring the skewness and mass at zero. This assumption is often the normal distribution and consequently, healthcare expenditure data do not meet the distributional requirement of these methods. This has resulted in some debate about the most appropriate method for modelling healthcare costs for individual patients. Suggestions include the use of distributional transformations, the use of non-parametric methods, and separate modelling of zero and non-zero costs in a two-step process (Mullahy, 2009, Manning and Mullahy, 2001, Jones et al., 2015, Basu and Manning, 2009).

Analysis of the determinants of healthcare expenditure and patterns of variation in costs on patient level is an important aspect of health econometrics research (Dunn et al., 2003). Such econometric modelling of large patient level data can help to understand how the individual and clinical characteristics of the patients influence the overall costs. Earlier works traditionally relied on transformation of the cost data, often using logarithmic transformation, before implementing a regression model (Jones, 2017, Mullahy, 2009). However, if the actual relationship between the explanatory variables or the predictors and the reported costs is not linear, this could result in wrong specification of the model potentially producing biased estimates. In such data, the appropriate model specification might be through the use of non-linear regression.

In recent years, a number of non-linear regression methods including the popular generalised linear models (GLMs) and even more flexible approaches such as the extended estimating equations (EEEs) have become commonplace in the literature on modelling healthcare costs

(Hill and Miller, 2010, Jones, 2017). Previous literature reviews that have compared econometric methods for analysing healthcare costs reported the lack of a single best approach for expenditure modelling (Gregori et al., 2011, Griswold M., 2004, Mullahy, 2009). Several diagnostics checks and validations are instead conducted to find the most appropriate regression model for any given healthcare cost data. Although these diagnostic checks may detect problems, they have various limitations that require careful considerations including their inability to provide solutions (Mihaylova et al., 2011, Basu et al., 2006). Therefore, the choice of appropriate econometric modelling techniques should be a subject of rigorous model comparison and testing, and it should be tailored to the intended aim of the research and the type of data to be used.

6.2 Aims and objectives

The aim of this chapter is to explore the main econometric methods for modelling healthcare costs. The specific objectives are to:

I - Describe the advantages and disadvantages of each method, their applicability and ability to address the characteristics of a cost data.

II - Provide guidance on the likely choice of econometric methods appropriate for assessing the association between predictors and healthcare costs of back pain.

6.3 Common econometric approaches for healthcare cost

6.3.1 Ordinary least squares (OLS) regression

OLS is a linear regression method that is based on the normal distribution assumption. It is the best known and most common estimation method for linear models, and thus it is generally used as a natural starting point for modelling costs (Basu et al., 2006, Jones, 2012).

The classical assumptions behind an OLS estimation include: i) The coefficients and the error term must be linear, meaning that the model is built by adding together terms that are either a constant or a product of a parameter and a predictor variable. With Y representing cost, the model specification follows:

$$Y_i = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_i X_i + \varepsilon \quad (6.1)$$

Where: βs are the parameter estimates, Xs are predictors and ε is the random error. ii) The error term should have constant variance or homoskedasticity where the variance per observation does not change, divergence from this leads to heteroskedasticity displaying unequal spread of the residuals. iii) The error terms should also be normally distributed in order to conduct hypothesis testing and produce reliable p-values and confidence intervals.

Various diagnostic checks based on the residuals in the model can be conducted to assess these assumptions. Linearity of the model is usually checked visually using plots of the residuals versus either predicted values or explanatory variables which are obtained as part of the regression output. The points should be symmetrically scattered around a diagonal line while evidence of systematic patterns reveal non-linearity indicating the model may be making systematic errors (Topp and Gomez, 2004, Tsai C., 1998). A scatter plot of the residuals against the predicted values may also be used to check heteroscedasticity that is often detected by the presence of a funnel or cone shaped pattern indicating errors increasing in one direction (Tsai C., 1998). Formal tests such as the Breusch-Pagan/Cook-Weisberg test for heteroscedasticity could also be conducted testing the spread of the errors against the null hypothesis of constant variance (Breusch and Pagan, 1979, Cook and Weisberg, 1983). Normality of the errors is usually checked with a normal probability plot (P-P plot) or a normal quantile plot (Q-Q plot) of the residuals (Kozak and Piepho, 2017). Significant

deviations of the points from the reference diagonal line indicate the presence of excessive skewness. These diagnostic checks and tests are not restricted to linear regression and may be extended to other models.

The advantages of an OLS estimation are ease of implementation, fast computation, and the coefficients are also easy to interpret since the cost data is on the original scale and no transformation is required. However, the skewed nature of healthcare costs may render untransformed OLS estimation impractical particularly in small samples. Healthcare cost data are also known to display a high degree of heteroscedasticity associated with the error terms further adding a disadvantage for the use of OLS (Basu et al., 2006, Jones, 2012). Transformation of the cost data usually on a logarithmic scale is typically performed to overcome these problems.

6.3.2 Log-transformed OLS regression

Transformation of the cost data results in a more symmetric distribution, and log transformation is the most popular to this end although square-root and other power transformations are sometimes considered as well. The log-transformed model discussed here is the log-linear model meaning that the transformation applies only to the Y variable (cost) and not to the linear part of the model or combination of explanatory variables. A log-linear model is specified as:

$$\ln(Y_i) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_i X_i + \varepsilon \qquad (6.2)$$

The diagnostic tests described in relation to raw-scale OLS equally apply to the log-transformed OLS regression models. The advantage of a log-transformed OLS regression

over OLS on raw scale is that more precise and robust estimates may be achieved (Mihaylova et al., 2011). One disadvantage of the log-linear method is its inability to handle zero values of the cost data. Since the log of zero is undefined, additional arbitrary transformations such as adding a small constant to the zero responses may be required. The alternative approach is to exclude observations with zero cost depending on the proportion. Another disadvantage is that comparison of means on a transformed scale do not directly translate to comparison on the original scale, requiring appropriate back transformation for interpretation of results. Methods for back transformation to the original scale are also not straight forward and may result in misleading and biased estimates on the untransformed scale, thus transforming the response is generally not recommended and should be applied very cautiously if used at all (Feng et al., 2014, Mihaylova et al., 2011). To avoid these problems, a regression method that does not require back-transformation and is more flexible in the distributional assumption will be required.

6.3.3 Generalised linear model (GLM)

The GLM is an extension and a flexible generalisation of the OLS or linear regression, and it allows the specification of models whose response variable follow a distribution other than the normal distribution (Hardin J.W., 2007). Two main components need to be defined in a GLM. The first is the probability distribution of the response variable also referred to as a variance function or a random component, and it specifies the relationship between the variance and the mean (Agresti, 2002, Jones, 2012). Common distributions of the exponential family include the Gaussian, Poisson, gamma, and binomial distributions and they provide flexibility in modelling the cost data. The second component is the link function which specifies the link between the random component and the explanatory variables as a combination of linear predictors (Agresti, 2002). The link function (eg. identity link, log link,

square root link) essentially states how the expected value of the response (mean cost) relates to the explanatory variables. A GLM with identity link and Gaussian distribution is equivalent to OLS, and similarly a log link with Gaussian distribution is comparable to log-OLS.

The most common GLM specification for modelling healthcare costs is with a log link and a gamma distribution (Basu et al., 2006, Deb and Norton, 2018, Manning and Mullahy, 2001). However, this is not always the case and the choice of these two components is guided by employing a series of diagnostic tests on candidate link functions and distributions. The Pregibon's link test (Pregibon, 1980) is usually performed to confirm adequacy of the link function selected by evaluating the linearity of the response on the scale of estimation (Murteira, 2016, Jones, 2012). The suitability of the distribution function can be tested using the modified Park test (Park, 1966) which estimates a coefficient to test the relationship between the variance and the mean. The value of the predicted coefficient provides guidance on which distribution family is preferred.

The main advantage of GLM is its ability to accommodate skewness of the data in natural ways providing considerable flexibility, making these models the dominant approach for modelling healthcare costs (Deb and Norton, 2018, Manning and Mullahy, 2001). GLM also allows for heteroscedasticity through the variance structure using a choice of distributional family. Another advantage is that analysis obtained with a GLM is directly on the scale of the original data, and therefore there is no need for back transformation. However, GLM is not a universal solution and it does have its own limitations. For example, the correct link function or distribution may not be one of the standard choices of link functions or distribution family available. The diagnostic tests described above may indicate problems with the functions or models being tested, but they do not provide solutions to the problems. A regression method

that allows for a wider range of values than the standard choices of link and distribution functions and hence is more flexible will be required to address these issues.

6.3.4 Extended estimating equations (EEE)

Basu and Rathouz (2005) proposed a flexible semi-parametric extension of the GLM approach known as extended estimating equations (EEE) to overcome the limitations of a standard GLM in selecting appropriate link functions and distributions. The EEE model determines the most appropriate scale by simultaneously estimating the link function and distribution using a Box-Cox transformation approach (Basu, 2005, Basu and Rathouz, 2005). Box-Cox transformation is a powerful method of transforming a non-normal response variable into an approximately normal distribution by finding the parameter value that provide the best normal distribution fit and running a number of tests to approximate this parameter by standard values representing known distributions (Box, 1964, Sakia, 1992). In the EEE application, a Box-Cox link function transforms the mean of the response and not the actual response variable, thereby avoiding problems of retransformation. Diagnostic tests employed for GLMs are generally applicable for EEE models.

The main advantage of an EEE model is that it overcomes the need for a priori selecting a specific link function and distribution family as in the case of a traditional GLM approach. As the appropriate link function in an EEE model is determined by an estimated parameter from the data, potential bias due to assuming wrong link functions is reduced. An EEE model is also semi-parametric, meaning that while a parametric method is used for the mean and variance, no further distributional assumptions are made resulting in better flexibility than conventional GLM. This also makes EEE a more efficient estimator for healthcare costs minimising prediction errors, which is especially desirable when the aim is to estimate

marginal or incremental effects (Basu and Rathouz, 2005, Hill and Miller, 2010). One disadvantage of EEE models is that large sample sizes in excess of 5000 are required to fit them well, making this method unlikely to be suitable for clinical trials data (Mihaylova et al., 2011). Secondly, both EEE as well as the underlying GLM methods do not explicitly model excess zero values requiring a further modelling approach when a mass zero problem is present in the data.

6.3.5 Two-part models

The one-part regression models described so far all employ a single regression equation to model healthcare costs irrespective of whether they utilised any services. In a severely skewed cost data with substantial proportion of zero values however, the use of a one-part model fails to distinguish between those who incur substantial costs from those who cost little or nothing. A common approach to deal with this problem is with the use of two part models or hurdle models which employ a two-part regression model allowing for a differential response to reflect the mass zeros (Dunn et al., 2003, Mihaylova et al., 2011). The first part predicts the probability of costs being incurred (response > 0), and the second part models the healthcare costs, conditional on health resource being utilised (Deb and Norton, 2018, Duan N., 1984). The predicted total healthcare expenditure will then be estimated by multiplying the predicted probabilities from the first part and the predicted costs from the second part of the model. This is specified mathematically as:

$$\mathrm{E}(\mathrm{Cost}) = \Pr(\mathrm{Cost} > 0) * \mathrm{E}(\mathrm{Cost} \mid \mathrm{Cost} > 0) \quad (6.3)$$

where: E is the expectation and Pr denotes probability

The method essentially decomposes the distribution of the cost data into a component with zero values, and another component with positive values and these are modelled through separate regressions. Probit or logit models which are standard regression models for a binary response (whether costs are incurred or not) are typically used in the first part, while the second part is usually modelled using OLS or GLM (Diehr et al., 1999, Mihaylova et al., 2011).All the diagnostic tests used for one-part models are generally applicable for two-part modes.

One advantage of a two-part model is that it enables the estimation of the probability of incurring costs in addition to predicting the general parameter of interest, the mean cost. By explicitly modelling mass zeros to reflect non-use of resources, two-part models may better describe relationships between healthcare costs and their predictors. However as with their one-part parametric counterparts, these models are intended to estimate the mean of the cost and they do not describe what happens outside of the mean. To overcome this problem, a non-parametric method that captures associations across the full range of the distribution may be required.

6.3.6 Quantile regression

Although important, the mean is not the only aspect in analysis of cost, and analysis entirely dependent on the mean may miss important information elsewhere in the distribution (Bitler et al., 2006). Thus, regression modelling techniques that facilitate going beyond the mean to model the entire distribution, such as the quantile regression, have become important (Fortin and Lemieux, 2009). The quantile regression method was originally proposed by Koenker and Basset (1978) as an extension and a non-parametric alternative to OLS when the distribution of the response variable is not normally distributed (Koenker and Bassett, 1978). Unlike

conventional regression methods that just estimate how the explanatory or predictor variables are related to the mean cost, quantile methods can describe the full range of the relationship by regressing at different points along the distribution, making this approach more efficient at capturing extreme costs in a skewed distribution (Buchinsky, 1998, Yang et al., 2012). Regression analyses can be done at any given quantile such as 0.1, 0.25, 0.5, 0.75, 0.9 (equivalent to the 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentile of the cost distribution), with the 0.5 regression being the median regression.

The main advantage of the quantile regression is that it enables the association between healthcare costs and predictors to be understood beyond the mean rather than just for an average patient. This is important for identifying how determinants of expenditure vary by subgroups of the population. By doing this a richer characterisation of the association between cost and the predictor variables can be obtained. Quantile regression also avoids the parametric distributional assumptions of the errors and it is more robust to outliers than OLS regression (Ranganai, 2016). Quantile regression thus compliments and adds a different dimension to analysis conducted by a parametric method such as OLS or GLM. The main disadvantages of quantile regression methods are that estimation of parameters are harder and more complicated compared to parametric methods, and excessive computing time is needed for bootstrapping hence fewer repetitions are specified (Olsen et al., 2012, Waldmann, 2018).

The ability of each econometric modelling approach discussed above to address key statistical issues for modelling healthcare cost data is shown in Table 6.1. The table presents a summary of the appropriateness of the alternative econometric methods based on the characteristics of the data and across different circumstances. Since there is no single model that addresses all

statistical issues, careful considerations will be required in order to arrive at the preferred and most appropriate econometric model.

Table 6.1: Key methodological issues addressed by commonly used econometric methods

	Key features (Yes/No/Medium)									
Model	Easy to perform/ estimate	Widely used for healthcare cost data	Requires normally distributed data	Assumes linear relationship	Flexible with distribut-ional assumption	Requires back transform-ation of estimates	Handles mass zero value issues	Allows modelling over the entire distribution	Model diagnostic checks widely available	Estimation takes long due to complex algorithm
OLS	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*No*	*No*	*No*	*Yes*	*No*
Log-OLS	*Yes*	*Yes*	*Yes*	*Yes*	*No*	*Yes*	*No*	*No*	*Yes*	*No*
GLM	*Yes*	*Yes*	*No*	*No*	*Medium*	*No*	*No*	*No*	*Yes*	*No*
EEE	*No*	*No*	*No*	*No*	*Yes*	*No*	*No*	*No*	*No*	*Yes*
Two-part model	*Medium*	*No*	*No*	*No*	*Medium*	*No*	*Yes*	*No*	*Medium*	*No*
Quantile regression	*Yes*	*No*	*No*	*Yes*	*Yes*	*No*	*No*	*Yes*	*No*	*Yes*

6.4 Model selection and specification

Model selection among candidate models involves both selection of variables for inclusion in the model as well as the specification of the functional forms of the variables. However, there is no consensus on the best method for selecting a regression model among competing models (Cherkassky and Ma, 2003). Selection of the best fitting model in the case of nested models where one model is a subset of another model is usually done by comparing the models using likelihood ratio test. The likelihood ratio test is a goodness of fit measure that assesses if the larger or more complex model significantly improves the model compared to the nested model. If no evidence is observed, the simpler model will be preferred. The process can be repeated until a parsimonious model is achieved where an addition of a variable does not significantly contribute more information.

Non-nested models such as models fitted with different specifications of link/distribution functions in a GLM can be compared using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) to aid selection between competing models. AIC and BIC are closely related to each other and they provide an indicator of the quality of a model by estimating the relative information lost in the process of fitting the model to represent a given data, hence the smaller the AIC or BIC value, the better the quality of that model (Aho et al., 2014, Burnham and Anderson, 2002). Prior knowledge of the data such as clinical variables may also be used to guide the model building process. Model diagnostic tests will then evaluate the performance of the selected model.

6.5 Assessing model performance

It is important to assess the quality or performance of a model, and residuals which are estimated as the difference between the actual observed value (y) and the model's predicted value (ŷ) play an important role in this process. One common measure is Pearson's chi-squared test for correlation between the residuals and the predicted values. The test determines systematic bias in the predicted values of the response by testing whether the predicted values are adequately representative of the observed values (Smyth, 2003). If the Pearson statistic is significantly different from zero, the predicted values fail to sufficiently represent the observed values due to systematic bias (Basu and Rathouz, 2005). In addition, the residuals can be plotted against the predicted values for visually inspecting the randomness of their distribution.

Error metrics can also be calculated to evaluate the quality of model predictions, and these include the mean percentage error (MPE), the mean absolute percentage error (MAPE) and the root mean squared error (RMSE). These error metrics are closely related to each other capturing slightly different aspects of the model with no method being superior. MPE is the computed mean of percentage errors, and it indicates the overall prediction bias by calculating how the mean of the predicted values of the outcome compares with the mean of the observed values, with lower values indicating smaller biases (Hill and Miller, 2010, Malehi et al., 2015). MPE is calculated as:

$$MPE = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i) \qquad (6.4)$$

Where: *n* is the number of observations, y_i is the observed cost, and $\hat{y}_i$ is the predicted cost.

MAPE is a similar concept to MPE in terms of its calculation and it measures the accuracy of the prediction as a percentage by calculating the mean of the absolute value of differences between the observed and predicted values with smaller values indicating better prediction accuracy of the model (Hill and Miller, 2010, Malehi et al., 2015). This is given as:

$$MAPE = \frac{1}{n}\sum_{i=1}^{n} |y_i - \hat{y}_i| \quad (6.5)$$

The third error metric RMSE measures the absolute fit of the model or how far from the regression line the data points are (spread of the residuals) using the square root of the mean of the squared residuals or deviations of the predicted values from the observed values (Dunn et al., 2003). This is algebraically defined as follows:

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2} \quad (6.6)$$

As with the other two metrics, lower values of RMSE are desired indicating better fit of the model, and hence better prediction accuracy.

6.6 Summary

Individual level healthcare cost data are typically characterised by a right-skewed, non-normal distribution with fewer patients accounting for a large proportion of the high costs. Healthcare cost data also often exhibit considerable heteroscedasticity of the errors and the relationship between the response and explanatory variables may be non-linear. These features pose several problems for analysing healthcare costs. Given the characteristics of these problems, no single

modelling technique will always be best for exploring the association between healthcare costs and various predictors. It is often the case that alternative modelling approaches may need to be considered to provide a degree of variation in the estimates due to uncertainties associated with each model. This has an added advantage of acting as a sensitivity analysis to assess the robustness of the methods.

Following the choice of regression methods for analysing the costs, appropriate explanatory variables need to be identified and correctly specified in the models. These steps are crucial for the entire process of estimating parameters and testing hypotheses about them. Specification errors, omission of important variables, or inclusion of irrelevant variables may result in biased prediction estimates. The underlying assumptions of the models and their goodness of fit must be assessed using appropriate diagnostic methods. Regression diagnostics using residual analyses apply to any investigation employing regression models. Based on the findings of the diagnostic procedures, re-examining of the include variables and their specifications may be required to remedy issues encountered. Finally, the performance of the final models should be assessed using error metrics to judge how well the predictions match up against observed values. This provides indication of the quality of the models and enables the performance of different regression methods to be compared.

This chapter explored the main econometric methods used for analysing healthcare costs, and the procedure for model selection, specification, and performance assessment. Depending on the research question and the nature of the cost data, a number of econometric methods from basic regression techniques to more complex extensions may be applied to appropriately analyse healthcare expenditure data. An empirical case study of the application of econometric methods

to model healthcare costs associated with back pain is given in the next chapter. Discussion of the methodological aspects of this chapter is also provided in the next chapter in conjunction with the empirical application.

CHAPTER 7. FACTORS ASSOCIATED WITH HEALTHCARE COSTS OF BACK PAIN

7.1 Introduction

The previous chapter explored the main econometric methods used for analysing healthcare cost data. It focussed on explaining the alternative regression models paying particular attention to the statistical methodology, selection and specification of models, and evaluation of the performance of the chosen model. This chapter presents an application of these methods to investigate the determinants of the economic burden of back pain related to medical costs. This is a prerequisite for the development and implementation of tailored interventions to treat or prevent back pain whose cost saving attributes may be assessed through economic evaluation. Although the total cost of back pain is generally dominated by indirect costs, the high healthcare resource use incurred by chronic patients and patients with recurring back pain, and their associated direct costs are also of serious concern to healthcare policy-makers (Sabariego et al., 2011).

The prognosis and prevalence of back pain has been widely studied both internationally and in the UK context (Dionne, 1999, Duthey, 2013, Hayden et al., 2009, Hoy et al., 2010a). Risk factors associated with back pain are explained in chapter 2. Older age, lack of exercise, excess weight, certain diseases, improper lifting, and psychological conditions are some of the factors believed to put people at greater risk of developing back pain (Burton et al., 1995, Church and Odle, 2007, Coenen et al., 2014, Dionne et al., 2006, Hestbaek et al., 2003, Hoy et al., 2010a, Shiri et al., 2018). However, little is known about the association of these factors with healthcare

resource utilisation and costs of back pain in UK primary care. A systematic review by Hayden et al. (2009) revealed a large body of evidence on back pain prognosis, in particular investigating its course and predicting outcomes in patients (Hayden et al., 2009). However, the outcomes of interest are generally focussed on pain, functional limitations, return to work and other clinical and occupational outcomes rather than resource use and costs (Hayden et al., 2010, Hayden et al., 2009).

This chapter employs appropriate econometric methods to determine factors which may be associated with the healthcare cost of back pain. It estimates the influence of demographic, socio-economic and clinical factors on the total costs of back pain which include consultation and prescription costs based on analysis of a large sample of patients from the THIN database. The literature on back pain in UK primary care is largely dominated by epidemiology, interventions, risk factors, and predictors of positive and negative health outcomes. It is proposed that an exploration of the determinants of costs given the specific characteristics of the patients will add a new dimension to the current literature.

7.2 Aims and objectives

The aim of this chapter is to investigate how patient and clinical characteristics affect healthcare costs for an individual with recorded back pain (confirmed with diagnostic codes). The specific objectives are to:

I. Demonstrate and compare empirical applications of alternative econometric methods relevant for the back pain cases dataset developed in chapter 5.

II. Perform appropriate multiple regression analyses to determine potential factors that may be associated with the healthcare costs of back pain.

7.3 Methods

7.3.1 Study population

The study population for the analyses in this chapter was the back pain diagnosed group (cases) established from the THIN database in chapter 5. These patients had at least one diagnostic Read code for back pain recorded between 01 January 2006 and 31 December 2015, and at least one prescription for pain medication during 2015. A total of 133,341 patients were eligible for the study, and the sample selection process was explained in detail in chapter 5. Due to missing values and other data inconsistencies (eg. patients with no resource use, and patients with outlying costs recorded), some patients were not included in the analyses. It was a very small number of patients who had no resource use recorded (25 patients) and two patients were deemed to have outlying costs. The final study sample included 108,013 patients with positive recorded total healthcare costs. All patients were at least 18 years old at the time of their back-pain diagnosis (first recorded Read code for back pain).

7.3.2 Study design

The present evaluation was a secondary analysis of patients with recorded back pain in UK primary care. It followed a cross-sectional study design where all patients had their annual healthcare resource use and costs estimated for 2015 in chapter 5. These estimates were used in this study to analyse the prediction of costs and their association with predisposing patient and clinical characteristics such as age, gender, deprivation, and comorbidities. The outcome measure

of interest was the total healthcare costs of back pain which comprised consultation costs and prescription costs from their medical records.

7.3.3 Overview of the data

The distribution of the outcome variable, the healthcare costs of back pain, was heavily skewed to the right (Figure 7.1). The skewness of the distribution was 4.6 with a kurtosis of 66.2, where for a symmetric data, skewness is expected to be near 0 and kurtosis not more than 3. The Jarque-Bera test of normality (p=0.000) confirmed the significant skewness of the outcome which was

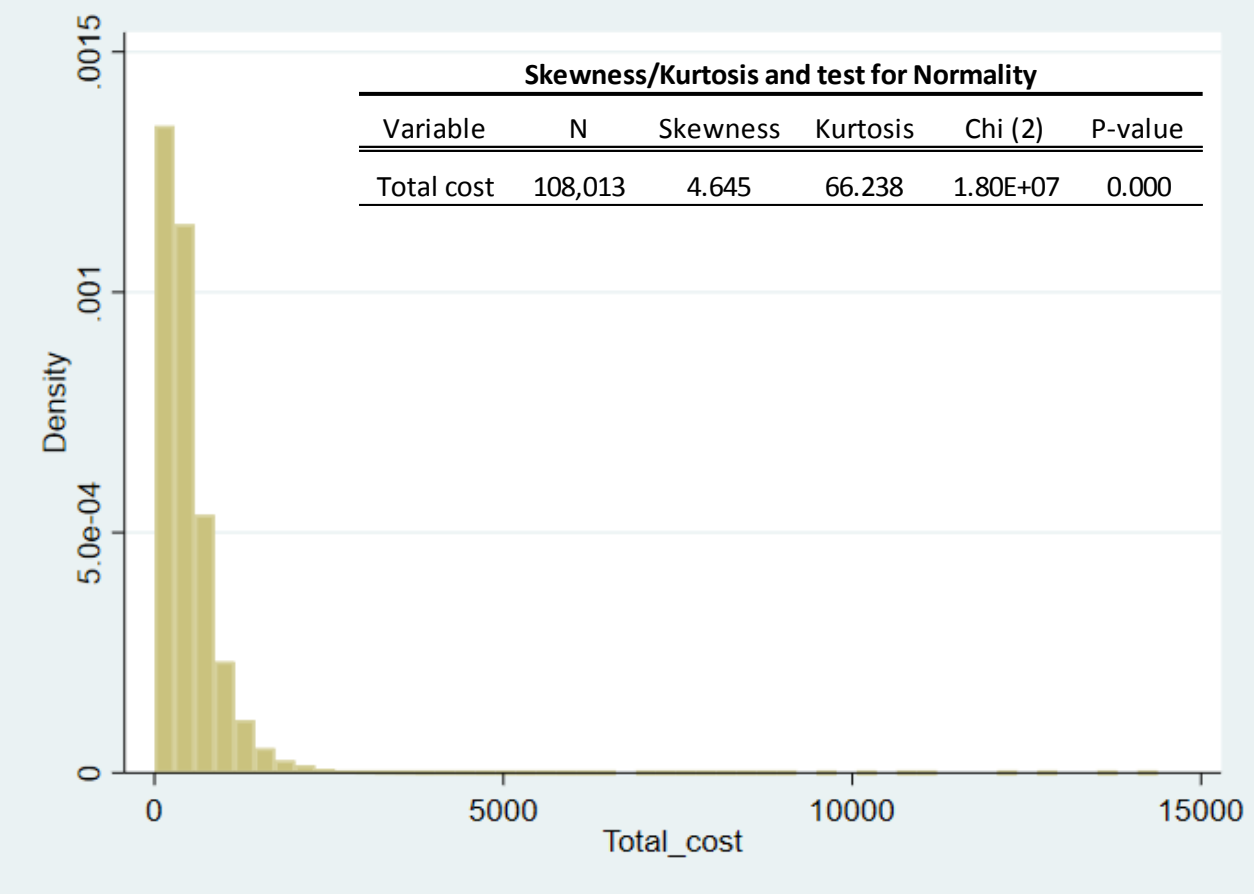
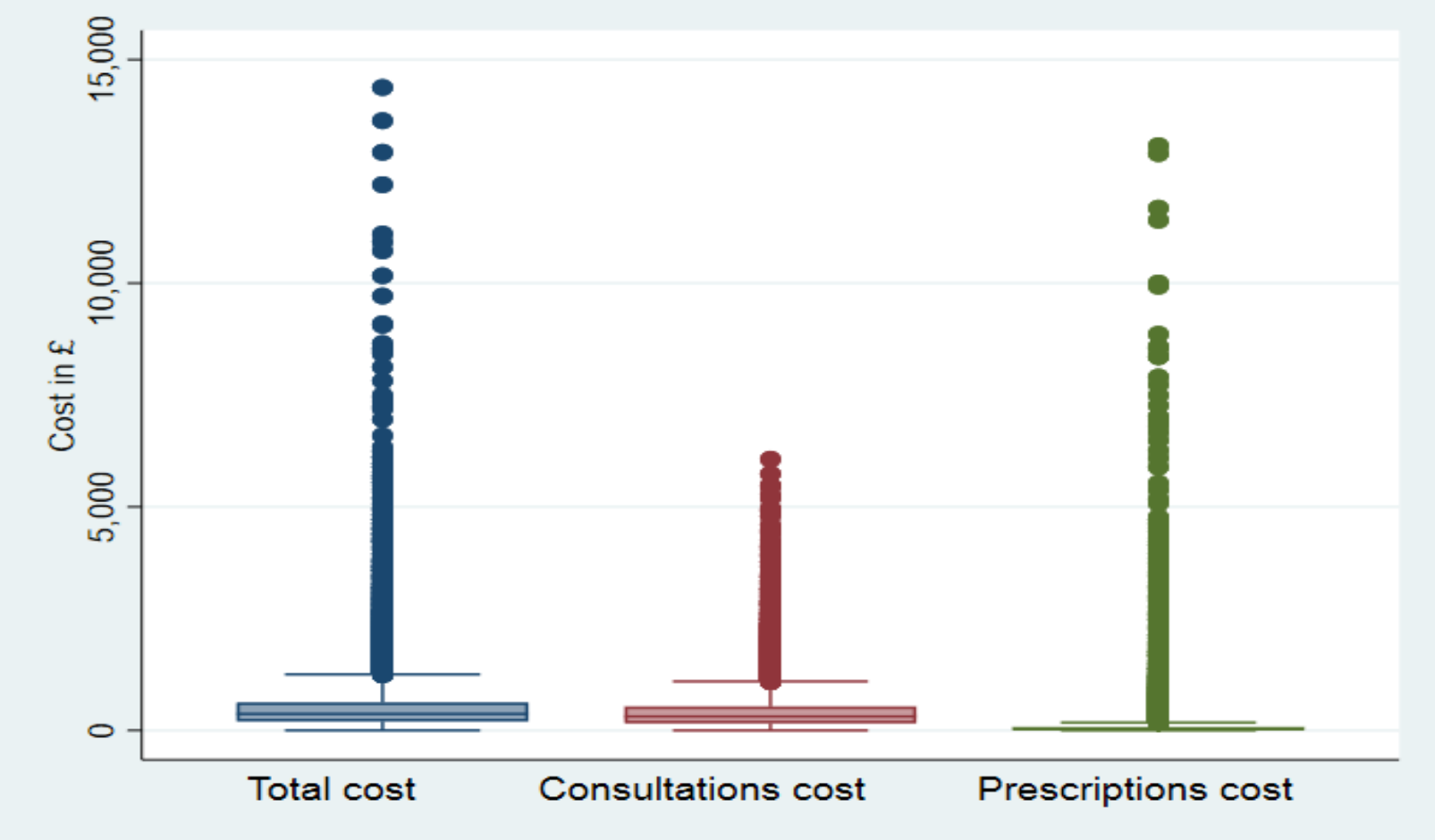


Figure 7.1: Skewed distribution of the total healthcare cost data

consistent with healthcare expenditure data in general. Almost all the patients had positive expenditure, with only 25 patients not utilising any resources and hence incurred zero cost. In order to further explore how the cost data were spread out by type of resource use, a boxplot was used displaying the distribution of the costs using a five number summary: the minimum, 1st quartile (Q1), median, 3rd quartile (Q3), and the maximum (Figure 7.2). The maximum in this summary represented an upper limit calculated with respect to Q3 and the interquartile range (IQR) (Maximum = Q3 + 1.5 * IQR). Hence, points outside of the maximum indicated extreme cost values with a potential to be outliers. The plot shows that due to the extremely skewed nature of the cost data in each of the cost group, the high cost values were much more spread out shrinking the IQR.



