Feasibility of identifying prognostic factors for total joint arthroplasty in electronic primary health care records

Matthew Alan Turner

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Keele University

Keele University

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Abstract

The ability to identify osteoarthritis (OA) patients at high risk of progressing to joint arthroplasty surgery could enable earlier, targeted nonsurgical management in primary care. The ability to do so using only information routinely recorded within the primary care electronic healthcare records (EHR) would have several advantages but the feasibility of this is unclear. The aim of this thesis was to identify factors associated with future primary total knee or hip arthroplasty (TKA/THA) that were available within the EHR. Initially, a systematic review identified 35 published articles reporting 42 factors potentially associated with primary TKA or THA in patients with osteoarthritis. A series of searches was then undertaken which obtained codelists based on Read morbidity and process of care codes and prescription medications based on the British National Formulary (BNF) subchapters for 13 of these factors. These codelists and a search of the consultation free text were then used in case-control studies of 874 patients receiving primary THA/TKA between 2005-2011 and 4,370 age-sex-practice-matched controls in the Consultations in Primary Care Archive (CiPCA) database. These analyses were used to determine which factors (i) met the minimum prevalence among cases and controls to warrant further analysis (3% in prior 5 years); (ii) were associated with the outcome of primary TKA/THA (unadjusted $p<0.05$). To identify other potential factors, an additional 'hypothesis-free' analysis was conducted examining the associations between outcome and all third- level Read codes and BNF subchapters (unadjusted odds ratio <0.75 or >1.33). In total 92 and 79 factors met the minimum prevalence and were associated with TKA and THA respectively. After adjusting for OA, 106 and 83 risk factors were associated with TKA and THA respectively. The studies in this thesis have identified 'building blocks' for a future multivariable risk prediction algorithm based within the primary care EHR.

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1 Introduction

Osteoarthritis is a common and disabling problem that affects many people within the UK, predominantly over the age of 45 years. Within the UK it is estimated that over 8 million adults have osteoarthritis which is painful and for which they have consulted their general practitioner (National Institute for Health and Clinical Excellence (NICE) 2014, Jordan et al. 2014). As with most long-term conditions, the majority of assessment and management takes place in primary care.

A range of non-pharmacological and pharmacological treatments are currently recommended (National Institute for Health and Clinical Excellence (NICE) 2014). These treatments are all directed towards symptom control; none appear to modify the course of the underlying disease. For a proportion of patients, these treatments may prove ineffective leading to a need for surgery. This reflects more generally the variation between individuals in the course of symptoms and the rate of disease progression (Nicholls et al. 2014).

For severe hip and knee osteoarthritis, total joint arthroplasty is highly effective (Carr et al. 2012) but it is also responsible for the vast majority of direct costs associated with osteoarthritis (Hiligsmann et al. 2014). The potential of more effective non-surgical management to prevent or delay the need for joint arthroplasty remains unclear but prognosis research may have an important contribution. By identifying prognostic factors associated with knee or hip arthroplasty, it may be possible to develop a risk prediction model to identify patients most at risk of requiring a future knee or hip surgery. The value of such a risk prediction model might be several-fold: to focus and intensify non-surgical management upon those persons at highest risk; to anticipate the increased likelihood of future need for surgical referral to enable a timely process of assessing appropriateness and willingness to undergo surgery; to provide researchers with a 'high-risk' group for enriched sampling for clinical trials.

It is important to consider how best to go about developing such a risk prediction model. The starting position taken in this thesis has been to base this solely on information held within the routine electronic health records (EHR). Information on specific prognostic factors may be identifiable from electronic health care records and this source may avoid the practical difficulty of requiring patients and clinicians to provide information needed to estimate risk of future joint replacement. Furthermore EHR databases can now provide long follow-up times for a large population. Other risk prediction models have been derived from EHR data in the UK, most notably within the QResearch® database. These include models to predict the risk of cardiovascular disease (Collins, Altman 2009). However, it is important to acknowledge from the outset some disadvantages with this approach. These include the complete absence of information on potentially important prognostic factors (e.g. severity of pain), and also potential for missing data and coding variability for those factors recorded. The purpose of this thesis was to undertake the preliminary studies necessary to inform future derivation of a risk prediction model for primary total hip replacement and total knee replacement.

The thesis aimed to identify a set of risk factors from within electronic health care records that could be feasibly obtained and were associated with the need for a future knee or hip arthroplasty.

1.1 Definition of Osteoarthritis

Osteoarthritis (OA) most commonly affects the knees, hips and hands (van Schoor et al. 2015) and it has been defined in a number of different ways (table 1-1).

Table 1-1: Definitions of osteoarthritis provided by different sources

Definitions of osteoarthritis
"A heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related changes in the underlying bone at the joint margins" pg. 1039 (Altman et al. 1986)
“Clinically, the condition is characterized by joint pain, tenderness, limitation of movement, crepitus, occasional effusion, and variable degrees of local inflammation.” Pg. 1 (Symmons, Mathers & Pfleger 2003)

"OA is usually a progressive disease of synovial joints that represents failed repair of joint damage that results from stresses that may be initiated by an abnormality in any of the synovial joint tissues, including articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves, or synovium. This ultimately results in the breakdown of cartilage and bone, leading to symptoms of pain, stiffness and functional disability. Abnormal intra-articular stress and failure of repair may arise as a result of biomechanical, biochemical and/or genetic factors. This process may be localized to a single joint, a few joints, or generalized, and the factors that initiate OA likely vary depending on the joint site." pg. 479 "OA is characterized by joint pain, stiffness and functional limitations resulting in reduced participation in valued activities, and downstream effects on fatigue, mood, sleep and overall quality of life" pg. 479 (Lane et al. 2011)
"Osteoarthritis refers to a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. It is the most common form of arthritis, and one of the leading causes of pain and disability worldwide." Pg. 4 "Osteoarthritis is characterised pathologically by localised loss of cartilage, remodelling of adjacent bone and associated inflammation. A variety of traumas may trigger the need for a joint to repair itself. Osteoarthritis includes a slow but efficient repair process that often compensates for the initial trauma, resulting in a structurally altered but symptom-free joint." Pg.4 (National Institute for Health and Clinical Excellence (NICE) 2014)

Together these definitions underline the fact that osteoarthritis is not a single condition and that the pathology involves multiple tissues. From the definitions it is evident that while there is a relationship between structural changes in the joint (considered as anatomical markers of OA "disease") and the occurrence and severity of symptoms such as pain and the associated limitation in function (markers of OA "illness"), there is also discordance between these two different aspects of OA. For example, a systematic review by Bedson and colleagues (Bedson, Croft 2008) identified that the proportion of those with knee pain who also had radiographic OA ranged from 15-76%. The 13 studies that were investigated had differing definitions of radiographic OA including x-raying separate parts of the knee joint or using a range of angles to take these x-rays.

The majority of the previous definitions used the Kellgren & Lawrence OA radiographic grading scale which uses certain aspects of the joint to assign a "score" as to how severe the OA is (e.g. the appearance of osteophytes). Others have used a symptomatic definition, resulting in possible

discrepancies in an overall OA definition. More recent studies using more sophisticated imaging techniques like magnetic resonance imaging (MRI) have identified some possible sources of discordance within symptomatic OA definitions by showing lesions not visible on plain radiography that contribute to pain (Yusuf et al. 2011). However, even with better imaging of all the joint tissues, substantial discordance of whether the patient had OA or not can still remain (Guermazi et al. 2012). A misconception about the pathogenesis of OA is that it is purely a degenerative disease process. Instead, OA is now understood to also involve repair processes in the joint (National Institute for Health and Clinical Excellence (NICE) 2014). It may be that successful repair may be one of the reasons for apparent structure-pain discordance

The above considerations have important implications for prognosis research in OA which is the focus of this thesis. The course of OA disease and symptoms is expected to be a more complex and variable course than a model of "inevitable decline" while the heterogeneous nature of osteoarthritis and the presumed existence of different phenotypes (Bijlsma, Berenbaum & Lafeber 2011) imply challenges in defining an appropriate "start point" (Hemingway et al. 2013) for prognosis studies.

1.2 Occurrence and impact

In the most recent Global Burden of Disease project, the global age standardised prevalence of osteoarthritis of the knee and hip was estimated to be 3.8% and 0.85% respectively (Cross et al. 2014). Within the UK, in 1995 incidence rate for knee OA was 100/100,000 persons years and for hip OA was 88/100,000 person years (Oliveria et al. 1995).

Of 291 different conditions, osteoarthritis of the hip and knee (combined) were ranked as the 11th highest contributor to global years lived with disability and 38th highest in disability-adjusted life years (Cross et al. 2014).

Within England, osteoarthritis contributed to 1.48% (IQR 1.13-1.86%) of the total years lived with disability after being standardised for age and 0.83% (IQR 0.62-1.09%) of the total disability adjusted life years (Institute for Health Metrics and Evaluation 2013). Within the West Midlands, where the current study is set, the contribution was 0.9% (IQR 0.65-1.2%) of the total disability adjusted life years after standardising for age. This was an increase from 1990 where the osteoarthritis contribution was 0.67% (IQR 0.46-0.91%) of the total disability adjusted life years after standardising for age. In a comparison of 5 musculoskeletal disorders presented by Public Health England (Institute for Health Metrics and Evaluation 2013), OA was the third ranked contributor to disability-adjusted life years behind low back/neck pain and a pooled category of other musculoskeletal conditions but ahead of both rheumatoid arthritis and gout.

Within North Staffordshire, the Consultations in Primary Care Archive (CiPCA) is a database that collects consultation data from 13 general practices (this is described further in Chapter 3). In 2010, there were 2,143 persons per 10,000 within the Consultations in Primary Care Archive (CiPCA) who had a record of consulting either primary or secondary care at least once for a musculoskeletal condition with 211 persons per 10,000 consulting for osteoarthritis. When investigating only primary care, this reduced to 1,967 persons per 10,000 consulting for a musculoskeletal condition and 176 persons per 10,000 consulting for osteoarthritis at least once in 2010. Of those patients that were aged 45 and over, 375 per 10,000 had consulted for OA in 2010 (Jordan et al. 2014). These values were not restricted to knee/hip OA but encompassed other joints affected by OA by using a set of Read-codes to identify the relevant population. Read-codes are used within primary care consultations to record a specific morbidity (described further in Chapter 3). For North Staffordshire, estimates of the incidence of OA have been obtained from the CiPCA database. By using a run in period of 10-years to exclude prevalent cases so only incidence cases were obtained, within 2010 the annual consultation incidence of osteoarthritis for any joint in patients aged 15 years and over was 8.6 per 1000 persons, lower for men at 6.3 per 1000 persons than women (10.8 per 1000 persons) (Yu et al. 2015). Among

patients aged over 45 years, the estimates for the incidence were 16.1 per 1000 persons (12.0 for men and 20.1 for women) suggesting an increased incidence in older patients. The estimates for the consultation incidence rate of knee OA among those aged 45+ was 6.5 per 1000 persons and for hip OA was estimated to be 2.4 per 1000 persons (Yu et al. 2015).

1.3 Prognosis and progression of OA

The "average prognosis" of symptomatic knee OA can be characterised by small annual losses in joint space width (an indirect measure of cartilage loss) and small annual increases in self-reported pain and disability (Nicholls et al. 2014). However, this group-average prognosis hides a much more heterogeneous course of structural disease progression, and change in symptoms and functional limitation.

Progression of OA can be investigated, with the measurement of radiographic joint space width still being the most accepted and widely used method of assessing OA progression (Emrani et al. 2008). The NICE guidelines for the care and management of osteoarthritis (National Institute for Health and Clinical Excellence (NICE) 2014) identified from observational studies that there are factors that affect the structural joint components and inflammation in and around the joint that influence the progression of OA. Many studies have sought to identify possible prognostic factors that are linked to the progression of OA in either the knee or the hip. Bastick and colleagues performed a systematic review and identified that the presence of knee pain and Herberden nodes were associated with the progression of knee OA whilst previous knee injury and regular performance of sports was not associated (Bastick et al. 2015). Although structure abnormalities can be seen as associated with the progression of OA, lifestyle factors have been looked at to determine their impact on the progression of OA. Nicholls and colleagues sort to examine the effect of reducing body mass index (BMI) on knee OA progression using a randomised control trial (Nicholls et al. 2014). The study team provided the cases with an exercise program to reduce the patients BMI. For those at high risk of having knee OA progression, the exercise program did not

show significant effects in reducing the progression of OA but particular features within the radiographs did diminish. From the definition above and the studies looking at prognostic factor, it can be seen that OA is a complex disease and progression can be affected by multiple factors. Certain techniques exist which are used to try to slow the progression of OA and relieve symptoms that can be caused by the disease (such as pain within the joint).

1.4 Management techniques available

1.4.1 Conservative management techniques

Throughout the clinical course of osteoarthritis, patients initiate and may receive a range of different treatments to alleviate the symptoms that they are experiencing. These treatments can be classed as education and self-management, pharmacological or surgical. Effective non-pharmacological treatment options recommended by NICE include advice to exercise, weight reduction techniques (if the patient is overweight) and use of superficial heat/cold techniques (National Institute for Health and Clinical Excellence (NICE) 2014). There is consistent evidence of small-to-moderate effects on pain and functional limitation of supervised excise programmes (Fransen et al. 2015). Within pharmacological treatments used for OA, the treatments are currently limited to symptomatic management with treatments including topical and oral non-steroidal anti-inflammatory drugs. However NICE guidelines have suggested that these pharmacological treatments are used before any possible surgery with the self-management techniques being offered first (National Institute for Health and Clinical Excellence (NICE) 2014).

Ongoing efforts to identify new disease-modifying non-invasive treatments have yet to produce convincing evidence of effectiveness. For example, Landmeer and colleagues' recent randomised controlled trial (RCT) in persons at high risk of knee OA found that a combination of glucosamine sulphate and exercise had no significant effect on knee OA progression defined by MRI (Landsmeer et al. 2015). Reginster and colleagues reported a beneficial structure-modifying effect of strontium ranelate in patients with knee OA (Reginster et al. 2013). However, at the

time of review NICE (2014) raised issues with using this particular treatment, primarily whether cardiovascular concerns would prevent approval of strontium ranelate for treating OA.

1.4.2 Total knee and hip arthroplasty

Total joint arthroplasty (TJA) is the most common surgical procedure for osteoarthritis that has not responded to conservative management and is regarded as an effective intervention (National Joint Registry 2015). The National Joint Registry of England, Wales and Northern Ireland identified that a total of 82,267 primary total knee arthroplasties (TKA) and 76,274 primary total hip arthroplasties (THA) were undertaken in 2013. This was an increase from 73,854 TKA and 66,707 THA in 2008. This increase could be due to a combination of factors which include the increase in an ageing population, as well as GP's referring more patients to secondary care to have a joint arthroplasty. Out of the patients that had received a joint arthroplasty in 2013, 93% of those that had received a primary hip arthroplasty, and 96% of those that had received a primary knee arthroplasty had been diagnosed with osteoarthritis prior to surgery (National Joint Registry 2015) indicating that OA was the predominant reason why patients received a joint arthroplasty.

The number of joint arthroplasties performed is set to increase in the coming years. Culliford and colleagues sought to provide estimates for the number of THA and TKA that will take place by 2035 by using different assumptions: (1) THA/TKA incidence rates fixed at 2010 levels, BMI distribution fixed at 2010 level; (2) THA/TKA incidence fixed, BMI changing over time; (3) THA/TKA incidence rates increasing log-linearly, BMI fixed; (4) THA/TKA incidence increasing log-linearly, BMI changing. The study obtained 50,000 THA and 45,609 TKA between 1991 and 2010 where the age, gender and BMI of the patient were recorded. By using these different assumptions, they estimated that the number of arthroplasties would increase by (assumption 1) 34.0%, (2) 32%, (3) 354%, and (4) 358% for primary THA and (1) 33.5%, (2) 39.6%, (3) 831% and (4) 913% for primary TKA (Culliford et al. 2015). However, the author acknowledged that results from

assumptions 3 and 4 seemed implausibly high but the results from assumptions 1 and 2 maybe underestimates. TJA is considered a cost-effective procedure although each procedure has been estimated to cost more than £8000 (Jenkins et al. 2013). The financial cost of joint arthroplasty extends beyond the surgery itself, impacting the economy and patients in regards to possible disabilities or care that is required after the surgery. A detailed list of UK unit costs for procedures, equipment and prescriptions that may be incurred after joint arthroplasty can be found in Marques et al. 2015. The financial burden of a total joint arthroplasty is an issue as the National Health Service (NHS) has come under increased financial constraints and had been set a target of saving £20 billion by 2015 which it was expected to fail to meet (Torjesen 2012).

Although total joint arthroplasties are considered as successful surgeries, certain recipients may require a revision surgery. In 2014, the National Joint Registry recorded a total of 8,925 hip revision procedures performed. The number of revision surgeries for the hip had been fairly consistent between 2009 and 2014 ranging from 7,478 in 2009 to 10,466 in 2012 (National Joint Registry 2015).

1.5 Rationale of study

Although the rates of hip and knee joint arthroplasties have increased in recent years, not all patients with OA will require or receive a joint arthroplasty. For example, in the Primary Care Society Hip Study set in 35 general practices in the UK, of patients aged 40 years and over presenting with a new hip problem 7% had been put on a waiting list for a hip arthroplasty by the first anniversary of attendance with this figure increasing to 23% by four years (Birrell et al. 2003). By establishing which factors predict future receipt of a joint arthroplasty, it would help GPs in determining who may require a joint arthroplasty years beforehand and provide treatments that can be used to decrease the risk of a joint arthroplasty or recommend those with a high risk for a joint arthroplasty sooner. With the increases in the amount of total joint arthroplasties performed and predictions that it is set to increase further, it would be of importance to identify

factors that appear to be related to a arthroplasty. By using this information, GP's could monitor closely the patients most at risk of requiring a joint arthroplasty and prioritise for surgery those who respond less well to conservative/ pharmacological management.

Prognostic factors for hip OA progression may not be the same as those for progression of knee OA. By studying the hip and knee joints independently of one another, the strengths of association of factors with arthroplasty between the two joints can be compared. This can be done using information collected within primary care routine electronic health records which keep a record of individual GP consultations. These store information collected by a GP, a nurse or other primary health care professional at each individual consultation with a patient and stores multiple pieces of information. While date of birth and gender are recorded at the patient's entry into the practice, the patient reason for consultation is recorded with additional information available within added prescriptions, referrals and test data, with text on the consultation also added by the GP. Included within the data will be records of any knee/hip arthroplasty that the individual had. This will be recorded in primary care from information that has been received from secondary care with the date the practice received this information being recorded. The recording of information at the time of the event or when information was received eliminates possible recall bias that can occur in cohort studies using questionnaires or other data collection methods through asking for retrospective information from patients or clinicians. By using primary care electronic records, additional risk factors related to comorbidity or process of care which have no prior evidence to an association with a knee/hip arthroplasty can also be investigated by looking at commonly occurring Read-codes and prescriptions. Although these factors may not have previously been investigated, they can still provide valuable insight as to the types of factors associated with an arthroplasty. Read-codes are used to record the purpose of the consultation and, within CiPCA (the database used for this study), GPs are encouraged to provide a Read-code per consultation with the informatics team providing training to achieve a high quality of coding (Porcheret et al. 2004). By using primary care records, a considerable

amount of information can be obtained. For example, CiPCA had an annual registered population of 94,565 by 2010 (Jordan et al. 2014) with 11 general practices providing information since 2003. At the time of this study a 12 year period of information from CiPCA practices was available for use (information obtainable from 1st January 2000 to 31st December 2011) which had dated records. Weakness of the electronic health records include the lack of information on potentially important risk factors such as severity of pain and the size and complexity of searching the coded information and information recorded in the text of the consultation.