Median: horizontal line inside the box, Interquartile range (IQR): upper and lower limits of the box,
Minimum and Maximum: the lines below and above the box, values above the maximum represent extreme values

Figure 7.2: Spread of high expenditure by type of resource use

In addition to the outcome variable, nine explanatory variables describing patient and disease characteristics were extracted from the THIN database as potential predictors (Table 7.1).

Table 7.1: Explanatory variables of patient and clinical characteristics

Variable	Description	Specification*
Age	Age in years in 2015	Continuous variable
Age-group	Age categorised into seven groups	Derived categorical variable: 18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75 & above
Gender	Gender code indicating 'male' or 'female'	Binary indicator variable: 0 = Male, 1 = Female
Country	Patients coded into one of the four countries of the UK	Categorical variable: 1 = England, 2 = N. Ireland, 3 = Scotland, 4 = Wales
Townsend	Patients coded into one of five deprivation quintiles based on the 2001 census	Categorical variable: 1 = Least deprived, 5 = Most deprived
BMI	BMI in kg/sq. meter	Continuous variable
BMI category	Patients coded into one of three BMI categories	Categorical variable: 1 = <25kg/sq. meter , 2 = 25-30Kg/sq. meter, 3 = >30Kg/sq. meter
Smoking status	Patients coded into one of three smoking status categories	Categorical variable: 1 = Non-smoker, 2 = Smoker, 3 = Ex-smoker
CCI category	Patients coded into one of six Charlson comorbidity index category	Categorical variable: 0 = No comorbidity, 5 = Highest comorbidity

* Categorical groups are mutually exclusive. Lowest group indicator is used as a reference group in the models.

These were: age, age-group, gender, country, Townsend quintiles, BMI, BMI categories, smoking status, and CCI categories. Duration of back pain or time since diagnosis would have been an important variable to include with these candidate variables. However, unlike other conditions such as diabetes or cancer, a diagnosis code for back pain does not necessarily indicate the starting point for duration of the condition. Once a patient is diagnosed with diabetes or cancer, they remain a case unless the disease is fully resolved and patients are unlikely to receive multiple diagnoses of the same disease. Hence duration for such conditions could easily be derived from the records. Back pain on the other hand is recurrent, and patients may recover fully or have multiple episodes which makes it difficult to calculate duration. Since a reliable duration variable could not be derived from the data, it was not included as a potential predictor. The THIN database was explained in detail in Chapter 4 with a summary of the available variables from which the nine modelling variables were drawn shown in Appendix 7.1.

7.3.4 Regression analysis methods

The econometric modelling approaches explained in the previous chapter were each considered given the characteristics of the data. The alternative appropriate methods adopted in the analyses also acted as sensitivity analyses to assess variations in the estimates associated with uncertainties of the different models used. Regression coefficients from each model were presented to determine factors associated with healthcare costs of back pain. Where models were non-linear, marginal/incremental effects were obtained to enable interpretation in the original scale. Robust standard errors were used in all models unless specified otherwise.

***Ordinary least squares (OLS)*:** An OLS approach on untransformed cost data is generally not recommended in smaller samples which are highly skewed. Given the large sample size (n = 108,013) in this study, an OLS approach was considered viable to result in unbiased estimates. This method was therefore included in the analysis, and its appropriateness was assessed. It was also deemed important to demonstrate how the modelling of the mean using simple regression methods like OLS compared and contrasted with modelling the full distribution of the cost. Therefore, estimates from the OLS model and quantile regression models were tabulated and presented graphically to demonstrate how coefficients obtained may vary across the distribution of the cost.

***Log-OLS*:** Log transformation results in considerable reduction in the skewness of data. Therefore, OLS regression following log transformation of the cost data was used to model the outcome. As coefficients from log-transformed costs are not directly interpretable, exponentiated coefficients are presented. The predicted mean cost (marginal effect) was retransformed to the original scale using Duan's smearing estimator for comparison with predictions from other models. Duan (1983) introduced the smearing estimator which is a correction factor that is applied to the exponentiated mean prediction of the log model in order to address the retransformation bias. The method has been widely used since then but with caution since the back-transformation relies on the assumption that the errors are homoscedastic (have constant variance) while the true distribution of the errors is not known (Basu et al., 2004, Manning and Mullahy, 2001, Mullahy, 1998).

***Generalised linear models (GLMs)*:** Alternative modelling using a GLM approach was conducted as it offers flexibility by specifying a link and distribution function for the data.

Several combinations of relevant link functions and distributions were tested before selecting the final model(s). First, seven models were fitted with the following specification of link/distribution: identity/gamma, log/gamma, identity/normal (equivalent to OLS), log/normal (equivalent to log-transformed OLS), square-root/gamma, square-root/normal, and log/negative binomial. Next, AIC and BIC, the model selection criteria for non-nested models were obtained from each model and compared among the models to select the best fitting model for the data.

***Extended estimating equations (EEE)*:** This modelling approach offers more flexibility than a conventional GLM in terms of selecting the link function and distribution family. An EEE model was therefore used which employed a Box-Cox transformation to simultaneously estimate the link function and variance function. Marginal effects from the model were reported.

***Two-part model*:** The use of this modelling approach is warranted when there is a substantial proportion of zero values in the response. With only 25 patients in the data having zero healthcare cost, a two-part model would not be appropriate and therefore was not used in this study.

***Quantile regression*:** A quantile regression method was used in order to capture the varying effects of the predictors on cost at different quantiles. Comparison was made with estimates from standard OLS approach. Quantile regression was performed at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentile of the total cost to evaluate the influence of predictors across the full range of the cost distribution.

7.3.5 Variable selection and specification

Selection of variables was informed by clinical significance indicated in the literature and the contribution to the model assessed by model comparison statistics. Older age, female gender, obesity, and higher number of comorbidities were reported to have association with back pain (Chapter 2), therefore the variables age, gender, BMI categories and CCI categories were retained in the models based on clinical significance. Age was the only continuous potential predictor, and it was entered into the models as a continuous variable as there was no justification for categorising it. For BMI, the categorised variable was preferred rather than the continuous variable since BMI is naturally categorised into low/normal, overweight, and obese classes. However, it is acknowledged that categorising a variable will always lead to loss power due to multiple testing even though the BMI categorisation followed the standard medical classification.

The other three variables: Country (England, Scotland, Wales, and N. Ireland), Townsend quintiles, and smoking status were selected for retention into the model using an iterative process. This was done using the simpler model of log-OLS and following a stepwise forward selection of variables in the first instance. A forward selection method involves running a regression model with no or basic number of variables and adding the remaining variables one at a time checking its significance using the likelihood ratio (LR) test. If the test provides evidence of significant contribution (p-value < 0.05), the variable would be retained in the model, and the process repeated until all variables were selected or rejected. In this case, the basic model had the four variables selected on clinical significance, and the remaining three variables were only included if they each contributed significantly to the model.

In order to assess the robustness of the variable selection, a sensitivity analysis was conducted using a backward elimination method on GLM with a log link and gamma distribution. Backward elimination involves starting with a full model with all potential variables and eliminating the suspected three variables one at a time checking its significance by comparing it with the full model using the likelihood ratio test. If no evidence of contribution is observed (p-value > 0.05), the variable would be rejected, and the process repeated for the remaining two variables.

The inclusion of interaction terms between the selected variables were considered based on evidence from the literature. Known interactions between predictors would be tested using likelihood ratio test in a similar fashion and added to the model if significant until a parsimonious model was achieved. The inclusion of polynomial terms (quadratic or cubic) for the continuous age variable was considered by assessing graphically the relationship between age and cost, and if their inclusion contributed to the model. The inclusion of these terms may increase the explanatory power of the model (Heinze et al., 2018). The same variable specifications were maintained in all regression models for consistency and comparison of results. The amount and distribution of missing values in the included variables were checked to assess their randomness. Positive expenditure values were analysed in this study in order to make consistent comparison across the different modelling approaches. Log transformed OLS for example take only positive values on a continuous scale. The 25 patients in the sample with zero total cost were therefore excluded, and this was not deemed to affect the analysis given the very large sample size.

7.3.6 Model diagnostics and descriptive statistics

Various statistical tests and measures of model performance were used for each modelling approach. Pearson's chi-squared test was applied for detecting systematic bias in the predicted values, while the Pregibon's link (P-L) test was used to confirm adequacy of the specification of the models. In addition, the overall goodness-of-fit of the models were assessed using the coefficient of determination or R^2. Comparison between the models for quality of predictions were done using the three error metrics of MPE, MAPE, and RMSE which were explained in Chapter 6.

Correlations among the included variables, and between the explanatory variables and the response were assessed using a correlation matrix on a scale of 0 to 1. A correlation coefficient of 0 indicated no correlation while a value of 1 indicated perfect or full correlation. Descriptive methods were used to evaluate the variables (numbers and percentages for categorical variables, means with standard deviations for continuous variables). The distributions of the response variables were assessed using box plots, and histograms. These provided evidence of normality of the distributions and helped identify potential outliers in the data. Groups were compared using the t-test for continuous variables and the chi-square test for categorical variables. A p-value < 0.05 was considered statistically significant. It was possible that a 5% significance level might be somewhat generous with such a large sample size. Nevertheless, given the non-experimental nature of the study, the conventional 5% threshold was adopted in this study. All data analyses were conducted using Stata SE 15.1 (StataCorp, 2017). A summary of the statistical tests and criteria used in this chapter is reported in Table 7.2.

Table 7.2: Summary of the statistical tests and criteria used

Type of test /Criteria	Description and usage
Jarque-Bera test	Tests whether the skewness and kurtosis of the data matches a normal distribution. A significant p-value ($p< 0.05$) indicates that the normality assumption is violated.
Box-Cox transformation	Is a way to transform non-normal data into a normal shape without assuming a particular link function such as log or square root. It uses the actual exponent lambda (λ), which varies between -5 & 5, instead to find the optimal approximation to a normal curve.
Pearson's Chi-squared test	Is a formal test for model performance. It determines systematic bias by testing the correlation between the residuals and the predicted values. A significant p-value indicates that the predicted values fail to adequately represent the observed values due to bias.
Pregibon link test	Is a formal test for adequacy of the model specification and goodness of the link function. It tests if the assumed link agrees with the data. A significant p-value indicates presence of specification error.
Coefficient of determination (R-squared)	Is a statistical measure that assesses the goodness-of-fit of a model. It displays the level of variability (%) in the data explained by the model. Higher values of R-squared indicate better fit of the model.
Likelihood ratio (LR) test	Compares the goodness-of-fit of two competing, nested models using the ratio of their likelihoods. It is used for variable selection where a significant p-value indicates that the bigger model fits better and hence the additional variable will be retained.
Akaike Information Criterion (AIC)	Is a criterion that is used to compare the goodness-of-fit of two competing, non-nested models. It is indicative of the relative information lost in fitting the model to represent the given data. The smaller the AIC value, the better the fit or quality of the model.
Bayesian Information Criterion (BIC)	Is an alternative criterion for model selection and is closely related to AIC. A smaller BIC value is preferred indicating better fit. Neither criterion is superior, and one or both methods could be used at a time.

7.4 Results

7.4.1 Study Population

The eligible study population were the 133,341 back pain patients from the case group described in Chapter 5. The distribution of total healthcare cost data in the study population was highly skewed with many unusually high cost observations. However, two observations were clearly separated from the rest indicating that these were likely to be outliers (Figure 7.3). These two observations were excluded from all analyses to avoid skewing of the mean estimates. Further exclusion of high cost observations or putting a cap on the costs was not deemed necessary allowing for the full distribution of the expenditure to be modelled. Three variables in the data also had missing values and these observations were dropped from the full case analyses. These were Townsend categories (17,638 missing), BMI categories (8,836 missing), and Smoking status (183 missing). The distribution of these observations across the deciles of total cost was checked to assess if there was any systematic missingness. However, these observations were spread uniformly across the deciles of cost indicating that the level of missingness was random. Imputation of missing values was not deemed necessary due the large sample size available for the study.

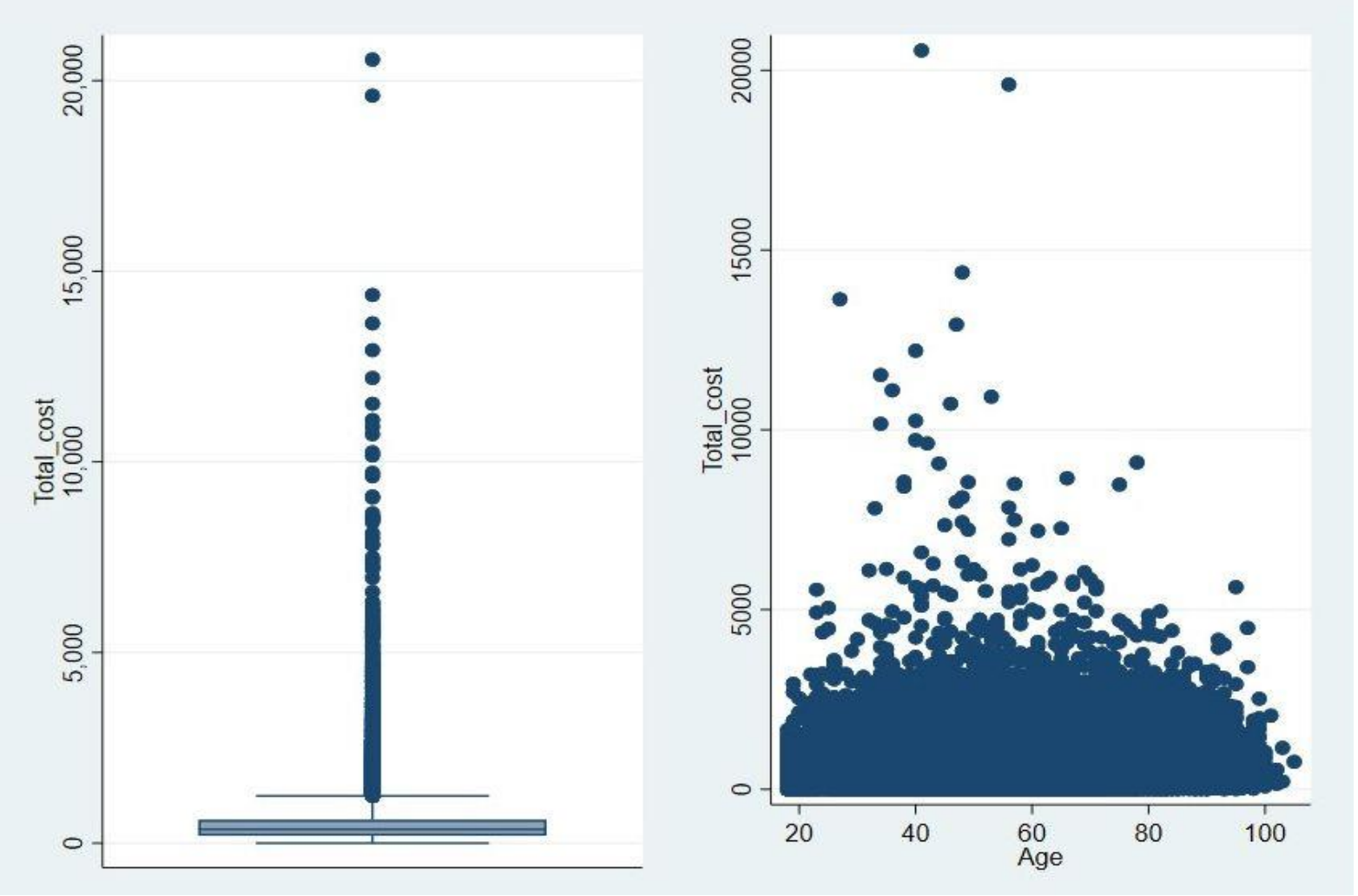


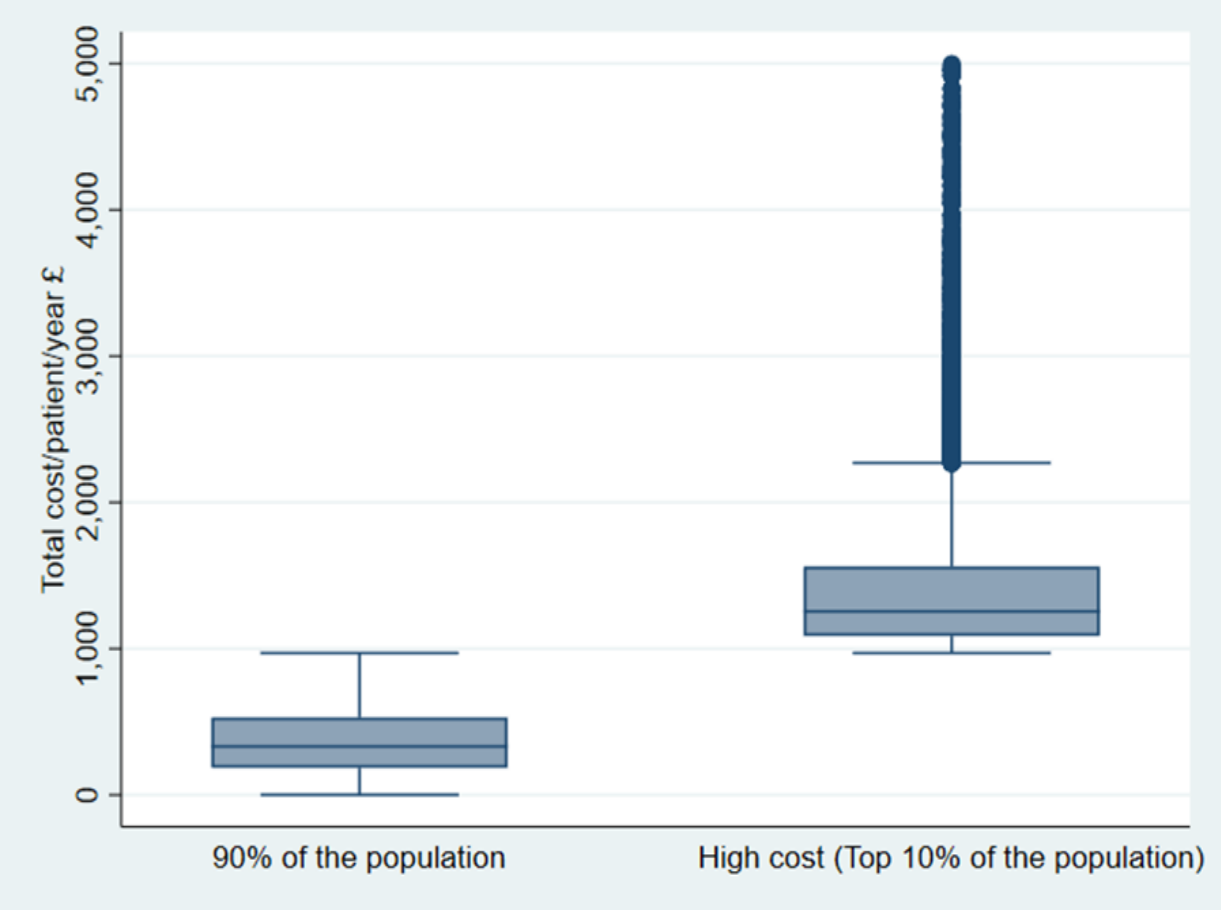
Figure 7.3: Distribution of the total healthcare cost and cost by age showing two outliers

The final study sample included 108,013 patients with back pain from 428 practices across the UK. The distribution of baseline characteristics in this sample is summarised in Table 7.3. The mean (SD) age was 57.5(16.5) years, and the majority of patients were female (63%). Patients were in general evenly distributed across deprivation quintiles and BMI categories. Half of the study population were from England followed by Scotland (24%). Just over half of the population also had no comorbidities, and patient numbers declined continuously across CCI categories.

Table 7.3: Summary statistics of the study population

Variables		n (%)
Gender		
	Male	40,185 (37.2)
	Female	67,828 (62.8)
Age (mean, SD)		57.5 (16.5)
Townsend quintiles		
	Least deprived 1	20,809 (19.3)
	2	21,752 (20.1)
	3	23,840 (22.1)
	4	22,750 (21.1)
	Most deprived 5	18,862 (17.5)
Country		
	England	54,037 (50)
	N. Ireland	10,571 (9.8)
	Scotland	25,829 (23.9)
	Wales	17,576 (16.3)
BMI category		
	< 25	31,211 (28.9)
	25 - 30	38,872 (36)
	> 30	37,930 (35.1)
Smoking status		
	Non-smoker	53,481 (49.5)
	Smoker	22,902 (21.2)
	Ex-smoker	31,630 (29.3)
CCI category		
	0	56,281 (52.1)
	1	27,368 (25.3)
	2	13,719 (12.7)
	3	6,279 (5.8)
	4	2,532 (2.3)
	5 and above	1,834 (1.7)

The distribution of healthcare costs in the study population is shown in Figure 7.4 comparing patients at the higher end of the expenditure against the rest of the population. Cost distribution in a small proportion of heavy users of healthcare is much more skewed than for the vast majority of patients in the sample. The median cost difference between the two groups was £925 while the minimum cost in the high cost group (£970) was equivalent to the maximum cost in the rest of the population.



M*edian: horizontal line inside the box, Interquartile range (IQR): upper and lower limits of the box, Minimum and Maximum: the lines below and above the box, values above the maximum represent extreme values, expenditures above £5,000 suppressed for clarity*

Figure 7.4: Distribution of expenditures in the high-cost group versus the rest

7.4.2 Variable selection and specification

The results from the stepwise forward selection of variables conducted using log-OLS models is reported in Table 7.4. A basic model (model 0) was first fitted to the data that included age, gender, BMI category, and CCI category. Model 1 was next fitted by including Townsend in addition to the four variables. The two models were then compared using likelihood ratio test. The highly significant p-value indicated that the larger model had a better fit than the basic model. Similarly, country was added in model 2 and it was compared against model 1. Finally, the full model (model 3) was compared against model 2. In both cases, the p-vales indicated that the larger models provided a better fit, and therefore the final model should include all seven variables.

Table 7.4: Forward selection of variables using likelihood ratio test on log-OLS model

Added variable	Models compared	LR test statistic ($\chi 2$)	p-value
Townsend	model 0 vs. model 1	414.88	<0.0001
Country	model 1 vs. model 2	141.14	<0.0001
Smoking status	model 2 vs. model 3	283.84	<0.0001

model 0 (basic model): age, gender, BMI category, CCI category

model 1: age, gender, BMI category, CCI category, Townsend

model 2: age, gender, BMI category, CCI category, Townsend, country

model 3 (full model): age, gender, BMI category, CCI category, Townsend, country, smoking status

The results of the sensitivity analysis conducted using the backward elimination technique on GLM models with a log-link and gamma variance is shown in Table 7.5. The full model (model 3) with all seven variables was compared subsequently against a model without smoking status (model 4), a model without country (model 5), and a model without Townsend (model 6). The tests (p-values < 0.0001) confirmed that the full model provided significant improvement in model fit compared to the smaller nested models.

Table 7.5: Backward elimination of variables using likelihood ratio test on GLM models

Removed variable	Models compared	LR test statistic ($\chi 2$)	p-value
Smoking status	model 3 vs. model 4	256.12	<0.0001
Country	model 3 vs. model 5	44.70	<0.0001
Townsend	model 3 vs. model 6	166.59	<0.0001

model 3 (full model): age, gender, BMI category, CCI category, Townsend, country, smoking status
model 4: age, gender, BMI category, CCI category, Townsend, country
model 5: age, gender, BMI category, CCI category, Townsend, smoking status
model 6: age, gender, BMI category, CCI category, country, smoking status

Correlation among the seven variables selected for modelling was examined using correlation matrix (Table 7.6). The correlation coefficients were generally very low indicating that no significant correlations exited among the variables. The highest correlation observed (0.358) was between age and CCI category followed by the correlation between CCI category and the response variable which was 0.219.

Table 7.6: Correlation matrix of the independent and dependent variables

Variables	Total cost	Age	Gender	Country	Town-send	BMI category	Smoking status	CCI category
Total cost	1.000							
Age	0.121	1.000						
Gender	0.079	-0.042	1.000					
Country	0.009	-0.037	0.005	1.000				
Townsend	0.051	-0.148	0.026	0.072	1.000			
BMI category	0.043	0.000	-0.022	0.022	0.050	1.000		
Smoking status	0.050	0.049	-0.124	0.024	0.074	0.023	1.000	
CCI category	0.219	0.358	-0.060	-0.009	0.006	0.065	0.093	1.000

After assessing the suitability of the seven variables for modelling, inclusion of interaction terms between the variables, and addition of polynomial terms (quadratic or cubic) for the continuous variable (age) were considered. Outputs of some models (eg. GLM, EEE) in this chapter are presented in the form of marginal effects due to lack of natural interpretations for the coefficients produced from the models. In such models, marginal effects of interaction terms are not meaningful. However, marginal effects may be estimated for each level of the first variable at specific level of the second variable. For example, interactions were expected between Townsend and CCI categories, both of which were categorical variables with 5 and 6 levels respectively. Assessing interactions here would require estimating marginal effects for each Townsend quintile

at each level of CCI categories. Therefore, interaction terms were not included in the models due to the complexity and interpretability issues. For inclusion of polynomial terms, graphical assessment of the relationship between age and the outcome (Figure 7.5) failed to indicate any quadratic or cubic patterns. The lowess (locally weighted smoothing) curve and the fitted values curve (line of best fit) were used which provide a flexible approach to representing data. The plot

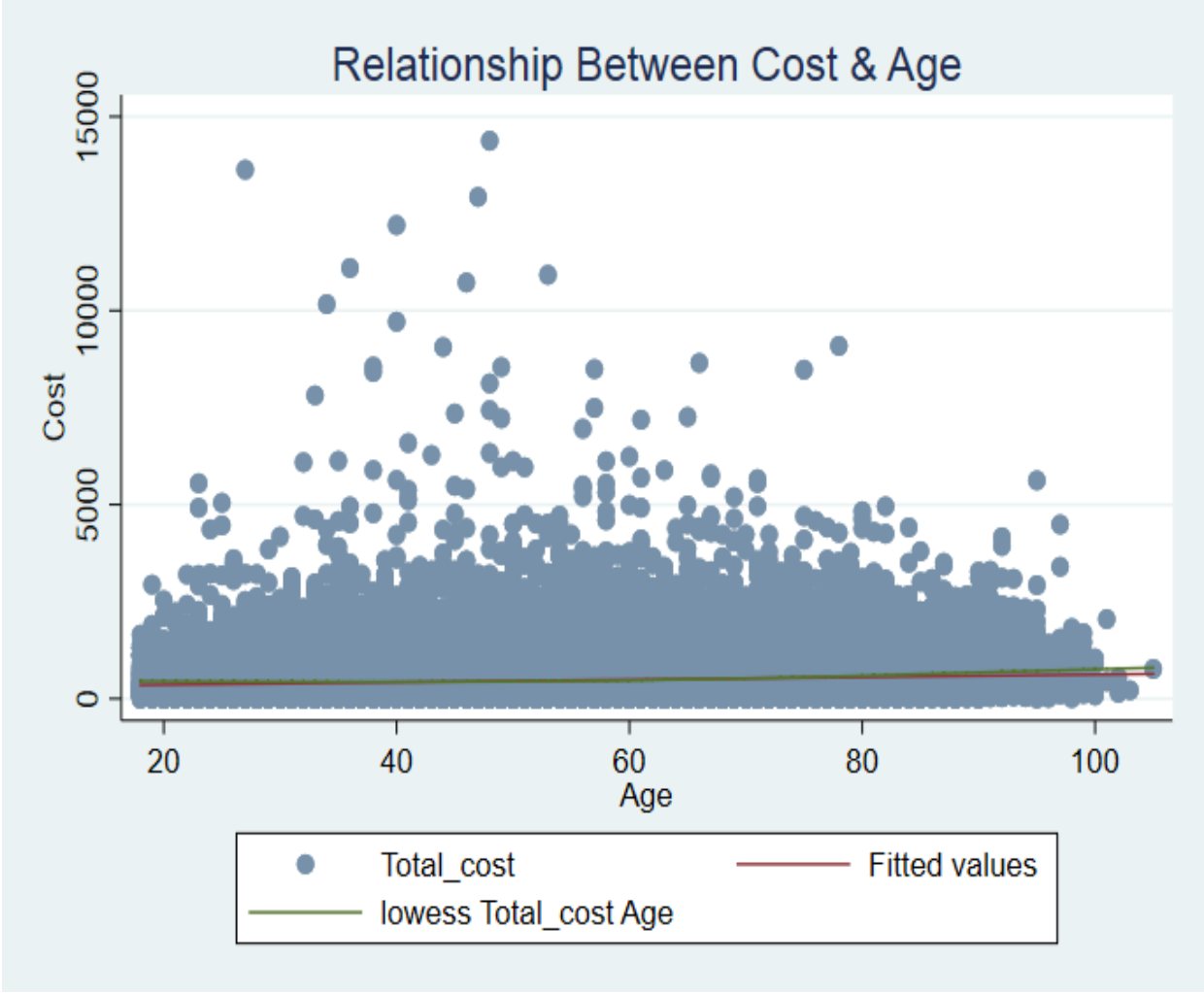


Figure 7.5: Association between total cost and age showing linear relationship

shows that both the lowess and fitted values curve indicate a linear relationship between total cost and age with little or no distortion due to noisy data values or sparse data points. Therefore, inclusion of polynomial terms for age was not required in the models.

7.4.3 OLS modelling

Linear regression estimates from the OLS model are reported in Table 7.7. The coefficients are interpreted as a direct change in total cost for a unit increase in the continuous predictor (age) or an incremental change in categorical predictors. With the exception of Wales and Townsend 2, all the coefficients obtained were highly significant. Females incurred about £88 more in total healthcare costs than males on average, while a one-year increase in age was associated with about £2 increase in costs. Healthcare costs increased considerably by deprivation quintiles and comorbidity indices. Both smokers and ex-smokers also incurred higher costs (£55 and £32 respectively) than patients who never smoked. While costs were higher in the obese group of patients (BMI > 30), the middle BMI group however resulted in lower total healthcare costs than the reference group (BMI < 25).

Table 7.7: Regression estimates of the OLS model

Variable	Coefficient	Robust Std. error	P-value	(95% Confidence interval)	
Age	1.955	0.093	0.000	1.772	2.137
Female	88.126	2.714	0.000	82.807	93.445
N. Ireland	17.256	4.541	0.000	8.355	26.157
Scotland	22.891	3.364	0.000	16.299	29.484
Wales	-3.389	3.760	0.370	-10.758	3.980
Townsend 2	2.751	3.980	0.490	-5.049	10.551
Townsend 3	14.486	3.979	0.000	6.687	22.285
Townsend 4	34.349	4.305	0.000	25.912	42.786
Townsend 5	50.782	4.537	0.000	41.889	59.675
BMI 25-30	-8.207	3.210	0.010	-14.498	-1.915
BMI >30	34.359	3.440	0.000	27.616	41.102
Smoker	55.613	3.829	0.000	48.109	63.117
Ex-smoker	32.091	3.059	0.000	26.096	38.087
CCI 1	108.166	3.247	0.000	101.801	114.531
CCI 2	149.665	4.840	0.000	140.179	159.150
CCI 3	221.423	6.985	0.000	207.733	235.113
CCI 4	307.198	12.367	0.000	282.958	331.437
CCI $\geq$ 5	381.44	15.520	0.000	351.022	411.859
Constant	183.884	6.599	0.000	170.950	196.819

7.4.4 The log-OLS model

Logarithmic transformation is a one way of transforming a non-normal data to an approximately normal distribution curve. Other feasible transformations were also conducted (Figure 7.6), and

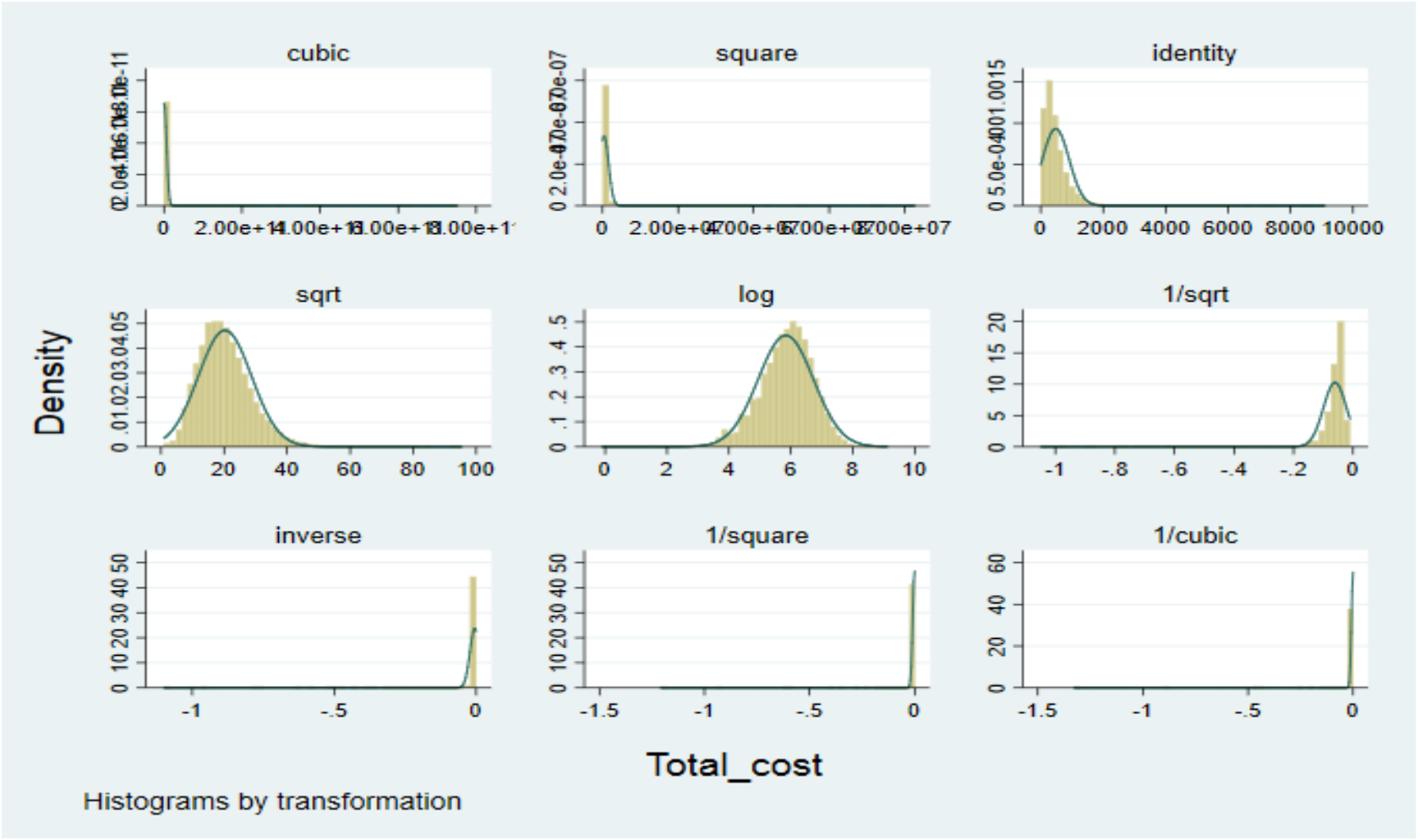


Figure 7.6: Comparison of the transformed total cost using common transformation types

comparison was made using histograms to find the transformation that best characterises a normal distribution. The plot shows that the log-transformed cost appears to have the best central tendency and spread of data around the center, while the square-root (sqrt) transformation was the next best as it was slightly skewed to the right. Other transformation types did not yield any meaningful transformation for the total healthcare cost data. Densities of the raw and log-scale total healthcare expenditure are shown in Fig. 7.7. The transformation has made the distribution much more symmetric compared to the original data. How close the transformed cost data is to a normal distribution curve is shown using a kernel density estimate in Appendix 7.2.

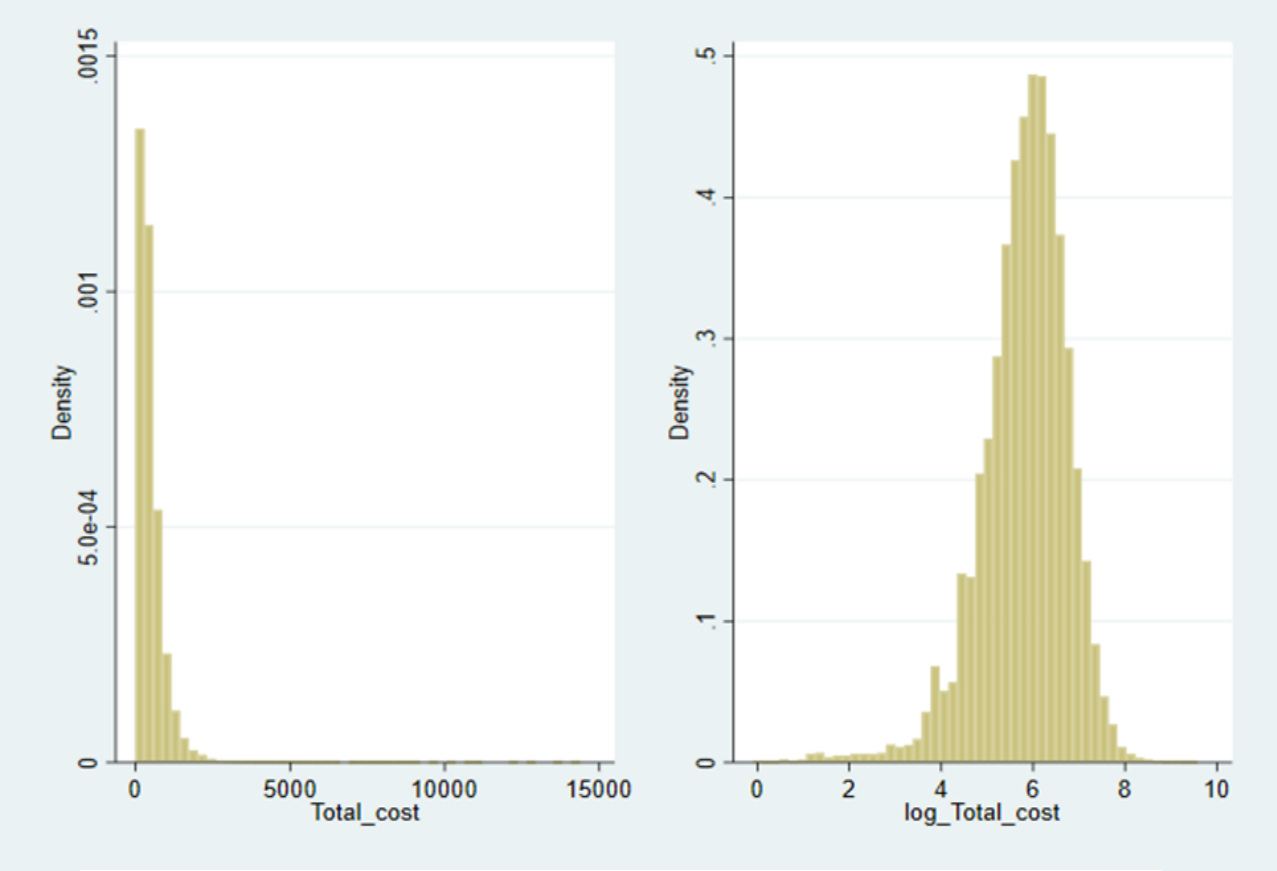


Figure 7.7: The log-transformed total healthcare cost versus the raw cost data

The exponentiated regression estimates from the log-OLS model are reported in Table 7.8. These are interpreted as percentage change in total cost for a one-year increase in age, and similarly for

Table 7.8: Exponentiated regression estimates of the log-OLS model

Variable	Coefficient	Robust std. error	P-value	(95% Confidence	interval)
Age	1.006	0.000	0.000	1.006	1.006
Female	1.274	0.008	0.000	1.259	1.289
N. Ireland	1.039	0.011	0.000	1.018	1.060
Scotland	1.083	0.007	0.000	1.069	1.098
Wales	1.037	0.008	0.000	1.022	1.053
Townsend 2	0.994	0.009	0.528	0.977	1.012
Townsend 3	1.018	0.009	0.045	1.000	1.036
Townsend 4	1.073	0.010	0.000	1.054	1.092
Townsend 5	1.128	0.011	0.000	1.107	1.149
BMI 25-30	1.013	0.007	0.076	0.999	1.027
BMI >30	1.114	0.008	0.000	1.099	1.130
Smoker	1.113	0.009	0.000	1.096	1.131
Ex-smoker	1.091	0.007	0.000	1.077	1.105
CCI 1	1.310	0.009	0.000	1.292	1.327
CCI 2	1.406	0.012	0.000	1.382	1.431
CCI 3	1.617	0.019	0.000	1.581	1.654
CCI 4	1.833	0.031	0.000	1.773	1.895
CCI $\geq$ 5	2.038	0.040	0.000	1.961	2.118
Constant	146.947	2.192	0.000	142.712	151.307

increments in the categorical predictors. The significance of the coefficients remained largely the same as in the OLS model with a couple of exceptions. Wales showed a 3.7% increase in cost compared to England and this was significant, while the middle BMI group indicated a 1.3% increase in cost compared to the lower group but without being significant. Increments of costs by smoking status, deprivation quintiles, and comorbidity categories were consistent with the OLS estimates. Patients in the five or more CCI category incurred twice as much cost as those without any comorbidities, while female patients showed a 27% increase in cost compared to males.

7.4.5 GLM modelling

The results of AIC and BIC model comparison criteria used to select the most appropriate link and variance functions for GLM modelling is shown in Table 7.9 in the order of the preferred model. The three models with the lowest AIC and BIC values were the GLM with identity link and a gamma variance, GLM with square root link and a gamma variance, and GLM with log link and gamma variance. These models also maximised the log-likelihood (LL) with the identity link model showing slightly better characteristics than the square root link or log link model based on these criteria. The three models were therefore selected for GLM modelling of the healthcare cost data.

Table 7.9: Comparison of GLM model selection in order of preference

GLM Model (Link/Variance)	Log-likelihood (LL)	AIC	BIC
Identity/Gamma	-772063.4	1544165	1544347
Square root/Gamma	-772071.5	1544181	1544363
Log/Gamma	-772098	1544234	1544416
Log/Negative Binomial	-772216.6	1544471	1544653
Identity/Normal	-809352.7	1618743	1618926
Square root/Normal	-809356.3	1618751	1618933
Log/Normal	-809382.6	1618803	1618985

GLM with an identity link and gamma variance

As this model was based on identity link function (no transformation needed), marginal effects would not be required. The regression estimates (Table 7.10) are interpreted in the same way as estimates from the OLS model. The significance and the direction of relationship between the predictor variables and the response in the GLM model were largely the same as those reported in the OLS model with some variations in the magnitude of p-values and the coefficients themselves. The only exception was the middle BMI group which showed a decrease of about £5.3 in total cost compared to the low BMI group under the GLM and this was not significant at 5% level. Under the OLS model however, a similar magnitude of decrease (£8.2) was reported and this was significant. Despite the slight variations observed, the two models produced consistent and comparable results.

Table 7.10: Regression estimates of the GLM model with identity link and gamma variance

Variable	Coefficient	Robust Std. error	P-value	(95% Confidence	interval
Age	1.982	0.079	0.000	1.828	2.137
Female	90.032	2.573	0.000	84.989	95.074
N. Ireland	10.975	4.233	0.010	2.678	19.271
Scotland	19.489	3.167	0.000	13.282	25.696
Wales	-1.517	3.578	0.670	-8.531	5.496
Townsend 2	4.179	3.771	0.270	-3.213	11.571
Townsend 3	15.591	3.813	0.000	8.117	23.065
Townsend 4	36.051	4.105	0.000	28.005	44.097
Townsend 5	53.550	4.414	0.000	44.898	62.202
BMI 25-30	-5.290	3.037	0.080	-11.242	0.663
BMI >30	35.489	3.288	0.000	29.045	41.933
Smoker	55.577	3.662	0.000	48.400	62.753
Ex-smoker	33.229	2.991	0.000	27.367	39.091
CCI 1	104.200	3.298	0.000	97.735	110.665
CCI 2	146.957	4.818	0.000	137.514	156.400
CCI 3	220.661	7.019	0.000	206.904	234.418
CCI 4	304.106	11.942	0.000	280.699	327.512
CCI $\geq$ 5	379.008	15.547	0.000	348.536	409.480
Constant	180.574	6.070	0.000	168.678	192.471

GLM with a square root link and gamma variance

Regression coefficients from a square root link GLM model do not have natural interpretation, hence marginal effects are produced instead (Table 7.11) to provide an equivalent output to the OLS and the identity link GLM models. The estimates reported were more consistent with the latter. The changes observed were generally a slight increase in the coefficients of the square root GLM model compared to the identity link GLM. The exceptions to these were the comorbidity categories above CCI 2 as well as the non-significant coefficients of Wales, Townsend 2, and the middle BMI group which showed minimal decline in healthcare costs. The significance of the middle BMI group was now marginal at 0.049 which sat somewhere between the level reported by the OLS and the identity link GLM. The original output from the GLM model with square root link and gamma variance are shown in Appendix 7.3.

Table 7.11: Marginal effects of the GLM model with a square root link and gamma variance

Variable	Margins (dy/dx)	Robust std. error	P-value	(95% Confidence	interval)
Age	2.065	0.085	0.000	1.899	2.231
Female	92.332	2.661	0.000	87.117	97.548
N. Ireland	12.862	4.424	0.004	4.191	21.533
Scotland	20.949	3.265	0.000	14.549	27.349
Wales	-2.480	3.705	0.503	-9.741	4.781
Townsend 2	4.030	3.925	0.305	-3.663	11.723
Townsend 3	15.720	3.951	0.000	7.976	23.464
Townsend 4	36.975	4.253	0.000	28.640	45.310
Townsend 5	54.618	4.533	0.000	45.734	63.503
BMI 25-30	-6.199	3.156	0.049	-12.384	-0.014
BMI >30	36.847	3.374	0.000	30.233	43.461
Smoker	58.610	3.849	0.000	51.065	66.154
Ex-smoker	34.313	3.034	0.000	28.366	40.260
CCI 1	106.763	3.279	0.000	100.338	113.189
CCI 2	148.279	4.800	0.000	138.872	157.686
CCI 3	220.286	6.977	0.000	206.611	233.961
CCI 4	301.819	11.824	0.000	278.644	324.994
CCI $\geq$ 5	376.565	15.437	0.000	346.308	406.821

GLM with a log link and gamma variance

Unlike the GLM model with square root link, estimates from a log link GLM model could be exponentiated and reported as percentage changes (in line with log-OLS estimates). However, in order to make consistent comparison, marginal effects from the GLM model with a log link and gamma variance are reported (Table 7.12). The significance of the coefficients and the direction of the relationships remained largely the same as the previous two GLM models and the OLS model with only minor changes in magnitude. Following the pattern from the previous model, the estimates have shown slight increase compared with the square root link model while the exceptions mentioned before also showing slight decline. The significance of the middle BMI group has gone from being non-significant in the identity link model (0.08) to marginally significant in the square root link model (0.049), and to being fully significant in this model (0.033). The original output from the GLM model with log link and gamma variance is shown in Appendix 7.4.

Table 7.12: Marginal effects from the GLM model with a log link and gamma variance

Variable	Margins (dy/dx)	Robust std. error	P-value	(95% Confidence	interval)
Age	2.111	0.090	0.000	1.935	2.288
Female	92.684	2.711	0.000	87.370	97.997
N. Ireland	14.418	4.582	0.002	5.436	23.399
Scotland	22.033	3.332	0.000	15.502	28.564
Wales	-3.265	3.779	0.388	-10.671	4.141
Townsend 2	3.872	4.021	0.336	-4.009	11.754
Townsend 3	15.605	4.033	0.000	7.700	23.510
Townsend 4	36.858	4.344	0.000	28.344	45.373
Townsend 5	54.339	4.604	0.000	45.316	63.361
BMI 25-30	-6.891	3.228	0.033	-13.218	-0.563
BMI >30	37.507	3.433	0.000	30.779	44.236
Smoker	60.569	4.012	0.000	52.706	68.433
Ex-smoker	34.599	3.043	0.000	28.635	40.563
CCI 1	108.562	3.265	0.000	102.163	114.961
CCI 2	148.829	4.776	0.000	139.467	158.188
CCI 3	218.816	6.912	0.000	205.268	232.364
CCI 4	298.476	11.731	0.000	275.484	321.468
CCI $\geq$ 5	372.690	15.276	0.000	342.751	402.630

7.4.6 Extended Estimating Equations (EEE) modelling

The iterative algorithm in the EEE modelling of the raw total healthcare cost data did not converge at all. Therefore, the outcome variable was scaled down by dividing it by its mean as recommended by the developers of the EEE method Basu & Rathouz (Basu, 2005, Basu and Rathouz, 2005) and convergence was achieved. The regression estimates obtained are shown in Table 7.13. The regression output also provided parameter estimates for the link and variance functions as standard. The λ value of 0.928 (95% CI: 0.732 - 1.124) indicated that the appropriate link function was closer to an identity link (where $\lambda = 1$) rather than to square root link ($\lambda = 0.5$) or log link ($\lambda = 0$). Similarly, the value of θ_2 from the model was 1.484 (95% CI: 1.288 - 1.679) which suggested that the optimal variance function was somewhere between a Poisson (where $\theta_2 = 1$) and a gamma (where $\theta_2 = 2$) distribution.

Table 7.13: Original regression estimates of the EEE model

Variable	Coefficient	Robust std. error	P-value	(95% Confidence interval)	
Age	0.004	0.000	0.000	0.004	0.005
Female	0.187	0.006	0.000	0.175	0.198
N. Ireland	0.027	0.009	0.000	0.009	0.044
Scotland	0.043	0.007	0.000	0.030	0.056
Wales	-0.004	0.007	0.550	-0.019	0.010
Townsend 2	0.008	0.008	0.320	-0.008	0.023
Townsend 3	0.032	0.008	0.000	0.016	0.047
Townsend 4	0.075	0.009	0.000	0.058	0.091
Townsend 5	0.110	0.009	0.000	0.092	0.128
BMI 25-30	-0.013	0.006	0.040	-0.025	0.000
BMI >30	0.074	0.007	0.000	0.060	0.087
Smoker	0.116	0.008	0.000	0.101	0.131
Ex-smoker	0.069	0.006	0.000	0.057	0.081
CCI 1	0.220	0.007	0.000	0.207	0.234
CCI 2	0.307	0.010	0.000	0.288	0.327
CCI 3	0.457	0.015	0.000	0.427	0.486
CCI 4	0.627	0.026	0.000	0.576	0.677
CCI $\geq$ 5	0.777	0.035	0.000	0.707	0.846
Constant	-0.628	0.016	0.000	-0.658	-0.597
λ	0.928	0.100	0.000	0.732	1.124
θ_1	0.798	0.020	0.000	0.759	0.837
θ_2	1.484	0.100	0.000	1.288	1.679

λ: *Parametric family of the link function*

$\theta 1$ & $\theta 2$: *Parametric family of the variance function*

As with the GLM with square root link function, the regression coefficients of the EEE modelling did not have natural interpretation and marginal effects were needed. However, unlike the other methods, EEE modelling in Stata did not have provision for full marginal effects output. Therefore, the marginal effects and their confidence intervals were estimated (Table 7.14) individually for each predictor and categorical levels scaling it back to its original value using the mean total cost. The table shows that, once again, the estimates were consistent with the previous models both in significance and direction of relationships between the predictor variables and total healthcare cost. The middle BMI group, showing a decrease of about £6 compared with the lower BMI group, was also significant in this model ($p = 0.04$) in line with the OLS and the log link GLM models.

Table 7.14: Estimates of marginal effects and CIs derived from the EEE model

Variable	Margins (dy/dx)	P-value	(95% Confidence interval)	
Age	1.984	0.000	1.786	2.182
Female	89.624	0.000	83.266	95.981
N. Ireland	12.822	0.000	4.518	21.126
Scotland	20.477	0.000	14.198	26.756
Wales	-2.129	0.550	-9.133	4.875
Townsend 2	3.732	0.320	-3.665	11.129
Townsend 3	15.225	0.000	7.747	22.703
Townsend 4	35.852	0.000	27.631	44.074
Townsend 5	53.053	0.000	44.138	61.968
BMI 25-30	-6.136	0.040	-12.120	-0.152
BMI >30	35.375	0.000	28.742	42.009
Smoker	55.981	0.000	48.297	63.665
Ex-smoker	33.053	0.000	27.013	39.094
CCI 1	106.197	0.000	98.293	114.101
CCI 2	148.793	0.000	137.552	160.034
CCI 3	222.324	0.000	206.186	238.463
CCI 4	306.810	0.000	280.285	333.334
CCI $\geq$ 5	381.919	0.000	348.480	415.358

7.4.7 Quantile regression (QR)

Quantile regression can be conducted at any chosen quantiles across the full range of the cost distribution. A quantile plot (Figure 7.8) was used to guide the choice of quantiles for modelling. The plot shows the quantiles of the total healthcare cost plotted against the fraction of the data they correspond to, and an inverse relationship was observed which is typical of a highly skewed data. High healthcare costs corresponded to a small fraction of the data, while very small patient-level costs represented a high proportion of the cost data.