1.6 Aims

The overall aim of the thesis was to obtain a set of potential risk factors for either a total hip or knee arthroplasty that were available and could be extracted from healthcare records, in order to determine the feasibility of deriving a multivariable prediction model for primary total hip and knee arthroplasty based on information routinely available within the primary care electronic health care record. The objectives were:

1. To undertake a **systematic review** to identify a list of possible prognostic factors associated with the need for total joint arthroplasty for the knee or hip in patients with osteoarthritis and identify and critically appraise any existing multivariable risk prediction algorithms or models for predicting risk of total hip or knee arthroplasty for osteoarthritis.
2. To undertake a **feasibility study** in the CiPCA database to determine, the extent to which each of the prognostic factors identified from the systematic review are obtainable within routinely collected healthcare data.
3. To undertake a **case-control study** in the CiPCA database to identify additional candidate prognostic factors which may be associated with the outcome of total hip or knee arthroplasty

1.7 Structure of thesis

Within the thesis there will be three main chapters which address each of the aims set out for the thesis

1.7.1 Systematic Review (chapter 2)

The systematic review is the next chapter. This chapter aimed to identify a set of possible prognostic factors for a future knee of hip arthroplasty from previously published literature within those who had been diagnosed with osteoarthritis. For factors within this part of the study to be taken forward for further analysis, there had to be strong evidence for an association or inconclusive evidence due to studies having conflicting results.

1.7.2 Feasibility Study (chapter 3)

For those factors taken forward from the systematic review a further search of the literature was undertaken to identify Read-code lists and definitions applicable to health care databases. Only those with an available list were considered for analysis. The prevalence of the different factors was assessed by searching within consultation records (using the CiPCA database) of those who had had a recorded joint arthroplasty of the knee or hip. This search was conducted using the code lists previously obtained and then the consultation free-text. Free-text is additional text that can be added during each consultation by the health care professional. Those factors with prevalence greater than 3% were taken forward to the next stage.

1.7.3 Case-control study (chapter 4)

A case-control study was then performed to assess the association of the identified factors from chapter 3 with knee and hip arthroplasty and identify further potential risk factors. The cases used in chapter 3 were matched to 5 controls by age-gender-practice-consultation year. The prevalence of the factors brought forward from chapter 3 were first determined within the controls. Additional morbidities and prescriptions were then searched for using a "hypothesis free" analysis to identify 3rd level Read Codes and prescriptions defined at BNF section level which

had prevalence greater than 3%. BNF chapters are a set of chapters that collect different drugs into different sections relating to different types of prescriptions (e.g. 4.7.2 Opioid analgesics). Once these were obtained, univariable logistic regressions were performed on the factors to identify which factors were associated with either a knee or hip arthroplasty.

2 Prognostic factors and multivariable risk models for predicting future primary hip or knee arthroplasty in osteoarthritis: A systematic review of observational studies

2.1 Introduction

Within the UK, not all patients with osteoarthritis will go on to have a joint arthroplasty. In one instance, in regards to hip arthroplasty, only 23% of patients who presented with OA for the first time received a hip arthroplasty after 4 years had passed (Birrell et al. 2003). Variability in progression of OA is one reason why certain patients will not require a joint arthroplasty. For certain patients, the progression of OA can be slow and the patient may not experience any significantly problematic symptoms for many years. In other patients disease progression and the appearance and worsening of symptoms may happen over a shorter time scale. Surgical options should be considered as the last possible alternative and NICE recommends that at least the core treatments for osteoarthritis have been offered (National Institute for Health and Clinical Excellence (NICE) 2014).

Patients may not receive the offer or accept an offer for a joint arthroplasty if the management techniques or prescriptions they are currently using are working for them. However there would be other possible reasons for patients not having a joint arthroplasty. These can include the patients not being willing to undergo the surgery if they do not believe it will benefit them in the long run. Cost may be a further reason why a patient would not receive a joint arthroplasty. The NHS was tasked with saving £20 billion by 2015 and a report anticipated that they would fail to achieve this target (Torjesen 2012). Each arthroplasty was estimated to cost on average £8000 per procedure in 2013 (Jenkins et al. 2013) and then the after care for patient would create additional costs. The area that the patient' lives within might also have an influence on the receipt of a joint arthroplasty. NICE recommends that before surgery, patients are given

information on how the care pathways are organised in the local area (National Institute for Health and Clinical Excellence (NICE) 2014)

There are many factors which may relate to a joint arthroplasty being offered to a patient and the patient actually accepting. Many of these factors will not be patient specific (e.g. area level deprivation). This may mean that a possible prediction model that is developed will perform poorly since there will be external factors that may influence the performance of a prediction model based purely on patient-specific factors. However, there will be certain key factors that will increase the likelihood that a patient will actually undergo surgery. The identification of these types of factors is what this systematic review aimed to discover as well as factors which were consistently seen as not being associated with surgery.

This systematic review aimed to obtain prognostic factors for knee/hip arthroplasty in patients with osteoarthritis; and factors that have been assessed in previous studies but with consistent evidence for lack of association with arthroplasty. The review also aimed to identify and appraise previous prediction models for arthroplasty.

2.2 Aims and objectives

The aims and objectives of this systematic review were:

1. Identify prognostic factors significantly associated with the prospective risk of knee/hip arthroplasty from observational studies
2. Identify prognostic factors consistently found to be non-significant with having an association with the prospective risk of knee/hip arthroplasty from observational studies
3. Appraise multivariable prognostic models relating to arthroplasty obtained from observation studies to determine their quality and how generalizable the models are.

2.3 Methods

2.3.1 Identification of studies and selection

To identify the appropriate observational studies regarding this specific topic, a search was conducted for all relevant papers published prior to the final search date of December 2014. An initial search strategy was trialled on two databases (Medline and EMBASE), testing its ability to correctly identify original research articles known to be eligible for inclusion in the review. This initial search strategy was developed by MT and reviewed by DY, GP and KJ with minor revisions undertaken accordingly. The search strategies of previously published systematic reviews were reviewed to inform this search strategy (e.g. (Ajuied et al. 2014)). Advice was also gained from the systematic review group within the Research Institute on which terms to include and training was completed on how the search strategy would need to be modified to allow for coverage in different search engines.

The databases that were searched were: Medline (1946-2014), EMBASE (1974-2014), Allied and Complementary Medicine (AMED 1985-2014), Cumulative Index to Nursing and Allied Health Literature (CINAHL 1981-2014) and Web of Science™ core collection (1970-2014). Each of these databases were searched individually due to the need to use different terms to identify possible articles. The search engines used to perform these searches were; Ovid (Medline and EMBASE), the Healthcare Databases Advanced Search (AMED and CINAHL) and Web of Science's own search engine. Since some of these databases went as far back as 1946, a limit to the date of the study could have been enforced. However, to ensure that all relevant papers were captured, no limit was used on the age of the studies. Specific keywords were used within the search to identify the studies in the different databases. These included: osteoarthritis, knee, hip, degenerative, arthroplasty, replacement, prognosis, factor, predict, risk, epidemiologic studies, cohort, case control and longitudinal. The final version of the full search strategy used for Medline is included in Appendix 1 table 7-1. The reference lists of all included studies were searched for additional

potentially eligible studies. Citation tracking of all included studies (using Web of Knowledge) was also performed to help identify further possible studies to include.

A study was eligible for inclusion if it met the systematic review's inclusion criteria. The eligibility criteria used to select studies for inclusion in the review is provided in table 2-1. "Virtual joint replacement indication" refers to attempts to define "pain and physical function cutpoints that would, coupled with structural severity, define a surrogate measure of 'need for joint replacement surgery,'" (Gossec et al. 2011).

Identified studies were downloaded into RefWorks and duplicate studies removed by MT. Titles were then screened by MT against the exclusion criteria. A random sample of 15 titles was independently checked by a second rater (DY). If any large disagreements (60% or more on which titles to include) occurred then a further 15 titles were selected and checked for consistency. Titles not meeting any of the exclusion criteria were moved to a separate folder within RefWorks for the abstract review.

Table 2-1: List of the Inclusion and Exclusion Criteria used for the Systematic Review

Inclusion Criteria	
1	patients within the study were 18 years of age or over
2	the hip and/or knee osteoarthritis was defined by certain clinical (diagnosis of OA, health care database read-code) and/or imaging criteria (Kellgren and Lawrence)
3	risk factors that were being measured were at the joint-level (e.g. joint abnormalities), patient- level (e.g. age, gender), practitioner-level (willingness to provide surgery), service-level (waiting levels) or area-level (e.g. area-deprivation)
4	the multivariable risk algorithms comprised of any of the risk/prognostic factors identified at the different levels (in point 3)
5	the end point of the study was that the patient received a primary total hip or knee arthroplasty, were listed for a primary hip or knee arthroplasty or satisfied criteria for "virtual joint replacement indication" (Gossec et al. 2011)
6	the study was based in either a cohort comprised of OA patients, the general population with OA or primary or secondary care patients with OA
7	the study design was an observational study which could include etiological, case-control, longitudinal and cohort studies
8	if the study's design allowed for a follow-up period then the follow-up period would need to be greater than 1 year
Exclusion Criteria	
1	the study was either an animal or laboratory study
2	the study focused on revision arthroplasty or any other form of hip/knee surgery as the

	outcome
3	studies that were comparing two different types of surgery or design of the prosthesis
4	studies investigating post-operative prognostic factors or comparing pre-operative factors to the post-operative factors
5	full texts or abstracts were not available or could not be retrieved
6	articles had incomplete data
7	any non-English study that could not be translated
8	any non-peer reviewed studies
9	the study was a randomised control trial or a qualitative study
10	the article was a conference abstract

All remaining abstracts were screened for eligibility by MT and a random sample of 15 abstracts was independently checked by a second rater (DY). Abstracts that met some inclusion criteria or failed to meet any exclusion criteria were taken through for full text review, being moved again into a separate folder within RefWorks. Full-text articles were retrieved and reviewed by MT against the eligibility criteria with the assistance of a second rater if required (DY). This assistance would be taken if there were full-texts in which there was some uncertainty on inclusion by MT. If during the review of these full-texts, a disagreement occurred which could not be resolved between MT and DY during a consensus meeting, then a third rater (GP or KJ) was consulted to resolve this disagreement.

2.3.2 Data Extraction

Prior to creating a data extraction form for the study, published systematic reviews were searched to determine what sort of data should be included within the form (Chapple et al. 2011, Lievense et al. 2002). The Critical appraisal and data extraction for systematic reviews of prediction modelling studies (CHARMS) checklist was also read and used (Moons et al. 2014) to assist with this. This paper gave information on how to critically appraise and extract data from prediction modelling studies which was valuable for the possible studies that had reported a prediction model. The extraction form contained five different sections to help gather all the appropriate data. These were: 1) general information containing the general study details (the last name of the lead author, date of publication and journal of publication), study title and country of origin; 2) population which includes the mean age (with standard deviation), proportion and counts by

gender, the sample size, whether the study was developed for this purpose or was it secondary analysis of a study developed for another purpose, the inclusion/exclusion criteria required for patients and the outcome measure used; 3) study characteristics including study design (e.g. cohort), study setting (e.g. primary care), aims and objectives of the study, the recruitment procedure used and the length of follow-up (where applicable); 4) the condition of interest including the joint being investigated (hip or knee) and the definition of osteoarthritis (e.g. using a radiographic definition or clinical definition); 5) the analysis performed including the prognostic factors assessed with the appropriate p-values and estimates of effect size for either the knee or hip, type of analysis performed and the covariates with effect sizes within identified prognostic models as well as any additional comments that could be added by MT. All of the information from the chosen studies was extracted by MT with the information from 15 studies being verified by DY. All information was recorded using an Excel Spreadsheet (a blank form is available in appendix 1 table 7-2).

2.3.3 Quality Assessment and Analysis

Each of the studies included for the analysis received a quality assessment by using the Quality of Prognosis Studies (QUIPS) tool (Hayden et al. 2013). This tool looked at six different elements of the study to analyse the quality of the study, first in individual domains which could then be used to assess the overall quality. The domains that were assessed included the **study participation domain** which assessed how the participants were selected in regards to the inclusion/exclusion criteria and the source population, **the study attrition domain** which assessed how the study accounted for non-responders and drop-outs in regards to attempting to collect the data from those who dropped out**, prognostic factor measurements domain** which addressed how the prognostic factors identified were measured, **the outcome measurement domain** which looked for a clear definition of the outcome as well as making sure the setting of the outcome was the same for all study participants, the **study confounders domain** which investigated whether all important confounders were measured as well as a clear definition of the important confounders,

and the **statistical analysis and reporting domain** which assessed the presentation and analysis of the data as well as checking for selective reporting of results (if this occurred).

For each of these domains, the study could be rated as having high, moderate or low bias. A higher overall bias from the different categories meant that the study would be of a lower quality and that the results obtained from the study might not be truly comparable to other studies. This check for overall bias was conducted by assessing the bias over the six categories. This was assessed by applying the level of bias that the majority of domains were recorded as. For this systematic review, if 4 out of the 6 domains were a certain level of bias then the overall study would be labelled as such. For example if there were 4 domains of low bias, 1 of moderate bias and 1 of high bias then the study would be recorded as having low bias. For studies that reported a multivariable risk prediction model, the TRIPOD statement was used (Collins et al. 2015). Although not designed as a quality assessment or "risk of bias" checklist, this statement provided a list of what information should be included for different types of studies reporting some form of risk prediction models. Quality assessment was performed by MT with a sample of studies (n=15) being reviewed independently by DY.

For this systematic review, a meta-analysis of the data was not applicable. A high level of heterogeneity between prognostic studies is a common problem that other systematic reviews have identified (Chapple et al. 2011, Shan et al. 2014). Although heterogeneity between studies can be dealt with to some extent in a meta-analysis by using a random effects model instead of a fixed effects model, the level of heterogeneity cannot be too high. This level can be assessed using the I^2 statistic which assesses heterogeneity as a percentage with a higher percentage meaning more heterogeneity. An I^2 of 60% (moderate heterogeneity) has been suggested as the maximum level for a random-effect meta-analysis (Higgins, Green 2008)) but the expected heterogeneity in this review would make this approach less viable. Therefore, the main approach that was taken in this review was a best evidence synthesis.

The main focus within the best evidence synthesis was to report the different prognostic factors. The QUIPS tool was used to assess the quality of the individual studies as high, moderate or low quality. All studies that were deemed as being a high quality study were used for the best evidence synthesis. These studies did not need to be high quality in all the domains of the QUIPS tool but were seen as high quality in most domains (at least 4). The different study factors were split into those factors that, from the evidence obtained, could be considered prognostic factors, those that were not prognostic factors and those factors that had conflicting or lack of evidence. This was judged by MT. Factors were deemed as being prognostic factors in a study if there was statistically significant evidence that there was an association with a knee or hip arthroplasty, meaning the p-value for the factor was less than 0.05 or the confidence interval provided did not contain 1. The information that was compared regarding these specific factors were the effect sizes reported (crude or adjusted) as well as the sample size and study population. Strong evidence was deemed as a factor that had statistically significant evidence that the factor was significantly associated with arthroplasty in most of the literature which was deemed as having a high quality. This was similar for strong evidence against. Inconclusive evidence was deemed as factors that had studies which had differing opinions on whether it was a prognostic factor. For the factors that were only identified by one particular study, these factors were still grouped into the categories of having strong evidence for being a factor, strong evidence against being a factor or had inconclusive evidence (e.g. a categorical variable where certain categories had an association whilst others did not). This best evidence approach was performed for factors regarding the knee and hip separately.

Assessment of multivariable prediction models did not use a best evidence synthesis approach. Instead, each of the models were analysed individually. These were assessed by looking more in-depth at how the model had been built and presented, as well as any model checks that were undertaken. This was assessed by using the TRIPOD statement and the CHARMS checklist (Moons

et al. 2014, Collins et al. 2015) as guidance. When determining if the model was viable or not, one of the main factors looked into was whether the model had been externally validated or not.

2.4 Results

2.4.1 Literature Selection

The initial search strategy used for searching the different databases yielded 1,352 articles, of which 926 remained after the removal of duplicate articles. This search strategy was reviewed and modified with assistance from DY, GP and KJ to enable more relevant articles to be identified. After applying this revised strategy (see appendix 1 table 7-1) 17,982 articles were identified from the search (6,923 from MEDLINE, 6,350 from EMBASE, 2,769 from Web of Science, 1,752 from CINAHL and 188 from AMED). 11,211 articles remained after the removal of duplicate studies (Figure 2-1). Of the 11,211 articles, a total of 55 were seen as potentially relevant and full texts were obtained for review. Of these 55, 28 were excluded from the final analysis, most commonly because they did not focus on osteoarthritis (n=13). 5 additional studies from the reference list search and 3 from citation tracking met the required criteria, so were included within the study. This resulted in 35 studies being included for analysis.

2.4.2 Study Characteristics

Table 2-2 provides details of the characteristics for the included studies. 35 studies (11 knee, 10 hip, 14 combined hip/knee) were undertaken in 22 unique datasets from 12 different countries. 11 studies were conducted in Australia, 6 of which sampled from the Melbourne Collaborative Cohort Study (Giles, English 2002) but used different inclusion criteria. The separation of the hip and knee joints allowed for individual risk factors for each joint to be assessed whereas the studies that investigated both joints allowed for a comparison of factors to be made. Two different types of study design were used, with studies being either cohort studies (77%) or case-control studies (23%). The majority of the studies performed some form of multivariable analysis, adjusting for specific confounders (which were not judged as prognostic factors) but only 3

studies reported multivariable prognostic models. 31 (86.1%) studies were designed to allow for a follow-up period to be used with the follow-up times ranging from 2-16 years.

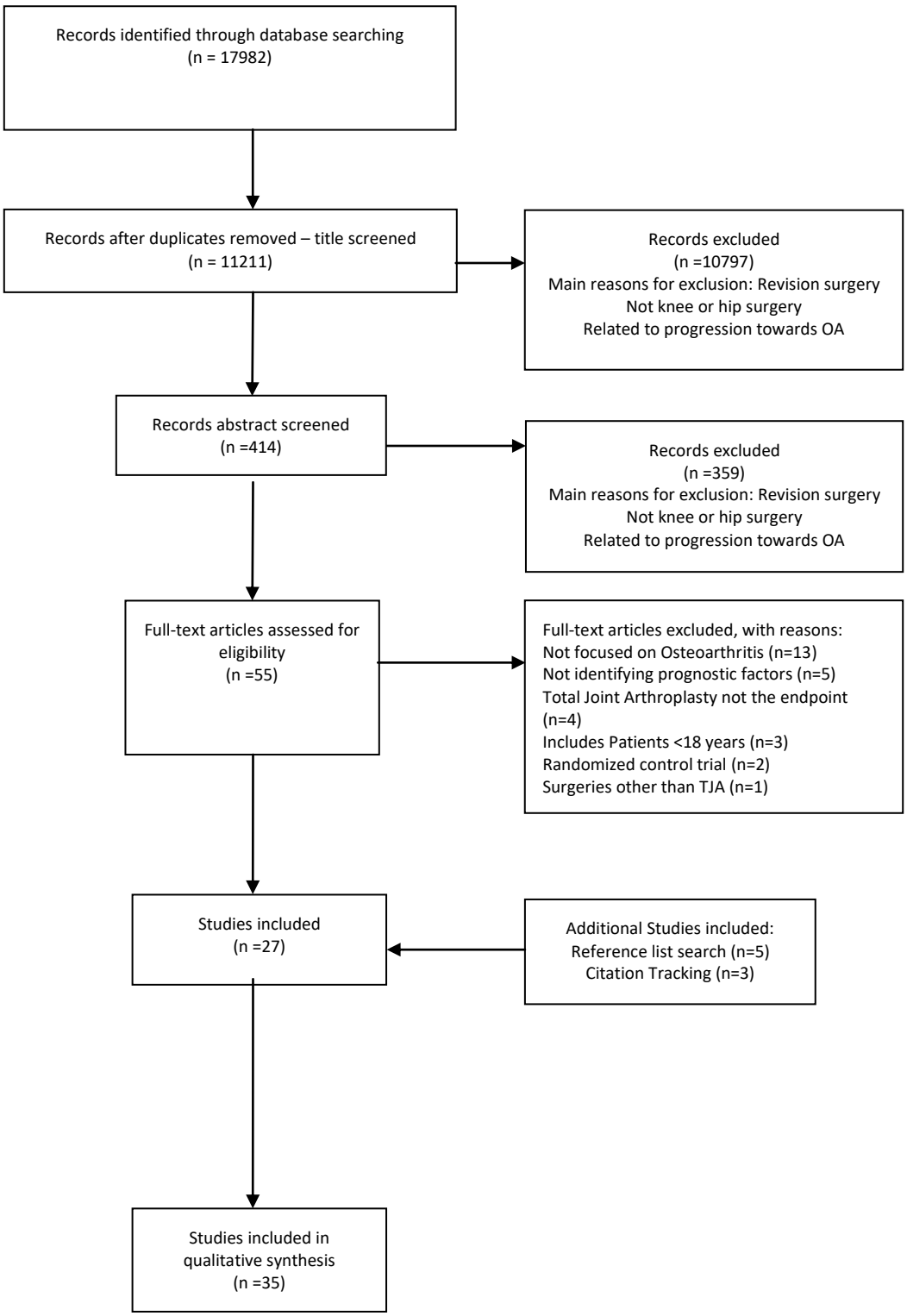

Figure 2-1: Flow chart of the systematic review progression at each stage of the review