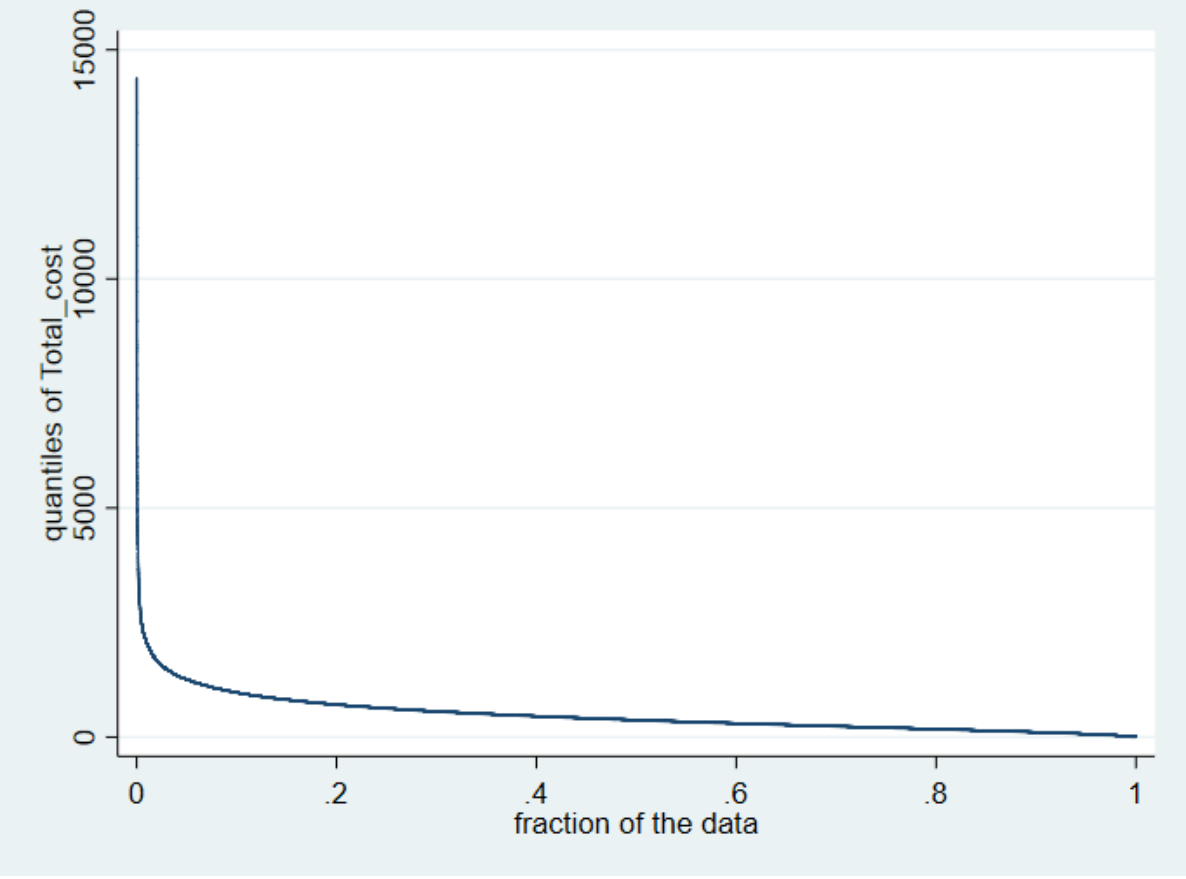


Figure 7.8: Quantile plot of the total healthcare cost data

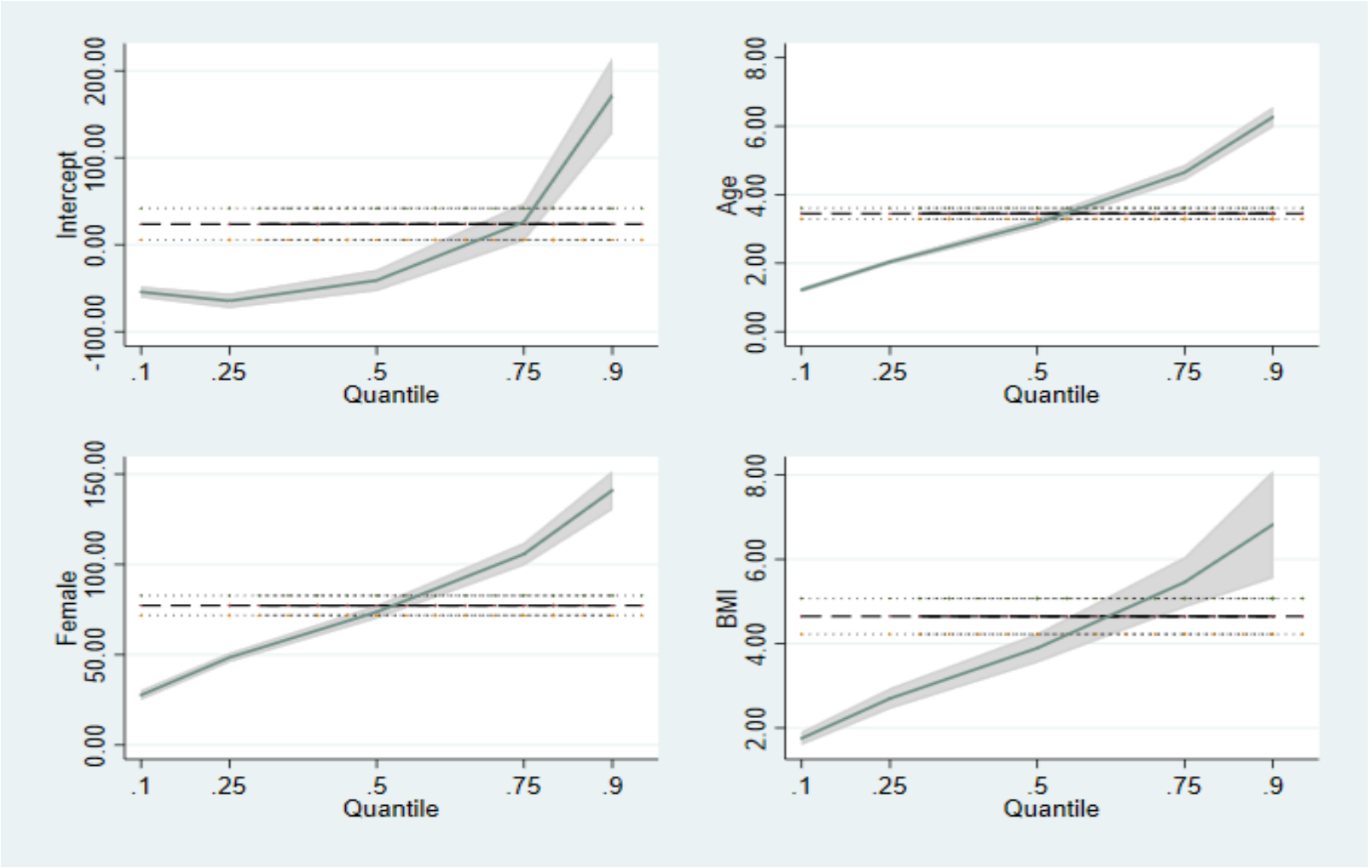
In order to capture the relationships across the full range of the distribution, quantile regressions were conducted for the 0.1, 0.25, 0.5, 0.75 and 0.9 quantiles of the total healthcare cost data. The estimates obtained are shown in Table 7.15 along with the OLS estimates for comparison. The results showed that estimates of QR varied depending on the quantile of the distribution being modelled. For most of the predictors, the change was generally an increase in coefficients across the quantiles. For example, a one-year increase in age resulted only in 78p increase in healthcare costs at 0.1 quantile, while the same change in age was associated with £3.83 increase in costs at 0.9 quantile. The same pattern was observed for female, Northern Ireland, Townsend quintiles (except Townsend 2), BMI >30, smoking status groups, and the CCI categories. Variations in the other coefficients, some of which were non-significant, were more mixed.

Table 7.15: Quantile regression estimates alongside OLS estimates

Variable	OLS Coef. (se)	0.1 Coef. (se)	0.25 Coef. (se)	0.5 Coef. (se)	0.75 Coef. (se)	0.9 Coef. (se)
Age	1.955	0.775	1.326	2.024	3.051	3.831
	(0.093)**	(0.045)**	(0.053)**	(0.074)**	(0.128)**	(0.205)**
Female	88.126	31.231	53.792	80.089	116.275	156.64
	(2.714)**	(1.288)**	(1.546)**	(2.21)**	(3.659)**	(6.706)**
N. Ireland	17.256	7.625	11.914	15.54	20.631	33.359
	(4.541)**	(2.347)*	(2.753)**	(3.776)**	(6.64)*	(12.848)**
Scotland	22.891	14.903	13.899	18.768	27.249	41.41
	(3.364)**	(1.59)**	(1.965)**	(2.931)**	(4.586)**	(8.126)**
Wales	-3.389	13.92	8.951	-0.591	-9.294	-27.012
	(3.760)~	(1.807)**	(2.113)**	(2.963)~	(4.943)~	(7.985)**
Townsend 2	2.751	-3.606	-3.675	-0.606	13.007	21.211
	(3.980)~	(1.956)~	(2.365)~	(3.28)~	(5.552)*	(9.758)*
Townsend 3	14.486	-2.29	1.167	9.185	27.996	44.071
	(3.979)**	(1.95)~	(2.331)~	(3.329)~	(5.36)**	(9.931)**
Townsend 4	34.349	6.191	12.575	20.967	48.58	68.96
	(4.305)**	(2.033)*	(2.416)**	(3.372)**	(5.567)**	(10.318)**
Townsend 5	50.782	13.683	23.21	39.845	74.316	117.535
	(4.537)**	(2.191)**	(2.648)~	(3.744)**	(6.329)**	(11.305)**
BMI 25-30	-8.207	5.542	6.58	1.258	-14.449	-34.828
	(3.210)*	(1.555)**	(1.901)*	(2.687)~	(4.476)*	(8.26)**
BMI >30	34.359	17.642	25.206	30.331	38.086	44.515
	(3.440)**	(1.655)**	(1.983)**	(2.838)**	(4.83)**	(8.517)**
Smoker	55.613	8.07	15.425	34.516	63.07	114.601
	(3.829)**	(1.711)**	(2.064)**	(2.969)**	(4.979)**	(8.758)**
Ex-smoker	32.091	11.512	17.335	27.814	38.234	48.71
	(3.059)**	(1.553)**	(1.885)~	(2.607)**	(4.287)**	(7.436)**
CCI 1	108.166	36.756	55.612	87.824	126.027	190.269
	(3.247)**	(1.686)**	(1.916)~	(2.718)**	(4.756)**	(7.917)**
CCI 2	149.665	46.533	73.162	121.14	176.828	270.867
	(4.840)**	(2.321)**	(2.832)**	(4.235)**	(6.674)**	(11.588)**
CCI 3	221.423	77.266	120.206	180.763	269.011	397.369
	(6.985)**	(4.565)**	(4.82)**	(6.191)**	(10.562)**	(16.586)**
CCI 4	307.198	107.312	164.395	249.489	369.946	547.891
	(12.367)**	(6.026)**	(8.231)**	(9.331)**	(12.669)**	(43.161)**
CCI 5	381.44	122.395	202.582	331.989	468.395	668.96
	(15.520)**	(8.987)**	(11.782)**	(14.932)**	(19.631)**	(40.256)**
Constant	183.884	6.892	36.996	107.072	216.521	397.98
	(6.559)**	(3.023)*	(3.6)**	(5.226)**	(8.972)**	(15.657)**

** p<0.05, ** p<0.01, ~ not significant (p>0.05), Coef. (se): Coefficient with standard errors*

Unlike the QR method, an OLS model assumes fixed regression coefficients for the entire distribution of the response. The mean estimates from the OLS were to some extent comparable to the median regression estimates (0.5 quantile) although the latter generally underestimated the costs. The assumptions of the OLS and the QR methods are demonstrated graphically in Figure 7.9 using selected predictors of age, gender, BMI and the intercept from the model. The plot shows that, while the OLS estimates remained flat (fixed coefficients and CIs), the QR estimates varied showing an upward trend across the quantiles. The OLS and QR estimates overlapped near the 0.5 quantile indicating that the mean estimates of the OLS fell largely within the confidence intervals of the median regression estimates from the QR and vice versa.



Solid lines and shaded areas: QR coefficients and 95% CIs respectively.
Dashed and dotted lines: OLS coefficients and 95% CIs respectively

Figure 7.9: Graphical representation of the QR vs. OLS estimates

7.4.8 Comparison between alternative models

Specification, bias, predictive accuracy and goodness-of-fit

Comparison of the performance of the alternative estimators is summarised in Table 7.16. For each model, p-values from test of specification using Pregibon's link (P-L) test, and test of systematic bias in the predicted values using Pearson's chi-squared test are reported. In addition, measure of predictive performance using error metrics values for MPE, RMSE, and MAPE are reported along with R^2, the overall indicator of goodness-of-fit for the models. Models that passed the tests at 5% significance level and the best performing two models under each measure of predictive performance and goodness-of-fit are shown in bold. Explanation of these measures and tests were given in Chapter 6.

Table 7.16: Comparison of model specification, predictive performance and goodness-of-fit

Estimator	P-L Test	Pearson Test	MPE	MAPE	RMSE	R^2
OLS	**0.3705**	**0.9999**	**0.0000**	282.1640	**434.4869**	**0.0675**
Log-OLS	<0.0001	0.0054	-0.3579	282.4193	434.8965	0.0658
GLM (identity)	**0.7542**	**0.7633**	0.0307	**282.1462**	434.4997	**0.0675**
GLM (log)	<0.0001	0.0014	-0.3234	282.3849	434.6717	0.0668
GLM (sq. root)	0.0018	**0.1191**	-0.2173	282.2319	434.5257	0.0674
EEE	NA	**0.9312**	**0.0021**	282.1533	**434.4905**	**0.0675**
QR (median)	**0.5960**	<0.0001	102.2517	**268.9426**	446.8076	0.0668

P-L test: Pregibon link test, MPE: mean percentage error, MAPE: mean absolute percentage error, RMSE: root mean squared error, R^2 denotes the R-squared from a regression of actual costs on the predicted values.

For the link test, the OLS (p = 0.3705), the GLM with identity link (p = 0.7542), and the QR (p = 0.5960) models were not rejected by the specification test at 5% level of statistical significance. Link test was not applicable for the EEE model as the optimal link function was calculated directly from the data rather than assumed apriori. The Pearson test failed to reject four out of the seven models (highlighted in bold in Table7.16) indicating that there was no evidence that the correlation coefficient between the prediction error (residuals) and the predicted values were different from 0 (systematic bias) in these models. The goodness-of-fit and predictive performance measurements (MPE, MAPE, and RMSE) of the models were highly similar to each other with the exception of the QR model. Goodness-of-fit measured by R^2 revealed that the best performing models (highest value) were the OLS, GLM with identity link, and the EEE models which had identical value of 6.75% (0.0675). The related measure of RMSE also corroborated the results of R^2 with the OLS and EEE models showing the lowest RMSE values followed by the GLM with identity link model.

In terms of prediction bias, the top two performing models were the OLS and the EEE models respectively while the QR model suffered largest bias. MPE values for some of the models were negative, but it is the magnitude of the values that is considered in comparison of the models. The signs of the values denote the direction of the bias, indicating whether the models underpredicted or overpredicted the outcome. In contrast to MPE, the QR model produced the lowest MAPE score indicating highest accuracy followed by the GLM with identity link model. The third best performing model in terms of accuracy was the EEE model, and the OLS was no longer dominant. No model came top at both prediction bias and accuracy suggesting that there may be a trade-off between the two performances. The overall best performing models were the OLS and

the EEE models although it is notable that the EEE applied accurately derived link function and was not testable. The GLM model with identity link was the third preferred GLM model in terms of the goodness of the link function at the model selection stage, however, it turned out to be the best performing GLM model at prediction. The worst performing models were the log-OLS and the GLM model with log link. Although these two models did not come top at any of the criteria, their predictive performance and goodness-of-fit scores were still largely similar to the other models.

The models were also compared in terms of the behavior of their residuals using scatter plots of residuals against predicted values (Figure 7.10). Residuals being the difference between observed and predicted values for each observation, they are generally desired to be near zero in ideal situation. The residuals are also expected to be symmetrically distributed around the zero-line indicating a linear relationship, and they also need to be scattered randomly (no particular patterns) indicating constant variance of the error terms (homoskedasticity). The models with the best-behaved residuals were the GLM models followed by the log-OLS model. The GLM models in this case were preferred since the residuals were narrowly scattered around the zero-value (smaller residuals) compared to the log-OLS model.

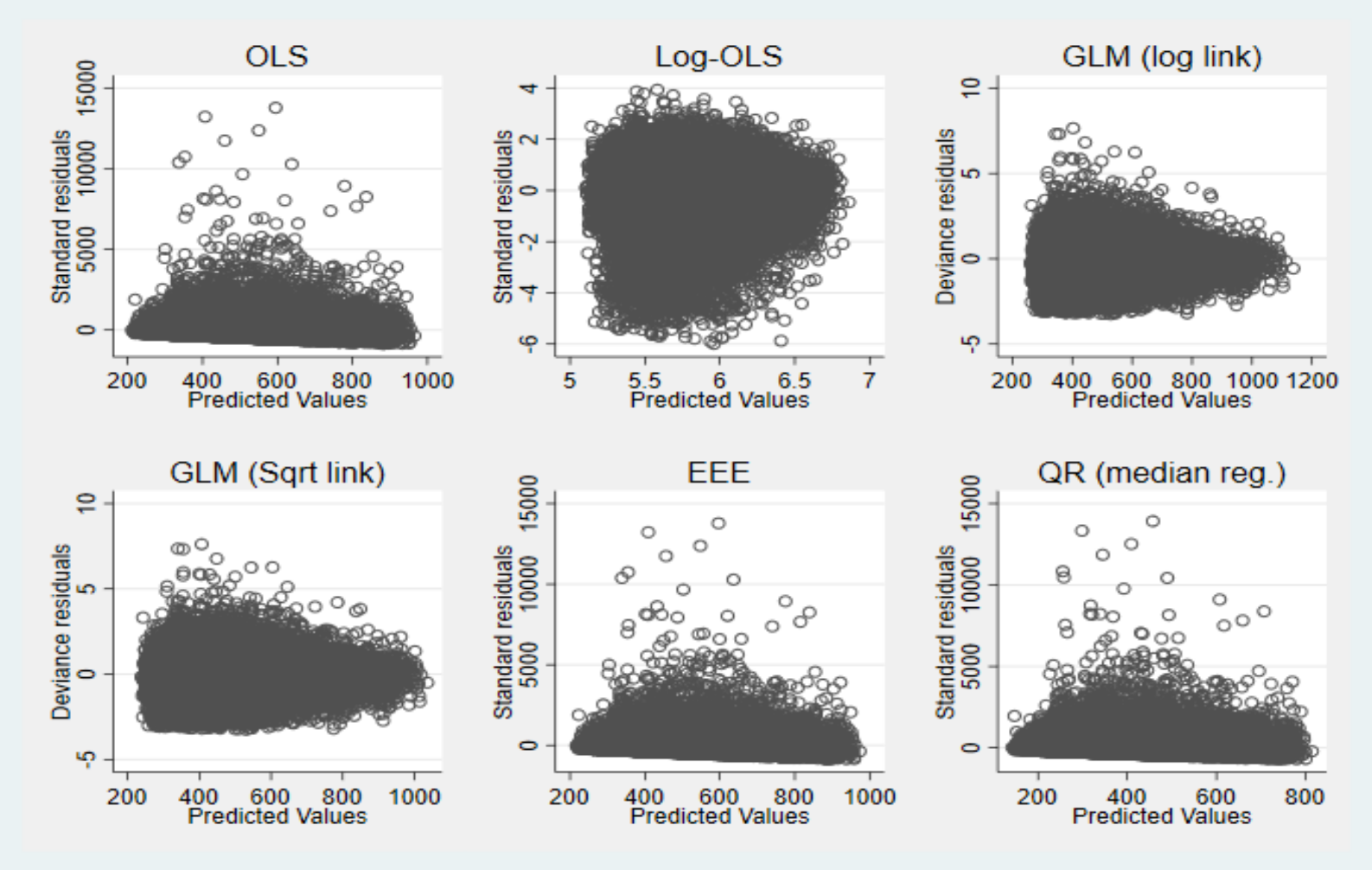


Figure 7.10: Scatter plot of the residuals against predicted values for the alternative estimators

Marginal effects of back pain on healthcare costs

The estimated average marginal effects of back pain on total healthcare costs obtained from each model (median for QR, mean for all other models) are shown in Table 7.17. The estimates are ordered highest to lowest with the log-OLS estimate also given in the original scale after applying Duan's smearing estimator. The observed mean (SD) total healthcare cost of the sample for comparison was £481.3 (449.95), while the observed median (IQR) cost was £369.07 (203.42 – 623.89). The back-transformed log-OLS estimate was the highest mean prediction among the models while the QR model produced the lowest estimate. However, the QR estimate was a median estimate, and the figure was actually slightly higher than the observed median cost of the sample, and within the interquartile range. There was little to separate the marginal effects produced by the other models.

Table 7.17: Predicted marginal effects for patients with back pain

Estimator	Margin	Standard error	(95% Confidence interval)	
Log-OLS	5.807* 487.448~	0.003	5.802	5.812
GLM (log Link)	481.628	1.325	479.031	484.224
GLM (sqrt link)	481.522	1.324	478.927	484.117
OLS	481.305	1.322	478.713	483.896
EEE	481.302	1.380	478.598	484.006
GLM (identity link)	481.274	1.324	478.680	483.868
QR (median)	379.053	1.162	376.775	381.331

** estimates are on log-scale,*

~ log-scale estimate back-transformed using Duan's smearing estimator.

The result of t-tests conducted to investigate differences between the EEE estimates and estimates from the other six models is shown in Table 7.18. The EEE estimate was used as a reference since it was the closest estimate to observed mean cost, and marginal effects from the models were compared against it. Significant differences were observed between the estimates of the EEE and the log-OLS model as well as between the EEE and the QR estimates. However, there were no statistically significant differences between the predictions of the other four models and that of the EEE model.

Table 7.18: Statistical tests of differences in the predictions of the models

Estimates compared	Mean difference	Standard error	T-test p-value	(95% Confidence interval)	
EEE vs. Log-OLS	-6.1459	0.5626	<0.0001	-7.2487	-5.0432
EEE vs. GLM (log Link)	-0.3255	0.5107	0.5239	-1.3265	0.6754
EEE vs. GLM (sqrt link)	-0.2195	0.5071	0.6651	-1.2133	0.7744
EEE vs. OLS	-0.0021	0.5029	0.9966	-0.9878	0.9835
EEE vs. GLM (identity link)	0.0285	0.5019	0.9547	-0.9553	1.0123
EEE vs. QR (median)	102.2495	0.4689	<0.0001	101.3304	103.1686

The predicted total healthcare costs of back pain from the models were also plotted against the observed costs (Figure 7.11). This enabled comparison of the models' prediction ability by deciles of age since there may be concern that models perform with varying success at different points in the distribution. The plot shows that the distribution of the predictions from the five models (OLS, EEE, and the three GLM models) were consistent with the observed cost across deciles of age. This also corroborated the point estimates reported in Table 7.17. The models slightly underpredicted at the lower and top end of the distribution (below the 2nd and above the 8th deciles) while they also slightly overpredicted in the middle deciles of the distribution.

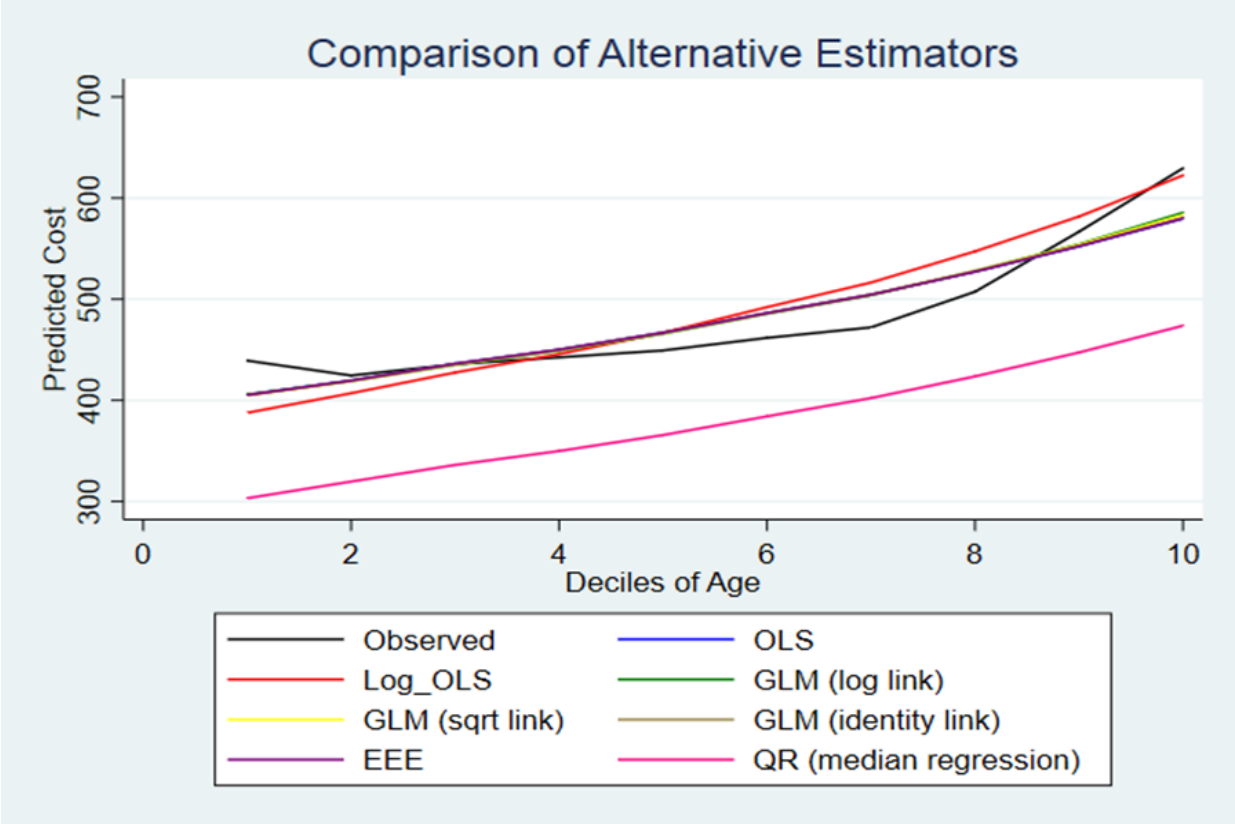


Figure 7.11: Plot of the predicted costs across deciles of age for the alternative estimators

The log-OLS model showed more pronounced deviation from the observed cost at the lower and middle parts of the distribution. The median regression estimates from the QR model underestimated the cost of this highly skewed data across the full deciles of age.

7.5 Discussion

7.5.1 Principal findings

This chapter aimed to investigate the impact of patient and clinical characteristics on healthcare costs of individuals with back pain. Several econometric methods were applied and compared using a 2015 healthcare cost data from THIN database. The seven models fitted were OLS on untransformed, and log transformed data, gamma distributed GLMs with identity, log, and square root links, an EEE model, and a quantile regression approach. All models included age, gender, BMI category, CCI category, Townsend quintiles, country, and smoking status as predictors.

In general, all models confirmed that the seven variables used in the analyses were significantly associated with healthcare costs of back pain. The only exceptions were living in Wales and being in the second deprivation quintile which were not found to have significant association with cost compared with England and the least deprived quintile respectively. High deprivation, having comorbidities, female, smoker, and obese patients incurred much higher healthcare costs compared with their respective reference groups. The higher healthcare costs in females compared to males may be explained by the fact women are also more likely to consult their GP than men in general (Hunt et al., 2011, Wang et al., 2013). While obese patients incurred significantly higher costs than patients in the low BMI group, being an overweight patient

(middle BMI group) on the contrary resulted in lower costs than the reference group. A possible explanation for this might be that the middle BMI group might reflect individuals who are more affluent and potentially accessing private healthcare and hence incurring less cost to the NHS.

The five models (OLS, EEE and the three GLMs) produced consistent and almost identical results, while the log-OLS model showed slight difference in estimates. The quantile regression approach characterised the association between the predictors and response in more detail across the full distribution of the cost. The observed relationship between the predictors and cost varied conditional on the quantile function. Regression estimates generally increased across the quantiles modelled (0.1, 0.25, 0.5, 0.75, and 0.9). The median regression produced comparable estimates with the mean-based regression methods in comparison with other conditional quantiles. Statistical tests showed no significant difference in the marginal effects of the five models, although the EEE and OLS models were preferred based on specification tests, predictive performance, and goodness-of-fit of the models.

7.5.2 Strengths and limitations of the study

To the researcher's knowledge, this was the first study in the UK to characterise and quantify the association of clinical and demographic factors with healthcare costs of back pain. The study used a large sample of patients from one of the largest primary care databases in the UK. The demographic groups were a representative sample of patients with back pain in the general population of the UK, so the findings of this study may be generalisable. A range of econometric regression methods were applied from the simpler OLS to the more flexible, and advanced EEE models. Despite considerable methodological differences, many of the models provided

consistent and largely similar results. The models that did not perform well were not expected to do so either because of their limitations (in the case of log-OLS) or because they serve a slightly different purpose (in the case of quantile regression). Variable selection and model specification were conducted methodically applying alternative variable selection methods as sensitivity analysis and following criteria for selection of appropriate models. The fitted models were also subjected to rigorous tests of specifications as well as assessing their predictive performance and goodness-of-fit.

There were, however, some limitations to the study. The current study was based on prescriptions and consultations costs in primary care using them as exemplars for assessing the different costs components associated with back pain. The full range of healthcare costs of back pain could be modelled using the same analyses approach developed in this study. Some important risk factors for back pain such as fitness/exercise level, employment type, and mental health conditions were also not available for analysis. Inclusion of such confounders, and some interaction terms may have resulted in a richer regression model. Healthcare expenditures for back pain are also likely to vary by diagnoses type (Luo et al., 2004), but the current study did not distinguish between diagnoses types due to difficulty in accurately categorising the Read medical codes used in the study.

7.5.3 Comparison with other studies and conclusion

The demographics of the sample in this study were comparable to a previous UK study conducted to estimate costs associated with treatment of chronic low back pain using CPRD (Hong et al., 2013). The proportion of female to male was 60:40, and the mean (SD) CCI index was 0.73(1.17)

in the previous study, while these were 63:37 and 0.86(1.16) respectively in the current study. The spread of age across the sample in the two studies was also similar. Although Hong et al. used a regression method to estimate healthcare costs, predictors of costs were not reported in the study and there was no other UK study to make a direct comparison with the estimates from the current study.

The findings of this study were consistent with those of previous US and other European studies. A US study on healthcare expenditure of back pain patients (Luo et al., 2004) found that at least 75% of the total costs were attributed to those with top 25% costs, and per-capita costs were higher for female and older patients. Other studies on musculoskeletal and chronic pain also confirmed that higher costs were associated with female patients (Azevedo et al., 2016, Boonen et al., 2005, Gaskin and Richard, 2012), and with older age groups (Azevedo et al., 2016). Previous studies generally did not control for comorbidity and deprivation indices in their analyses, but focussed more on other socio-economic factors like employment, education and income levels. Pain intensity and depression were reported to be strong predictors for healthcare costs of back pain (Becker et al., 2010, Engel et al., 1996) as well as costs of pain in general (Gaskin and Richard, 2012), but the current study was unable to investigate these factors due to constraints of the available dataset. On the other hand, most of the previous studies that analysed factors associated with healthcare costs of back pain were conducted with smaller sample size usually from survey data. So far, only the study by Luo et al. (2004) included a larger sample size than the current study.

While the empirical findings of this study were plausible and in line with expectations, the methodological contributions of the analyses were equally important. The choice of a particular

regression model for analysing healthcare cost data is hardly straight forward. Several studies have compared alternative statistical methods either empirically (Basu et al., 2006, Carreras et al., 2016, Dodd et al., 2006, Dunn et al., 2003, Griswold M., 2004, Lipscomb et al., 1998, Powers et al., 2005) or theoretically as a review of methods (Diehr et al., 1999, Gregori et al., 2011, Manning and Mullahy, 2001, Mihaylova et al., 2011). No single method is best under all conditions and several alternative models can usually be applied without necessarily deducing major analytic improvements (Diehr et al., 1999, Manning and Mullahy, 2001, Mihaylova et al., 2011). The result of model comparisons in the current study also confirmed this with little to separate between the five models out of a total of seven model that were fitted. The simplest method (OLS), and the most advanced and complex method (EEE) applied in the analyses fared slightly better than the three GLM models. This was consistent with the findings of other studies that a simple OLS model may provide equivalent predictive performance and accuracy as the more advanced econometric models in large samples where the asymptotic properties assure unbiasedness and efficiency of the OLS estimator (Dunn et al., 2003, Mihaylova et al., 2011, Powers et al., 2005).

Contrary to the popularity of a GLM model with log link and gamma distribution as the most common specification for analysing healthcare cost data, this study showed that it was not necessarily the best model overall, and not even the most appropriate in the GLM family. Although the three GLM models produced highly similar predictions, the model with the identity link in particular showed better performance than the log link model, and this emphasises the need for comparing model fit using model selection criteria.

To the researcher's knowledge, this is the largest study in the UK to investigate the distribution of comorbidities, deprivation, and other patient and clinical characteristics and their association with healthcare costs of patients back pain. This chapter focussed on the costs associated with cases since interest lies in the characteristics of back pain patients. However, it is acknowledged that it was possible to include the controls in the regression modelling and derive incremental cost estimates that could be compared with estimates obtained from Chapter 5. The results presented in this chapter demonstrated a strong link between healthcare costs and the factors examined, and that per-capita expenditure increased significantly with age, deprivation, comorbidities as well as for female, smokers, and obese patients. These findings suggest that back pain patients in primary care utilise healthcare resources in response to a combination of clinical factors and patients' characteristics. The results of these analyses may therefore be used inform the question of what to target when designing cost-saving interventions or rehabilitation programs which may be tailored according to individual morbidity profiles. Special attention to high resource utilisers, and those with comorbidities may improve the outcomes for these patients, and possibly reduce both the short- and long-term costs associated with back pain (Carey and Freburger, 2005, Nordin et al., 2002, Ritzwoller et al., 2006).

The study also demonstrated the application of a variety of econometric methods for modelling healthcare costs associated with back pain. The evidence puts emphasis on the advantages of considering appropriate alternative models through sensitivity analysis to ensure robust conclusions. It also shows that model selection and performance assessment should be evidence-based and suitable for the purpose as this could vary from one dataset to another. Future studies should aim to control for additional variables such as pain severity, chronicity, depression,

employment type, and education levels to assess the impacts of a broader range of confounders and add further information about the predictors of healthcare costs of back pain.

CHAPTER 8. DISCUSSION

8.1 Introduction

The overarching aims of this thesis were to estimate the healthcare costs of back pain from electronic health records (EHRs) data, and to appropriately predict the relationship between reported back pain and its consequent economic burden given the characteristics of the dataset. In brief, the research consisted of four phases corresponding to each of the objectives set out in Chapter 1.

- *Phase I* was a systematic review of the existing literature aimed at ascertaining the most appropriate method of estimating healthcare costs of back pain from EHR data.
- *Phase II* was a review of routinely collected data sources in the UK exploring and identifying the cost components that could be estimated.
- *Phase III* was the application of a retrospective case-control study to estimate the healthcare costs of back pain using the database established in phase II.
- *Phase IV* was the comparison of alternative and appropriate econometric modelling techniques to identify the determinants of costs from the back pain cohort developed in phase III.

In this final chapter, the findings from the thesis are drawn together and presented. First, the principal findings from the systematic review, the estimation of healthcare costs, and the

econometric modelling studies are presented. Next, the strengths and weaknesses of the research within this thesis are discussed, also in relation to other studies. Then, the implications of the research to stakeholders such as healthcare providers, and implications in relation to other research such as economic evaluation studies are discussed. The chapter ends with some recommendations for future research and policy, and a concluding remark is given.

8.2 Statement of principal findings

8.2.1 Systematic review of existing studies

A methodological systematic review of studies that assessed the direct and indirect costs of back pain was presented in Chapter 3. The review examined 43 COI studies that used significantly heterogeneous methodologies to derive cost estimates. The findings of the review confirmed that back pain is a costly problem worldwide. The national cost estimates in 2015 USD ranged from $259 million ($29.1 per capita) in Sweden to $71.6 billion ($868.4 per capita) in Germany. It was also clear from the review that indirect costs were the main cost drivers for back pain. Many studies did not explicitly describe their methodologies posing challenges in assessing them. Sensitivity analyses were not routinely conducted to assess the robustness of the approaches taken. The lack of clarity and apparent discrepancies within the studies have direct impact on the reported costs and the credibility of the studies. The main methodological challenges in terms of comparability of reported costs stemmed from variations in the case definition of back pain, the source of data used, the cost components included, and the methods of estimation adopted in the analyses.

The majority of studies were conducted using large surveys or compensation claims databases rather than EHRs and hence commonly adopted a direct method of summing up back pain related costs. As the focus of this thesis is on the use of patient level data from EHRs, an incremental cost approach which isolates the actual costs due to back pain and accounts for costs that would otherwise be missed (eg. mental healthcare costs due to back pain) was deemed appropriate for the analysis. Back pain has important mental health implications with depression or other psychiatric disorders being common among patients with back pain and being generally associated with increased healthcare resource utilisation (Carstensen et al., 2012, Holmes et al., 2013, Rayner et al., 2016). Despite the methodological variations in the included studies, the national estimates reported in this review represented significant costs of back pain. However, costs have not been updated in the UK in nearly 20 years.

8.2.2 Estimating resource utilisation and costs

In order to address the scarcity of COI studies on back pain using routine medical records, a matched control study using incremental cost approach was conducted in Chapter 5. This retrospective study utilised the THIN database and included 133,341 patients with back pain that were matched 1:1 with patients without back pain. The base-case (primary care) annual healthcare cost of patients in the back-pain group (£63 million) was double that of the control group (£30.5 million). In the sensitivity analysis that used a smaller group of patients with more recent diagnosis, the result was consistent at £12 million and £5.3 million for the case and control groups respectively. The mean incremental cost per patient was £244 and £270 in the main and sensitivity analysis respectively. Nearly 80% of the cost difference between the case and control groups was attributed to consultations. The incremental healthcare cost of back pain in 2015

extrapolated to a UK national level amounted to £3.2 billion. This indicates that the direct cost of back pain has at least doubled in nearly 20 years since it was last estimated in 1998 (Maniadakis and Gray, 2000). However, the current study did not assess changes in unit costs of resources since the previous estimate due to heterogeneity of the two studies (patient-level vs aggregated data). Therefore, it was not possible to separate out the contribution of resource use intensity from changes in unit costs of resources when comparing the two estimates. The mean healthcare costs of patients with back pain varied significantly by gender, age-groups, deprivation quintiles, and comorbidity categories. Costs generally increased with age-groups and comorbidity indices, as well as for female patients. A five-year trend in healthcare costs between 2011 and 2015 showed a slight peak in 2013 which was consistent with the general trends in average number of prescriptions per GP consultation reported in a recent study (Curtis and Burns, 2018).

8.2.3 Econometric modelling of healthcare costs

The systematic review also revealed scarcity of studies reporting on factors associated with the reported costs of back pain. The econometric modelling study in Chapter 7 addressed this by providing the first estimates of the predictors of healthcare costs of back pain using a comparative regression modelling approaches to overcome the issues of analysing skewed healthcare expenditure data. This cross-sectional study analysed a sample of 108,013 patients with back pain from 428 practices across the UK. The distribution of cost was highly skewed requiring appropriate modelling approaches to determine factors associated with healthcare cost of back pain. Regression analysis methods applied included OLS, log-transformed OLS, generalised linear models (GLMs), extended estimating equations (EEE) models, and a quantile regression approach. The performance of the alternative estimators in terms of bias, accuracy and goodness-

of-fit was compared by examining regression diagnostics, and predictive performance of the models in line with standard approaches.

Per-capita expenditures increased significantly with age, deprivation, comorbidities as well as for smokers, female, and obese patients. No single model was clearly dominant across all measures, but the simpler model (OLS) and the most flexible and advanced model (EEE) performed as well, or better, than the commonly used GLM models. Predictions from five of the models (the OLS, EEE, and the three GLM models) were highly concurrent with the observed mean (SD) total healthcare cost of £481.3 (449.95) indicating the robustness of the models in such a large sample. Nevertheless, none of the models were best at both prediction bias and accuracy of predictions suggesting that there may be a trade-off between the two as measured by mean percentage error (MPE) and mean absolute percentage error (MAPE) respectively. The findings demonstrate that in large samples, a simple OLS model may provide predictive performance comparable to that of more advanced econometric models such as the EEE model.

8.3 Strengths and limitations of the research

8.3.1 Strengths of the research

This thesis presented the first comprehensive and rigorous systematic review of the methodologies used to estimate the direct and indirect costs associated with back pain. A major strength of this review was that a high number of studies were included from a diverse range of countries with different socio-economic and healthcare systems. The search strategy was robust and multiple databases were searched with no restriction on publication date. The previous review by Dagenais et al. (2008) focussed on synthesising results rather than methodologies. The

findings of their review were also limited as the search was restricted to one database and included only studies published in the previous 10 years. The main issues highlighted in the current review have provided support for updating back pain costs estimates in the UK.

The matched control study provided the first estimates of healthcare resource utilisation and costs associated with back pain in the UK using EHR data. It is one of the largest population-based COI studies conducted to date. The distribution of the sample was also comparable with the general population making the findings of the study generalisable to the wider population. Another major strength of the study was that a validated and comprehensive list of diagnoses was used to identify patients with back pain. By matching patients with several factors including comorbidities, the analysis in this study also accounted for the excess cost of back pain related comorbidities such as depression which has important implications for healthcare expenditure. This was done by study design overall rather than attempting to estimate the costs associated with each comorbid condition. The matched control study (incremental method) has been used previously in spine-related studies, and is known to capture expenditure resulting from related comorbid conditions (Hong et al., 2013, Luo et al., 2004, Martin et al., 2008). Conditions unrelated to back pain should theoretically be the same in the case and control groups allowing back pain related comorbidities (which are only present in the cases) to be captured. However, it was not possible to separate out the costs associated with each comorbid condition due to the design of the study (resource utilisations are attached to the index condition rather than the individual comorbid conditions). COI studies are underestimated if comorbid conditions associated with the disease of interest are not accounted for in the analysis (Blakely et al., 2019, Carstensen et al., 2012, Cortaredona and Ventelou, 2017, Norlund et al., 2001). The approach

used in this study may provide guidance on how to estimate the true costs of an illness using individual level data.

The econometric modelling work, a cross-sectional analysis of THIN database, provided detailed estimates of the association between healthcare costs of back pain, and patient and clinical characteristics. To the researcher's knowledge, this was the first study in the UK to characterise and quantify this relationship by comparing several alternative econometric modelling techniques. A comprehensive illustration of econometric methods in the analysis of EHR is provided. A major strength of the study was that a large nationally representative sample was used. As a result, the analyses were sufficiently powered to detect differences in model performance. The variable selection and model specification stages were also subjected to rigorous tests and sensitivity analyses enabling a valid comparative evaluation of the various models.

8.3.2 Limitations of the research

Although the thesis had several strengths, there were limitations which may provide grounds for further research. The systematic review only considered studies conducted in high income countries and published in English. Given the large number of studies included however, the findings of the review could be considered robust. The estimation of healthcare resource use and costs was based on primary care consultations and prescriptions. Data on other components such as inpatient and outpatient care are limited in primary care databases and therefore posed limitation in the analyses. The analysis of trends in healthcare costs was also restricted to a five-year period by conducting three separate analyses for 2011, 2013 and 2015. This was due to time

limitation to extract separate datasets for several years and repeat the analysis in each dataset which was a highly intensive and time-consuming process. As the eligibility of patients for each year of the study varied, the inclusion criteria needed to be applied for each year of the study prior to extraction, and the data were extracted accordingly on a year by year basis. The latest estimate that could be derived from THIN database was for 2015 as that was the latest year with the most complete record at the time of data extraction in 2017.

Another limitation was that identification of back pain was based on recorded Read codes where miscoding and different recording practices might be present (van der Bij et al., 2017). However, a comprehensive list of Read codes with a large study population was used, making the findings of the analysis robust. A major limitation of the econometric modelling work was that some important risk factors and confounders for back pain such as exercise level and occupation type could not be included in the models due to limitations of the EHR data. The analyses also did not make a distinction between the different back pain diagnosis types to be able to examine expenditure patterns in subgroups of morbidity such as by pain duration or severity. This was because the Read diagnostic codes were not specific enough to categorise the diagnosis types.

8.4 Implications of the research

8.4.1 Methodological contributions

The research within this thesis has important methodological implications. There are currently no formal guidelines for conducting a COI analysis (Clabaugh and Ward, 2008, Coughlan et al., 2014, Jo, 2014). The systematic review demonstrated that significant variation exists among others in the cost components included, the source of data, and the method of analysis used. The

literature therefore provided competing estimates for the healthcare costs of back pain. Two types of costs can generally be estimated in a COI analysis: an incremental cost and the total cost. Total healthcare costs can be estimated by summing all medical costs for patients with a diagnosis of the disease (sum_all_medical) or by summing the medical costs for treating that particular diagnosis (sum_diagnosis_specific) (Akobundu et al., 2006, Mattingly et al., 2016, Onukwugha et al., 2016). The sum_diagnosis_specific method was the most commonly used method for estimating the healthcare costs of back pain. However, both methods of estimating total healthcare costs have major flaws within them. The sum_all_medical approach is bound to significantly overestimate the costs since it follows an all-encounter approach rather than the costs being tied to the specific diagnosis. On the other hand, the sum_diagnosis_specific approach could underestimate the costs since it does not take into account the cost of co-morbid conditions, and clinical codes may also not be specific enough to capture all clinical encounters related to the disease (Hopkins et al., 2016, Martin et al., 2008).

Back pain being multifaceted involving various intricate structures of the spine, it can be difficult to isolate the costs directly associated with the problem without comparison to a similar reference population. In the absence of an appropriate comparator, there is a risk of confounding effects that some of the healthcare resource utilisation could be due to difference in baseline comorbidities (Hong et al., 2013). The best alternative is an incremental cost approach which requires a control group to estimate the excess cost attributed to back pain. However, this approach was hardly used in COI studies of back pain as shown in the systematic review. Two reasons are likely to have influenced this decision. First, the complexity of matching the case and control groups on a number of patient and clinical characteristics or adjusting for these covariates

in an econometric model. Second, as most of the COI studies of back pain were conducted using survey-based data or compensation claims databases, they are bound to have limitations in terms of capturing detailed baseline comorbidities and other clinical characteristics compared to GP records in an EHR. The matched control analysis in this thesis therefore offered an important methodological contribution to the COI literature on back pain through the use of propensity score matching to appropriately match the case and control groups and obtain more reliable estimates.

It is also evidenced that COI studies largely fail to account for comorbidities (Cortaredona and Ventelou, 2017, Segel, 2006b, Blakely et al., 2019), carrying out the analysis as if comorbidities did not exist. This is partly due to the lack of application of the incremental cost approach as discussed above. It is further complicated by difficulty of deciding how many comorbid conditions and which comorbidities to account for in the analysis. The cost of comorbidities appear to be accounted for in COI studies of some high profile medical conditions with more obvious comorbidities such as diabetes (Honeycutt et al., 2009, Seuring et al., 2015, Tunceli et al., 2010), or obesity (Anis et al., 2010, Pelone et al., 2012, Sander and Bergemann, 2003). However, in conditions such as back pain where the role of comorbidities is less obvious (Schneider et al., 2007), the inclusion of comorbidities costs in COI studies does not appear to receive much attention. A systematic review on chronic low back pain (CLBP) and psychological comorbidity by Bletzer et al (2007) reported a significant association between LBP and depression (Bletzer et al., 2017). Other studies found that depressed patients were twice as likely to report LBP compared to those without depression (Li, 2015, Bair et al., 2003), and the various complications associated with chronic pain such as sleep disorder, depression, and anxiety

disorders incurred significant economic burden (Fine, 2011). The Charlson Comorbidity index (CCI) used in this thesis included most of the chronic conditions listed in the Quality and Outcomes Framework (QOF). By accounting for these conditions, the healthcare cost estimation in this thesis provided an additional contribution to the COI methodology of back pain.

The matched control study in this thesis also revealed a key potential pitfall in the selection of an appropriate counterfactual or reference population in a case-control study. Cases in this study were defined as patients with a diagnosis of back pain who were required to have at least one prescription drug for pain during the study year to ensure that they were relevant cases. Controls on the other hand were patients without a diagnosis of back pain who may or may not have received prescription drugs for pain. This posed a methodological challenge in the choice of appropriate control group. On one hand, the controls needed to be representative of the general population in order to make a valid inference about the incremental healthcare cost of back pain nationally. This meant not having a requirement that patients in the control group should also have at least one prescription drug since the general population could not be assumed to be on analgesics. On the other hand, it made sense from an epidemiological point of view to stipulate that controls should also receive at least one prescribed analgesic to make sure that we have a balanced case and controls groups. This is to avoid having healthier population in the control group compared to the cases.

The World Health Organisation (WHO) guide on identifying the economic consequences of disease and injury stress the importance of identifying an appropriate counterfactual or reference population which requires careful consideration of various issues (WHO, 2009). Separate analyses were conducted in this thesis for each control-group scenario since the economic

consequence of the choice of controls was unknown. The resulting incremental cost obtained from the second scenario where the controls were also required to have prescription record to qualify as a control represented a surprisingly significant underestimation of the costs. The explanation is likely to be that the controls had some underlying painful medical conditions which increased their healthcare resource utilisation making them different from the general population. This work therefore revealed a key methodological implication in the choice of controls or reference population for a case-control study.

The econometric modelling work presented in this thesis investigated the methodological challenges posed by various features of healthcare cost data. Several studies have analysed healthcare costs of back pain/LBP to identify determinants of costs or for prediction of estimated costs (Becker et al., 2010, Boonen et al., 2005, Engel et al., 1996, Hong et al., 2013, Maeng et al., 2015, Ritzwoller et al., 2006, Sabariego et al., 2011, Sharma et al., 2009, Martin et al., 2008, Gore et al., 2012, Luo et al., 2004, Mapel et al., 2004, Mehra et al., 2012). Various statistical methods were reported in these studies but none of the studies analysed healthcare expenditure by applying and comparing a variety of alternative econometric models. Using seven regression models and a nationally representative dataset, the study in this thesis provided an empirical modelling of the healthcare costs of back pain examining the appropriateness of each model. While there was no previous comparative modelling work for back pain, similar analyses have been conducted in other disease areas (Basu et al., 2006, Basu and Rathouz, 2005, Carreras et al., 2016, Deb and Norton, 2018, Diehr et al., 1999, Griswold M., 2004, Hill and Miller, 2010, Honeycutt et al., 2009, Jones et al., 2013, Lipscomb et al., 1998, Malehi et al., 2015, Powers et al., 2005, Trogdon et al., 2007).

The exploration in this thesis presented detailed methodological approaches to variable selection, model specification, and testing. Regression analysis methods applied included OLS, log transformed OLS, generalised linear models (GLMs), a flexible extended estimating equations (EEE) model, and a quantile regression approach. How well the alternative estimators performed in terms of bias, accuracy and goodness-of-fit was compared by examining regression diagnostics, and predictive performance of the models. This work highlighted that no single model is best for analysing healthcare cost data, and that researcher should examine their assumptions about the most appropriate model given the characteristics of the data. In sufficiently large samples, a simpler model such as OLS could perform as well as the most complex model such as the EEE model.

The methodological findings of the study were consistent with some of the previous work done in other disease areas (Hill and Miller, 2010, Jones et al., 2013, Malehi et al., 2015, Powers et al., 2005). As there is no dominant model for analysing healthcare costs data, policy makers must weigh up several factors in arriving at their preferred model, including prediction accuracy, bias and goodness-of-fit of the models. This work and the steps followed within it could be applied in a wide range of settings particularly in musculoskeletal disorders and other chronic pain conditions in addition to replicating it in other datasets, and it could be used as a guide to econometric modelling of healthcare cost data in general. The study contributed significantly to the methodology by estimating and interpreting the effects of a natural experiment in healthcare expenditure modelling.

8.4.2 Implications for the NHS and economic evaluation

According to the UK Health Accounts compiled by the Office for National Statistics (ONS), total healthcare expenditure in the UK in 2015 was £185 billion which accounted for 9.9% of the gross domestic product (GDP) (ONS, 2015). Breakdown of the costs in this national statistics source is provided by healthcare function, provider, and financing schemes but not by disease/illness type. The England level expenditure on musculoskeletal conditions in 2011 was £5.1 billion or 4.7% of the NHS England program budget (Harker, 2012). The Department of Health's Programme Budgeting national level expenditure data are the best data available in terms of how much the NHS is spending on different medical conditions. Their estimates are categorised by specialty such as musculoskeletal, respiratory, and circulation rather than providing detailed costs by specific conditions. Nevertheless, previous studies have shown that back pain is the most prevalent condition within the musculoskeletal (MSK) disorders (Briggs et al., 2018, Woolf and Pfleger, 2003) and the disability burden of low back pain (LBP) alone is higher than all other MSK disorders put together (Hay et al., ET AL. (G. B. D. 2016 DALYs and HALE Collaborators) 2017). This may give an indication of the expenditure level for back pain although the national data from government bodies are not directly comparable to the estimates presented by the study in this thesis.

Two previous studies have estimated healthcare costs of back pain in the UK, although the comparability between them is limited due to inherent differences in the focus of the studies. The earlier study by Maniadakis and Gray (2000) estimated the direct costs of back pain in 1998 to be £1.6 billion. The study was based on the Office of Population Censuses and Surveys (OPCS) data as the primary source of data in combination with other epidemiological, unit costs, and

aggregated resource utilisation data sources. The latter study by Hong et al. (2013) found total healthcare costs associated with chronic low back pain (CLBP) to be double those of patients without the condition (£1,074 vs. £516). This was an incremental cost analysis based on CPRD, however it focused only on chronically ill LBP patients which is a subset of the analysis reported by the study in this thesis. Extrapolated to a national level, the incremental healthcare cost of CLBP was equivalent to £1.5 billion in 2009 (Hong et al., 2013). Since this estimate did not include costs for a full range of back pain conditions, it did not serve as an update to the previous estimates but potentially captured expenditure in the most costly patients.

The incremental healthcare cost of back pain estimated by the study in this thesis (£3.2 billion) represents double the costs reported by both studies. However, this is not considered an over estimation but rather reflective of the nature of the study and the time period elapsed. The estimate from Hong et al. (2013), although narrow in its scope (focussing on CLBP), was largely equivalent to the Maniadakis and Gray (2000) estimate for the whole of back pain and produced about a decade earlier. That means, the costs of back pain had already risen significantly in the first 10 years since the first study. Maniadakis and Gray (2000) had argued that the costs of back pain were expected to increase in the future. The definition of back pain used in the study in this thesis was the same as that of Maniadakis and Gray (2000), so the cost difference observed may primarily be attributed to the increase in healthcare costs of back pain in almost 20 years and the significant costs associated with comorbidities that was captured in this study. It is however acknowledged that other methodological differences such as the cost components included, and the sources of data used would have contributed to the differences in costs reported by the two studies.

Hong et al. (2013) found significant differences in baseline comorbidities between the CLBP group and the matched controls (mean CCI (SD): 0.73(1.17) vs. 0.47(0.98)), and they adjusted for comorbidities in their analysis. The importance of capturing back pain related costs of comorbidities was also stressed by the US study Martin et al. (2008) which employed both the incremental approach and the direct method of summing up expenditures specifically for spine problems (Martin et al., 2008). The authors reported that the direct method resulted in substantially lower estimates which was expected ($85.9 billion Vs. $32.7 billion in 2005) (Martin et al., 2008). The added economic burden of comorbidities will have implications for economic evaluation of interventions that aim to prevent or manage back pain. Since the presence of comorbidities is associated with increased healthcare resource utilisation, the effect of comorbidities should be considered in evidence-based policies and guidelines with regard to 'holistic approaches' for back pain management. The current NICE guideline on assessment and management of low back pain and sciatica which came to effect in 2016 however, does not address the issue of comorbidities. With regard to measuring and valuing health effects, the NICE guidance on methods of technology appraisal 2013 recommends making adjustments to utility values for certain circumstances such as comorbidities (NICE, 2018). However, no further detail is given in the guideline. The study in this thesis provided current evidence about the excess cost of back pain taking into account the presence of comorbidities. However, further research may be needed to quantify the extent of the comorbidity burden on healthcare costs of back pain.

The NICE guideline to the methods of technology appraisal 2013 also recommends analysis of data for patient subgroups since the benefit of the technology/treatment may differ based on patient characteristics (NICE, 2018). The matched control study in this thesis provided detailed

information on how the mean healthcare costs varied by sub-groups of back pain patients as well as by healthcare professional and prescription drugs type. These estimates along with estimates from the main analysis can be applied to the economic evaluation of back pain prevention and management strategies, and they may provide vital information for health service resource allocation.

8.5 Conclusions

The research within this thesis investigated the primary care consultation and prescription costs of back pain in the UK using routinely collected electronic health records (EHRs). The two overarching research aims of this thesis were estimating the healthcare costs of back pain in primary care settings in the UK using EHRs and identifying the determinants of these costs using econometric modelling approaches. To achieve these aims, specific objectives were set out and a series of inter-related studies were conducted. It was hypothesised that the economic burden of back pain was likely to have increased since it was last estimated almost 20 years ago. The findings of this thesis indicate that the healthcare resource utilisation and costs of back pain have indeed risen substantially in the intervening period. The mean incremental cost of back pain based on consultations and prescriptions was estimated at £244 per patient in 2015. Assuming a similar prevalence level as estimated in this thesis (25.7%), the national cost amounted to an estimated £3.2 billion. Further research may be warranted to investigate the long-term trends and prediction of future costs including costs due to inpatient, and other outpatient services such as physiotherapy and diagnostic imaging. Although the relevance of COI studies in priority setting have been criticised over the years, these estimates can provide valuable information for policy makers particularly as input into further economic evaluation analysis.

To the researcher's knowledge, the matched control study in this thesis was the first study to use the THIN electronic health records (EHR) database for estimation of back pain costs in the UK. The large sample size and the advanced matching techniques used are distinct strengths of this study. The resulting methodology and findings contribute to the validation of using routinely collected EHR data to estimate healthcare costs of illnesses and can be applied to other disease areas. This thesis also quantified the effects of patient and clinical characteristics on total healthcare costs for patients with back pain. Although the focus of this study was the back pain patients, future studies could include the controls in the regression models for the purpose of estimating the incremental costs associated with the disease of interest. This enables the results obtained from a case-control design to be replicated and act as a sensitivity analysis.

The mean healthcare costs of patients with back pain increased significantly with age, deprivation, comorbidities as well as for smokers, female, and obese patients. Given the significant costs associated with back pain, these findings can be used to target high cost individuals using tailored back pain management programs to achieve cost savings and potential improvements in outcomes. The econometric modelling study provided a novel framework for analysing healthcare costs of back pain overcoming the several challenges posed by healthcare expenditure data. The application included model selection and performance assessment of a variety of econometric models. This can be applied to expenditure data for a wide range of diseases to identify the most appropriate model and to ensure that robust conclusions are drawn from multiple competing models.

APPENDICES

Appendix 3.1: Search strategies used in the systematic review by database type.

MEDLINE (1946 to March, 2019), **Total hits:** 1,610

1. exp Back Pain/ (34,476)
2. ((lumb* or spin* or vertebra*) adj5 pain).ti,ab. (13,336)
3. (backache or lumbago).ti,ab. (3,261)
4. (back adj5 (disorder* or ach*)).ti,ab. (1,742)
5. (back adj5 pain).ti,ab. (35,387)
6. or/1-5 (58,838)
7. exp "Costs and Cost Analysis"/ (217,015)
8. economic*.ti. (35,418)
9. cost*.ti. (93,479)
10. (health care adj5 (us* or utili* or expen*)).ti,ab. (33,098)
11. (financ* adj5 (burden or impact)).ti,ab. (5,222)
12. (resource* adj5 (us* or utili*)).ti,ab. (41,041)
13. (los* adj5 (product* or earn*)).ti,ab. (10,899)
14. ((sick* or absen*) adj5 expen*).ti,ab. (267)
15. or/7-14 (333,380)
16. 6 and 15 (1,733)
17. limit 16 to (english language and humans) (1,610)

EMBASE (1974 to March 2019), **Total hits:** 2,100

1. exp backache/
2. (backache or lumbago).ti,ab.
3. (back adj5 pain).ti,ab. (3,261)
4. (back adj5 (disorder* or ach*)).ti,ab.)
5. ((lumb* or spin* or vertebra*) adj5 pain).ti,ab.
6. or/1-5
7. exp economics/
8. exp "cost of illness"/
9. economic*.ti.
10. cost*.ti.
11. (health care adj5 (us* or utili* or expen*)).ti,ab.
12. (financ* adj5 (burden or impact)).ti,ab.
13. (resource* adj5 (us* or utili*)).ti,ab.