Table 2-2: Study characteristics of the included studies in the systematic review

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Vinciguerra et al. 1995)	France	Primary Care	Cohort	Original	149	58 (14)	99 (66.4)	Hip	American College of Rheumatology criteria	Evaluated medical records to assess if a THA was recorded	5 years	Cox proportional hazards	Low
(Cooper et al. 1998)	UK	Populati on-based	Case-Control	Original	611	70 (9.0)	401 (65.6)	Hip	Radiological (cases)	Placed on waiting list for THR/TKR over a 18 month period	2 years	Logistic regression	Low
(Dougados et al. 1999)	France	Multi-centre	Cohort	Original	421	COUNTS <55: 63(15%) 55-60: 74 (18%) 60-65: 97 (23%) 65-70: 96 (23%) >70: 89 (21%)	246 (58.4)	Hip	American College of Rheumatology criteria	Decision for THA made by rheumatologist with the surgery date noted	3 years	Cox proportional hazards	Low
(Michaëlsson et al. 2011)	Sweden	Populati on-based	Cohort	Original	53,983	38.8 (12.3)	5409 (10.02)	Knee/ Hip	Arthroplasty due to OA	Linked the subjects to the National Patient Registry on for received a TKR/THR after the last race	10 years	Cox proportional hazards	High Quality
(Karlson et al. 2003)	United States	Study of Nurses	Cohort	Original	93,442	30-55 yrs (no mean given)	Female Study	Hip	Self-reported	Self-reported total hip arthroplasty on a questionnaire	6 years	Logistic regression	Low
(Chan et al. 2010)	Taiwan	Primary Care	Case-Control	Original	326	TKA: 69.6 No TKA: 69.5	TKA: 156 (80.8) No TKA: 87 (65.4)	Knee	-	Received a TKA from one of five orthopaedic surgeons	N/A	Logistic regression	Moderate Quality

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Sigurjonsdottir et al. 2010.)	Iceland	Population-based	Cross-sectional	Original	5,170	76 (6.0)	2975 (57.5)	Knee/ Hip	Arthroplasty due to OA	Identified from database who received a THR/TKR	N/A	Logistic regression	Low
(Nicholls et al. 2012)	UK	Population-based	Cohort	Original	1,414	53	Female Study	Knee	Arthroplasty due to OA	Received a TKA and verified by general practitioner records	10 years	Logistic regression	Moderate Quality
(Wang et al. 2009)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	39,023	Knee Arthroplasty : 68.1 (6.9) Hip Arthroplasty : 67.3 (7.2) No Arthroplasty : 62.6 (8.8)	Knee Arthroplasty : 344 (63.6) Hip Arthroplasty : 283 (60.5) No Arthroplasty : 22699 (59.7)	Knee/ Hip	Arthroplasty due to OA	Identified cases from the AOA NJRR	8 years	Cox proportional hazards	High Quality
(Wang et al. 2011a)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	35,331	62.2 (8.8)	21580 (61.1)	Knee/ Hip	Arthroplasty due to OA	Identified cases from the AOA NJRR	8 years	Cox proportional hazards	Moderate Quality
(Wang et al. 2011b)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	39,023	66.0 (7.63)	23326 (59.8)	Knee/ Hip	Arthroplasty due to OA	Identified cases from the AOA NJRR	8 years	Cox proportional hazards	High Quality

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Wang et al. 2012)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	27,848	62.3	16940 (60.8)	Knee/ Hip	American College of Rheumatology criteria	Identified cases from the AOA NJRR	8 years	Cox proportional hazards	High Quality
(Wang et al. 2013)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	38,149	Female: 57.2 (7.7) Male: 57.5 (8.03)	22849 (59.9)	Knee/ Hip	- American College of Rheumatology criteria	Identified cases from the AOA NJRR	8 years	Cox proportional hazards	Moderate Quality
(Hussain et al. 2014)	Australia	Population-based	Cohort	Melbourne Collaborative Cohort Study (Giles, English 2002)	14,511	56.3 (7.63)	8598 (59.3)	Knee/ Hip	American College of Rheumatology criteria	Identified cases from the AOA NJRR	10.5 years	Cox proportional hazards	High Quality
(Lohmander et al. 2009)	Sweden	Population-based	Cohort	Malmö Diet and Cancer Cohort (Berglund et al. 1993)	27,960	Female: 57.4 (7.8) Male: 59.2 (7.0)	16934 (60.6)	Knee/ Hip	Arthroplasty due to OA	Based on record linkage with national Swedish hospital discharge register	11.2 years	Cox proportional hazards	Moderate Quality
(Engström et al. 2009)	Sweden	Population-based	Cohort	Malmö Diet and Cancer Cohort (Berglund et al. 1993)	5194	Severe Knee OA: 59.7 Severe Hip OA: 60.0 (5.1)	Knee OA: 3029 (58.6) Hip OA: 3024 (58.6)	Knee/ Hip	Diagnosis of OA according to ICD-9 and ICD-10	Received a knee/hip arthroplasty in combination with a diagnosis of OA according to ICD-9 and ICD-10	N/A	Cox proportional hazards	Moderate

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Ageberg et al. 2012)	Sweden	Population-based	Cohort	Malmö Diet and Cancer Cohort (Berglund et al. 1993)	28,449	58 (7.6)	17203 (60.4)	Knee/ Hip	Arthroplasty due to OA	First hip arthroplasty in combination with a diagnosis of OA	5 years	Cox proportional hazards	High
(Leung et al. 2014)	China	Population-based	Cohort	Taken from (Hankin et al. 2001)	63,129	67.8 (6.6)	35191 (55.7)	Knee	Matched to database	TKR identified via record linkage analysis with hospital discharge databases	14.5 years	Cox proportional hazards	High
(Leung et al. 2015)	China	Population-based	Cohort	Taken from (Hankin et al. 2001)	52,780	56.02 (7.91)	28844 (54.65)	Knee	Arthroplasty due to OA	Identified TKR via record linkage using Medic Claim System hospital discharge database	Mean: 14.5 (4.1)	Cox proportional hazards	Moderate
(Cicuttini et al. 2004)	Australia	Community based	Cohort	Original	113	Arthroplasty : 64.1 (9.3) No Arthroplasty : 63.1 (10.3)	Arthroplasty : 12 (67) No Arthroplasty : 53 (56)	Knee	Radiological	Contacted subjects 4 years later to determine if they had had a TKR	4 years	Logistic regression	High
(Podsiadlo et al. 2014)	Australia	Population-based	Cohort	Taken from Cicuttini et al (2004)	114	Arthroplasty : 63.9 (8.8) No Arthroplasty : 63.8 (10.8)	Arthroplasty : 16 (57.1) No arthroplasty : 49 (57)	Knee	American College of Rheumatology criteria	Contacted subjects 6 years later to determine whether they had a JR	6 years	Logistic regression	Moderate
(Franklin et al. 2009)	Iceland	Multi-centre	Case-Control	Original	2,578	Case: 74.1 (6.82) Control: 70.9 (6.75)	Case: 872 (59.2) Control: 599 (54.3)	Knee/ Hip	Radiological	Identified using hospital records patients with OA diagnosis who had undergone a THR/TKR	median 5 years (range 0-26)	Logistic regression	High

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Franklin et al. 2010)	Iceland	Multi-centre	Case-Control	Taken from Franklin et al (2009)	2,490	Case: 74.25 (7.25) Control: 70.75 (7.05)	Case: 832 (59.1) Control: 592 (54.7)	Knee/ Hip	Radiological	Identified using hospital records patients with OA diagnosis who had undergone a THR/TKR	median 5 years (range 0-26)	Logistic regression	High
(Manninen et al. 2001)	Finland	Population-based	Case-Control	Original	805	Female case: 69.2 (5.37) Male case: 67.5 (5.67) Female control: 67.2 (5.55) Male control: 67.2 (5.64)	Case: 226 (80.4) Control: 384 (73.3)	Knee	Arthroplasty due to OA	Cases received they first TKA between 1992-1993, identified through Finnish Registry of Arthroplasty	N/A	Logistic regression	High
(Manninen et al. 2004)	Finland	Population-based	Case-Control	Taken from Manninen et al. (2001)	635	Case: 66.7 (5.6) Control: 68.6 (5.5)	394 (62)	Knee	Arthroplasty due to OA	Cases received they first TKA between 1992-1993, identified through Finnish Registry of Arthroplasty	N/A	Logistic regression	Low
(Rubak et al. 2013)	Denmark	Population-based	Cohort	Original	1,910,493	Female: 48.2 Male: 49.1	889,549 (46.6)	Hip	Arthroplasty due to OA	First THR due to OA, collected form the NPR	10 years	Logistic regression	High
(Rubak et al. 2014)	Denmark	Population-based	Case-Control	Taken from Rubak et al. (2013)	5,495	Female: 64.7 Male: 64.3	2744 (49.9)	Hip	Arthroplasty due to OA	First THR due to OA, collected using specific read codes	11 years	Logistic regression	Moderate

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Tanamas et al. 2010.)	Australia	Population-based	Cohort	Original	109	63.2 (10.3)	56 (51.4)	Knee	Radiological	Contacted subjects 4 years later to determine if they had received a TKR, verified by the treating physician	4 years	Linear regression	Moderate
(Tanamas et al. 2010)	Australia	Population-based	Cohort	Taken from Tanamas et al. (2010)	109	63.2 (10.3)	56 (51.4)	Knee	Radiological	Contacted subjects 4 years later to determine if they had received a TKR, verified by the treating physician	4 years	Logistic regression	Moderate
(Flugsrud et al. 2002)	Norway	Multi-centre	Cohort	(National Health Screening Service 1988)	50,034	46.6	25,037 (50.0)	Hip	Arthroplasty due to OA	First THR due to OA from arthroplasty register	10 years	Cox proportional hazards	High
(Liu et al. 2007)	UK	Population-based	Cohort	(Million Women Study Collaborative Group 1999)	490,532	50-64 (range)	Female Study	Knee/ Hip	Arthroplasty due to OA	Primary hip/knee arthroplasty codes were identified	2.9 years	Cox proportional hazards	Moderate

Authors, Year of Publication, Study	Country of Origin	Study setting	Study Design	Sample Used	Sample Size	Age (mean SD)	Female (n and %)	Type of OA	OA definition used (or eligibility)	Outcome Measure	Length of Follow-up	Type of Analysis	Quality of study
(Flugsrud et al. 2006)	Norway	Population-based	Cohort	Nationwide screening for tuberculosis in Norway (Waaler 1984)	1,200,000	Female: 55.9 (12.6) Male: 56.9 (12.7)	625,034 (54.3)	Hip	Arthroplasty due to OA	Matched codes from tuberculosis screening with information in hip arthroplasty surgery from arthroplasty registry	16 years	Cox proportional hazards	High
(Mnatzaganian et al. 2013)	Australia	Population-based	Cohort	Second Australian National Blood Pressure Study (Wing et al. 2003)	44,614	72.8 (5.0)	24761 (55.5)	Knee/ Hip	Arthroplasty due to OA	Identified cases from the AOA NJRR	11 years	Cox proportional hazards	Moderate
(Bruyere et al. 2013)	Czech Republic	Primary Care	Cohort	Taken from (Pavelká et al. 2002)	202	With surgery: 65.3 (6.6) Without surgery: 61.4 (6.7)	170 (84.2)	Knee	American College of Rheumatology criteria	First OA Surgery	8 years	Logistic regression	High
(Gossec et al. 2005)	France	Secondary care	Cohort	Taken from (Ravaud et al. 2004)	741	64.0 (10.1)	309 (61.2)	Hip	American College of Rheumatology criteria	Contacted rheumatologist to obtain if patients had received surgery	2 years	Logistic regression	High

Original sample corresponds to the sample being collected specifically for use in that study

The ages of patients investigated in the studies ranged from 30-76 with the majority of the studies having a mean age of above 50 years. The sample sizes that each study used varied, ranging from 109 patients to 1,910,493.

Certain studies had used arthroplasty as an alternative means of determining who had arthroplasty. These studies had used a retrospective design and had determined that the patients in the study had OA by only selecting those who had received an arthroplasty due to OA.

Over the 35 different studies, the two main forms of analysis used were logistic regression and Cox proportional hazards analysis. The use of Cox proportional hazards analysis meant that time-to-event data was used for these studies. The final end point for the time to event analysis was receiving a total joint arthroplasty or being put on a waiting list for a total joint arthroplasty or the patient was censored, whichever occurred first. The censored information could take the form of the patient dropping out of the study or the end of follow-up being reached before the event of interests occurred.

2.4.3 Factors identified by the systematic review

The included studies presented evidence for possible factors in various ways. The direction and magnitude of association between predictors and outcome were reported as odds ratios, relative risks or hazard ratios in all but one study (which provided only p-values). For the knee, there were a total of 38 factors with reported information and for the hip there were a total of 58 factors with reported information. 29 factors with reported information were investigated for both joints. There were certain factors included from particular studies that might only be possible to use for a specific population of people (e.g. number of competitive skiing races (Michaëlsson et al. 2011)) or were designed to include specific time components for specific factors (pain over 6 months (Gossec et al. 2005)) which could be difficult to investigate on a different population outside of these studies. Details on all these factors can be seen in the appendix 1 (tables 7-3 & 7-4). Many of the factors which were investigated by more than one

study were categorical variables but did not use comparable categories across studies. An example of this includes smoking status within patients with knee OA in the Leung at el. (2014) study which used 21 different categories whilst the Manninen at el. (2001) study used only 4 for the same factor.

2.4.4 Best Evidence Synthesis

For the best evidence synthesis, only papers that were of high quality were used within the analysis (a histogram of how the quality compared over the six elements of the QUIP's tool can be seen in figure 2-2 with further details in the appendix 1 table 7-5). Many of the studies did poorly within the study attrition section and the statistical analysis and confounding section with 11.4% having low bias within the study attrition section and 37.1% having low bias in the statistical analysis section. Of the 35 studies identified, 16 rated as high quality were used in the best evidence synthesis. Overall there were 21 factors investigated for the knee and 29 investigated for the hip in these studies of which 15 factors were investigated for both the knee and hip. For the purpose of taking through all possible risk factors forward, low and moderate quality studies were assessed separately to obtain possible factors to take through for further analysis (chapters 3 and 4). For the purpose of this systematic review however, only high quality studies were assessed. The factors included in the lower quality studies were assessed outside of this systematic review. The conclusions drawn for these factors were not identical across joints as certain factors had an association with arthroplasty in one joint but not the other. Table 2-3 provides the factors investigated for the knee and table 2-4 provides the factors investigated for the hip from the 16 high quality studies. Since many studies split the specific factors into multiple categories, the number of levels used is shown and example categories were chosen to demonstrate the effect size. One of the studies (Gossec et al. 2005)) only provided p-values so a direction of association for the factors investigated in this study could not be determined.

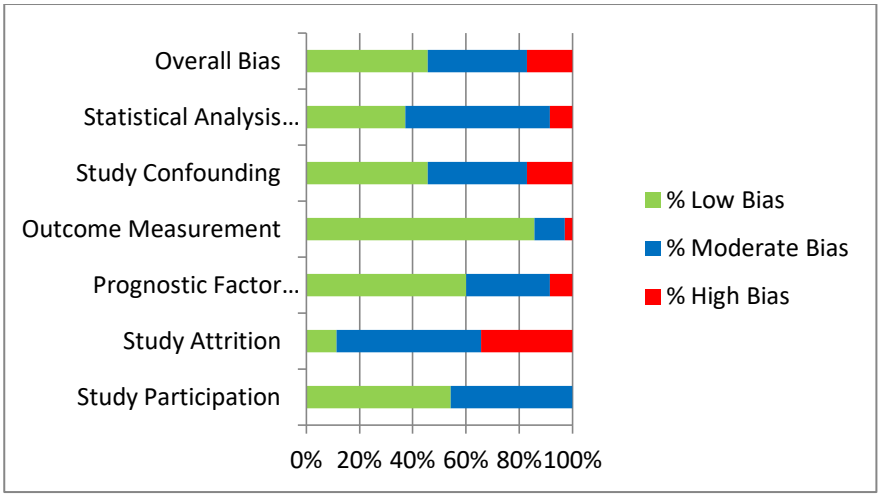

Figure 2-2: Histogram representing the level of bias shown in each category of the QUIP's tool across studies as well as the overall bias

2.4.5 Prognostic factors for Total Knee Arthroplasty

Table 2-3 lists the 21 factors identified by the high quality papers. Of these factors, 5 were investigated by more than one study. Of these 5, only BMI, physical activity (in general) and radiological grade had generally consistent evidence as to whether the specific factor was associated with the need for a future arthroplasty. Studies assessing BMI indicated a positive association with requiring a knee arthroplasty in the future (Franklin et al. 2009, Manninen et al. 2001) whilst studies investigating physical activity (Wang et al. 2011b, Ageberg et al. 2012, Manninen et al. 2001) provided consistent evidence that neither were associated with predicting future knee arthroplasty s in patients with OA. Both smoking status (Leung et al. 2014, Manninen et al. 2001), radiological grade (Cicuttini et al. 2004, Bruyere et al. 2013) and age (Cicuttini et al. 2004, Manninen et al. 2001) had conflicting evidence of associations as the included studies reported different conclusions for those factors. With smoking status, one study identified no association with the need for a knee arthroplasty whilst the second study identified a negative association for current smokers, meaning they were less at risk of requiring a knee arthroplasty than non-smokers. For age, one study identified no association for the entire population whilst the second study identified a positive (increased risk for those of older age) association for

females only. This study also investigated BMI (Manninen et al. 2001) which also divided the category by gender. For this study, a positive association occurred in females for BMI but no association was present for males.