14. (los* adj5 (product* or earn*)).ti,ab.
15. ((sick* or absen*) adj5 expen*).ti,ab.
16. or/7-15
17. 6 and 16
18. limit 17 to (human and english language)

CINAHL Plus (March 2019, **Total hits:** 2,185)

S17 S6 AND S16 (Limiters - English Language)
S16 Or/S7-S15
S15 TX ((sick* or absen*) N5 expen*)
S14 TX (los* N5 (product* or earn*))
S13 TX (resource* N5 (us* or utili*))
S12 TX (financ* N5 (burden or impact))
S11 TX (health care N5 (us* or utili* or expen*))
S10 AB cost*
S9 AB economic*
S8 (MH "Economic Aspects of Illness")
S7 (MH "Costs and Cost Analysis+")
S6 Or/S1-S5
S5 TX (back N5 pain)
S4 TX (back N5 (disorder* or ach*))
S3 TX (backach* or lumbago)
S2 TX ((lumb* or spin* or vertebra*) N5 pain)
S1 (MM "Back pain+") or (MM "Low Back Pain+") or (MM "Back Injuries+")

Web of Science (1900 to March 2019, **Total hits:** 1,833)

#17 #6 AND #16 (Limit to English)
#16 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#15 TS=((sick* or absen*) NEAR/5 expen*)
#14 TS=(los* NEAR/5 (product* or earn*))
#13 TS=(resource* NEAR/5 (use or utili*))
#12 TS=(financ* NEAR/5 (burden OR impact))
#11 TS=(health care NEAR/5 (use OR utili* OR expen*))
#10 TI=(cost*)
#9 TI=(economic*)
#8 TS=("Economic Aspect*")
#7 TS=("Cost of illness")
#6 #1 OR #2 OR #3 OR #4 OR #5
#5 TS=(back NEAR/5 pain)

#4	TS=(back NEAR/5 (disorder* OR ach*))
#3	TS=(backach* OR lumbago)
#2	TS=((lumb* OR spin* OR vertebra*) NEAR/5 pain)
#1	TS=(Back Pain OR Low Back Pain OR Back Injuries)

EconLit (March 2019, **Total hits:** 13)

S17 S6 AND S16
S16 Or/S7-S15
S15 TX ((sick* or absen*) N5 expen*)
S14 TX (los* N5 (product* or earn*))
S13 TX (resource* N5 (us* or utili*))
S12 TX (financ* N5 (burden or impact))
S11 TX (health care N5 (us* or utili* or expen*))
S10 TI cost*
S9 TI economic*
S8 TX "Economic Aspects of Illness"
S7 TX "Cost of illness"
S6 Or/S1-S5
S5 TX (back N5 pain)
S4 TX (back N5 (disorder* or ach*))
S3 TX (backach* or lumbago)
S2 TX ((lumb* or spin* or vertebra*) N5 pain)
S1 "back pain" or "low back pain" or "back injuries"

CRD Databases (March 2019, **Total hits:** 247)

(back pain) AND (cost) OR (economic burden) in DARE, NHS EED, HTA

Appendix 4.1: Read codes list developed for identification of back pain diagnosis from the THIN database

Read code	Description
N100.00	Ankylosing spondylitis
N101.00	Spinal enthesopathy
N102.00	Sacroiliitis NEC
N10y.00	Other inflammatory spondylopathies
N10y000	Inflammatory spondylopathies in diseases EC
N10yz00	Other inflammatory spondylopathies NOS
N11..00	Spondylosis and allied disorders
N110.00	Cervical spondylosis without myelopathy
N111.00	Cervical spondylosis with myelopathy
N112.00	Thoracic spondylosis without myelopathy
N113.00	Thoracic spondylosis with myelopathy
N114.00	Lumbosacral spondylosis without myelopathy
N114.12	Lumbar spondylosis
N115.00	Lumbosacral spondylosis with myelopathy
N116.00	Kissing spine
N117.00	Ankylosing vertebral hyperostosis
N118.00	Traumatic spondylopathy
N11z.00	Spondylosis NOS
N11z000	Spondylosis without myelopathy, NOS
N11z100	Spondylosis with myelopathy, NOS
N12..00	Intervertebral disc disorders
N12..11	Displacement of intervertebral disc
N120.00	Cervical disc displacement without myelopathy
N120.12	Cervical disc displacement
N121.00	Thoracic disc displacement without myelopathy
N122.00	Lumbar disc displacement
N123.00	Disc displacement, site unspecified, without myelopathy
N124.00	Schmorl's nodes
N124000	Schmorl's nodes of unspecified region
N124100	Schmorl's nodes of the thoracic region
N124200	Schmorl's nodes of the lumbar region
N124z00	Schmorl's nodes, region NOS
N125.00	Cervical disc degeneration
N126.00	Thoracic disc degeneration
N127.00	Lumbar disc degeneration
N128.00	Degenerative disc disease NOS

N129000	Unspecified disc disorder with myelopathy
N129100	Cervical disc disorder with myelopathy
N129200	Thoracic disc disorder with myelopathy
N129300	Lumbar disc disorder with myelopathy
N129z00	Disc disorder with myelopathy NOS
N12A.00	Postlaminectomy syndrome
N12A000	Postlaminectomy syndrome of unspecified site
N12A100	Cervical postlaminectomy syndrome
N12A200	Thoracic postlaminectomy syndrome
N12A300	Lumbar postlaminectomy syndrome
N12Az00	Postlaminectomy syndrome NOS
N12z.00	Other and unspecified disc disorders
N12z000	Other disc disorders of unspecified site
N12z100	Other cervical disc disorders
N12z200	Other thoracic disc disorders
N12z300	Other lumbar disc disorders
N13..00	Other cervical disorders
N130.00	Cervical spinal stenosis
N131.00	Cervicalgia - pain in neck
N132.00	Cervicocranial syndrome
N133.00	Cervicobrachial syndrome
N134.00	Brachial (cervical) neuritis
N134.11	Brachial radiculitis
N135z00	Torticollis NOS
N136.00	Panniculitis of neck
N137.00	Cervical posterior longitudinal ligament ossification
N13y.00	Other cervical syndromes
N13z.00	Cervical and neck disorders NOS
N14..00	Other and unspecified back disorders
N140.00	Spinal stenosis, excluding cervical region
N140.11	Spinal stenosis
N140000	Spinal stenosis of unspecified region
N140100	Thoracic spinal stenosis
N140200	Lumbar spinal stenosis
N140z00	Spinal stenosis NOS
N141.00	Pain in thoracic spine
N142.14	Lumbago
N143.00	Sciatica
N144000	Thoracic neuritis, unspecified
N144100	Lumbosacral neuritis, unspecified
N145.00	Backache, unspecified

N145.11	Acute back pain - unspecified
N145.12	Back pain, unspecified
N146.00	Disorders of the sacrum
N147.00	Disorders of the coccyx
N147000	Unspecified disorder of the coccyx
N147100	Hypermobility of the coccyx
N147z00	Coccyx disorder NOS
Nyu6100	(X) Other specified inflammatory spondylopathies
Nyu6200	(X) Other spondylosis with myelopathy
Nyu6400	(X) Other spondylosis
S560.00	Sprain, lumbosacral ligament
S561.00	Sacroiliac ligament sprain
S562.00	Sprain, sacrospinous ligament
S563.00	Sprain, sacrotuberous ligament
S56y.00	Other specified sacroiliac sprains
S56z.00	Sacroiliac sprain NOS
S57..00	Sprain of other parts of back
S570.00	Neck sprain
S571.00	Thoracic sprain
S572.00	Lumbar sprain
S573.00	Sacrum sprain
S574.00	Coccyx sprain
S57X.00	Sprain & strain of other & unspecified parts of lumb spine & pelvis
S57z.00	Back sprain NOS

Appendix 4.2: Pain relief drug list used for identification of prescription drugs from the THIN database

BNF	Drug group	Drug description and dose
10.1.1	6	Aceclofenac Tablets 100 mg
10.1.1	6	Acemetacin Capsules 60 mg
4.7.1	6	Aloxiprin Tablets 600 mg
4.7.1	1	Aspirin Dispersible Tablets 300 mg
4.7.1	1	Aspirin Tablets 300 mg
10.1.1	6	Azapropazone Capsules 300 mg
10.1.1	6	Azapropazone Tablets 600 mg
10.1.1	6	Benorylate Tablets 750 mg
10.3.2	1	Benzydamine Hydrochloride Cream 3 %
4.7.2	3	Buprenorphine Sublingual Tablets Sugar Free 2 mg
4.7.2	3	Buprenorphine Sublingual Tablets Sugar Free 200 micrograms
4.7.2	4	Buprenorphine Sublingual Tablets Sugar Free 400 micrograms
4.7.2	3	Buprenorphine Transdermal Patches 10 micrograms/hour
4.7.2	4	Buprenorphine Transdermal Patches 20 micrograms/hour
4.7.2	4	Buprenorphine Transdermal Patches 35 micrograms/hour
4.7.2	3	Buprenorphine Transdermal Patches 5 micrograms/hour
4.7.2	4	Buprenorphine Transdermal Patches 52.5 micrograms/hour
4.7.2	4	Buprenorphine Transdermal Patches 70 micrograms/hour
10.3.2	1	Capsaicin 0.025% cream
10.3.2	1	Capsaicin Cream 0.075%
10.3.2	1	Capsicum Ointment bpc
10.1.1	6	Celecoxib Capsules 100 mg
10.1.1	6	Celecoxib Capsules 200 mg
4.7.1	3	Co-Codamol 15/500 Tablets
4.7.1	4	Co-Codamol 30/500 Capsules
4.7.1	4	Co-Codamol 30/500 Effervescent Powder
4.7.1	4	Co-Codamol 30/500 Effervescent Tablets
4.7.1	4	Co-Codamol 30/500 Tablets
4.7.1	4	Co-Codamol 60/1000 Effervescent Powder
4.7.1	2	Co-Codamol 8/500 Capsules
4.7.2	3	Codeine Phosphate Tablets 15 mg
4.7.2	4	Codeine Phosphate Tablets 30 mg
4.7.2	4	Codeine Phosphate Tablets 60 mg
10.1.1	6	Dexibuprofen Tablets 400 mg
10.1.1	6	Dexketoprofen Trometamol Tablets 25 mg
4.7.2	5	Dextromoramide Tablets 5 mg

4.7.2	3	Dextropropoxyphene Hydrochloride Capsules 65 mg
4.7.2	5	Diamorphine Hydrochloride Tablets 10 mg
10.1.1	6	Diclofenac 50mg dispersible tablets sugar free
10.3.2	1	Diclofenac Diethylammonium Gel 1.16 %
10.1.1	6	Diclofenac Potassium Tablets 12.5 mg
10.1.1	6	Diclofenac Potassium Tablets 25 mg
10.1.1	6	Diclofenac Potassium Tablets 50 mg
10.1.1	6	Diclofenac sodium 50mg gastro-resistant tablets
10.1.1	6	Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets
10.1.1	6	Diclofenac sodium 75mg modified-release tablets
10.3.2	1	Diclofenac Sodium Cutaneous Solution 16 mg/ml
10.1.1	6	Diclofenac Sodium Dispersible Tablets 50 mg
10.1.1	6	Diclofenac Sodium M/R Capsules 100 mg
10.1.1	6	Diclofenac Sodium M/R Capsules 75 mg
10.1.1	6	Diclofenac Sodium M/R Tablets 100 mg
10.1.1	6	Diclofenac Sodium Suppositories 100 mg
10.1.1	6	Diclofenac Sodium Suppositories 25 mg
10.1.1	6	Diclofenac Sodium Suppositories 50 mg
10.1.1	6	Diclofenac Sodium Tablets 25 mg
10.1.1	6	Diclofenac Sodium Tablets 50 mg
10.3.2	1	Diethylamine Salicylate Cream 10 %
10.1.1	6	Diflunisal Tablets 250 mg
10.1.1	6	Diflunisal Tablets 500 mg
4.7.2	4	Dihydrocodeine 60mg modified-release tablets
4.7.2	4	Dihydrocodeine Tablets 30 mg
4.7.2	4	Dihydrocodeine Tartrate Elixir 10mg/5 ml
4.7.2	4	Dihydrocodeine Tartrate M/R Tablets 120 mg
4.7.2	4	Dihydrocodeine Tartrate M/R Tablets 90 mg
4.7.2	4	Dihydrocodeine Tartrate Tablets 30 mg
4.7.2	5	Dipipanone 10mg / Cyclizine 30mg tablets
10.1.1	6	Etodolac 600mg modified-release tablets
10.1.1	6	Etodolac Capsules 200 mg
10.1.1	6	Etodolac Capsules 300 mg
10.1.1	6	Etoricoxib 120mg tablets
10.1.1	6	Etoricoxib Tablets 120 mg
10.1.1	6	Etoricoxib Tablets 30 mg
10.1.1	6	Etoricoxib Tablets 60 mg
10.1.1	6	Etoricoxib Tablets 90 mg
10.3.2	1	Felbinac Foam 3.17 %
10.3.2	1	Felbinac Gel 3 %
10.1.1	6	Fenbufen Effervescent tablets 450 mg

10.1.1	6	Fenbufen Capsules 300 mg
10.1.1	6	Fenbufen Tablets 300 mg
10.1.1	6	Fenbufen Tablets 450 mg
10.1.1	6	Fenoprofen Tablets 300 mg
10.1.1	6	Flurbiprofen Tablets 100 mg
10.1.1	6	Flurbiprofen Tablets 50 mg
4.7.2	5	Hydromorphone Hydrochloride Capsules 1.3 mg
4.7.2	5	Hydromorphone Hydrochloride Capsules 2.6 mg
4.7.2	5	Hydromorphone Hydrochloride M/R Capsules 16 mg
4.7.2	5	Hydromorphone Hydrochloride M/R Capsules 2 mg
4.7.2	5	Hydromorphone Hydrochloride M/R Capsules 24 mg
4.7.2	5	Hydromorphone Hydrochloride M/R Capsules 4 mg
4.7.2	5	Hydromorphone Hydrochloride M/R Capsules 8 mg
10.3.2	1	Ibuprofen 10% gel
10.1.1	1	Ibuprofen 400mg tablets
10.3.2	1	Ibuprofen 5% gel
10.1.1	6	Ibuprofen 600mg tablets
10.3.2	1	Ibuprofen and Levomenthol Gel 5 % + 3 %
10.1.1	1	Ibuprofen Capsules 200 mg
10.3.2	1	Ibuprofen Cream 5 %
10.1.1	6	Ibuprofen Fc Tablets 800 mg
10.1.1	6	Ibuprofen Granules 600 mg/sachet
10.1.1	1	Ibuprofen M/R Capsules 300 mg
10.1.1	6	Ibuprofen M/R Tablets 800 mg
10.1.1	1	Ibuprofen Oral Suspension Sugar Free 100 mg/5 ml sachet
10.3.2	1	Ibuprofen Pump Spray 5 %
10.1.1	1	Ibuprofen Sugar-Free Suspension 100 mg/5 ml
10.1.1	1	Ibuprofen Suspension 100 mg/5 ml
10.1.1	1	Ibuprofen Tablets 200 mg
10.1.1	6	Indometacin 25mg capsules
10.1.1	6	Indometacin 50mg capsules
10.1.1	6	Indometacin M/R Capsules 25 mg
10.1.1	6	Indometacin M/R Capsules 75 mg
10.1.1	6	Indometacin M/R Tablets 25 mg
10.1.1	6	Indometacin M/R Tablets 75 mg
10.1.1	6	Indometacin Oral Suspension 25 mg/5 ml
10.1.1	6	Indometacin Suppositories 100 mg
10.1.1	6	Ketoprofen And Omeprazole M/R Capsules 100 mg + 20 mg
10.1.1	6	Ketoprofen Capsules 100 mg
10.1.1	6	Ketoprofen Capsules 50 mg
10.3.2	1	Ketoprofen Gel 2.5 %

10.1.1	6	Ketoprofen M/R Capsules 100 mg
10.1.1	6	Ketoprofen M/R Capsules 150 mg
10.1.1	6	Ketoprofen M/R Capsules 200 mg
10.1.1	6	Ketoprofen Suppositories 100 mg
10.1.1	6	Lumiracoxib Tablets 100 mg
10.1.1	6	Mefenamic Acid Capsules 250 mg
10.1.1	6	Mefenamic Acid Tablets 500 mg
10.1.1	6	Meloxicam 15mg orodispersible tablets sugar free
10.1.1	6	Meloxicam Suppositories 15 mg
10.1.1	6	Meloxicam Suppositories 7.5 mg
10.1.1	6	Meloxicam Tablets 15 mg
10.1.1	6	Meloxicam Tablets 7.5 mg
4.7.2	4	Meptazinol 200mg tablets
4.7.2	5	Morphine Hydrochloride Suppositories 15 mg
4.7.2	5	Morphine Sulphate Concentrated Oral Solution 20 mg/ml
4.7.2	5	Morphine Sulphate M/R Capsules 10 mg
4.7.2	5	Morphine Sulphate M/R Capsules 100 mg
4.7.2	5	Morphine Sulphate M/R Capsules 120 mg
4.7.2	5	Morphine Sulphate M/R Capsules 150 mg
4.7.2	5	Morphine Sulphate M/R Capsules 200 mg
4.7.2	5	Morphine Sulphate M/R Capsules 30 mg
4.7.2	5	Morphine Sulphate M/R Capsules 50 mg
4.7.2	5	Morphine Sulphate M/R Capsules 60 mg
4.7.2	5	Morphine Sulphate M/R Capsules 90 mg
4.7.2	5	Morphine Sulphate M/R Suspension 100 mg/sachet granules sugar free
4.7.2	5	Morphine Sulphate M/R Suspension 20 mg/sachet granules sugar free
4.7.2	5	Morphine Sulphate M/R Suspension 200 mg/sachet granules sugar free
4.7.2	5	Morphine Sulphate M/R Suspension 30 mg/sachet granules sugar free
4.7.2	5	Morphine Sulphate M/R Suspension 60 mg/sachet granules sugar free
4.7.2	5	Morphine Sulphate M/R Tablets 10 mg
4.7.2	5	Morphine Sulphate M/R Tablets 100 mg
4.7.2	5	Morphine Sulphate M/R Tablets 15 mg
4.7.2	5	Morphine Sulphate M/R Tablets 200 mg
4.7.2	5	Morphine Sulphate M/R Tablets 30 mg
4.7.2	5	Morphine Sulphate M/R Tablets 5 mg
4.7.2	5	Morphine Sulphate Oral Solution (Unit Dose) Sugar Free 10 mg/5 ml vial
4.7.2	5	Morphine Sulphate Oral Solution 10 mg/5 ml
4.7.2	5	Morphine Sulphate Suppositories 10 mg
4.7.2	5	Morphine Sulphate Tablets 10 mg
4.7.2	5	Morphine Sulphate Tablets 20 mg
4.7.2	5	Morphine Sulphate Tablets 50 mg

10.1.1	6	Nabumetone Dispersible Tablets 500 mg
10.1.1	6	Nabumetone Suspension Sugar Free 500 mg/5 ml
10.1.1	6	Nabumetone Tablets 500 mg
10.1.1	6	Naproxen Granules 500 mg
10.1.1	6	Naproxen 250mg gastro-resistant tablets
10.1.1	6	Naproxen 250mg tablets
10.1.1	6	Naproxen 500mg gastro-resistant tablets
10.1.1	6	Naproxen 500mg tablets
10.1.1	6	Naproxen and Esomeprazole M/R Tablets 500 mg + 20 mg
10.1.1	6	Naproxen and Misoprostol Tablets 500 mg + 200 micrograms
10.1.1	6	Naproxen M/R Tablets 500 mg
10.1.1	6	Naproxen Sodium Tablets 275 mg
10.1.1	6	Naproxen Suppositories 500 mg
10.1.1	6	Naproxen Suspension 125 mg/5 ml
4.7.1	3	Nefopam Hydrochloride Tablets 30 mg
4.7.2	5	Oxycodone 5mg/5ml oral solution sugar free
4.7.2	5	Oxycodone and Naloxone M/R Tablets 10 mg + 5 mg
4.7.2	5	Oxycodone and Naloxone M/R Tablets 20 mg + 10 mg
4.7.2	5	Oxycodone and Naloxone M/R Tablets 40 mg + 20 mg
4.7.2	5	Oxycodone and Naloxone M/R Tablets 5 mg + 2.5 mg
4.7.2	5	Oxycodone Hydrochloride Capsules 10 mg
4.7.2	5	Oxycodone Hydrochloride Capsules 20 mg
4.7.2	5	Oxycodone Hydrochloride Capsules 5 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 10 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 120 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 15 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 20 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 30 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 40 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 5 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 60 mg
4.7.2	5	Oxycodone Hydrochloride M/R Tablets 80 mg
4.7.2	5	Oxycodone Hydrochloride Solution Sugar Free 10 mg/ml
4.7.1	1	Paracetamol 1g suppositories
4.7.1	1	Paracetamol 325mg / Isometheptene 65mg capsules
4.7.1	1	Paracetamol 500mg soluble tablets
4.7.1	1	Paracetamol 500mg tablets
4.7.1	1	Paracetamol Capsules 500 mg
4.7.1	1	Paracetamol Mixture 250 mg/5 ml
4.7.1	1	Paracetamol Oral Suspension (Sugar-Free) 250 mg/5 ml
4.7.1	1	Paracetamol Oral Suspension 250 mg/5 ml

4.7.1	1	Paracetamol Oral Suspension 500 mg/5 ml
4.7.1	1	Paracetamol Suppositories 240 mg
4.7.1	1	Paracetamol Suppositories 250 mg
4.7.1	1	Paracetamol Suppositories 500 mg
4.7.2	4	Pentazocine Capsules 50 mg
4.7.2	4	Pentazocine Tablets 25 mg
4.7.2	4	Pethidine 50mg tablets
4.7.2	4	Phenazocine Hydrobromide Tablets 5 mg
10.1.1	6	Phenylbutazone Tablets 100 mg
10.1.1	6	Phenylbutazone Tablets 200 mg
10.1.1	6	Piroxicam Capsules 10 mg
10.1.1	6	Piroxicam Capsules 20 mg
10.1.1	6	Piroxicam Dispersible Tablets 10 mg
10.1.1	6	Piroxicam Dispersible Tablets 20 mg
10.3.2	1	Piroxicam Gel 0.5 %
10.1.1	6	Rofecoxib Oral Suspension Sugar Free 12.5mg/5ml
10.1.1	6	Rofecoxib Oral Suspension Sugar Free 25mg/5ml
10.1.1	6	Rofecoxib Tablets 12.5 mg
10.1.1	6	Rofecoxib Tablets 25 mg
10.3.2	1	Salicylic Acid and Mucopolysaccharide Polysulphate Cream 2 % + 0.2 %
10.3.2	1	Salicylic Acid and Mucopolysaccharide Polysulphate Gel 2 % + 0.2 %
4.7.1	1	Solpadeine Tablets
10.1.1	6	Sulindac Tablets 100 mg
10.1.1	6	Sulindac Tablets 200 mg
4.7.2	5	Tapentadol 100mg modified-release tablets
4.7.2	5	Tapentadol 150mg modified-release tablets
4.7.2	5	Tapentadol 200mg modified-release tablets
4.7.2	5	Tapentadol 250mg modified-release tablets
4.7.2	5	Tapentadol 75mg tablets
4.7.2	4	Tapentadol M/R Tablets 50 mg
10.1.1	6	Tenoxicam Tablets 20 mg
10.1.1	6	Tiaprofenic Acid S/R Capsules 300 mg
10.1.1	6	Tiaprofenic Acid Tablets 200 mg
10.1.1	6	Tiaprofenic Acid Tablets 300 mg
4.7.2	4	Tramadol 100mg effervescent powder sachets sugar free
4.7.2	4	Tramadol 100mg modified-release capsules
4.7.2	4	Tramadol 150mg modified-release capsules
4.7.2	4	Tramadol 200mg modified-release capsules
4.7.2	4	Tramadol 50mg capsules
4.7.2	2	Tramadol and Paracetamol Effervescent Tablets Sugar Free 37.5 mg + 325 mg
4.7.2	2	Tramadol and Paracetamol Tablets 37.5 mg + 325 mg

4.7.2	4	Tramadol Hydrochloride Effervescent Powder Sugar Free 50 mg/sachet
4.7.2	4	Tramadol Hydrochloride M/R Tablets 100 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 150 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 200 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 300 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 400 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 50 mg
4.7.2	4	Tramadol Hydrochloride M/R Tablets 75 mg
4.7.2	4	Tramadol Hydrochloride Oral Drops 100 mg/ml
4.7.2	4	Tramadol Hydrochloride Orodispersible Tablets (Sugar Free) 50 mg
4.7.2	4	Tramadol Hydrochloride Soluble Tablets Sugar Free 50 mg
10.1.1	6	Valdecoxib Tablet 10 mg
10.1.1	6	Valdecoxib Tablet 20 mg
10.1.1	6	Valdecoxib Tablet 40 mg

Drug group: 1 - Basic analgesics, 2 - Weak analgesics, 3 - Moderate analgesics
4 - Strong analgesics, 5 - Very strong analgesics, 6 - NSAIDS

Appendix 4.3: List of additional drugs usually prescribed with some pain relief medications

BNF	Drug description and dose
1.6.3	Arachis oil 130ml enema
1.6.3	Arachis oil liquid
1.6.2	Bisacodyl 10mg suppositories
1.6.2	Bisacodyl 5mg gastro-resistant tablets
1.6.2	Co-danthramer 25mg/200mg capsules
1.6.2	Co-danthramer 25mg/200mg/5ml oral suspension sugar free
1.6.2	Co-danthramer 37.5mg/500mg capsules
1.6.2	Co-danthramer 75mg/1000mg/5ml oral suspension sugar free
1.6.3	Co-danthrusate 50mg/60mg capsules
4.1.2	Diazepam 10mg tablets
4.1.2	Diazepam 10mg/2.5ml rectal solution tube
4.1.2	Diazepam 10mg/2ml emulsion for injection ampoules
4.1.2	Diazepam 10mg/2ml solution for injection ampoules
4.1.2	Diazepam 2.5mg/1.25ml rectal solution tube
4.1.2	Diazepam 2mg tablets
4.1.2	Diazepam 2mg/5ml oral suspension
4.1.2	Diazepam 5mg tablets
4.1.2	Diazepam 5mg/2.5ml rectal solution tube
1.6.3	Docusate 100mg capsules
1.3.5	Esomeprazole 10mg gastro-resistant granules sachets
1.3.5	Esomeprazole 20mg gastro-resistant capsules
1.3.5	Esomeprazole 20mg gastro-resistant tablets
1.3.5	Esomeprazole 40mg gastro-resistant capsules
1.3.5	Esomeprazole 40mg gastro-resistant tablets
1.3.5	Esomeprazole 40mg powder for solution for injection vials
1.3.5	Esomeprazole 40mg/5ml oral suspension
4.1.1	Flurazepam 15mg capsules
4.1.1	Flurazepam 30mg capsules
1.6.2	Generic CitraFleet oral powder 15.08g sachets sugar free
1.6.2	Generic CitraFleet oral powder 16.11g sachets sugar free
1.6.4	Generic Klean-Prep oral powder 69g sachets sugar free
1.6.4	Generic moviprep oral powder sachets sugar free
1.6.2	Generic picolax oral powder 16.1g sachets sugar free
1.6.2	Glycerol 1g suppositories
1.6.2	Glycerol 2g suppositories
1.6.2	Glycerol 4g suppositories
1.6.1	Ispaghula husk 3.5g effervescent granules sachets gluten free sugar free

1.6.1	Ispaghula husk 3.5g granules sachets gluten free
1.6.1	Ispaghula husk oral powder sugar free
1.6.4	Lactulose 10g/15ml oral solution 15ml sachets sugar free
1.6.4	Lactulose 3.1-3.7g/5ml oral solution
1.3.5	Lansoprazole 15mg gastro-resistant capsules
1.3.5	Lansoprazole 15mg orodispersible tablets
1.3.5	Lansoprazole 30mg gastro-resistant capsules
1.3.5	Lansoprazole 30mg orodispersible tablets
4.1.1	Loprazolam 1mg tablets
4.1.1	Lormetazepam 1mg capsule
4.1.1	Lormetazepam 1mg tablets
4.1.1	Lormetazepam 500mcg tablets
1.6.4	Macrogol compound half-strength oral powder sachets npf sugar free
1.6.1	Methylcellulose 500mg tablets
10.1.2	Methylprednisolone 40mg/1ml / Lidocaine 10mg/1ml (1%) suspension for injection vials
4.1.1	Nitrazepam 2.5mg/5ml oral suspension
4.1.1	Nitrazepam 5mg tablets
1.3.5	Omeprazole 10mg dispersible gastro-resistant tablets
1.3.5	Omeprazole 10mg gastro-resistant capsules
1.3.5	Omeprazole 10mg gastro-resistant tablets
1.3.5	Omeprazole 20mg dispersible gastro-resistant tablets
1.3.5	Omeprazole 20mg gastro-resistant capsules
1.3.5	Omeprazole 20mg gastro-resistant tablets
1.3.5	Omeprazole 40mg dispersible gastro-resistant tablets
1.3.5	Omeprazole 40mg gastro-resistant capsules
1.3.5	Omeprazole 40mg gastro-resistant tablets
1.3.5	Omeprazole 40mg powder and solvent for solution for injection vials
1.3.5	Omeprazole 40mg powder for solution for infusion vials
4.1.1	Oxazepam 10mg tablets
4.1.1	Oxazepam 15mg tablets
1.3.5	Pantoprazole 20mg gastro-resistant tablets
1.3.5	Pantoprazole 40mg gastro-resistant tablets
1.3.5	Pantoprazole 40mg powder for solution for injection vials
1.3.5	Rabeprazole 10mg gastro-resistant tablets
1.3.5	Rabeprazole 20mg gastro-resistant tablets
1.6.2	Senna 7.5mg tablets
1.6.2	Sodium picosulfate 5mg/5ml oral solution sugar free
1.6.1	Sterculia 62% granules 7g sachets gluten free
4.1.1	Temazepam 10mg tablets
4.1.1	Temazepam 10mg/5ml oral solution sugar free
4.1.1	Temazepam 20mg tablets
10.1.2	Triamcinolone hexacetonide 20mg/1ml suspension for injection ampoules

Appendix 4.4: Overlap between the Charlson Comorbidity Index (CCI) and the Quality Outcomes Framework (QOF) Conditions

Medical Conditions included in Charlson Comorbidity Index (CCI) assessment	Quality Outcomes Framework (QOF) condition
Myocardial Infarction (MI)	Yes
Heart Failure	Yes
Peripheral Vascular Disease (PVD)	Yes
Stroke and transient ischemic attack (TIA)	Yes
Chronic Obstructive Pulmonary Disease (COPD)	Yes
Dementia	Yes
Respiratory/Asthma	Yes
Paraplegia and Hemiplegia	No
Diabetes	Yes
Diabetes Complications	No
Renal Disease	Yes
Mild Liver Disease	No
Moderate or Severe Liver Disease	No
Leukemia	No
Rheumatic Disease	Yes
Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS)	No
Cancer	Yes
Metastatic cancer/tumour	No

Appendix 4.5: Study protocol submitted to Scientific Review Committee for using the THIN database

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Title of the study

Healthcare resource use and costs of back pain in UK primary care

Version 1, 23 April 2018

Background

Back pain is a common health problem affecting people from all walks of life, children to elderly. Nearly everyone will experience back pain at some point during their life. Although back pain has low impact in terms of mortality, it imposes great costs on patients, employers, health care providers and society as a whole (2014b). As society is aging worldwide, these costs are set to rise due to increased utilisation of health care resources, putting further pressure on health care services. There is a large body of evidence to support estimates of the prevalence and prognosis of back pain. However, there is a gap in terms of estimating its economic burden, with the latest study estimating the total costs for the UK originating from 1999 (Maniadakis and Gray, 2000). Given the aging population, advances in medical treatment, and the increasing UK retail price over the past two decades, an up-to-date estimate for the costs of back pain are required.