Table 2-3: List of factors investigated for the knee and the associations identified within high quality studies

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
Socio-demographic	Age*	Cicuttini at el. (2004)	Logistic	Odds-Ratio	1	0.9 (0.7, 1.3)	No Association	Inconclusive
		Manninen at el. (2001)	Logistic	Odds-Ratio	2	Men: 1.01 (0.43, 1.04) Women: 1.07 (1.03, 1.10)	Men: No Association Women: Positive	
	Sex (F v M)*	Cicuttini at el. (2004)	Logistic	Odds-Ratio	1	9.9 (1.5, 65.4)	Positive	Positive
Body Composition	BMI*	Cicuttini at el. (2004)	Logistic	Odds-Ratio	1	0.9 (0.8, 1.1)	No Association	Positive
		Franklin at el. (2009)	Logistic	Odds-Ratio	4	Men BMI >30: 5.3 (2.8, 10.1) Women BMI >30: 4.0 (2.6, 6.1)	Positive	
		Manninen at el. (2001)	Logistic	Odds-Ratio	2	Men: 1.09 (0.98, 1.21) Women: 1.11 (1.06, 1.18)	Men: No Association Women: Positive	
		Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.88 (1.76, 2.00)	Positive	
	Weight*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.58 (1.51, 1.65)	Positive	Positive
	Waist/Hip Ratio*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.43 (1.29, 1.58)	Positive	Positive
	Body Fat*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	2.84 (2.47, 3.26)	Positive	Positive
	Waist Circumference*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.62 (1.53, 1.72)	Positive	Positive
	Fat mass*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.88 (1.76, 2.00)	Positive	Positive
Lifestyle	Physical Activity	Ageberg at el. (2012)	Cox PH	Relative	3	Moderate-high: 1.36	Association	No

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
	(General)*			-Risk		(1.04, 1.77)		Association
		Manninen at el. (2001)	Logistic	Odds-Ratio	8	Men Low Cumulative: 0.76 (0.29, 1.97) Women Low Cumulative: 0.55 (0.29, 1.03)	No Association	
		Wang at el. (2011)	Cox PH	Hazard-Ratio	13	Moderate : 1.13 (0.87, 1.46)	No Association	
	Smoking Status	Leung at el.(2014)	Cox PH	Hazard-Ratio	21	Current Smoker: 0.49 (0.40, 0.60)	Negative	Inconclusive
		Manninen at el. (2001)	Logistic	Odds-Ratio	4	Men ex or current: 0.84 (0.42, 1.68) Women ex or current: 0.59 (0.35, 0.99)	No Association	
	No of competitive skiing races*	Michaëlsson at el. (2011)	Cox PH	Hazard-Ratio	1	1.09 (1.02, 1.16)	Positive	Positive
	Time completed skiing races*	Michaëlsson at el. (2011)	Cox PH	Hazard-Ratio	1	1.10 (0.96, 1.26)	No Association	No Association
	Occupation*	Franklin at el. (2010)	Logistic	Odds-Ratio	14	Technicians and Clerks >Men: 2.0 (0.71, 5.7) Farmers >Men: 5.1 (2.1, 12.4)	Inconclusive	Inconclusive
	Physical work stress	Manninen at el. (2001)	Logistic	Odds-Ratio	6	Heavy: 0.61 (0.29, 1.27)	No Association	No Association
	Previous Knee Injury	Manninen at el. (2001)	Logistic	Odds-Ratio	4	Yes: 2.90 (1.48, 5.66)	Positive	Positive
Biomarkers (imaging, biochemical)	Radiological Grade/Progression	Bruyere at el. (2013)	Logistic	Odds-Ratio	2	new definition: 3.92 (1.44-10.67)	Positive	Inconclusive
		Cicuttini at el. (2004)	Logistic	Odds-Ratio	1	1.8 (0.6, 6.1)	No Association	

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
	HFE Genotype group*	Wang at el. (2012)	Cox PH	Hazard-Ratio	9	Recessive 2 copies: 0.48 (0.15, 1.49)	No Association	No Association
	Tibial Bone Area	Cicuttini at el. (2004)	Logistic	Relative-Risk	1	1.2 (1.0, 1.4)	Positive	Positive
	Cartilage loss	Cicuttini at el. (2004)	Logistic	Relative-Risk	1	1.2 (1.1, 1.3)	Positive	Positive
Clinical	WOMAC (Pain score)	Cicuttini at el. (2004)	Logistic	Relative-Risk	1	1.5 (1.1, 2.0)	Positive	Positive
Other	2D:4D index to finger ratio*	Hussain at el. (2014)	Cox PH	Hazard-Ratio	3	Left 2D:4D : 0.93 (0.86, 1.01)	No Association	No Association
*** - Factors identified for both the knee and the hip** **COX PH; Cox proportional Hazard model; logistic, Logistic regression model**								

Table 2-4: List of factors investigated for the hip and the associations identified within high quality studies

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
Socio-demographic	Age*	Rubak at el. (2013)	Logistic	Odds-Ratio	2	Women: 1.11 (1.11, 1.11) Men: 1.09 (1.09, 1.09)	Positive	Inconclusive
		Gossec at el. (2005)	Logistic	P-Value	1	0.09	No Association	
	Sex (F v M)*	Gossec at el. (2005)	Logistic	P-Value	1	0.53	No Association	No Association

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
Body Composition	BMI*	Flugsrud at el. (2002)	Cox PH	Relative -Risk	8	Men 23.5-25.2: 1.3 (0.9, 1.9) 27.4 +: 2.0 (1.4, 2.9) Women 22.3-24.2: 1.3 (0.9, 1.8) 27.1+: 3.0 (2.1, 4.1)	Inconclusive	Positive
		Franklin at el. (2009)	Logistic	Odds-Ratio	4	Men BMI >30: 1.7 (1.0, 2.9) Women BMI >30: 1.0 (0.6, 1.5)	Inconclusive	
		Flugsrud at el. (2006)	Cox PH	Relative -Risk	20	Men 32.0+: 3.4 (2.9, 4.0) Women 32.0+: 2.3 (2.1, 2.4)	Positive	
		Gossec at el. (2005)	Logistic	P-Value	1	0.55	No Association	
		Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.26 (1.15, 1.38)	Positive	
	Weight*	Flugsrud at el. (2002)	Cox PH	Relative -Risk	8	Men 85.1+: 2.1 (1.4, 3.2) Women 72.1+:3.4 (2.4, 4.9)	Positive	Positive
		Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.22 (1.15, 1.30)	Positive	
	Height*	Flugsrud at el. (2006)	Cox PH	Relative -Risk	10	Men 181+: 1.3 (1.2, 1.4) Women 168+: 1.9 (1.9, 2.0)	Positive	Positive
	Waist/Hip ratio*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.01 (0.85, 1.19)	No Association	No Association
	Body Fat*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.37 (1.19, 1.57)	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
	Waist Circumference*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.10 (1.01, 1.38)	Positive	Positive
	Fat Mass*	Wang at el. (2009)	Cox PH	Hazard-Ratio	1	1.29 (1.18, 1.41)	Positive	Positive
Lifestyle	Occupation*	Franklin at el. (2010)	Logistic	Odds-Ratio	14	Technicians and Clerks >Men: 1.6 (0.85, 3.0) Farmers >Men: 3.6 (2.1, 6.2)	Inconclusive	Inconclusive
		Rubak at el. (2013)	Logistic	Odds-Ratio	10	Men top managers (upper level): 0.63 (0.58, 0.68) Women Employees (intermediate level): 0.91 (0.82, 1.02)	Inconclusive	
	Physical Activity (General)*	Ageberg at el. (2012)	Cox PH	Relative-Risk	3	moderate-high: 0.91 (0.72 ,1.16)	No Association	No Association
		Wang at el. (2011)	Cox PH	Hazard-Ratio	13	Moderate (3-4): 0.89 (0.67, 1.16)	No Association	
	Physical Activity (at leisure)	Flugsrud at el. (2002)	Cox PH	Relative-Risk	8	Men Intermediate: 0.9 (0.7, 1.4) Women Intermediate: 0.9 (0.6, 1.2)	No Association	No Association
	Physical Activity (at work)	Flugsrud at el. (2002)	Cox PH	Relative-Risk	8	Men Intermediate: 1.7 (1.1, 2.4) Women Intermediate: 1.4 (0.9, 2.0)	Inconclusive	Inconclusive

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
	Physical Workload	Rubak at el. (2013)	Logistic	Odds-Ratio	2	Women Worked in industry 5-point year increments: 1.00 (0.99, 1.01) Men Worked in industry 5-point year increments:1.02 (1.02, 1.03)	No Association	No Association
	No of competitive skiing races*	Michaëlsson at el. (2011)	Cox PH	Hazard-Ratio	1	1.08 (1.03, 1.14)	Positive	Positive
	Time completed skiing races*	Michaëlsson at el. (2011)	Cox PH	Hazard-Ratio	1	1.10 (0.96, 1.26)	No Association	No Association
Biomarkers (imaging, biochemical)	HFE genotype group*	Wang at el. (2012)	Cox PH	Hazard-Ratio	9	Codominant 1 Copy: 1.05 (0.87, 1.28)	No Association	No Association
	Radiological Grade/Progression*	Gossec at el. (2005)	Logistic	P-Value	1	<0.0001	Association†	Association
Clinical	Location of hip OA	Gossec at el. (2005)	Logistic	P-Value	3	Global: 0.53	No Association	No Association
	Duration of symptoms (years)	Gossec at el. (2005)	Logistic	P-Value	1	0.28	No Association	No Association
	OA in contralateral hip	Gossec at el. (2005)	Logistic	P-Value	1	0.27	No Association	No Association
	Previous Treatment	Gossec at el. (2005)	Logistic	P-Value	2	NSAIDs: 0.003 Hip intra-articular injections: 0.81	NSAIDs: Association Hip intra-articular injections: No Association	Inconclusive
	Baseline Pain	Gossec at el. (2005)	Logistic	P-Value	1	0.03	Association†	Association

Type of Factor	Prognostic Factor	Studies	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (example categories)	Association	Overall Association
	Baseline WOMAC (Pain Score)	Gossec at el. (2005)	Logistic	P-Value	1	0.17	No Association†	No Association
	Baseline patient global assessment	Gossec at el. (2005)	Logistic	P-Value	1	0.006	Association†	Association
	Mean pain over first 6 months >42	Gossec at el. (2005)	Logistic	P-Value	1	<0.0001	Association†	Association
	Mean WOMAC function score over first 6 months >26	Gossec at el. (2005)	Logistic	P-Value	1	0.001	Association†	Association
	Mean patient global assessment over the first 6 months >47	Gossec at el. (2005)	Logistic	P-Value	1	<0.0001	Association†	Association
Other	2D:4D index to finger ratio*	Hussain at el. (2014)	Cox PH	Hazard-Ratio	3	Average 2D:4D : 0.97 (0.89, 1.06)	No Association	No Association

*** - Factors identified for both the knee and the hip**
† - Factors specific to the particular study and are not comparable to other studies. Only the p-values are assigned, therefore preventing the direction of the association being obtained.
COX PH; Cox proportional Hazard model; logistic, Logistic regression model

Apart from the two factors already noted, there were 8 more factors that overall gave a positive association with the need for future knee arthroplasty. Of these 8, there were 3 factors linked to BMI: weight, percentage of body fat and fat mass (Wang et al. 2009). Waist circumference and waist/hip ratio are related to each other as the waist/hip ratio is calculated as waist circumference divided by the hip circumference, meaning that the larger the waist circumference, the larger the ratio would be so long as the hip circumference did not increase. Since these factors were both measured as continuous variables and were both positively associated factors, this meant that as the waist circumference or the WHR increased, the likelihood of requiring a TKA increased. The other three factors that were deemed as positively associated factors were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (Cicuttini et al. 2004), previous knee injury (Manninen et al. 2001) and number of competitive skiing races the individual had participated in (Michaëlsson et al. 2011). The skiing races factor was a factor which would not be relevant to many individuals but may indicate a link to competitive sport in general. Unlike general physical activity, competitive sports can put a larger strain on the joints due to a larger physical excursion being used. Unfortunately, this systematic review did not identify studies for the knee that investigated other competitive sports to see if this link existed.

Of the factors that were seen as having inconclusive evidence, occupation was one of interest. This factor was split into 7 different categories ranging from more physical labour to desk work (Franklin et al. 2010). From this factor, the jobs which required more physical excursion (e.g. farming) had an association attributed to it meaning they were more likely to require knee arthroplasty surgery in future. However, other jobs which were less physical (e.g. technicians and clerks) had no association in either direction compared to the reference category of “managers”. Manual occupation would be worth investigating further as it would be related to physical workload (which was not investigated for the knee) in a similar way to how the competitive sports differs from general exercise.

Apart from the two factors already identified as having an association with future knee arthroplasty (BMI and age), there was a further 4 factors identified including: 2D:4D index to finger ratio (Hussain et al. 2014), HFE genotype group (Wang et al. 2012), physical work stress (Manninen et al. 2004) and time that the skiing races were completed in (Michaëlsson et al. 2011). Both the studies assessing 2D:4D ratio and the HFE genotype group were investigating if other bodily features appeared to affect the need for a joint arthroplasty. Whilst the 2D:4D ratio looked at the three different possible types of ratios (index finger longer, index ring finger the same size and ring finger longer), the HFE genotype group investigated different combinations of genes and whether the HFE genotype was dominant or recessive. These however, all produced no association with requiring a knee arthroplasty. The time that skiing races were completed in was taken from the same study that investigated the amount of races as previously discussed (Michaëlsson et al. 2011). Unlike the amount of races however, this factor was not seen to have an association with requiring a knee arthroplasty. This could be due to the times not corresponding with the amount of races completed, meaning someone could compete in only a couple of races but have a faster time and will not experience as much stress on the joint as someone who might have completed multiple races but have slow times.

2.4.6 Prognostic factors for Total Hip Arthroplasty

Table 2-4 lists the 29 factors with reported information identified by the high quality studies. Of these factors, 5 were investigated by more than one study. Of these 5 factors, BMI, weight and physical activity (in general) gave a clear indication as to whether they were factors associated with predicting the need for a hip arthroplasty or not. Similar to the results for the knee, both BMI (Wang et al. 2009, Franklin et al. 2009, Flugsrud et al. 2002, Flugsrud et al. 2006, Gossec et al. 2005) and weight (Wang et al. 2009, Flugsrud et al. 2002) were considered as factors positively associated with predicting whether a patient would require a hip arthroplasty in the future. As explained for the knee, these two factors are related due to how BMI is calculated. Another similarity to the knee was that moderate physical activity (in general) factor (Wang et al. 2011b,

Ageberg et al. 2012) was seen as having no association with future hip surgery, suggesting that, for both joints, moderate physical activity was not an important factor. For the hip, both age and occupation provided conflicting evidence as to whether they were factors. For age, one study discovered a positive association with the need for a hip arthroplasty (Rubak et al. 2013) whilst another found no association (Gossec et al. 2005). Occupation (Franklin et al. 2010, Rubak et al. 2013), like the knee, was seen as inconclusive in its nature as some of the occupations that were listed in each study were considered positively associated factors whilst others had no association at all. Some of the positively associated factors included those which entailed more manual labour (e.g. farming) whilst factors which had little physical labour (e.g. clerks) provided no association and in some cases gave a negative association (e.g. upper management). This suggests that patients with those types of jobs were actually less likely to require a hip arthroplasty.

There were 11 other factors that were identified as having an association with requiring a hip arthroplasty in future. However, 5 of these were study specific values (e.g. mean pain over 6 months) which may be available for other populations but they would be very population specific. Of the remaining 6 factors, 5 were also investigated for the knee which included waist circumference, percentage of body fat, fat mass (Wang et al. 2009), radiological grade/progression (Gossec et al. 2005) and the number of competitive skiing races participated in (Michaëlsson et al. 2011). All of these factors, apart from radiological grade which was seen as associated with a hip replacement, came to the same conclusion on these factors being associated with the need for a joint arthroplasty. The final factor, which was not investigated for the knee, was height (Flugsrud et al. 2006) which was seen as having a positive association with the requirement for a future hip arthroplasty. This factor, as well as weight, was also associated with BMI due to how BMI is calculated.

There were two others factors investigated for the hip which had inconclusive evidence as to whether they were prognostic factors or not. These were physical activity (at work) and previous

treatment. Physical activity (at work) was split by gender and by the amount of physical activity obtained, ranging from sedentary to intensive (Flugsrud et al. 2006). Both males and females that experienced extensive physical activity at work were more likely to require a hip arthroplasty in future. However, the male/female categories differ more on importance of the lower categories of physical activity with an association with requiring a hip arthroplasty for females only appearing for the higher physical activity categories, whereas males had a reported association at lower levels compared to those that had never worked in an industry with either an intermediate or high physical workload (risk ratio of 1.5 (1.0, 2.2)). This factor could be linked to the occupation factor which had inconclusive evidence due to the different jobs investigated requiring different physical workloads. Previous treatment was assessed in one study (Gossec et al. 2005) which investigated two different treatments: NSAIDs and Hip intra-articular injections. From these two treatments, NSAIDs gave evidence of an association with the requirement for future hip arthroplasty whilst hip intra-articular injections found no evidence of an association. Whilst this provided mixed evidence, it would be worth investigating to see if other treatments provided prior to arthroplasty had an association with the need for arthroplasty surgery.

Apart from the previously mentioned factors, there were 11 other factors that found no association with joint arthroplasty. 5 of the factors that were seen as having no association were also investigated for the knee joint which included: gender (Gossec et al. 2005), waist/hip ratio (WHR) (Wang et al. 2009), 2D:4D finger length ratio (Hussain et al. 2014), HFE genotype group (Wang et al. 2012) and time taken to complete the skiing race (Michaëlsson et al. 2011). Of these factors, gender and WHR were seen as factors associated with the need for joint arthroplasty for the knee but not for the hip. This could be due to the different joints experiencing different stresses. There were two more physical factors which were found to be not associated (physical activity (at leisure) (Flugsrud et al. 2002) and physical workload (Rubak et al. 2013)). Of these two, the physical workload factor, unlike physical activity (at work), investigated how long the person had been in physically active work but did not specify the jobs investigated. This means

that this factor could have investigated a range of jobs which had varying physical workloads and so would change the resulting association. Both location of hip OA and if the patient had OA in the contralateral hip (Gossec et al. 2005) also found no association which showed that where on the hip the OA occurred does not affect how much sooner the patient might require a hip arthroplasty . The duration of symptoms factors (Gossec et al. 2005) is interesting in that the study does not specify the symptoms that are being investigated. It also does not state how bad the symptoms had to be to be recorded. This could be linked to pain as in certain cases if the symptoms became painful to the patient this could lead to the patient receiving a joint arthroplasty. However, patients could have certain symptoms for years without any pain which is why this factor appears to have no association. The final factor was baseline WOMAC pain score (Gossec et al. 2005). The data obtained from this study suggested that the baseline WOMAC for those that did and did not receive a THA was similar (45.7 and 43.7 respectively) meaning that the level of the severity of OA was similar at the start, hence why this was a non-statistically significant factor.

2.4.7 Multivariable prediction models

Most of the studies investigated in this systematic review were primarily focusing on identifying possible prognostic factors rather than creating specific multivariable prognostic models. Many studies performed some form of multivariable analysis on factors to evaluate the effect sizes after adjustment for other prognostic factors. However, these studies did not present a model designed to evaluate a patient's overall need for future joint arthroplasty. There were however studies which primarily focused on the model rather than identifying the prognostic factors. Out of the 35 studies initially included, only 3 studies (Chan et al. 2010, Cicuttini et al. 2004, Gossec et al. 2005) generated a final multivariable prediction model from the findings in their papers (table 2-5). Due to the small number of studies that identified specific models, all of the models were reviewed irrespective of study quality. 2 of the studies (Cicuttini et al. 2004, Gossec et al. 2005) included for the main analysis of the prognostic factors provided final prognostic models in their

analysis whilst the other paper (Chan et al. 2010) did not give results for individual factors and so it was not included within the best evidence synthesis.

Chan at el.(2010) provides a logistic regression prediction model based on 193 patients consulting in a hospital in Taiwan who had intractable knee pain with OA and underwent primary TKA surgery. These were compared to the 133 patients who had OA without surgery in the previous 5 years. This model was used to determine the probability of requiring a knee arthroplasty which was reported as:

Equation 2-1: Model from Chan at el (2010) to determine the probability of a subject requiring a future knee arthroplasty surgery

$$\hat{p} = \frac{\exp(\beta' X)}{1 + \exp(\beta' X)}$$

where β'X denotes a linear combination of the coefficients for the factors shown in table 2-5. All variables in the model were statistically significant. The model suggested that the higher the age, if the patient was female or if they had a higher joint space narrowing (JSN) value (i.e. lower joint space width (JSW)) in either the medial or lateral tibiofemoral compartment then the probability of requiring a future knee arthroplasty would increase. However, for an increase of self-care and osteophytes in the medial compartment of the tibia the probability will decrease. There was some assessment to determine the goodness of fit of the model. The study investigated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the receiver operating characteristic (ROC) curve. These were high at 83.9% (sensitivity), 83.1% (specificity), 84.4% (PPV) and 82.7% (area under ROC curve) meaning that the model had fit the data well. In theory the possibility exists that a better model could be obtained but the model obtained was a good fit for the data. This model was created to help in the decision making process for those that might require an immediate knee arthroplasty rather than predicting the need for a future knee arthroplasty with a probability of 0.5 being the cut-off point for deciding if that patient should receive an arthroplasty.

Table 2-5: Models identified within the systematic review with the relevant coefficients and effect sizes reported

Study	Quality of Paper	Joint Assessed	Analysis Reported	Model Factors (with effect size)	Confidence intervals/P-values
Chan at el. (2010)	Moderate Quality	Knee	Regression Coefficients	Intercept: -5.27	p<0.001
				Age: 0.43	p=0.02
				Female: 1.26	p=0.001
				Self-Care ability: -2.64	p<0.001
				JSN in medial tibiofemoral compartment: 3.94	p<0.001
				JSN in lateral tibiofemoral compartment: 2.59	p<0.001
				Osteophytes in medial tibia: -0.97	p=0.03
Cicuttini at el. (2004)	High Quality	Knee	Relative Risks	Age: 0.9	0.7, 1.3
				Female: 9.9	1.5, 65.4
				BMI: 0.9	0.8, 1.1
				Change in Tibial Bone Area: 1.2	1.0, 1.4
				% of Tibial cartilage loss: 1.2	1.1, 1.3
				WOMAC (pain score): 1.5	1.1, 2.0
				Radiological grade of OA: 1.8	0.6, 6.1
Gossec at el. (2005)	High Quality	Hip	Odds-Ratios	Radiological grade of OA	
				> III: 3.3	1.7, 6.4
				> IV: 5.3	2.6, 10.8
				Previous NSAIDs intake: 1.5	1.0, 2.4
				Baseline patient global assessment: 2.2	1.4, 3.2

One of the study limitations was that there had been no external validation of the actual predictive value of the model. This would be required to determine how generalizable the model would be in other populations. The study however mentions this, stating that a further longitudinal or multicentre study needs to be performed to test the validity of the model. There was also missing data within the study with interviews performed for the study not being available. To try and compensate for the missing data, self-care ability was taken from a separate source and used as a confounding factor for TKA which was taken from the standard nursing evaluation form based on how well the patient could perform functions in daily living. Although this explains some of the missing data, this could lead to the model being potentially misleading for certain patients. This is why validation of this final model is needed to verify this model.

Cicuttini at el. (2004) is one of the studies that provided information on prognostic factors as well as creating a model. Patients were recruited with early knee OA in Australia resulting in 123 subjects entering the study with 113 completing the follow-up of 4 years. At the 4 year time point, subjects were asked if they had undergone an arthroplasty in the same knee in which they had the baseline MRI. This study generated a model with some factors which were also included in the previous model such as age and gender. In this model, not all of the final factors within the model were statistically significant (age, BMI and radiological grade). The tibial bone area and tibial cartilage loss are factors that could only be used for the knee joint. Both the tibial bone factors provided a positive association with the requirement for future knee surgery suggesting that the more cartilage that has been lost, the likelihood for requiring future knee surgery increases. The gender variable is the most significant within this model with an odds ratio of 9.9 meaning the odds of requiring a knee surgery for females is 9.9 times higher than males. However, this odds ratio was large and the confidence interval for this factor was also large due to the small sample (113 patients).

For this model, there did not appear to be any sort of model testing performed meaning the performance of the model has not been verified. It is therefore unknown how well the model fits the given dataset. Since the model predicted the coefficients using a sample of only 113 patients, the model generated might not be generalizable across a larger population. There is a mention of how some of the factors might not be generalizable in other datasets due to the study purposefully trying to investigate these factors which include the relationship between loss of knee cartilage and progression to knee arthroplasty. This would make the model less generalizable as a whole due to these specific factors but there is no mention within the study regarding testing how generalizable the model may be or attempting to apply it to a secondary dataset. This was a prediction model however rather than simply being a multivariable model. This would therefore mean that although it might fit the data (which is also unknown), it will be difficult to apply to other studies.

Gossec at el. (2005) is the second study that also provided information on prognostic factors as well as creating a prediction model. This was a 2 year longitudinal cohort study of 741 patients based in France. Patients were selected if they were aged 40 years or over and had hip OA according to the American College of Rheumatology. Patients were asked if they had a THR during the 2 year follow-up period. This study only included factors within the model that were seen as statistically significant within the uni-variable analysis. Therefore there are only three factors included within the model: radiological grade, previous intake of NSAIDs and baseline patient global assessment. The patient global assessment was the assessment of pain using a visual analogue scale (VAS). The radiological grade of OA in this model only has two possible grades. In this study, these were the only two classification grades used. These grades are taken from the Kellegren-Lawrence grading scale for OA (Kellegren, Lawrence 1957) which ranges from 0 which is no radiological features of OA to 4 which shows large osteophytes, marked joint space narrowing and definite bone deformity. This study uses grades 3 which correspond to multiple osteophytes, definite joint space narrowing and possible bone deformity as well as grade 4. This

study therefore only looked at the grades which show more advanced OA whereas the lower grades show either less developed OA or no OA at all. Both of these grades had a positive association with the need for a hip arthroplasty compared to having grade 0-2 with the higher grade leading to a higher effect size meaning the more advanced the OA, the more likely the patient would require a future hip arthroplasty. The use of NSAIDs is a type of treatment used to relieve pain and reduce inflammation. If a patient had had to use these drugs in the past then they had been in pain which they could not manage themselves. This leads to a positive association for the requirement for hip surgery. This model provides valuable information on what factors could be included within future models,

The model used was a logistic regression model designed to determine the occurrence of THR after 2 years. This allowed for clear predictive values of whether a patient would actually receive a THR. The cut-off point provided by the study was a p-value of $p \leq 0.20$. Once the procedure was complete, 3 factors remained that were seen as statistically significant ($p \leq 0.05$). This provided a 2 year rate of THR of 37.4% which was seen as high compared to other studies which could be down to the amount of missing data. The design of the study was highlighted as a possible source of why the study had this high rate of THR as the study was designed to follow-up patients from a therapeutic trial. This meant that the patients within the study would have high symptomatic severity when entering the study which would be likely to be the main reason to the high rate of THR. This meant that the results would not be as generalizable in other healthcare systems or other populations. This could be assessed using external validation but this had not been performed for this particular study. There is no mention of how the model actually fits the data. This meant that although the model provided statistically significant values, these effects sizes may not be representative of the entire sample population.

2.5 Discussion

From the 35 studies that were obtained from this systematic review, 16 were seen as high quality studies. From these studies, a total of 12 factors had an association with the requirement for knee arthroplasty and 13 factors had an association with the requirement for a hip arthroplasty. An additional 4 factors for the knee joint and 4 factors for the hip joints had inconclusive evidence as to whether they were associated with the requirement for a joint arthroplasty or not.

2.5.1 Strengths and Weaknesses

The review had a clear protocol laid out before any form of analysis was taken. The PRISMA guidelines (Moher et al. 2009) outline the steps that should be taken to identify relevant papers for a systematic review and how to present the obtained information. It provides a 27-point checklist which was used as a basis on how to lay out the systematic review and present the findings of the systematic review accordingly. The different elements in the guidelines include: the clear outline of the inclusion/exclusion criteria, clear presentation on how the studies are selected and study characteristics that were identified. By using this as guidelines for the systematic review, the study could be conducted easier. The use of the PRISMA flow diagram allowed the results of the number of studies identified by the systematic review and the number of studies removed during each stage to be easily displayed. The reasons for why certain papers did not make it through to the main review were also included in this diagram. The guidelines do not however give a clear representation on how to approach a best evidence synthesis as it focusses on a meta-analysis approach. However the best evidence synthesis has been described as a logical alternative to a meta-analysis if one cannot be performed (Slavin 1995).

35 studies were identified. This allowed for a greater number of factors possibly associated with the need for total joint arthroplasty to be assessed as well as providing sufficient information to allow the knee and hip to be studied separately. The larger amount of studies also meant that there was a high probability that there would be factors identified by more than one study

allowing for possible comparisons between different populations. The initial search strategy provided only a small amount of studies in comparison to the final review and appeared to have not comprehensively identified appropriate papers; hence the strategy was reviewed before any further screening was performed. The exclusion criteria was useful in reducing the initial number of titles and abstracts available, reducing the possible studies to less than 1% of those that were initially identified whilst the inclusion criteria was able to identify correctly out of the remaining studies which were relevant to the question asked. Although some studies were not captured by the search, only a few additional studies were required to be included by other methods (reference list search and citation tracking).

The data extraction form created for this systematic review allowed for the relevant information from each of the studies to be identified and catalogued. This allowed comparisons between the different studies to be made more clearly, such as the amount of studies using a specific form of analysis or the distribution of the countries in which studies were based. One particular piece of information collected was whether the studies had been developed for the purpose of determining risk factors for arthroplasty or it had used data from a previous study. This allowed a comparison between the different studies from the same sample and additional studies to be identified for the systematic review through citation tracking. This was seen with the Melbourne Collaborative cohort study (Giles, English 2002) which had 5 studies that had used this dataset identified through the review and a sixth (Wang, 2009) identified through citation tracking. There had also been some studies that had used datasets from other studies already within the systematic review including Gossec et al. 2005 which had used data from a cohort taken by Ravaud at al. 2004. Some of the papers however did not contain all the information that the data extraction form was collecting. The most prominent missing value was the date the study was undertaken. This field would have allowed certain comparisons to be made across the separate studies including how associations have changed over time.

One of the weaknesses that this study had experienced is that a second rater was not employed for all stages of the systematic review procedure. The second reviewer was part of the initial screening procedure, was used to assess consistency over the studies by evaluating random samples of the titles and abstracts, screening them separately and comparing the results obtained by MT to determine if similar decisions on inclusion/exclusion were reached. However, DY was only contacted for the full paper review if there was an uncertainty on whether to include the study or not. Using a procedure similar to the title and abstract screening by reviewing a selection of papers independently would help to improve the credibility of the systematic review by reducing possible bias that might occur. This was not performed due to time constraints. A second rater was employed to review a sample of the data that was extracted within the data extraction form and apply quality appraisal for a sample of the studies. This allowed further consistency in the data to be obtained and reduce possible selection bias that might occur. To improve the validity of the results obtained in future, a second rater should be used throughout the entire process and the manner in which the rater is used should remain consistent over all stages of the systemic review process.

The QUIPs tool provided a clear outline of judging bias of the prognostic studies. However, the QUIPs tool does have its own weakness in judging the level of bias overall. One problem encountered within this study was that within certain domains, there was a difficulty making judgements across all items within a domain. Whilst the study might have accomplished a certain item within a domain, there would be others that were less clear that made it challenging to determine the state of bias within that specific domain. The QUIPs tool also does not provide overall bias estimates. Instead this decision was made by determining how the bias ranged over the different domains and using the most common level of bias (low, moderate or high risk of bias). The QUIPs study does not suggest this action but the decision was taken after looking at other quality assessment tools. This is a judgement call which could lead to the study being labelled with an inacuarate level of bias which is why the sample of studies was investigated by a

second rater to improve how the bias is decided. There are alternatives to the QUIPs tool for assessing bias within studies. One possible alternative is the 42 point epidemiological appraisal instrument (EAI) (Genaidy et al. 2007). Each of the points falls under different sections (similar to the domains with the QUIPs tool) with each point providing detailed explanations regarding each choice with possible options for responses being "yes" (information is complete), "partial" (information is partially complete), "no" (information is not described but should be provided), "unable to determine" (insufficient evidence to answer the question) or "not applicable". The items are then scored and an average taken to obtain the overall score for the study. The possible scoring suggested was "yes" is given 2, "partial" is 1 and "no" or "unable to determine" is scored 0. This means that a study with a higher score will be of higher quality. This method allows the overall level of bias of the studies to be determined with more ease. However, whilst an overall score can be determined there is no recommended cut-offs that can be used to determine from that score what the overall level of bias is. The overall bias obtained from this method would be dependent therefore on the reviewer's own decision.

Whilst it would have been ideal to use a meta-analysis, due to how the data collected was compiled and the heterogeneous nature of the data a best evidence synthesis approach had to be performed. Whilst it has been described as a logical alternative to a meta-analysis (Slavin 1995), this method only allowed a narrative form to be taken for the overall systematic review whereas a meta-analysis would have enabled the estimates from the different studies to be pooled to allow an overall effect size to be identified. This would have made the decision as to whether factors had an association with total joint arthroplasty clearer to identify across the different studies. Instead the judgement as to whether the factors were associative or not were determined by the quality of the study and the effect sizes obtained in each study. This also meant that it could only be said that the association was present and not what the pooled overall effect size was. Further the factors were often split into multiple categories which differed over the different studies making the pooling of the evidence for the meta-analysis difficult. This meant a best evidence

synthesis approach was taken. A problem with this approach within this study meant that studies of high quality were the only studies taken forward for a possible narrative synthesis due to the decisions made. This meant that information regarding different factors could have been lost and the conclusion from the factors taken through might have altered. To determine if this was the case, the full set of factors were investigated in a sensitivity analysis to determine if any of the conclusions gained for the factors within the best evidence synthesis changed once all studies were included. This is included in appendix 1 tables 7-3 and 7-4. All of the factors taken through for the best evidence synthesis within the knee had similar conclusions when compared to the full factor list whereas the list for the hip factors did not match. The age factor had an overall positive association with the need for future hip when including lower quality studies whilst it originally had inconclusive evidence. Gender was seen as having an inconclusive association as the effects sizes varied over the studies that investigated it when including lower quality studies compared to having no association with the requirement for a total hip arthroplasty when just including high quality studies. Despite these differences in the associations, the factors would still have been taken to the next stage of analysis so this does not affect the results obtained.

A possible weakness within the study is the possibility of further evidence from grey literature. Grey literature refers to studies that are not peer-reviewed. This type of literature can be problematic in that the studies may be more likely to only report findings that support their initial hypothesis. The problem meant that although the systematic review may have identified factors that were seen as associated with the requirement for a joint arthroplasty, these factors would be subject to reporting bias. Sometimes, this can easily be identified. For example, in this systematic review, if all of the factors from one particular study were associated with the requirement for a joint arthroplasty then the indication for possible reporting bias is clearer. However, in other cases this may not be as clear. The statistical analysis and reporting domain within the QUIPs looked to address this issue but it may not always be obvious that there is bias in the reporting. This is an issue that may not have affected the result but it would be worth being cautious.

2.6 Conclusion

Overall, there were 21 possible knee factors investigated and 28 possible hip factors investigated in the studies included within the best evidence synthesis. Of these factors there were 12 knee factors and 13 hip factors which provided evidence of an association with the need for a joint arthroplasty in those who had osteoarthritis. From these two lists, there were 6 factors that were identified in both lists; BMI, weight, percentage of body fat, waist circumference, fat mass and number of competitive skiing races (a marker of high levels of regular physical activity/competitive sports participation). There were also 4 factors for the knee and 4 factors for the hip which had inconclusive evidence as to whether these were factors associated with the need for total joint arthroplasty or not. Most of the factors which had inconclusive evidence were lifestyle factors. Two of these factors were also seen in both lists: age and occupation. All of the factors that were seen as having either a positive association with joint arthroplasty or had inconclusive evidence as to whether they are factors or not were taken forward for further analysis.

Of the prognostic models that were identified, all three used logistic regression to model. However, only one study provided sufficient model checking whilst the others either did not mention or had not performed this in the given dataset. All three of the models had not been validated within another database. This validation process would be useful to assess if the models are generalizable or is limited to the population that the model was created within. The model that had undergone model testing (Chan et al. 2010) was designed to estimate the immediate probability of requiring a joint arthroplasty unlike the other models.

For the purpose of this thesis, factors from all the 35 studies were investigated separately to determine the factors to take through for further analysis. Overall, by including factors from all the papers and not just the high quality studies, 42 possible prognostic factors were identified which were taken through. Table 2-6 below provides the list of factors that were taken through.

Table 2-6: Prognostic factors identified by the systematic review as having an association with either a knee or hip arthroplasty or had inconclusive evidence

Domain	Factor	Identified for the Knee?	Identified for the Hip?
Demographic	Age	✓	✓
	Sex	✓	✓
Body Composition/Lifestyle	Body mass index	✓	✓
	BMI Change (over time)	✓	✓
	Weight (kg)	✓	✓
	Weight Change (over time kg)	✓	✓
	Waist/hip Ratio	✓	
	Waist Size	✓	
	Body fat	✓	✓
	Waist circumference	✓	✓
	Fat mass	✓	✓
	Height	✓	✓
	Smoking status	✓	
Occupation, occupational/leisure time physical activity	Occupation	✓	✓
	Socioeconomic Status (Seifa Score)	✓	✓
	Physical activity (at work)		✓
	Participation in Contact Sports		✓
	No. of competitive skiing races	✓	✓
Medical History	Previous Injury	✓	✓
	Previous Fracture		✓
	Familial predisposition		✓
	Blood Pressure	✓	✓
	Metabolic Syndrome	✓	
	Hyperglycemia	✓	
Comorbidities	Charlson Index	✓	✓
Disease Severity (Imaging)	Tibial bone area	✓	
	Cartilage loss	✓	
	Radiological Grade/Progression	✓	✓
	Trabecular bone texture	✓	
	Bone Marrow Lessions	✓	
	Joint Space Width		✓
	Superolateral migration of femoral head		✓
	Kellgren-Lawrence Grade		✓
Clinical severity (patient reported)	WOMAC (Pain)	✓	✓
	Baseline pain (VAS)		✓
	Baseline patient global assessment		✓
	Mean pain over first 6 months (VAS)		✓
	Mean WOMAC function score over first 6 months		✓
	Mean patient global assessment over the first 6 months (VAS)		✓
	Lequesne index (pain score)		✓

Domain	Factor	Identified for the Knee?	Identified for the Hip?
Previous/current non-surgical treatments	NSAID (source of treatment not identified)		✓
	Hip intra-articular injections		✓

3 Are prognostic factors for primary knee/hip arthroplasty available in primary care records? A feasibility study in CiPCA

3.1 Introduction

Within the UK, about 98% of people are registered with a general practice for all routine primary care (Bowling 2014). In England, general practices are the first points of access to formal healthcare and constitute 90% of all NHS contacts (Goodwin et al. 2011). Each year an estimated 300 million consultations take place in general practices in England with this number set to rise (Hippisley-Cox, Fenty & Heaps 2007). With the mass adoption of electronic health records in general practice, information that is routinely recorded in general practice for clinical care is increasingly recognised as a valuable source of data for research, including risk prediction modelling and prognosis research. A prominent example of this are QRISK scores, multifactor cardiovascular disease risk prediction algorithms, which were developed within the Qresearch database and externally validated in the Heath Improvement Network (THIN) database (Collins, Altman 2009).

As with all research using data recorded and intended for use in clinical care, the quality of data is an important consideration when undertaking prognosis research using primary care electronic health record data. The primary care electronic healthcare records (EHR) surpass many existing registries in terms of volume of information and the reuse of such data may provide a relatively efficient and low-cost means of conducting clinical research compared to cohort studies requiring a new data collection (Weiskopf, Weng 2013). However, it is important to remember that the quality and scope of the data within such databases may be limited. This limitation arises due to the differing priorities between the clinical and research settings (Weiner, Embi 2009). There still remains no consensus in regards to the quality of electronic clinical data and what data quality actually means in regards to EHRs (Weiner, Embi 2009).

In the context of a primary care EHR-based risk model for estimating the risk of primary hip or knee arthroplasty for osteoarthritis, risk factors and outcome must be defined based on information contained within the primary care record. The availability, completeness and accuracy of this information cannot be assumed. For example, the recording of clinical osteoarthritis as a problem may be recorded under a range of diagnosis (osteoarthritis) and symptom (for example, knee pain) codes and so its identified prevalence will depend on the codes used. Similarly, primary knee arthroplasty is associated with several codes in the Read system (described in section 3.3.1). The validity of diagnoses identified by the Read-codes has been investigated within different studies that have used healthcare databases. Khan and colleagues (Khan, Harrison & Rose 2010) performed a systematic review of literature that aimed to assess the accuracy and completeness of diagnostic coding within the General Practice Research Database (GPRD). The studies included within the systematic review had sent out questionnaires to patients within the GPRD to determine if the diagnosis was correct. The study identified that from the 40 studies included, most of the diagnoses were accurately recorded in the patient's electronic records but acute conditions were not as well recorded in terms of completeness. However, although this was identified for the GPRD it cannot be assumed that this is true for all EHR databases (Weiskopf, Weng 2013). The accuracy and completeness of available code lists and of the data are considerations that require attention before proceeding to statistical modelling. Appropriate code lists may be publicly available for some risk factors identified in the previous systematic review conducted in the thesis. For others, they may need to be derived through clinical consensus or some other process. Further, potential risk factors such as BMI may not be recorded in the EHR for all patients

This chapter describes the process involving both the opinions of primary care researchers and previously published literature to determine which of the factors identified by the systematic review (see chapter 2 table 2-6), were unlikely to be obtained from an EHR. It also describes the process in which, of factors that were seen as obtainable, how Read-code lists to identify the

specific factors were obtained from the previously published literature and applied within the Consultations in Primary Care Archive (CiPCA). It describes how the population for the study was obtained and how both the coded and free-text information within the database was searched to obtain the prevalence of the risk factors identified from the systematic review that were seen as obtainable.