Specific aims and objectives

The aim of the study is to assess healthcare resource utilisation and associated direct medical costs in patients with back pain from the NHS perspective, and to compare these with previous estimates available. It is hypothesised that the consumption of resources and medical costs incurred by back pain patients has increased since it was last estimated 20 years ago. The specific objectives of the study are to:

1 - Extract healthcare resource utilisation data from THIN database.

2 - Identify unit costs for healthcare resource use from available data sources.

3 - Estimate annual healthcare costs (2011-2015 £) associated with treatment of back pain from NHS perspective.

4 - Describe how these estimates vary by age, gender, socio-economic status (SES) and over time.

5 - Determine factors associated with increased economic burden.

Data source

Data for the study will be obtained from THIN database, which is one of the main primary care databases in the UK and is available for this research. A healthcare resource utilisation data will be extracted from THIN, and this will be used to estimate costs of patients with back pain in primary care settings. This is achievable with THIN, since patients included in the database are representative of the UK in relation to patients demographics and prevalence of medical conditions (Blak et al., 2011). Prior to data extraction for analysis, the following important steps will be completed using the database, which will define the study population and outcomes. These are identification of Read clinical codes for back pain, identification of drug codes to be costed, and identification of co-morbid conditions and their Read codes to be taken into account in the analyses. In order to ensure data quality, patients will be eligible for selection only after 12 months of acceptable mortality recording (AMR) date, Vision date (date practice started using Vision software) and patient registration dates.

Methods

Study design

This is a retrospective, matched case-control study of patients registered in THIN during the study period. Patients with back pain will be 1:1 matched with those without back pain based on age, gender, GP practice, deprivation index, BMI categories, smoking status, and Charlson comorbidity index (CCI) categories. Index date is defined as the date of diagnosis for the cases, and the same index date is assigned to matched controls. For prevalent cases, the index date will be the first day of the study year (eg. 01 Jan 2011).

Inclusion and exclusion criteria

The following inclusion and exclusion criteria will be applied for all eligible patients:

Inclusion criteria:

1 - All patients must be aged 18 years or older at the index date.

2 - Both the case and control cohorts are required to have continuous registration with the GP practices during the study year unless they died.

3 - Cases (new and old diagnosis) are required to have at least one diagnostic Read code for back pain in the previous ten years including the study year. They must also have had at least one prescription for pain medication during the study year.

4 - Control cohort are required to be without a diagnosis of back pain recorded in THIN to be eligible for inclusion. They must, however, have had at least one prescription for pain medication during the study year in line with the cases.

Exclusion criteria:

1 - Patients with under 12 months of AMR, Vision and patient registration dates recorded in THIN.

2 - Patients aged under 18 years old.

3 - Patients not registered for the full study period unless they died.

Selection of study population

Diagnoses of back pain will be identified from THIN database using the Read medical codes in the patient's record. The case and control cohorts will initially be extracted from the eligible population in THIN using 1:4 matching of GP practice, age (+/- 1 year), gender, and Townsend index category. After applying the inclusion and exclusion criteria, the remaining population will be matched again more closely using propensity score matching and by applying additional matching variables of BMI categories, smoking status, and CCI.

Extraction of healthcare resource use data

The following components of healthcare resource utilisation data will be extracted for all patients in the study:

***Prescription drugs*:** Information on all identified pain medications and additional drugs that may be prescribed along with the analgesics will be extracted from the therapy file of THIN using

their drug codes. The data includes date of prescription, quantity prescribed, formulation and dosage, and prescription type (acute or repeat prescription).

Consultations: Consultation in this study is defined as direct contact with healthcare professionals, and this does not include administrative and repeat prescription issues. Three major groups of consultations will be constructed from the consultation types extracted from THIN. These are surgery consultations, home visits, and telephone consultations. The healthcare professionals who conducted the consultations will be obtained from the staff file in THIN, and two staff groups (GP and nurse) will be created. Each consultation will then be attached to a staff group for assessing resource use and costs associated it.

Assigning costs to healthcare resource utilisation

Healthcare resource use and costs for each cost component and the total for each patient will be calculated for the calendar years 2011, 2013, and 2015. All costs will be valued in £ Sterling using unit costs for the respective years. The costs of prescribed pain medications and the additional drugs identified will be obtained from Electronic Drug Tariffs. Each prescribed drug in the patient's record will be matched to the unit costs using drug name and formulation. Multiple drug codes representing a single prescription drug will be assigned same unit cost. The estimated total costs of drugs will reflect the quantities specified in the prescription.

The unit cost of each consultation will be based on a combination of consultation type and primary staff role. Unit cost per visit for each type of consultation for the relevant year will be derived from the Unit Costs of Health and Social Care. The total costs of consultation will take into account the duration of each consultation recorded for the patients.

Statistical analysis plan

De***scriptive analysis and costing***

Descriptive statistical methods will be used to evaluate the different variables as appropriate for both cohorts (numbers and percentage for categorical variables, means with standard deviations, and medians with interquartile ranges for continuous variables). Comparisons between case and control cohorts will be conducted using t-tests, chi-square tests, and Wilcoxon rank-sum tests

(depending on the data type and distribution) to test differences between groups for resource utilisation and costs.

Healthcare resources used will be identified and enumerated, assigning a unit to each component. The annual costs of the individual healthcare resources for each cohort will then be estimated as a product of the quantities of the resource per year and the attached unit costs. The total costs of all healthcare resource utilisation for each patient will be aggregated to make up the total direct costs of healthcare resource utilisation. The total direct cost per patient per year will be derived from total direct cost for both the case and control cohorts. The incremental costs associated with the treatment of back pain will be calculated as the difference between the total direct costs for the cases and the controls. Sensitivity analysis will be conducted by restricting the study population to patients with the most recent back pain diagnoses (two years) and their matched controls; and assessing costs in this population. Estimates from the sensitivity analysis will then be compared to the results from the main analysis that included ten years of diagnoses history. Total direct costs will also be presented stratified by age group, gender and Townsend deprivation index. Trends over time will be assessed using the total direct costs for 2011, 2013 and 2015. Costs will be extrapolated to a national level using UK prevalence rates.

Modelling

The distribution of healthcare costs at patients' level is generally characterised by a long positive skew with a mass zero or close to it reflecting little or no resource use. This has resulted in some debate about the most appropriate method for modelling healthcare costs for individual patients with suggestions including the use of transformations (log, square root, Box-Cox transformations) Generlised Linear Models (GLMs), and two-part models or hurdle models (Mullahy, 2009, Manning and Mullahy, 2001, Jones et al., 2015, Basu and Manning, 2009). Both GLMs and two-part models perform well as explanatory modelling techniques, but the two-part model has more value and is much richer than the simpler one-part GLM model (Mihaylova et al., 2011, Diehr et al., 1999).

The association of annual healthcare costs with patient and disease characteristics such as gender, age-group, comorbidity category, and deprivation category will be modelled using a two-part model including interaction terms. A probit model will be employed in the first part predicting

the probability of costs being incurred allowing for the proportion of patients not utilising resources. A GLM with a log-link and gamma errors will be employed in the second part to model healthcare costs, conditional on health resource being utilised. The predicted total healthcare expenditure will then be estimated by multiplying the predicted probabilities from the first part and the predicted costs from the second part of the model. Park test will be used to determine appropriate variance function for the GLM, while the model specification will be examined using link test. Model performance will be checked using goodness of fit measures. All data analyses will be conducted using suitable statistical software.

Implications and limitations

Data collected in electronic health records (EHRs) for patients in primary care can have important benefits for research. They contain comprehensive prescribing, consultation, and other clinical information which allows for healthcare research in many areas. However, the data collected in these databases are routine clinical care information that general practices record and therefore, they are not particularly collected for research purposes. Data are only available from patients who chose to consult their GP. Limitations with respect to accuracy of coding, missing or insufficient data have been recognised for some time (Powell et al., 2017, Shephard et al., 2011). Ethnicity data for example, are known to be poorly recorded (Shephard et al., 2011). There are also limitations with access to linked secondary care data. Nevertheless, this study is likely to have a very large sample size, and data will be representative of the general population. The study will generate reliable estimates for the first time in 20 years for healthcare utilisation and costs using a comprehensive list of back pain diagnosis. The findings of this study will provide a foundation for research into cost-effectiveness interventions to prevent or treat back pain. Therefore, the results of this study may serve as an important resource for policymakers in informing effective service planning and provision for people with back pain.

Appendix 4.6: Scientific Review Committee (SRC) approval of protocol

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SRC Feedback

Researcher Name: Dawit Zemedikun
Organisation: University of Birmingham
SRC Reference Number: 18THIN041
Date: 31st May 2018
Study title: Healthcare resource use and costs of back pain in UK primary care

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN041_v1_23-04-2018	1	23-04-2018
SRC_Researcher_responses_18THIN041		

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend

that you include the words “The Health Improvement Network (THIN)” within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.



Mustafa Dungarwalla
Consultant

SRC
Scientific Review Committee

Appendix 5.1: Grouping of consultation types for costing

THIN Code	Consultation Type	Grouping
9	Surgery consultation	Surgery consultation
22	Third Party consultation	
1	Clinic	
11	Acute visit	
18	Emergency consultation	
3	Follow-up/routine visit	
100	Community clinic	
34	Walk-in Centre	
7	Out of hours, practice	
36	Co-op surgery consultation	
27	Home visit	Home visit
8	Out of hours, non-practice	
30	Nursing home visit	
31	Residential home visit	
37	Co-op home visit	
4	Night visit, local rota	
33	Triage	Telephone consultation
21	Telephone call to a patient	
10	Telephone call from a patient	
35	Co-op telephone advice	

Appendix 5.2: Grouping of healthcare professional staff roles for costing

THIN Code	Staff role	Grouping
2	Partner	GP
1	Senior partner	
7	Locum	
47	Salaried partner	
8	GP registrar	
50	GP retainer	
4	Associate	
10	Sole practitioner	
9	Consultant	
11	Practice nurse	Nurse

Appendix 5.3: Unit cost of prescription drugs used in the analysis for 2015

The list includes both analgesics and additional drugs prescribed with some analgesics. The main source of the unit costs was the Electronic Drug Tariff (EDT) for July 2015 from the NHS Prescription Services which produces the drug tariff on a monthly basis on behalf of the Department of Health and Social Care. Two additional sources of unit costs, the Prescription Cost Analysis (PCA), and the British National Formulary (BNF) were also used when unit costs could not be found from EDT. In a minority of cases, where unit cost could be not be identified for a specific drug from any of the three sources, a group cost by BNF sub-paragraph was obtained from the PCA to approximate the individual drug's unit cost.

Drug description and dose	Source of cost	Unit cost (£)	Pack size	Item/ unit
Aceclofenac Tablets 100 mg	EDT	9.63	60	tablets
Acemetacin Capsules 60 mg	EDT	28.2	90	capsules
Arachis oil 130ml enema	PCA 15	37.85	130	ml
Arachis oil liquid	EDT	3.49	200	ml
Aspirin Dispersible Tablets 300 mg	EDT	1.04	32	tablets
Aspirin Tablets 300 mg	EDT	3.35	32	tablets
Bisacodyl 10mg suppositories	EDT	3.53	12	piece
Bisacodyl 5mg gastro-resistant tablets	EDT	2.22	60	tablets
Buprenorphine Sublingual Tablets Sugar Free 2 mg	EDT	2.13	7	tablets
Buprenorphine Sublingual Tabs Sugar Free 200 micrograms	EDT	5.04	50	tablets
Buprenorphine Sublingual Tabs Sugar Free 400 micrograms	EDT	1.6	7	tablets
Buprenorphine Transdermal Patches 10 micrograms/hour	EDT	31.55	4	piece
Buprenorphine Transdermal Patches 20 micrograms/hour	EDT	57.46	4	piece
Buprenorphine Transdermal Patches 35 micrograms/hour	EDT	15.8	4	piece
Buprenorphine Transdermal Patches 5 micrograms/hour	EDT	17.6	4	piece
Buprenorphine Transdermal Patches 52.5 micrograms/hour	EDT	23.71	4	piece
Buprenorphine Transdermal Patches 70 micrograms/hour	EDT	31.6	4	piece

Capsaicin 0.025% cream	EDT	17.71	45	grams
Capsaicin Cream 0.075%	EDT	14.58	45	grams
Capsicum Ointment bpc	PCA15 gp	6.05	45	grams
Celecoxib Capsules 100 mg	EDT	21.55	60	capsules
Celecoxib Capsules 200 mg	EDT	21.55	60	capsules
Co-Codamol 15/500 Tablets	EDT	9.11	100	tablets
Co-Codamol 30/500 Capsules	EDT	4.45	100	capsules
Co-Codamol 30/500 Effervescent Tablets	EDT	2.78	32	tablets
Co-Codamol 30/500 Tablets	EDT	1.58	30	tablets
Co-Codamol 60/1000 Effervescent Tablets	PCA15 gp	3.77	100	tablets
Co-Codamol 8/500 Capsules	EDT	3.3	32	capsules
Co-danthramer 25mg/200mg capsules	EDT	12.86	60	capsules
Co-danthramer 25mg/200mg/5ml oral suspension sugar free	EDT	125.45	300	ml
Co-danthramer 37.5mg/500mg capsules	EDT	15.55	60	capsules
Co-danthramer 75mg/1000mg/5ml oral suspension sugar free	EDT	269.47	300	ml
Co-danthrusate 50mg/60mg capsules	EDT	42.5	63	capsules
Codeine Phosphate Tablets 15 mg	EDT	1.33	28	tablets
Codeine Phosphate Tablets 30 mg	EDT	1.55	28	tablets
Codeine Phosphate Tablets 60 mg	EDT	2.88	28	tablets
Dexibuprofen Tablets 400 mg	EDT	9.97	60	tablets
Dexketoprofen Trometamol Tablets 25 mg	EDT	9.18	50	tablets
Diamorphine Hydrochloride Tablets 10 mg	EDT	24.09	100	tablets
Diazepam 10mg tablets	EDT	1.18	28	tablets
Diazepam 10mg/2.5ml rectal solution tube	EDT	7.35	5	piece
Diazepam 10mg/2ml emulsion for injection ampoules	EDT	4.5	10	piece
Diazepam 2.5mg/1.25ml rectal solution tube	PCA 15	8.12	5	piece
Diazepam 2mg tablets	EDT	1.05	28	tablets
Diazepam 2mg/5ml oral suspension	EDT	19.09	100	ml
Diazepam 5mg tablets	EDT	1.07	28	tablets
Diazepam 5mg/2.5ml rectal solution tube	EDT	5.85	5	piece
Diclofenac 50mg dispersible tablets sugar free	EDT	6.19	21	tablets
Diclofenac Diethylammonium Gel 1.16 %	EDT	5.63	100	grams
Diclofenac Potassium Tablets 12.5 mg	PCA15 gp	4.93	30	tablets
Diclofenac Potassium Tablets 25 mg	EDT	3.46	30	tablets
Diclofenac Potassium Tablets 50 mg	EDT	6.62	30	tablets
Diclofenac Sodium Cutaneous Solution 16 mg/ml	PCA15 gp	6.02	30	ml
Diclofenac Sodium Dispersible Tablets 50 mg	EDT	6.19	21	tablets
Diclofenac Sodium M/R Capsules 100 mg	EDT	6.97	28	capsules
Diclofenac Sodium M/R Capsules 75 mg	EDT	9.69	56	capsules
Diclofenac Sodium M/R Tablets 100 mg	EDT	9.47	28	tablets
Diclofenac Sodium Suppositories 100 mg	EDT	3.03	10	piece

Diclofenac Sodium Suppositories 25 mg	EDT	1.03	10	piece
Diclofenac Sodium Suppositories 50 mg	EDT	1.7	10	piece
Diclofenac Sodium Tablets 25 mg	EDT	3.46	30	tablets
Diclofenac Sodium Tablets 50 mg	EDT	6.62	30	tablets
Diclofenac sodium 50mg gastro-resistant tablets	EDT	0.91	28	tablets
Diclofenac sodium 75mg g-r / Misoprostol 200microgram	EDT	15.83	60	tablets
Diclofenac sodium 75mg modified-release tablets	EDT	12.92	56	tablets
Dihydrocodeine 60mg modified-release tablets	EDT	5.2	56	tablets
Dihydrocodeine Tablets 30 mg	EDT	1.32	28	tablets
Dihydrocodeine Tartrate Elixir 10mg/5 ml	BNF 15	3.5	150	ml
Dihydrocodeine Tartrate M/R Tablets 120 mg	EDT	10.95	56	tablets
Dihydrocodeine Tartrate M/R Tablets 90 mg	EDT	8.66	56	tablets
Dipipanone 10mg / Cyclizine 30mg tablets	EDT	129.74	50	tablets
Docusate 100mg capsules	EDT	2.09	30	capsules
Esomeprazole 10mg gastro-resistant granules sachets	EDT	25.19	28	piece
Esomeprazole 20mg gastro-resistant capsules	EDT	3.4	28	capsules
Esomeprazole 20mg gastro-resistant tablets	EDT	3.62	28	tablets
Esomeprazole 40mg gastro-resistant capsules	EDT	3.96	28	capsules
Esomeprazole 40mg gastro-resistant tablets	EDT	4.28	28	tablets
Esomeprazole 40mg powder for solution for injection vials	BNF 15	3.13	40	mg
Etodolac 600mg modified-release tablets	EDT	15.5	30	tablets
Etodolac Capsules 300 mg	EDT	8.14	60	capsules
Etoricoxib Tablets 120 mg	EDT	24.11	28	tablets
Etoricoxib Tablets 30 mg	EDT	13.99	28	tablets
Etoricoxib Tablets 60 mg	EDT	20.11	28	tablets
Etoricoxib Tablets 90 mg	EDT	22.96	28	tablets
Felbinac Foam 3.17 %	EDT	8.41	100	mg
Felbinac Gel 3 %	EDT	2.26	30	grams
Fenbufen Capsules 300 mg	PCA 15	5.32	56	capsules
Fenbufen Tablets 300 mg	PCA 15	6.81	84	tablets
Fenbufen Tablets 450 mg	PCA 15	11.71	84	tablets
Fenoprofen Tablets 300 mg	BNF 15	9.62	100	tablets
Flurazepam 15mg capsules	BNF 15	6.91	30	capsules
Flurazepam 30mg capsules	BNF 15	8.63	30	capsules
Flurbiprofen Tablets 100 mg	EDT	38.1	100	tablets
Flurbiprofen Tablets 50 mg	EDT	21.3	100	tablets
Generic CitraFleet oral powder 15.08g sachets sugar free	PCA 15	9.75	5	piece
Generic CitraFleet oral powder 16.11g sachets sugar free	PCA 15	11.2	5	piece
Generic Klean-Prep oral powder 69g sachets sugar free	PCA 15	19.02	10	piece
Generic moviprep oral powder sachets sugar free	PCA 15	13.34	4	piece
Generic picolax oral powder 16.1g sachets sugar free	PCA 15	10.3	5	piece

Glycerol 1g suppositories	EDT	0.88	12	piece
Glycerol 2g suppositories	EDT	1.28	12	piece
Glycerol 4g suppositories	EDT	2.29	12	piece
Hydromorphone Hydrochloride Capsules 1.3 mg	BNF 15	8.82	56	capsules
Hydromorphone Hydrochloride Capsules 2.6 mg	BNF 15	17.64	56	capsules
Hydromorphone Hydrochloride M/R Capsules 16 mg	BNF 15	106.53	56	capsules
Hydromorphone Hydrochloride M/R Capsules 2 mg	BNF 15	20.98	56	capsules
Hydromorphone Hydrochloride M/R Capsules 24 mg	BNF 15	159.82	56	capsules
Hydromorphone Hydrochloride M/R Capsules 4 mg	BNF 15	28.75	56	capsules
Hydromorphone Hydrochloride M/R Capsules 8 mg	BNF 15	56.08	56	capsules
Ibuprofen 10% gel	EDT	5.79	100	grams
Ibuprofen 400mg tablets	EDT	1.04	24	tablets
Ibuprofen 5% gel	EDT	2.12	50	grams
Ibuprofen 600mg tablets	EDT	1.31	84	tablets
Ibuprofen Fc Tablets 800 mg	PCA11 gp	4.98	84	tablets
Ibuprofen Granules 600 mg/sachet	EDT	6.8	20	piece
Ibuprofen M/R Capsules 300 mg	BNF 11	9.64	120	capsules
Ibuprofen M/R Tablets 800 mg	EDT	7.74	56	tablets
Ibuprofen Pump Spray 5 %	PCA 15	7.35	100	ml
Ibuprofen Sugar-Free Suspension 100 mg/5 ml	EDT	1.48	100	ml
Ibuprofen Suspension 100 mg/5 ml	EDT	8.88	500	ml
Ibuprofen tablets 200 mg	EDT	1.02	24	tablets
Indometacin 25mg capsules	EDT	1.26	28	capsules
Indometacin 50mg capsules	EDT	1.58	28	capsules
Indometacin M/R Capsules 25 mg	PCA15 gp	4.98	28	capsules
Indometacin M/R Capsules 75 mg	EDT	8.05	100	capsules
Indometacin M/R Tablets 25 mg	PCA15 gp	4.98	28	tablets
Indometacin M/R Tablets 75 mg	PCA15 gp	4.98	28	tablets
Indometacin Oral Suspension 25 mg/5 ml	PCA15 gp	4.98	237	ml
Indometacin Suppositories 100 mg	EDT	17.61	10	piece
Ispaghula husk 3.5g efferv gran sachets gluten & sugar free	EDT	3.75	10	piece
Ispaghula husk 3.5g granules sachets gluten free	EDT	2.2	30	piece
Ispaghula husk oral powder sugar free	EDT	2.44	30	piece
Ketoprofen And Omeprazole M/R Capsules 100 mg + 20 mg	BNF 15	13.8	30	capsules
Ketoprofen Capsules 100 mg	PCA15 gp	4.98	56	capsules
Ketoprofen Capsules 50 mg	EDT	15.14	112	capsules
Ketoprofen Gel 2.5 %	EDT	2.14	50	grams
Ketoprofen M/R Capsules 100 mg	EDT	23.93	56	capsules
Ketoprofen M/R Capsules 150 mg	BNF 15	13.66	28	capsules
Ketoprofen M/R Capsules 200 mg	EDT	23.85	28	capsules
Ketoprofen Suppositories 100 mg	BNF 15	6.65	10	piece

Lactulose 10g/15ml oral solution 15ml sachets sugar free	EDT	2.5	10	piece
Lactulose 3.1-3.7g/5ml oral solution	EDT	3.17	500	ml
Lansoprazole 15mg gastro-resistant capsules	EDT	1.17	28	capsules
Lansoprazole 15mg orodispersible tablets	EDT	3.04	28	tablets
Lansoprazole 30mg gastro-resistant capsules	EDT	1.54	28	capsules
Lansoprazole 30mg orodispersible tablets	EDT	5.49	28	tablets
Loprazolam 1mg tablets	EDT	18	28	tablets
Lormetazepam 1mg tablets	EDT	22.11	30	tablets
Lormetazepam 500mcg tablets	EDT	23.14	30	tablets
Macrogol compound half-strength oral sachets npf sugar free	EDT	4.27	30	piece
Mefenamic Acid Capsules 250 mg	EDT	6.86	100	capsules
Mefenamic Acid Tablets 500 mg	EDT	5.64	28	tablets
Meloxicam Suppositories 15 mg	BNF 15	5.58	12	piece
Meloxicam Suppositories 7.5 mg	PCA15 gp	4.98	12	piece
Meloxicam Tablets 15 mg	EDT	1.32	30	tablets
Meloxicam Tablets 7.5 mg	EDT	1.13	30	tablets
Meptazinol 200mg tablets	EDT	22.11	112	tablets
Methylcellulose 500mg tablets	EDT	3.22	112	tablets
Methylprednisolone 40mg/1ml / Lidocaine 10mg/1ml (1%)-suspension for injection vials	EDT	3.94	1	piece
Morphine Hydrochloride Suppositories 15 mg	BNF 15	8.85	12	piece
Morphine Sulphate Concentrated Oral Solution 20 mg/ml	EDT	19.5	120	ml
Morphine Sulphate M/R Capsules 10 mg	EDT	3.47	60	capsules
Morphine Sulphate M/R Capsules 100 mg	EDT	38.5	60	capsules
Morphine Sulphate M/R Capsules 120 mg	BNF 15	29.15	28	capsules
Morphine Sulphate M/R Capsules 150 mg	BNF 15	36.43	28	capsules
Morphine Sulphate M/R Capsules 200 mg	EDT	43.6	60	capsules
Morphine Sulphate M/R Capsules 30 mg	EDT	8.3	60	capsules
Morphine Sulphate M/R Capsules 50 mg	PCA15 gp	13.45	60	capsules
Morphine Sulphate M/R Capsules 60 mg	EDT	16.2	60	capsules
Morphine Sulphate M/R Capsules 90 mg	EDT	22.04	28	capsules
Morphine Sulphate M/R Suspension 100 mg/sachet gran SF	BNF 15	85.15	30	piece
Morphine Sulphate M/R Suspension 20 mg/sachet gran SF	BNF 15	24.58	30	piece
Morphine Sulphate M/R Suspension 200 mg/sachet gran SF	BNF 15	170.3	30	piece
Morphine Sulphate M/R Suspension 30 mg/sachet gran SF	BNF 15	25.54	30	piece
Morphine Sulphate M/R Suspension 60 mg/sachet gran SF	BNF 15	51.09	30	piece
Morphine Sulphate M/R Tablets 10 mg	EDT	5.18	60	tablets
Morphine Sulphate M/R Tablets 100 mg	EDT	38.5	60	tablets
Morphine Sulphate M/R Tablets 15 mg	EDT	9.1	60	tablets
Morphine Sulphate M/R Tablets 200 mg	EDT	81.34	60	tablets
Morphine Sulphate M/R Tablets 30 mg	EDT	12.47	60	tablets