3.2 Aims

The aims of this feasibility study were to:

1. Assess the availability of code lists that could be applied to primary care databases for risk factors identified within the systematic review described in Chapter 2
2. Obtain available code lists for risk factors identified within studies using healthcare databases
3. Assess the extent to which information is recorded in patients undergoing knee/hip arthroplasty for each of the risk factors with an available code list

3.3 Methods

3.3.1 The Consultations in Primary Care Archive (CiPCA) and related primary care databases

The setting for the next stages of the thesis was the Consultations in Primary Care Archive (CiPCA) which is a database containing consultation information from 13 practices in North Staffordshire, with 94,965 registered patients in 2010 (Jordan et al. 2014). At the time of this analysis, consultation information was available up to the end of 2011

CiPCA is an anonymised database with the practices supplying information to the database regularly undergoing training, assessment and feedback with respect to the quality of the coding (Porcheret et al. 2004). These practice staff are trained to enter at least one Read-code relating to the patient's reason for consultation during each individual consultation. At each consultation,

the subject of the consultation will be recorded in the form of a Read-code with the GP given the option to include additional information within free text. The GP can include as much additional text that they deem relevant to the consultations but the anonymised data that is included within CiPCA is limited to 255 characters due to the limitation of the Egton Medical Information Systems (EMIS) software in extracting information from practice records. Read-codes are a hierarchical coding structure of clinical terms most commonly used in medicine, surgery, nursing and the professions allied to medicine and is the preferred terminology for clinical systems in UK primary care (Stuart-Buttle et al. 1996). Higher hierarchical terms within the Read-codes cover a wider range of conditions whilst lower hierarchical terms are more precise on the condition or symptoms of a particular individual. For example, codes starting N05 cover osteoarthritis in different forms whilst N05z5 refers to OA of the hip joint and N05z6 is OA of the knee joint. Any prescriptions that are issued by a GP are automatically coded according to the British National Formulary (BNF) and entered into the Prescriptions in Primary Care Archive (PiPCA), a sister database to CiPCA linked via unique patient ID ensuring a complete record of all prescriptions issued (Roddy et al. 2013). The Demographics in Primary Care Archive (DiPCA) contain socio-economic status data on the patients in CiPCA. This is linked by the patients unique ID and provides area-level deprivation scores using the Index of Multiple Deprivation 2007 score. The Investigations in Primary Care Archive (IiPCA) is another sister database linked to CiPCA via unique patient ID which contains investigation data regarding tests performed (e.g. Body Mass Index (BMI), blood pressure). The IiPCA database only contains data for the most recent years (2009 to 2011).

Neither ethnic composition nor deprivation in the CiPCA population is nationally representative. North Staffordshire is considered as a more deprived area compared to the rest of England as a whole although CiPCA does cover both deprived and less deprived areas (Yu et al. 2015) and hence relative deprivation can be assessed within the geographical area covered by the CiPCA practices. Although CiPCA only provides information on patients within North Staffordshire, the

CiPCA estimates for the consultation prevalence of musculoskeletal conditions (including OA) have been shown to be similar or slightly higher than other national databases in a population over 15 years of age (Jordan et al. 2007).

General practices that do participate within CiPCA inform their patients that their anonymised records will be used for research purposes. All patients are offered the opportunity to withdraw their records from inclusion in CiPCA (Shraim et al. 2014b).

3.3.2 Identification of Read-code lists

From the systematic review, there were a total of 42 possible risk factors found to be associated or with conflicting or less evidence of their association with a knee/hip arthroplasty (see chapter 2). Although these factors would be of interest to study, not all of them would be obtainable within CiPCA and by extension, any primary care database. Therefore, steps were taken to identify the factors that were obtainable and those that were not (a flow chart of this process can be seen in figure 3-1).

In the first step, informal discussions between MT, GP, KJ and DY led to the exclusion of certain factors that were deemed highly unlikely to be obtainable from the primary care EHR. The factors were excluded if they were deemed to be unobtainable. There would be no further action taken with these factors. Remaining factors were taken forward.

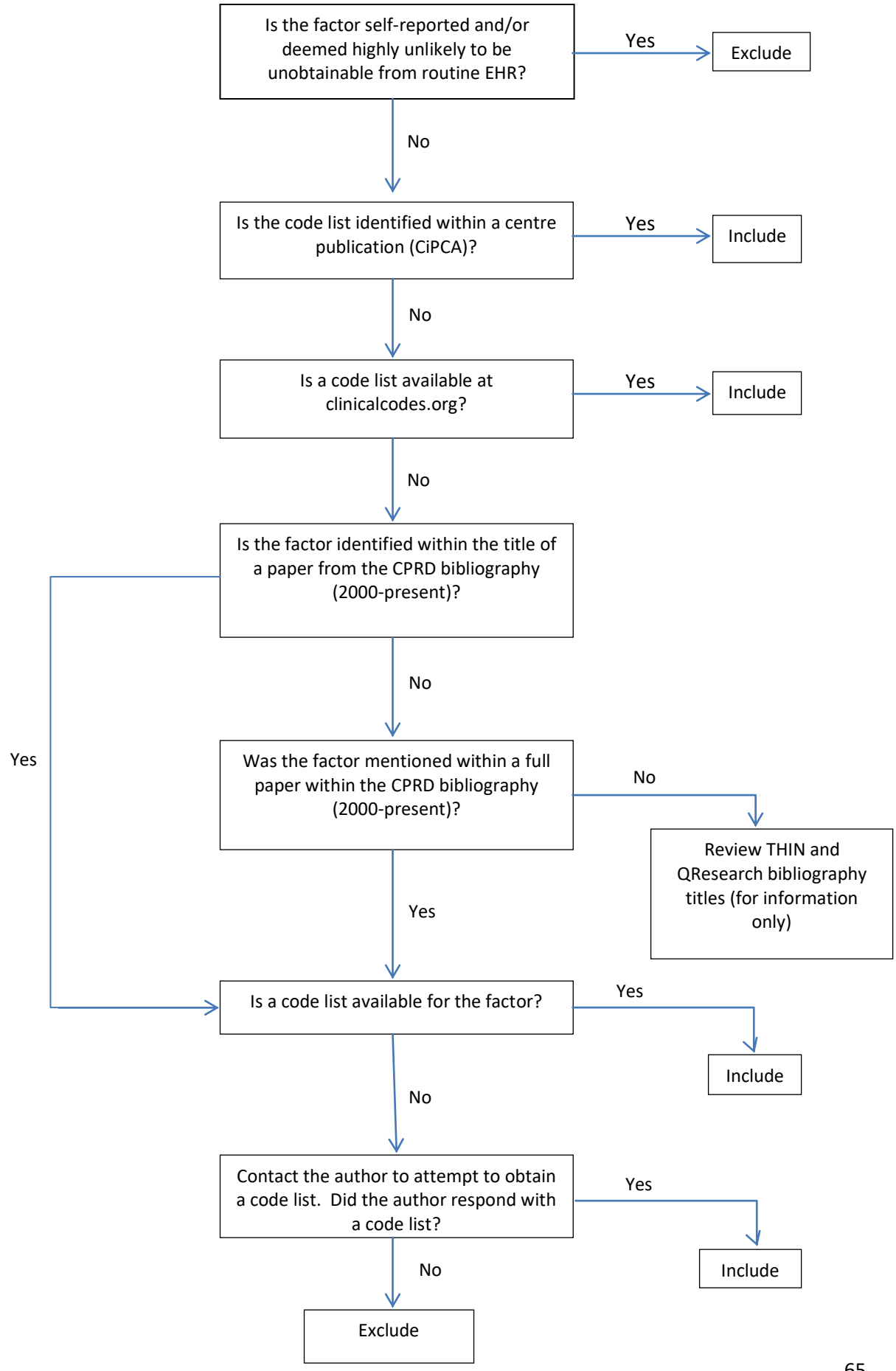

Figure 3-1: Flow chart showing the process taken for identifying the Read-code lists for factors identified by the systematic review

In the second step, previously published studies using CiPCA were searched. This was to identify possible Read-code lists for the remaining factors. Identifying code lists from papers that used CiPCA meant that the code lists would be more applicable for this study. These CiPCA papers were identified by accessing a bibliography of published papers that had used CiPCA data held within the centre. To identify the code lists, MT searched full texts of all the papers that used CiPCA to establish whether the factor had been investigated. If the factor had been identified within the study, the full text was searched along with any supplementary data to identify any relevant code lists. Where no code lists were identified, authors were contacted to obtain the code list.

In the third step, code lists for the remaining risk factors that were not found within CiPCA based studies were sought within Clinicalcodes.org. Clinicalcodes.org is a repository created by the University of Manchester which contains a code list or a collection of code lists that have been uploaded to the site for specific studies. These articles may be peer-reviewed papers published in medical journals or other important sources of code lists (Springate et al. 2014). Each of the code lists are detailed, with the codes being assigned a code name, what coding system had been used (e.g. Read, OXMIS etc.), description of what the code represents and the entity type (e.g. diagnosis). If the code list obtained for a specific factor uses a mixture of coding systems then only the Read-codes were taken from the list for use in identifying the factor within CiPCA. This was done for all the remaining factors.

In the fourth step, for factors that did not have a code list in either CiPCA publications or in Clinicalcodes.org, a search within the Clinical Practice Research Datalink (CPRD) bibliography was undertaken. The CPRD is an EHR containing information from 674 practices across the UK (Herrett et al. 2015). The CPRD bibliography contains the titles of all published CPRD papers from 1988 to present along with the titles of posters and abstracts. This provides a larger amount of possible papers to search with no guarantee that a code list will be obtained. Due to time constraints and to ensure code lists were reasonably up-to-date, only papers from 2000 to January 2015, when

the bibliography was last updated at the time of this study, were searched. Factors were first searched for within the titles of the papers. If a factor was identified within a title then the full paper was searched to identify a relevant code list. If a factor appeared in more than one title then the most recent study was first searched to identify a code list. If a code list was not obtained from that study then the second most recent paper would be searched until no papers remained. For factors that did not appear within the titles of any CPRD papers, full texts were searched from the most recent till 2000 to identify papers that have reported using the factor. The factors were searched for electronically by first obtaining the full texts then, within an electronic reader, using the "find" function to determine if the term had been used. This record of the factor could have been reported as the outcome, as a factor that had been investigated within the analysis for its relationship with the outcome or a covariate that had been adjusted for within the main analysis. Within papers that had reported a factor, a Read-code list was searched for within the paper and the supplementary material of said paper. This continued until all papers had been searched that had identified the factor. If a code list was not identified then the papers' authors were contacted to attempt to obtain a code list.

In the fifth and final step, if a factor was not identified within a CPRD paper or the author did not release a code list then the factor was searched within the titles of The Health Improvement Network (THIN) and QResearch papers. This step was designed as a final check to assess whether it may be feasible to use this factor in an EHR-based prognostic study but any code lists identified by this means were not included in further analysis due to time.

3.3.3 Population for the study

All of the risk factors identified from the systematic review were potentially associated with the outcome of primary total joint arthroplasty of the hip or knee for osteoarthritis. To correspond to this, analysis in CiPCA began with the identification of patients who had received a primary total knee arthroplasty or a primary total hip arthroplasty between 1st January 2005 and 31st December

2011. To limit the potential for including revision arthroplasty there had to be no record of either a hip or knee arthroplasty in the previous 5 years. This population was defined by using Read-codes for primary total hip or knee arthroplasty which had previously been identified (Culliford et al. 2015) (available in appendix 2 table 8-1). The index date of each case was assigned as the date of the first identification of one of the Read-codes for either a hip arthroplasty or a knee arthroplasty. We assumed that the date the code was first recorded was an appropriate approximation of the date of surgery. It may not be the exact date since the date used would either be the consultation where GPs discusses the proposed surgery or, more likely, the date the practice received confirmation the surgery had been performed or the date of the actual operation based on hospital correspondence. For the future case-control study (Chapter 4), the outcomes of hip and knee arthroplasty were investigated separately. However, for the current feasibility study, a combined outcome of either knee or hip arthroplasty was used. If a patient had received both a knee and hip arthroplasty then the first arthroplasty that took place was used for the feasibility study. For inclusion in the study, patients had to be 45 years or older at the receipt of the arthroplasty , had at least 5 years prior registration in a CiPCA practice and had no previous arthroplasty in those 5 previous years.

3.3.4 Analysis of the obtained factors

Within the feasibility study, each factor identified in the systematic review was searched for using the Read-code lists previously obtained within the study population in CiPCA, PiPCA, the Demographics in Primary Care Archive (DiPCA) and the Investigations in Primary Care Archive (IiPCA). The factor was searched for first within the 12 months prior to date of arthroplasty, denoted as the 1st annual year. This was to allow the most recent recording of a specific factor to be used. If the factor was not identified within the previous 12 months, the period 12-24 months before date of arthroplasty was searched for the factor. This continued until either the factors had been identified in the records or 5 years prior to the recording of the arthroplasty was reached. This 5 year period was calculated as 5 years prior to the date the joint arthroplasty took

place. For example if a patient had an arthroplasty code on the 4th June 2010 then information on this patient was reviewed until the 4th June 2005. All recorded instances of the factor appearing were noted. The search for risk factors did not go further back than five years for two reasons: it was not possible for cases with primary hip or knee arthroplasty in 2005 (CiPCA records data from 2000 onwards); it present problems when investigating certain factors, notably those that can vary over such a time period e.g. BMI and smoking status).

In addition to the application of the Read-code lists within CiPCA, a free-text search was conducted to obtain additional information. Factors described within the free-text may not have been the subject of the consultation so the Read-code used would not correspond to that factor. A set of terms (keywords and phrases) were used to identify the factors within the free-text over the same time period used for the coded factors. These terms were applied by searching for the first instance of the term within the free-text and searching the following characters for a value (for example, a BMI or weight value). The word "ideal" was also searched for to ensure the search did not simply identify a value which the GP sees as ideal for that patient (e.g. ideal BMI or weight). The values of factors obtained between 2009 and 2011 from this free-text search were compared to values obtained from IiPCA to assess whether IiPCA data allows better (more complete) identification of certain factors.

Frequencies of recording of the different factors were determined to establish their availability within CiPCA. Certain risk factors would not be expected to be recorded for all patients (e.g. previous fracture). The assumption that was made for these types of risk factor was that if there was no record of the risk factor then the patient did not have the risk factor. For these types of factors, a minimum prevalence of 3% was used as the criteria for inclusion in the case-control study in Chapter 4. This 3% was used so that there would be enough information for each factor in the cases when used in a case-control analysis (see chapter 4). Other risk factors should have measurements for all patients (e.g. BMI) in which case the absence of a recorded value would be

interpreted as missing data. For factors that would be expected to be available for all patients, such as BMI and smoking status, a minimum prevalence of 50% was desirable so that sensible imputation could be used. Although no clear indication had been made in regards to the amount of missing information the multiple imputation approach can handle, it is noted that larger amount of missing data can lead to misleading results (as seen in a QResearch paper which imputed for missing cholesterol values which had 70% missing data values giving the unexpected finding of a null association (Hippisley-Cox et al. 2007). All analysis was performed in Stata SE 14.0.

3.4 Results

3.4.1 Identification of Read-code lists

Of the 42 factors identified within the systematic review, 13 factors were seen as obtainable within CiPCA and identified to have code and hence were taken forward for further analysis. The process of the exclusions is summarised in Figure 3-2. The majority of those excluded (n=24) were deemed highly unlikely to be obtainable within the routine EHR at step 1, without the need for further search for code lists. These included factors related to patient-reported measures and scales for pain and function. In the systematic review, many of these factors had originated from one particular study (Gossec et al. 2005) with prospective collection of data performed by physicians as part of the research study. While demonstrating that these factors may be feasibly collected as part of a research study, it was felt unlikely that this information would be collected and recorded routinely in the primary care EHR. Specific measures of OA disease severity obtained from imaging (n=8 of the 24 factors excluded) were excluded including the radiological grade of osteoarthritis, joint space width measurements and semi-quantitative and quantitative measures of cartilage loss and bone marrow lesions from magnetic resonance imaging (MRI). These measurements (and MRI as an imaging modality for OA) are not routinely performed or recorded in practice. At best there may be a record of whether the patient has been referred to

radiography but the findings of these may be obtainable only from scanned letters/reports. Three factors related to physical activity at work or in contact sports were excluded at this first stage as being unlikely to be regularly collected and recorded with the EHR. The 4 non-physical activity related factors that were removed at this first stage were related to body composition. These factors included waist size, body fat, waist circumference and fat mass. It is possible that these factors may be investigated by a GP during a consultation but in discussions with primary care researchers, it was considered unlikely that they would appear in the EHR and, if they did appear, there would be only a small amount of the population that was likely to have a record.

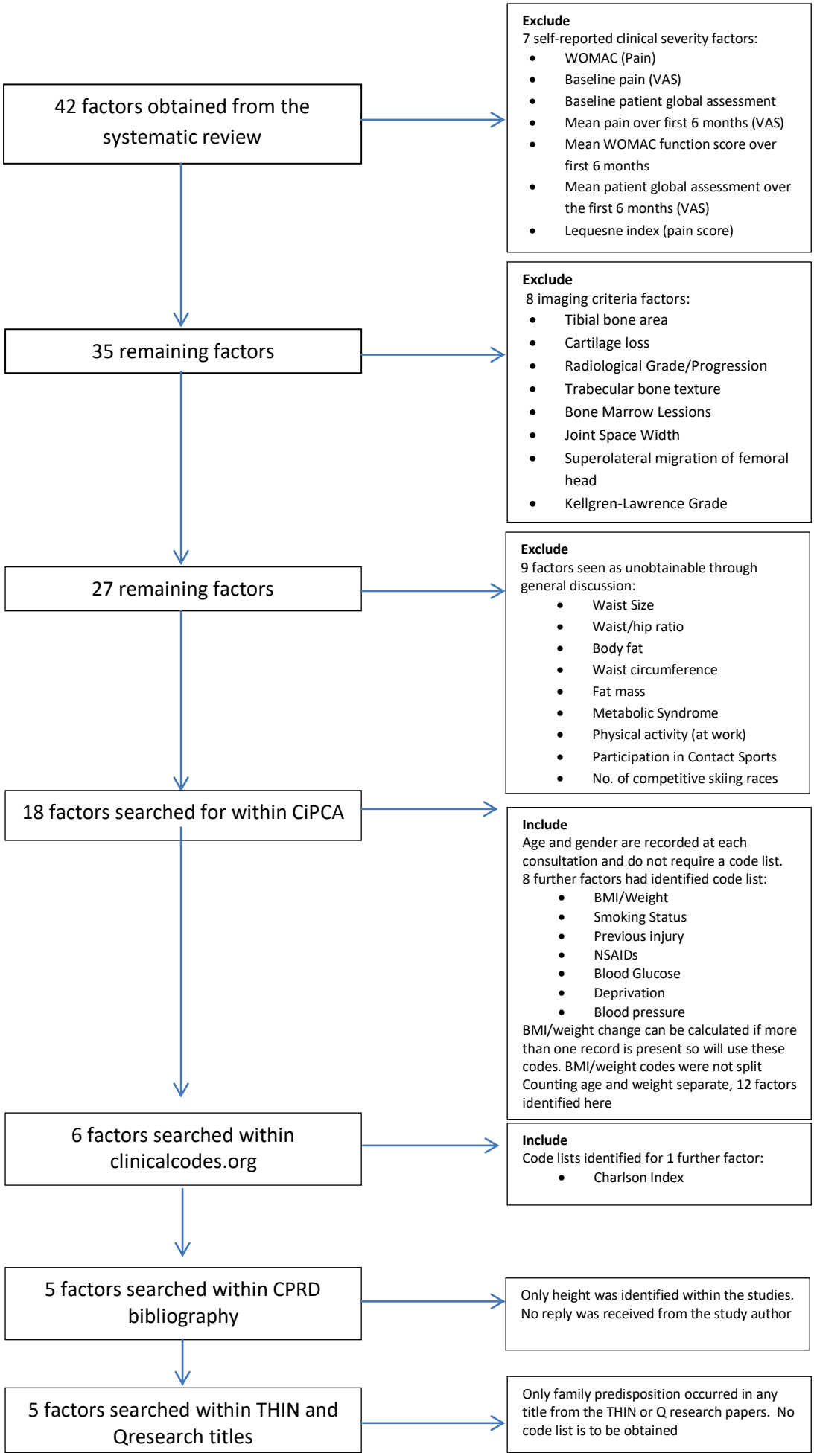

Figure 3-2: Flow chart identifying the source of the Read-code lists for each factor identified by the systematic review

18 factors were taken forward for investigation within CiPCA studies. Within the 29 published CiPCA studies, 8 risk factors had been previously investigated. Of these, age and gender were most commonly investigated. These factors are brought through from registration details and do not require a Read-code list to be obtained. Socioeconomic status/deprivation was investigated by one study (Shraim et al. 2014b) which used the Index of Multiple Deprivation (IMD) 2007 scores. The IMD scores are 3-yearly statistical indices that provide a ranking of areas across England by the level of socioeconomic deprivation based on seven different domains which include: income, education, employment, health, barriers to housing and local services, environment and crime (Sandford et al. 2015).Within the Demographic Database (DiPCA), this factor has been derived for registered patients at the practices. Therefore, within this study, a code list for deprivation was not required. Age, gender and deprivation were all taken through to the next stage.

The BMI and weight code lists were identified from one particular study (Monk et al. 2013) with blood glucose, blood pressure and smoking status code lists also presented and therefore these factors were all taken through to the next stage. The code list obtained from this study had combined the codes for BMI and weight together as, within the paper, they are reported as weight. The codes within the list did not specify which corresponded to weight and which corresponded to BMI from the codes meaning. Therefore, with the application of this specific code list in the next stage, weight and BMI was grouped as one factor with the codes being used jointly as indicators as to whether BMI or weight had been recorded. BMI change over time could be identified if at least two records of a BMI were recorded for an individual patient. There was the possibility that not all patients within the study would have more than one record of BMI but this was something that was investigated within the analysis to determine if it was feasible to obtain change in BMI over 5 years within the healthcare records. The identified blood pressure codes (Monk et al. 2013) did not specify which specific blood pressure reading had been recorded and so diastolic and systolic blood pressure readings were searched for as separate

measurements within the free text part of the CiPCA analysis. Furthermore, these codes within this list were a mixture of "diagnosis" codes (e.g. hypertension), less formal indicators of high blood pressure (e.g. raised blood pressure) or process of care codes (e.g. identifying that a blood pressure reading had been taken). A hypertension record would be an indicator of raised blood pressure and a code related to blood pressure reading having been performed would suggest a value should be recorded in the records. There was a similar issue with the glucose Read-codes (Monk et al. 2013) as diabetes had been used as a substitute for a possible glucose reading or identified that a glucose test had been performed.

Several studies in CiPCA had used NSAIDs prescriptions. We chose the list used by Bedson and colleagues (Bedson et al. 2013) in their original study rather than subsequent adaptations of this list (e.g. (Ndlovu et al. 2014)). Finally, a codelist for previous knee injury was obtained from Woods and colleagues (Wood, Muller & Peat 2011). However this was limited to fracture, dislocation and subluxation of the patella fracture.

Codelists for the remaining 6 factors were searched for within clinicalcodes.org. At the time of searching there were 26 studies that had provided code lists to the site. From the search, one factor was identified which was the Charlson index (identified within (Khan et al. 2010)). The Charlson index is a morbidity score calculated by assigning a score to individual morbidities which was originally developed in the 1980s (Charlson et al. 1987). The Khan study used CPRD data to adapt and validate the Charlson index within a UK primary care database. The Charlson index identified used 17 different morbidities to provide a weighted comorbidity score for an individual. The separate code lists for each of the individual factors within the index also contained Oxford Medical Information System (OXMIS) codes. For use within CiPCA, only the Read-codes within these lists were used.

The remaining 5 factors were searched for within the CPRD bibliography for the period of 2000-January 2015. This search looked for the remaining factors within 957 published CPRD papers.

Out of these 5 remaining factors, two had been used within the studies, which were height and occupation. Occupation was identified within one study (Rodríguez et al. 2000) but a code list was not derived for this factor. The paper had mailed the GP a follow-up questionnaire which included a question on the occupation the patient had. This meant that a code list had not been obtained to measure occupation within the database. Therefore, occupation was considered as not having an existing a code list. Height was used within one study (Odeyemi et al. 2006) from 2006. This paper was investigating associations with an overactive bladder with height being used primarily as a descriptive factor for the population with no analysis performed other than as a characteristic of the population of interest. The author of the study was contacted to obtain the code list but no reply was received. Therefore, this factor could not be used since there was no available code list.

A final search of the titles of THIN and QResearch publications (87 and 211 respectively) was used to gauge whether codelists for the remaining 5 factors were likely to be available from other sources (assuming time and resource to actually obtain these). This suggested that further off-the-shelf codelists were unlikely to be found for the 5 remaining factors not covered by either CiPCA studies or clinicalcodes.org. Out of the remaining factors, only familial predisposition for osteoarthritis was identified (one study within THIN and one within QResearch). There was no suggestion from THIN and QResearch titles that codelists were available for the remaining factors.

The list of codes used can be seen in appendix 2 tables 8-2 and 8-3. The factors with Read-code lists were BMI, weight, smoking status, previous injury (patella), prior use of NSAIDs, blood glucose level, blood pressure and Charlson Index Score. BMI change over time and weight change over time were calculated using the Read-codes' associated values if two BMI/weight records were available. Age, gender and deprivation score did not require a Read-code list. This provided 13 possible factors for analysis.

3.4.2 Identification of the study population

A flow chart of the case identification process for the study population can be seen in figure 3-3. The set of Read-codes for THA and TKA identified by Culliford et al. (2015) was used for the study. Not all of the codes identified were Read-codes, as some were OXMIS codes. Only the Read-codes (13 codes for total knee arthroplasty and 16 codes for total hip arthroplasty) were applied to CiPCA to identify all those that had received either a hip or knee arthroplasty. Prior to application of the codes, there were a total of 2,222 possible cases with a code for THA or TKA for the study within the CiPCA database. After applying the code lists obtained from the Culliford study to remove any revision surgeries, 1,708 (76.8%) possible cases remained. Not all of these cases had received their joint arthroplasty within the 2005-2011 period. After the removal of cases prior to 2005, 1,144 possible cases remained. An additional 25 patients were excluded since they were <45 years of age when they first received a joint arthroplasty and a further 23 patients were excluded since they were included within practice 1 between 2005-2006. This practice had used an earlier version of the Read coding system between 2000-2002 which would require an alternative Read code list. Therefore these records were excluded as those who had the arthroplasty within 2005 or 2006 would not have 5 years' worth of prior history. Out of the 1,096 remaining cases there were 490 total knee arthroplasties and 606 total hip arthroplasties. However, not all of these patients had been registered with the practice for 5 years prior to the first joint arthroplasty. 42 patients did not have any recorded history within a practice. These patients may have been transient patients who had been with a practice for less than 6 months and within CiPCA, registration history is collected every 6 months. Out of the remaining patients, there were 874 included cases (398 total knee arthroplasties and 476 total hip arthroplasties) that had at least 5 years' registration within CiPCA practices. The mean age of the cases was 69.82 (standard deviation 9.57) with 57.2% of the cases being female. When comparing the female cases to male cases, females were slightly older compared to males (70.0 (SD 9.86) compared to

68.6 (SD 8.99). The age distribution at the time of joint arthroplasty was approximately normal for both hip and knee arthroplasty cases.

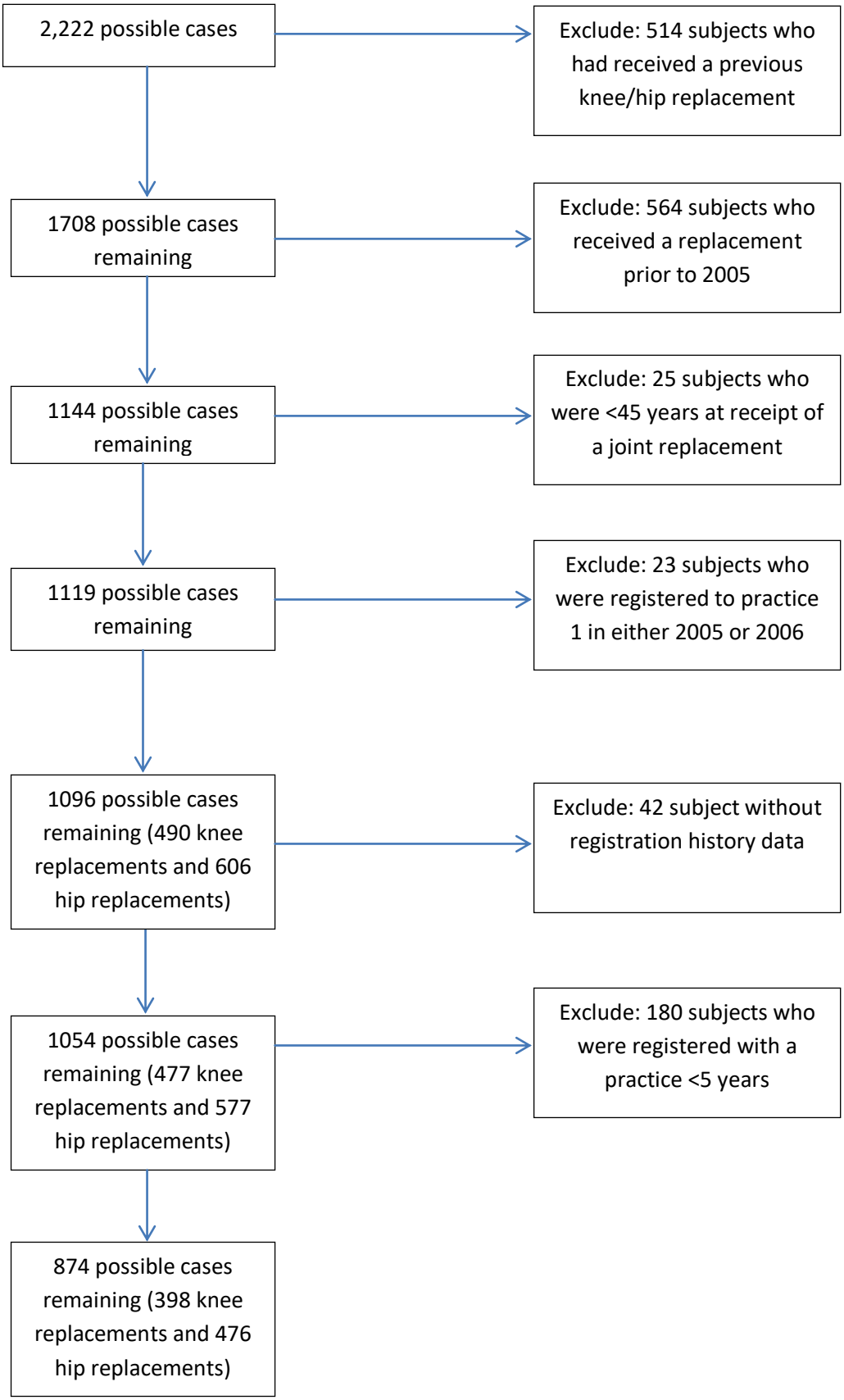

Figure 3-3: Flow chart displaying the process of identifying cases of hip or knee arthroplasty

The demographic characteristic of these primary THA and TKA cases in CiPCA was very similar to figures from the National Joint Registry (mean age for THA=69.7 years (female), 67.3 years (male) 60% female; TKR = 69.5 years (female), 69.2 years (male); 57% female (National Joint Registry 2015))

After removing consultations after the date of surgery and those consultations that occurred more than 5 years prior to the surgery, there was a total of 81,891 consultations within CiPCA for these patients which included both primary care consultations and secondary care information that had been received. The amount of recorded consultations that patients had received varied from 2 to 633 consultations (including the surgery record). After adjusting the data for each person to fall within the time frame used, 869 of the original 874 cases had received a prescription and there was a total of 182,093 prescriptions with the number of prescriptions ranging from 1 to 1023 for each patient within the specified time frame.

3.4.3 Coded factors within CiPCA and PiPCA

Each of the 22 Read-code lists (17 of which were for the Charlson index) and the list of BNF subchapters for NSAIDs were applied to the 81,891 consultations and 182,093 prescription records. If a patient had received at least one of the codes for a specific factor then the record with the code nearest in time to the date of joint arthroplasty was recorded within a separate field. All instances of a specific factor were also recorded.

Table 3.1 displays the number of times each of the factors was identified for the first time by number of years prior to the joint arthroplasty. Only 4 of the factors identified from the systematic review had been identified in all of the patients. These were: gender, age, area-level deprivation and the Charlson index. The overall deprivation ranks for the patients ranged from 222 to 31174 with a median of 13,450 where 1 represents the most deprived area in England. Out of the remaining factors that had a Read-code list, only NSAIDs and blood pressure were recorded for over half of the patients. As previously mentioned, 2 patients had no record of

receiving prescriptions within the time period identified. Apart from these two patients, 660 (77.5%) of the remaining patients had a record of receiving a NSAID with 485 (55.4%) of these receiving an NSAID prescription in the 12 months prior to the joint arthroplasty.

Table 3-1: Number of patients with coded records of individual factors by year closest to recording before index date

	Annual Year (prior to arthroplasty)					
Factors	1	2	3	4	5	Total, n (%)
Age	-	-	-	-	-	874 (100.0)
Gender	-	-	-	-	-	874 (100.0)
BMI/Weight recorded during the consultation	38	20	10	12	7	87 (10.0)
Smoking status recorded during the consultation	7	4	1	5	4	21 (2.4)
Blood glucose test recorded or identification of Type I/II diabetes	111	13	6	6	1	137 (15.7)
Hypertension or blood pressure recorded during consultation	467	78	30	24	15	614 (70.3)
Previous injury: patella	0	0	0	1	0	1 (0.1)
Received a prescription for an NSAID	485	61	50	36	28	660 (77.5)
Charlson Index	-	-	-	-	-	874 (100.0)
Area level Deprivation	-	-	-	-	-	874 (100.0)

BMI - Body Mass Index; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs
Deprivation was calculated using the overall rank of the Index of Multiple Deprivation 2007

614 (70.3%) patients had received one of the blood pressure codes in CiPCA with 467 of these patients receiving a code within the 12 months period prior to the joint arthroplasty. Only 137 (15.7%) patients had received a code for a glucose test being performed or where a glucose value may have been recorded. The BMI/weight (either category or value) had been coded in only 10% (n=87) of the cases. The code list for BMI/weight had used certain groupings for patients with different levels of BMI (e.g. obesity) but there were certain codes that could make it difficult to place a patient within a specific grouping (e.g. wants to lose weight). Only 21 (2.4%) patients had a smoking status coded. Similar to the other factors, over a third of the patients who received a code for smoking (n=7) had also received it within the same 12 months as the joint arthroplasty. Only 1 person had received one of the codes for patella injury confirming the narrow scope of this codelist.

The Charlson index that was obtained contained 17 different morbidities. Each coded morbidity was weighted from 1-6 with 10 of the items having a score of 1 (lowest weight), and these were

then summed for each individual. Certain conditions within the Charlson index were split into two separate categories dependent on the severity of the conditions (e.g. mild and moderate liver disease). No individual within the database had had all of the conditions during the period they were included within the database and 192 (22.0%) patients had a score of zero implying they had no code for any of the conditions included within the Charlson index during the 5 year period. The highest score obtained was a score of 15 which only one individual (0.1%) had obtained (figure 3-4 displays the distribution of the scores obtained by the included population).

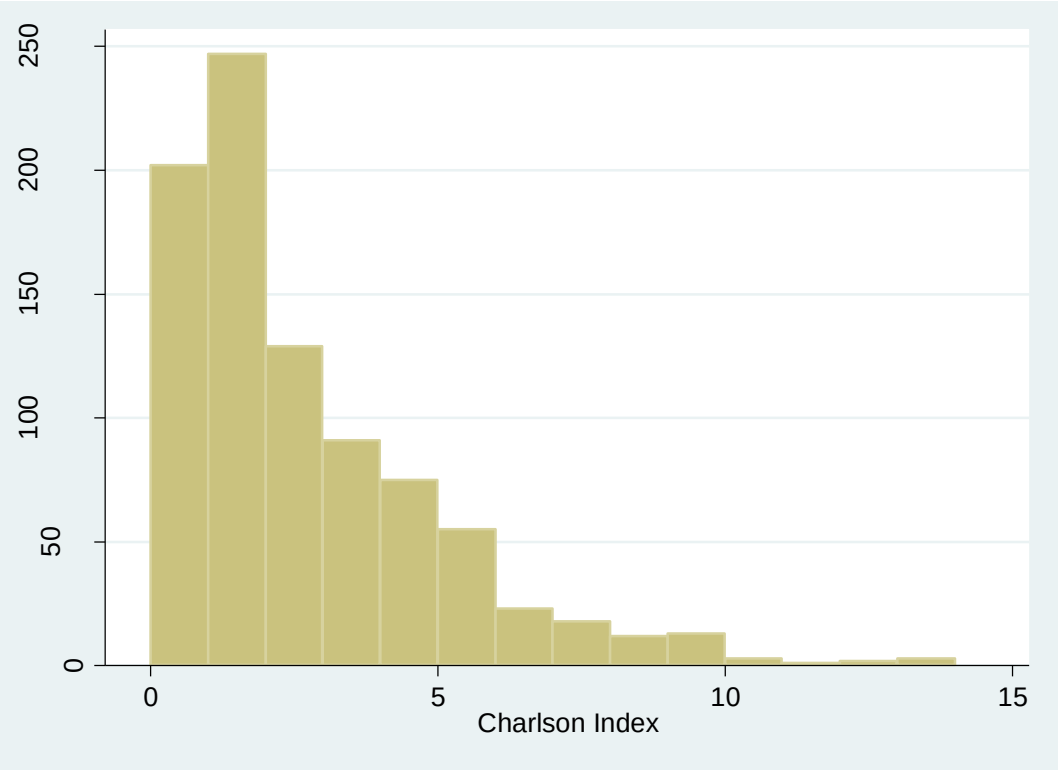

Figure 3-4: Distribution plot displaying the scores obtained from applying the codes for the different morbidities within the Charlson index to the study population and calculating the overall score

Certain morbidities contributed more towards the higher scores with metastatic tumour having the highest morbidity score of 6. While this morbidity was only seen within a small percentage of patients within the population (3 (0.34%)), the weighted score applied to this factor increased the overall Charlson score. The most commonly identified factor was rheumatological disease which was recorded within 469 individuals (53.7%). The rheumatological disease covered multiple conditions (e.g. Rheumatoid arthritis, non-articular rheumatism) but not osteoarthritis. Many of

the lower weighted morbidities were identified within a larger proportion of the study population (figure 3-5 displays all of the morbidities).

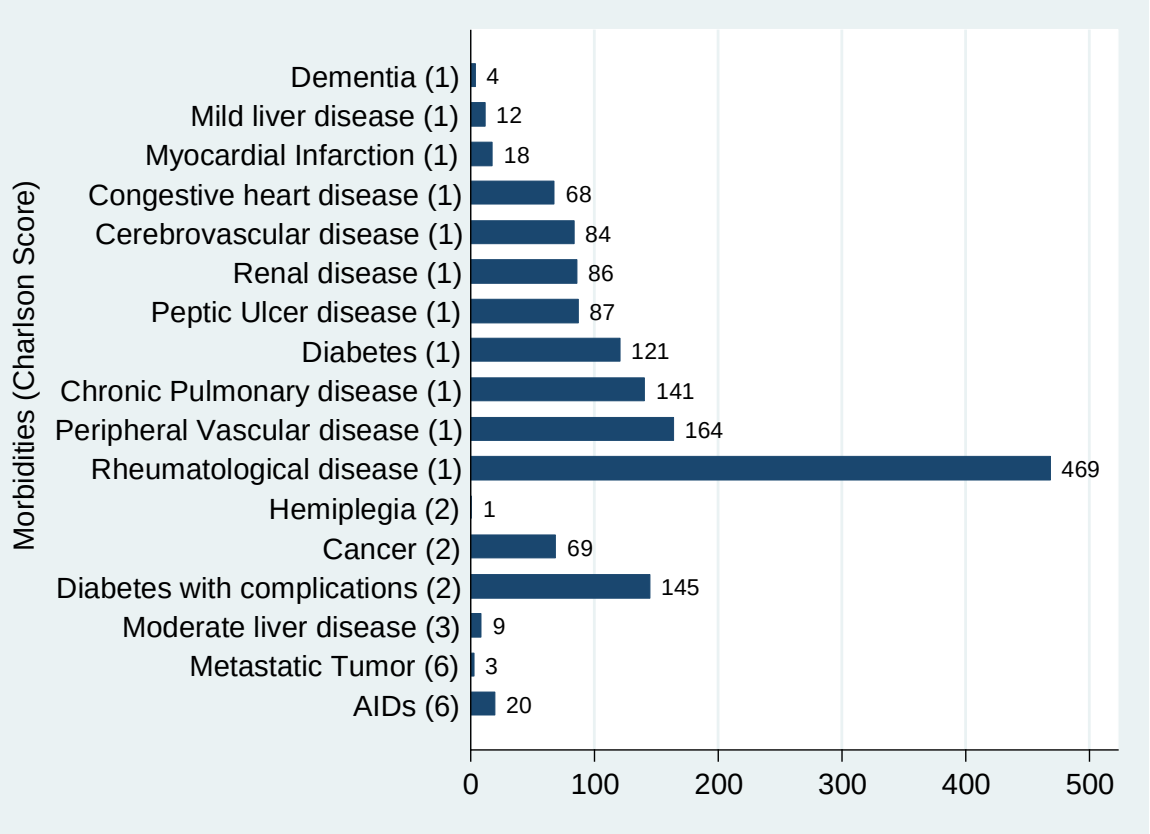

Figure 3-5: Bar graph displaying frequencies of the identified morbidities within the Charlson index and the morbidity score associated with that specific condition within the cases

3.4.4 Information from the free text

From the identified factors from the code lists, there was the possibility that more information could be obtained within the free text of the consultations. This additional information might include a possible grouping for the patients to be included within (e.g. non-smoker) or have a specific value recorded (e.g. blood pressure levels). The free text was therefore searched using appropriate search terms for all the factors (see appendix 2 table 8-4). The count of the number of times the factors were recorded in the text can be seen in table 3-2.