Morphine Sulphate M/R Tablets 5 mg	EDT	3.29	60	tablets
Morphine Sulphate Oral Solution Sugar Free 10 mg/5 ml vial	EDT	13.99	100	ml
Morphine Sulphate Oral Solution 10 mg/5 ml	EDT	5.45	300	ml
Morphine Sulphate Suppositories 10 mg	BNF 15	11.21	12	piece
Morphine Sulphate Tablets 10 mg	EDT	5.31	56	tablets
Morphine Sulphate Tablets 20 mg	EDT	10.61	56	tablets
Morphine Sulphate Tablets 50 mg	EDT	28.02	56	tablets
Nabumetone Suspension Sugar Free 500 mg/5 ml	EDT	28.9	300	ml
Nabumetone Tablets 500 mg	EDT	8.56	56	tablets
Naproxen 250mg gastro-resistant tablets	EDT	4.21	56	tablets
Naproxen 250mg tablets	EDT	1.23	28	tablets
Naproxen 500mg gastro-resistant tablets	EDT	10.51	56	tablets
Naproxen 500mg tablets	EDT	1.71	28	tablets
Naproxen and Esomeprazole M/R Tablets 500 mg + 20 mg	BNF 15	14.95	60	tablets
Naproxen and Misoprostol Tablets 500 mg + 200 micrograms	EDT	23.76	112	tablets
Naproxen M/R Tablets 500 mg	PCA15 gp	4.98	28	tablets
Naproxen Sodium Tablets 275 mg	EDT	7.1	60	tablets
Naproxen Suppositories 500 mg	EDT	12.77	56	piece
Nefopam Hydrochloride Tablets 30 mg	EDT	10.59	90	tablets
Nitrazepam 5mg tablets	EDT	1.88	28	tablets
Omeprazole 10mg dispersible gastro-resistant tablets	EDT	7.75	28	tablets
Omeprazole 10mg gastro-resistant capsules	EDT	1.25	28	capsules
Omeprazole 10mg gastro-resistant tablets	EDT	7.9	28	tablets
Omeprazole 20mg dispersible gastro-resistant tablets	EDT	11.6	28	tablets
Omeprazole 20mg gastro-resistant capsules	EDT	1.24	28	capsules
Omeprazole 20mg gastro-resistant tablets	EDT	5.98	28	tablets
Omeprazole 40mg dispersible gastro-resistant tablets	EDT	5.8	7	tablets
Omeprazole 40mg gastro-resistant capsules	EDT	1.12	7	capsules
Omeprazole 40mg gastro-resistant tablets	EDT	5.14	7	tablets
Omeprazole 40mg powder & solvent solution injection vials	BNF 15	5.18	40	mg
Omeprazole 40mg powder for solution for infusion vials	BNF 15	5.18	40	mg
Oxazepam 10mg tablets	EDT	1.42	28	tablets
Oxazepam 15mg tablets	EDT	1.5	28	tablets
Oxycodone 5mg/5ml oral solution sugar free	EDT	9.71	250	ml
Oxycodone and Naloxone M/R Tablets 10 mg + 5 mg	EDT	42.32	56	tablets
Oxycodone and Naloxone M/R Tablets 20 mg + 10 mg	EDT	84.62	56	tablets
Oxycodone and Naloxone M/R Tablets 40 mg + 20 mg	BNF 15	140.44	56	tablets
Oxycodone and Naloxone M/R Tablets 5 mg + 2.5 mg	EDT	21.16	28	tablets
Oxycodone Hydrochloride Capsules 10 mg	EDT	22.86	56	capsules
Oxycodone Hydrochloride Capsules 20 mg	EDT	45.71	56	capsules
Oxycodone Hydrochloride Capsules 5 mg	EDT	11.43	56	capsules

Oxycodone Hydrochloride M/R Tablets 10 mg	EDT	25.04	56	tablets
Oxycodone Hydrochloride M/R Tablets 120 mg	EDT	305.02	56	tablets
Oxycodone Hydrochloride M/R Tablets 15 mg	EDT	38.12	56	tablets
Oxycodone Hydrochloride M/R Tablets 20 mg	EDT	50.08	56	tablets
Oxycodone Hydrochloride M/R Tablets 30 mg	EDT	76.23	56	tablets
Oxycodone Hydrochloride M/R Tablets 40 mg	EDT	100.19	56	tablets
Oxycodone Hydrochloride M/R Tablets 5 mg	EDT	12.52	56	tablets
Oxycodone Hydrochloride M/R Tablets 60 mg	EDT	152.49	56	tablets
Oxycodone Hydrochloride M/R Tablets 80 mg	EDT	200.39	56	tablets
Oxycodone Hydrochloride Solution Sugar Free 10 mg/ml	EDT	46.63	120	ml
Pantoprazole 20mg gastro-resistant tablets	EDT	1.2	28	tablets
Pantoprazole 40mg gastro-resistant tablets	EDT	1.55	28	tablets
Pantoprazole 40mg powder for solution for injection vials	BNF 15	5.11	40	mg
Paracetamol 1g suppositories	BNF 15	60	12	piece
Paracetamol 325mg / Isometheptene 65mg capsules	BNF 15	5.5	30	capsules
Paracetamol 500mg soluble tablets	EDT	1.3	24	tablets
Paracetamol 500mg tablets	EDT	0.97	32	tablets
Paracetamol Capsules 500 mg	EDT	1.32	32	capsules
Paracetamol Oral Suspension (Sugar-Free) 250 mg/5 ml	EDT	1.72	200	ml
Paracetamol Oral Suspension 250 mg/5 ml	EDT	1.38	100	ml
Paracetamol Oral Suspension 500 mg/5 ml	PCA15 gp	4.96	500	ml
Paracetamol Suppositories 240 mg	EDT	22.01	10	piece
Paracetamol Suppositories 250 mg	EDT	27.6	10	piece
Paracetamol Suppositories 500 mg	EDT	36.5	10	piece
Pentazocine Capsules 50 mg	BNF 15	16.55	28	capsules
Pentazocine Tablets 25 mg	EDT	26.19	28	tablets
Pethidine 50mg tablets	EDT	50.82	50	tablets
Phenylbutazone Tablets 100 mg	PCA 15	89.84	84	tablets
Phenylbutazone Tablets 200 mg	PCA 15	92.66	84	tablets
Piroxicam Capsules 10 mg	EDT	4.68	56	capsules
Piroxicam Capsules 20 mg	EDT	4.42	28	capsules
Piroxicam Dispersible Tablets 10 mg	BNF 15	16.82	56	tablets
Piroxicam Dispersible Tablets 20 mg	BNF 15	17.6	28	tablets
Piroxicam Gel 0.5 %	EDT	6.32	60	grams
Rabeprazole 10mg gastro-resistant tablets	EDT	2.32	28	tablets
Rabeprazole 20mg gastro-resistant tablets	EDT	2.82	28	tablets
Senna 7.5mg tablets	EDT	4.8	60	tablets
Sodium picosulfate 5mg/5ml oral solution sugar free	EDT	6.55	300	ml
Solpadeine Tablets	PCA 15	7.43	84	tablets
Sterculia 62% granules 7g sachets gluten free	EDT	5.77	60	piece
Sulindac Tablets 100 mg	EDT	29.78	56	tablets

Sulindac Tablets 200 mg	EDT	38.29	56	tablets
Tapentadol 100mg modified-release tablets	EDT	49.82	56	tablets
Tapentadol 150mg modified-release tablets	EDT	74.73	56	tablets
Tapentadol 200mg modified-release tablets	EDT	99.64	56	tablets
Tapentadol 250mg modified-release tablets	EDT	124.55	56	tablets
Tapentadol 75mg tablets	EDT	18.68	28	tablets
Tapentadol M/R Tablets 50 mg	EDT	12.46	28	tablets
Temazepam 10mg tablets	EDT	17.97	28	tablets
Temazepam 10mg/5ml oral solution sugar free	EDT	70.68	300	ml
Temazepam 20mg tablets	EDT	17.46	28	tablets
Tenoxicam Tablets 20 mg	EDT	16.16	28	tablets
Tiaprofenic Acid Tablets 300 mg	EDT	14.95	56	tablets
Tramadol 100mg modified-release capsules	BNF15	15.28	60	capsules
Tramadol 150mg modified-release capsules	BNF15	22.92	60	capsules
Tramadol 200mg modified-release capsules	BNF15	30.55	60	capsules
Tramadol 50mg capsules	EDT	1.28	30	capsules
Tramadol and Paracetamol Efferv Tabs SF 37.5 mg + 325 mg	EDT	9.68	60	tablets
Tramadol and Paracetamol Tablets 37.5 mg + 325 mg	EDT	9.22	60	tablets
Tramadol Hydrochloride M/R Tablets 100 mg	BNF15	18.26	60	tablets
Tramadol Hydrochloride M/R Tablets 150 mg	BNF15	27.39	60	tablets
Tramadol Hydrochloride M/R Tablets 200 mg	BNF15	36.52	60	tablets
Tramadol Hydrochloride M/R Tablets 300 mg	BNF15	24.94	30	tablets
Tramadol Hydrochloride M/R Tablets 400 mg	BNF15	32.47	30	tablets
Tramadol Hydrochloride M/R Tablets 50 mg	BNF15	4.6	60	tablets
Tramadol Hydrochloride M/R Tablets 75 mg	PCA15 gp	13.45	60	tablets
Tramadol Hydrochloride Oral Drops 100 mg/ml	EDT	3.5	10	ml
Tramadol Hydrochloride Orodispersible Tablets SF 50 mg	BNF 15	7.12	60	tablets
Tramadol Hydrochloride Soluble Tablets Sugar Free 50 mg	BNF 15	2.79	20	tablets

EDT - Electronic Drug Tariff, BNF - British National Formulary, PCA - Prescription Cost Analysis, gp - group price

Appendix 5.4: Unit cost per visit for each type of consultation in 2015

Consultations	Unit cost	Comments*
GP consultation in surgery	£40 (lasting 11.7 minutes)	Table 10.8b. Cost including qualifications, excluding other direct care staff costs
GP home visit	£81.9 (lasting 23.4 minutes including travel)	Tables 10.8a & b. Cost based on a rate of £3.5/minute, including qualifications, excluding other direct care staff costs.
GP telephone consultation	£25 (lasting 7.1 minutes)	Table 10.8b. Cost including qualifications, excluding other direct care staff costs
Nurse consultation	£14.5 (lasting 15.5 mins)	Table 10.6. Cost based on £56 per hour face-to-face contact with practice nurse, including qualifications.

** All costs in 2015 prices from Unit Costs of Health & Social Care 2015, Personal Social Services Research Unit (PSSRU)*

Appendix 5.5: Back pain prevalence estimates in 2015 calculated from the THIN database

Overall prevalence:

Cases with BP	Total population	Point prevalence
817,322	3,175,379	25.7

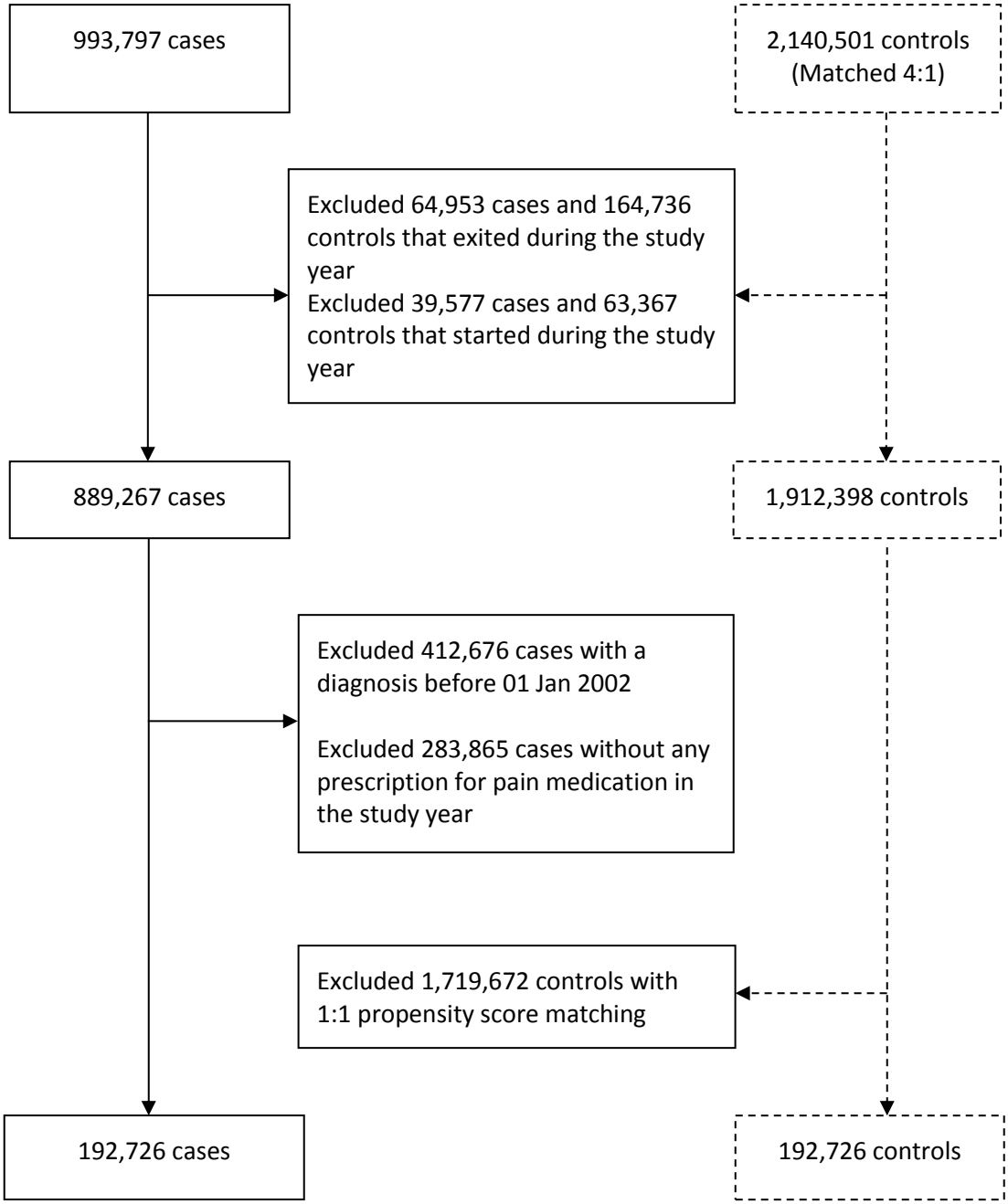
Prevalence stratified by gender:

Sex	Cases with BP	Sub-group population	Point prevalence
Male	1,209,321	1,563,096	22.6
Female	1,148,736	1,612,283	28.9

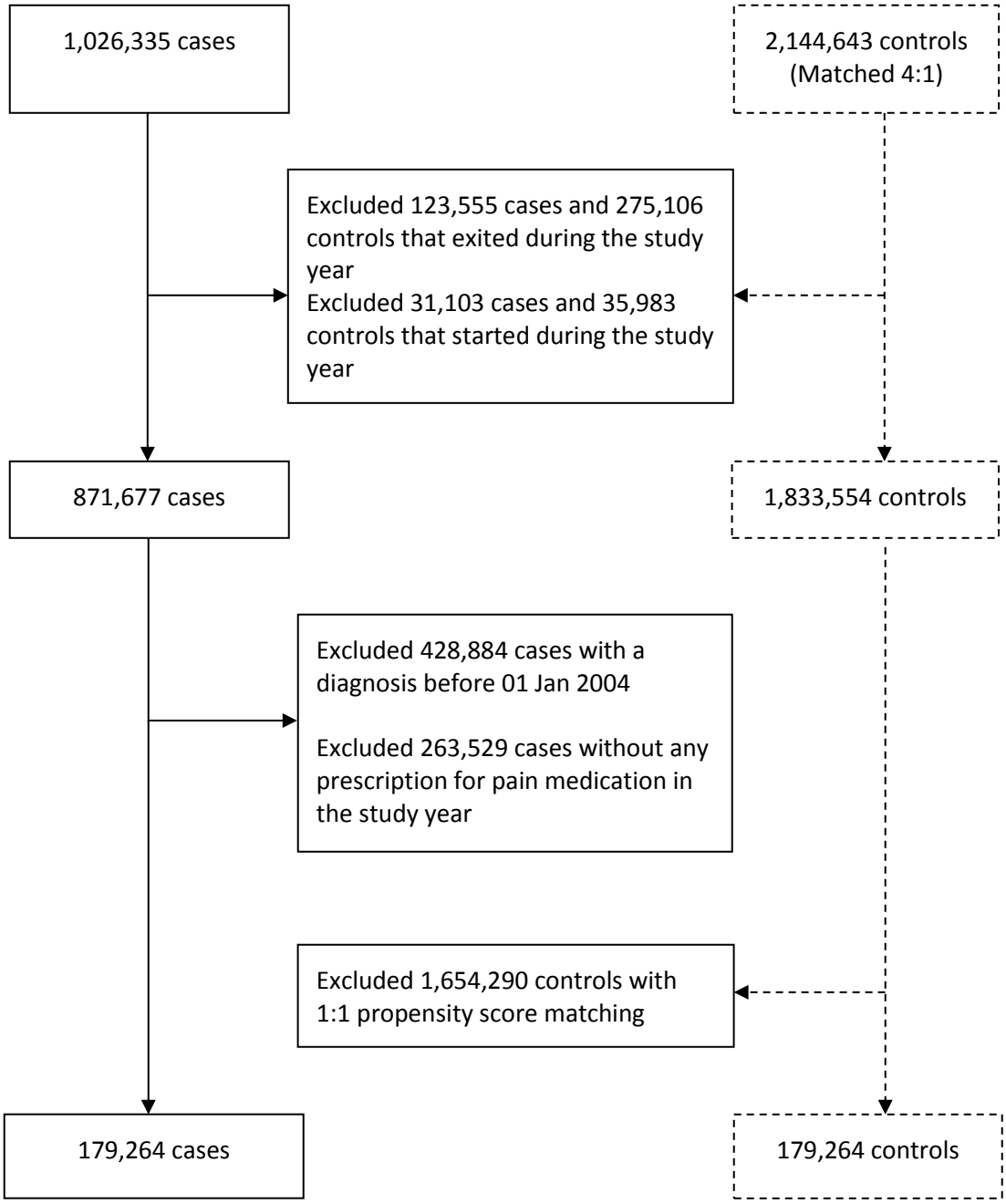
Prevalence stratified by age-groups:

Age-group	Cases with BP	Sub-group population	Point prevalence
18-24	17,003	259,822	6.5
25-34	61,647	500,112	12.3
35-44	107,382	531,820	20.2
45-54	169,823	612,968	27.7
55-64	165,559	501,250	33
65-74	156,136	421,700	37
75 & over	139,772	347,707	40.2

Appendix 5.6: Selection of study population in the 2011 study



Appendix 5.7: Selection of study population in the 2013 study



Appendix 5.8: Estimates of annual healthcare resource use and costs associated with the treatment of back pain in 2011

	Main analysis		Sensitivity analysis*	
Cost component	**Back pain** (n=192,726)	**No back pain** (n=192,726)	**Back pain** (n=39,448)	**No back pain** (n=39,448)
Consultations				
Count	1,835,210	1,037,642	384,695	203,472
Rate	9.52	5.38	9.75	5.16
Total costs	£61,100,000	£32,600,000	£13,000,000	£6,393,119
Per patient	£317.03	£169.15	£329.55	£162.06
Prescriptions				
Count	2,050,968	711,718	401,596	134,016
Rate	10.64	3.69	10.18	3.40
Total costs	£12,700,000	£3,704,276	£2,289,497	£729,878
Per patient	£65.90	£19.22	£58.04	£18.50
Sum				
Total costs	£73,800,000	£36,304,276	£15,289,497	£7,122,997
Per patient	£382.93	£188.37	£387.59	£180.57

* The sensitivity analysis was conducted by including only patients with most recent (2 years) back pain diagnoses and their matched controls

Appendix 5.9: Estimates of annual healthcare resource use and costs associated with the treatment of back pain in 2013

	Main analysis		Sensitivity analysis*	
Cost component	**Back pain** (n=179,264)	**No back pain** (n=179,264)	**Back pain** (n=34,522)	**No back pain** (n=34,522)
Consultations				
Count	1,734,148	969,213	342,970	177,970
Rate	9.67	5.41	9.93	5.16
Total costs	£73,900,000	£38,700,000	£14,900,000	£7,121,430
Per patient	£412.24	£215.88	£431.61	£206.29
Prescriptions				
Count	2,032,354	696,839	375,404	123,144
Rate	11.34	3.89	10.87	3.57
Total costs	£13,700,000	£4,200,363	£2,396,676	£731,450
Per patient	£76.42	£23.43	£69.42	£21.19
Sum				
Total costs	£87,600,000	£42,900,363	£17,296,676	£7,852,880
Per patient	£488.66	£239.31	£501.03	£227.47

* The sensitivity analysis was conducted by including only patients with most recent (2 years) back pain diagnoses and their matched controls

Appendix 5.10: Distribution of the study population in THIN vs. the general population

		THIN study population		ONS mid-year population*	
Demographic factor		**N**	**%**	**N**	**%**
Total adult population		266,682		51,339,161	
Gender					
	Male	100,960	37.86	25,020,726	48.74
	Female	165,722	62.14	26,318,435	51.26
Age (mean, SD)		56.58 (16.9)		48.3	
Age group					
	18 - 24	6,377	2.39	5,878,472	11.45
	25 - 34	23,223	8.71	8,822,757	17.19
	35 - 44	38,982	14.62	8,378,302	16.32
	45 - 54	54,422	20.41	9,196,082	17.91
	55 - 64	49,980	18.74	7,452,381	14.52
	65 - 74	49,103	18.41	6,339,752	12.35
	75 & overs	44,595	16.72	5,271,415	10.27

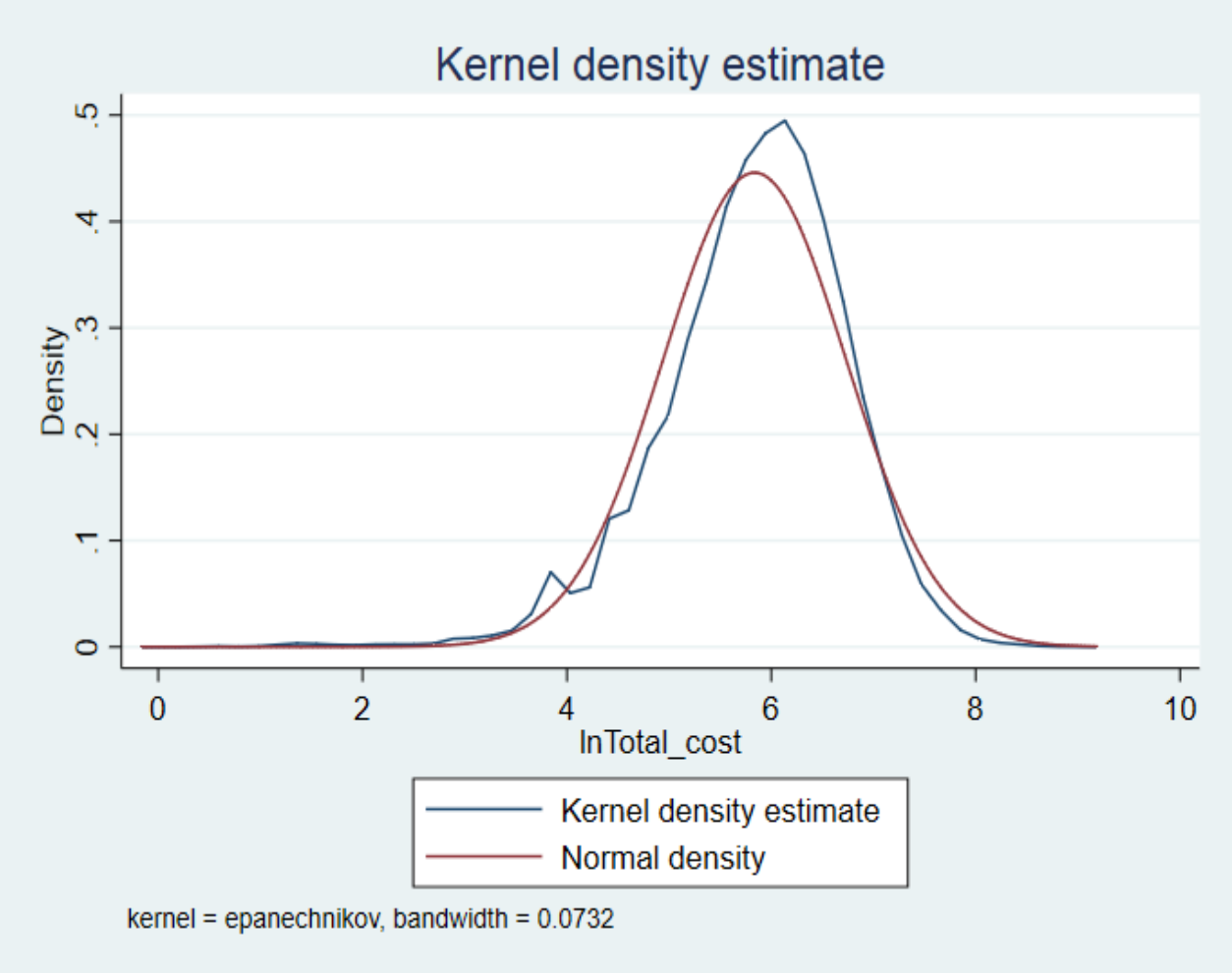
** Source: ONS data MYE2: Population estimates by single year of age and sex for local authorities in the UK, mid-2015*

Appendix 7.1: A full list of potential variables available for modelling from the THIN database

Variable	Type of data	Description
Patient factors		
year_of_birth	Date	Month and year of birth
sex	Categorical (1,2)	Gender indicator (1=male, 2=female)
country	Categorical (1-4)	England, Scotland, Wales & N.Ireland
death_date	Date	Date patient died
townsend	Categorical (1-5)	Deprivation index (1=least deprived)
weight	Continuous	Weight of patient in KG
smoking	Categorical (1-3)	Smoking status (1=non-smoker)
Clinical factors		
exposure	Date	Read code for back pain
exposure_date	Date	Date of back pain diagnosis (Read code)
25 other clinical diagnoses & diagnosis dates		Co-morbid conditions
drug_painkiller	Drug code	Prescribed analgesics (used to identify cases)
drug_painkiller_date	Date	Date of prescribed analgesics
bmi	Continuous	BMI in kg/sq.m
creatinine	Continuous	Serum creatinine in µmol/L
creatinine_date	Date	Date of creatinine measurement
egfr	Continuous	estimated Glomerular Filtration Rate (eGFR)
egfr_date	Date	Date eGFR measurement
cci	Continuous	Charlson comorbidity index (CCI)
consult	Continuous	Number of consultations
Practice factors		
patient_id	Letters & numbers	Patient ID number unique within practice

practice_id	Letters & numbers	Unique practice ID number
practice_patient_id	Letters & numbers	Unique patient identifier
comp_date	Date	Date practice became computerised
vision_date	Date	Date practice started using Vision software for medical recoding
amr_date	Date	Accepted mortality recording date
collection_date	Date	Date of last data collection
registration_date	Date	Date of patient registration at practice
transfer_date	Date	Date patient transferred to another GP
last_consultation_date	Date	Date patient had last consultation
Other (study related)		
start_date	Date	Study start date
index_date	Date	Date of start of patient follow-up
control	Binary (0,1)	Indicator of control patients (1=control)
case	Binary (0,1)	Indicator of case (1=case)
exit_date	Date	Date of end of patient follow-up
Derived variables		
age	Continuous	Calculated from year of birth
age_group	Categorised (1-7)	Categorised age (7 categories)
bmi_category	Categorised (1-3)	Categorised BMI (normal,overweight,obese)
cci_category	Categorised (0-6)	Categorised CCI
consultations_count	Continuous	Consultations count for each patient
consultations_cost	Continuous	Consultations cost for each patient
prescriptions_count	Continuous	Prescriptions count for each patient
prescriptions_cost	Continuous	Prescriptions cost for each patient
total_cost	Continuous	Total healthcare cost for each patient

Appendix 7.2: Comparison of the log-transformed cost data vs. a normal distribution curve



Appendix 7.3: Output of the GLM model with square root link and gamma variance

Variable	Coefficient	Robust std. error	P-value	(95% Confidence	interval)
Age	0.047	0.002	0.000	0.044	0.051
Female	2.146	0.063	0.000	2.024	2.269
N. Ireland	0.295	0.101	0.004	0.097	0.493
Scotland	0.479	0.101	0.000	0.333	0.624
Wales	-0.057	0.086	0.503	-0.225	0.111
Townsend 2	0.094	0.092	0.305	-0.086	0.275
Townsend 3	0.366	0.092	0.000	0.186	0.547
Townsend 4	0.851	0.098	0.000	0.660	1.043
Townsend 5	1.246	0.103	0.000	1.044	1.449
BMI 25-30	-0.144	0.073	0.049	-0.288	0.000
BMI >30	0.839	0.077	0.000	0.688	0.990
Smoker	1.336	0.863	0.000	1.167	1.505
Ex-smoker	0.792	0.070	0.000	0.655	0.928
CCI 1	2.494	0.075	0.000	2.348	2.641
CCI 2	3.393	0.104	0.000	3.189	3.597
CCI 3	4.875	0.142	0.000	4.598	5.153
CCI 4	6.454	0.278	0.000	6.015	6.893
CCI $\geq$ 5	7.824	0.278	0.000	7.280	8.368
Constant	14.693	0.153	0.000	14.394	14.993

Appendix 7.4: Output of the GLM model with a log link and gamma variance

Variable	Coefficient	Robust std. error	P-value	(95% Confidence	interval
Age	0.044	0.000	0.000	0.004	0.005
Female	0.198	0.006	0.000	0.186	0.209
N. Ireland	0.030	0.009	0.001	0.011	0.048
Scotland	0.045	0.007	0.000	0.032	0.059
Wales	-0.007	0.008	0.388	-0.023	0.009
Townsend 2	0.008	0.009	0.336	-0.009	0.025
Townsend 3	0.033	0.009	0.000	0.016	0.050
Townsend 4	0.077	0.009	0.000	0.059	0.095
Townsend 5	0.112	0.009	0.000	0.093	0.130
BMI 25-30	-0.015	0.007	0.033	-0.028	-0.001
BMI >30	0.077	0.007	0.000	0.063	0.090
Smoker	0.124	0.008	0.000	0.108	0.140
Ex-smoker	0.073	0.006	0.000	0.063	0.085
CCI 1	0.236	0.007	0.000	0.223	0.250
CCI 2	0.312	0.009	0.000	0.294	0.329
CCI 3	0.430	0.012	0.000	0.517	0.583
CCI 4	0.550	0.017	0.000	0.517	0.583
CCI $\geq$ 5	0.650	0.020	0.000	0.611	0.689
Constant	5.497	0.015	0.000	5.468	5.526

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