Table 3-2: Identification of individual factors within CiPCA/PiPCA/DiPCA using free text and the percentage of patients with a record of the factor. Identified factors recorded the instance closest to the receipt of a knee/hip arthroplasty

	Annual Year (prior to arthroplasty)					
Factors	1	2	3	4	5	Total, n (%)
BMI/weight status	59	34	21	22	12	148 (16.9)
BMI value (kg/m^2)	325	147	92	50	29	643 (73.6)
Weight value (kg)	376	142	86	46	27	677 (77.5)
Current smoking status	287	201	98	73	44	703 (80.4)
Blood glucose grouping	150	90	58	56	41	395 (45.2)
Blood Glucose value (mmol/L)	7	6	4	9	8	34 (3.9)
SBP value (mmHg)	516	120	53	29	25	743 (85.0)
DBP value (mmHg)	511	123	49	30	26	739 (84.6)
Any injury: any lower extremity fracture	14	7	0	2	3	26 (3.0)

BMI - Body Mass Index; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure
BMI/Weight groupings were groupings that had specifically been identified within the free-text without converting identified values of BMI/weight into groupings
Glucose groupings corresponds to either the results of a blood glucose test or identifying if a blood glucose test was performed

More patients were identified with a recorded BMI or weight status (for example, obesity, overweight) in the free text than identified by Read codes (16.9% vs 10.0%) (categories can be seen in table 3-3). There were additional BMI groupings obtained from the free-text, for example underweight. For the BMI categories, the majority of people either fell into the obesity or weight loss group. Both the weight loss and weight gain group would require a previous grouping to determine if they remain within the same category or have switched between categories.

To compensate for the lack of categorised BMI/weight groupings identified, both BMI and weight values were searched for instead of specific categories. From these searches, 643 (73.6%) patients had a BMI recorded value and 677 (77.5%) patients had a recorded weight value with over half of the recorded values being identified within the same 12 month period before the joint arthroplasty (325 and 376 respectively). By looking at all BMI and weight records, there were 2,723 BMI values and 3,126 weight values recorded within the consultation text. 475 (54.3%) patients had at least two BMI records and 530 (60.6%) had at least two weight records.

This provided the opportunity to obtain changes in BMI and weight between the values closest to the joint arthroplasty date and the value furthest from the joint arthroplasty date. Not all patients who were included within a BMI grouping (e.g. obese) also had a BMI value recorded. Out of the patients who were included within a BMI grouping from the free text, 131 (15.1%) had both a grouping and a BMI value. The free text did however catch a larger amount of information compared to the Read-codes alone as 220 (25.2%) patients had no BMI value or grouping within the free-text compared to 787 (90.0%) by using the Read-code list alone.

Table 3-3: Categories for the risk factors identified from the free-text in cases

Factor	Grouping	Total, n (%)
BMI	Obesity	62 (41.9)
	Overweight	10 (6.8)
	Weight gain	10 (6.8)
	Weight lose	56 (37.8)
	Want to lose weight	10 (6.8)
Current smoking status	Never Smoked	8 (1.1)
	Non-smoker	160 (22.8)
	Ex-smoker	351 (49.9)
	Ex-heavy smoker	6 (0.9)
	Ex-moderate smoker	20 (2.8)
	Ex-light smoker	7 (1.0)
	Smoke cessation	51 (7.3)
	Smoker	80 (11.4)
	Trivial smoker	6 (0.9)
	Light smoker	6 (0.9)
	Moderate smoker	3 (0.4)
	Heavy smoker	5 (0.7)
Blood Glucose	Fine	4 (1.0)
	Negative	337 (85.3)
	Abnormal	11 (2.8)
	Raised	17 (4.3)
	Tolerance	26 (6.6)
Any injury: any lower extremity fracture	Acetabulum	1 (3.8)
	Ankle	4 (15.4)
	Femur	6 (23.1)
	Fibula	2 (7.7)
	Fracture Pubis	1 (3.8)
	Hip	7 (26.9)
	Lateral Malleolus	1 (3.8)
	Metatarsal	3 (11.5)
	Toe	1 (3.8)

Figure 3-6 shows the distribution of the BMI and weight values amongst the cases that had been obtained from the free-text. From figure 3-6 (a) the distribution of the BMI values obtained from the free-text followed roughly a Normal distribution with a mean of 29.3 (SD 5.1). The mean values obtained were almost identical between genders (29.1 for female and 29.4 for males). The weight distribution as seen in figure 3-6 (c) also seemed to follow a roughly normal distribution. Height alone was not well recorded within the free-text as it does not change over short periods of time so was recorded less. BMI values were recorded more often weight. The

differences in weight for different genders can be seen more clearly in figure 3-6 (d) which shows that the mean for females was lower than the mean for males (73.8 for females and 86.4 for males). BMI and weight values were used to calculate BMI change over time and weight change over time.

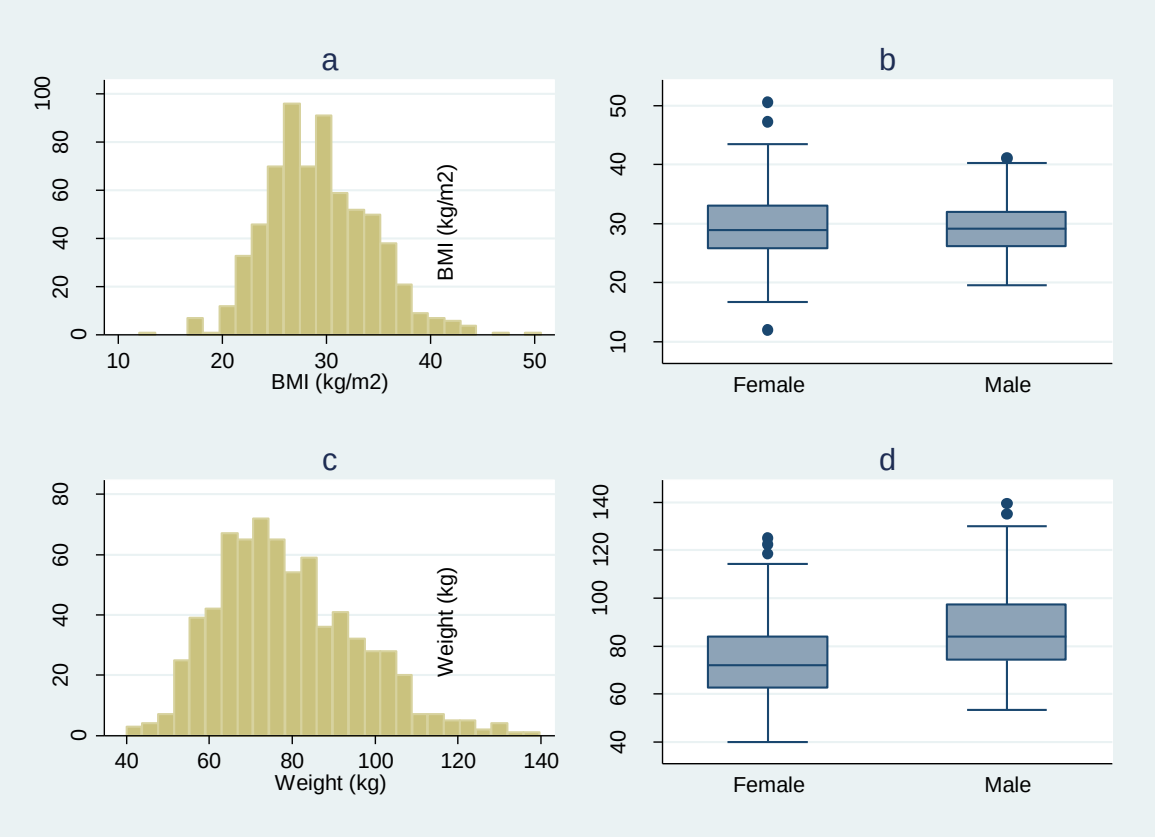

Figure 3-6: (a) distribution of the BMI values obtained from the free-text for the cases; (b) boxplot for the obtained BMI values for the males and females within the cases; (c) distribution of the weights obtained from the free-text for the cases; (d) boxplot for the obtained weight values for the males and females within the cases. Within boxplots, middle line represents the median, edges of the box represent the upper and lower quartiles (25% and 75% of the data) and the whiskers represent the maximum/minimum values once outliers have been excluded.

The proportion of patients whose smoking status could be classified in the EHR rose substantially from 21 (2.4%) to 703 (80.4%) once information from the free text was included (groupings for smoking status can be seen in table 3-3). This increase was due to free-text recording of smoking information in consultations for other Read-coded problems (e.g. breathing problems).

The amount of possible grouping categories available for blood glucose also increased when the free text was searched but still resulted in less than a half of patients having a blood glucose

record (see table 3-3). Fewer patients had received a glucose test as recorded within the free text with only 34 patients (3.9%) having a recorded glucose test result within the free text. Unlike a blood pressure reading, glucose tests are less regularly done and may only be investigated for specific conditions.

The majority of the patients within the database had a record of systolic and diastolic blood pressure readings within the free text (743 (85.0%) and 739 (84.6%) respectively). Within the free text, these were presented as SBP/DBP. Not all patients who had a SBP record also had a DBP record. Figure 3-7 (a) displays a boxplot for the SBP by gender and (b) shows the DBP by gender. From figure 3-7 (a) it can be seen that the mean of blood pressure readings for males and females are similar (SBP: female mean 139.4 (SD 14.63), male mean 139.3 (SD 15.46) DBP: female 78.2 (SD 9.69), male 78.3 (SD 8.97)).

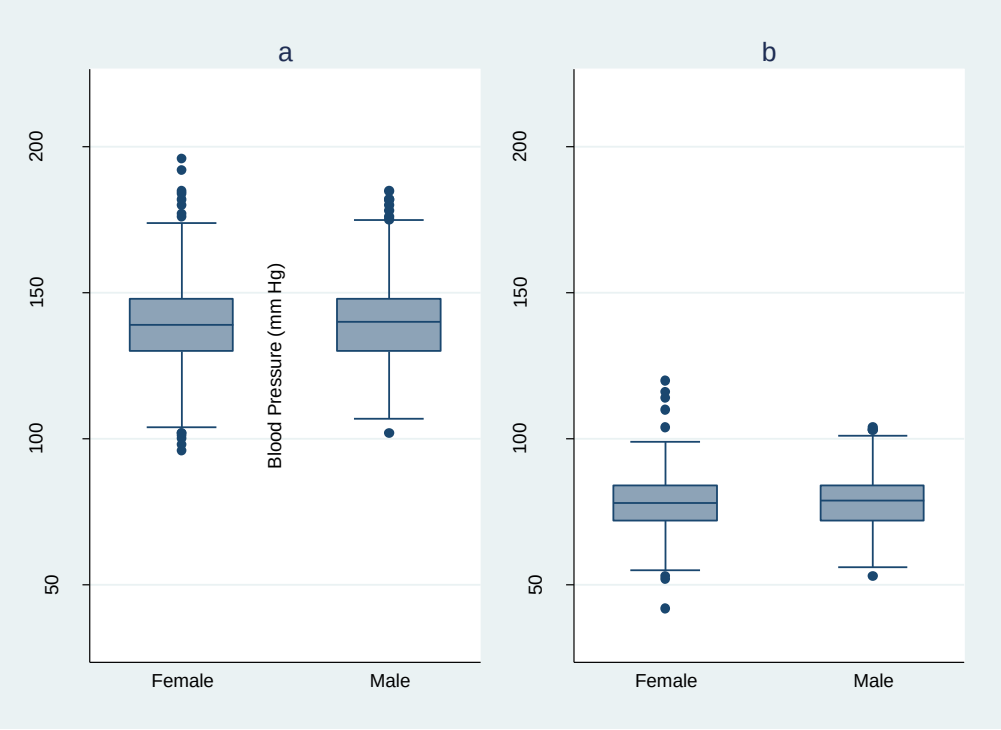

Figure 3-7: (a) Systolic blood pressures by gender within the cases; (b) box plot of the diastolic blood pressures by gender within the cases. Within boxplots, middle line represents the median, edges of the box represent the upper and lower quartiles (25% and 75% of the data) and the whiskers represent the maximum/minimum values once outliers have been excluded.

Only 26 patients (3%) had a record of any lower body fracture recorded in the text. These fractures were not limited to a specific limb (fractures identified can be seen in table 3-3). There were a total of 9 fracture types recorded within the healthcare database. Some of these could be grouped together into a specific joint area to reduce the number of categories that could be used. However hip fractures are one of the most common reasons for a hip arthroplasty. To combat this, hip fractures factors were first excluded completely and then only included if they did not occur within the 12 months prior to the arthroplasty. These results can be seen in table 3-4.

Table 3-4: Frequency of the recording of the fracture closest to the receipt of a knee/hip arthroplasty without the hip related fractures and without the hip fractures within the first annual year

	Annual Year (prior to arthroplasty)					
Factors	**1**	**2**	**3**	**4**	**5**	**Total, n (%)**
Lower body facture Fracture (excluding hip fractures)	2	5	0	2	3	12 (1.4)
Lower body facture Fracture (excluding hip fractures in first year)	2	8	0	2	3	15 (1.7)

The exclusion of the hip fractures reduced the amount of fractures that had occurred overall by 14. Originally there were 13 patients that had received a hip fracture within the same annual year as the joint arthroplasty (see table 3-2) meaning that one individual had suffered a different fracture prior to suffering a hip fracture. When the hip fractures were re-included but limited so that the fracture did not appear in the same annual year as the arthroplasty, an additional 3 patients were included. This showed that most of the hip fractures that had occurred had been in the same annual year as the arthroplasty. After this removal, the fracture group did not meet the required prevalence level so was not included within further analysis.

3.4.5 Comparisons of factors from CiPCA to IiPCA

The values obtained from the free-text were not the only available source of information for the BMI, weight, blood pressure and smoking status. IiPCA was searched from 2009 onwards as the database does not contain data from before 2009. Including only information prior to an individual's surgery, 510 unique patients had records within IiPCA for this time period. Each of

these factors was searched for within IiPCA and the results of where each of the individual's factors was identified can be seen in table 3-5.

Table 3-5: Indication of where cases had information available for 5 different risk factors

	Body mass index	Weight	Systolic blood pressure	Diastolic blood pressure	Smoking status
Not Identified	213 (41.8)	204 (40.0)	126 (24.7)	126 (24.7)	163 (32.0)
IiPCA only	99 (19.4)	79 (15.5)	91 (17.8)	97 (19.0)	178 (34.9)
CiPCA only	2 (0.39)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.4)
Identified in both	196 (38.4)	227 (44.5)	292 (57.3)	286 (56.1)	167 (32.8)

CiPCA - Consultations in Primary Care Archive; IiPCA - Investigations in Primary Care Archive

Together, CiPCA and IiPCA provided a large amount of information for each of the factors with over 30% of patients having a value in both parts of the databases. Using CiPCA alone did not provide a large amount of information on its own. With BMI, CiPCA identified 2 (0.39%) more BMI values not obtained from IiPCA compared to the 99 (19.4%) that IiPCA identified alone.

Although both CiPCA and IiPCA may both include a recorded value for (for example) BMI, the actual values recorded may be different. Table 3-6 identifies, out of the patients that had both a recording in CiPCA and IiPCA within the time period of 2009-2011, the frequency of those values that were equal (±1 unit) to each other and those that were not.

Table 3-6: Comparison of the values for the factors obtained from CiPCA's free text and IiPCA

	Body mass index	Weight	Systolic blood pressure	Diastolic blood pressure
Values Equal (± 1 unit)	175 (89.3)	188 (82.8)	199 (68.2)	187 (65.4)
IiPCA>CiPCA	11 (5.6)	12 (5.3)	47 (16.1)	55 (19.2)
IiPCA<CiPCA	10 (5.1)	27 (11.9)	46 (15.8)	44 (15.4)

CiPCA - Consultations in Primary Care Archive; IiPCA - Investigations in Primary Care Archive

From the table, over 65% of the patients who had a recorded value for the specific factor in both of the database had similar values within the ±1 unit range. For those values that were outside of this range, many of the values were not vastly different. Upon inspection of the BMI factors, the overall range of the difference between the values was -7.9 to +4.4 kg/m^2. This is not a large range meaning that although the values of BMI identified from CiPCA came from the free-text, the values that were obtained were almost identical to those stored within the investigations database. This was the same for the weights values which had a range of differences of -7 to +14

kg. This is not the same for the blood pressures which had a larger range of differences in the values compared to BMI and weight. The blood pressures readings had a larger range of values (SBP -48 to +59 mmHg, DBP -22 to +29 mmHg). Although certain readings were not equal, it would be worth using a combination of both IiPCA and the free-text obtained values within CiPCA to identify risk factors.

3.5 Discussion

From the study, 13 of the original 42 factors from the systematic review were seen as being obtainable within CiPCA with available Read-code lists or BNF subchapters for prescription codes in PiPCA. When applied to the 874 cases of knee or hip arthroplasty, only age, gender, area level deprivation and Charlson Index score were complete. A free-text search provided additional information for the obtained factors. For BMI, weight, SBP and DBP available in both CiPCA and IiPCA, values obtained were consistent across the two parts of the database. After splitting the blood pressure into SBP and DBP, 13 factors were seen as obtainable, achieving the 3% prevalence required. These 13 factors were age, gender, SBP, DBP, BMI, BMI change over time, weight, weight change over time, smoking status, Charlson Index Score, glucose test value, area-level deprivation score and prior use of NSAIDs.

3.5.1 Factors to be included within the case-control study

Many of the factors that had been identified by the systematic review had been self-reported factors on the patient's well-being (e.g. pain) or the patient's occupation and physical activity. These pieces of information are not regularly recorded during consultations so would not be available within CiPCA. There is a section within the Read-codes that addresses a patient's occupation but these Read-codes are rarely used by GP's meaning there would be little information for this factor. By having to exclude these factors before any analysis could actually be performed was a significant loss as all of these factor were seen as either having an association

with a knee/hip arthroplasty or had inconclusive evidence to support if they were factors or not. However, one of the aims of the study was to assess the feasibility of using these factors in EHR.

12 of these remaining factors had the minimum 3% recorded prevalence to be included within the case-control study. However, this 3% was only achieved in certain factors through looking into the free-text for additional information on the specific factor. Smoking status would not have initially been taken through to the case-control study as the coded prevalence of this factor fell below the 3% mark (2.4%) but once a search of the free-text had been performed the prevalence increased to allow it to be taken through (80.4%). The free-text proved valuable in providing additional information that could be used to obtain information on the different factors identified. Initially, values of BMI, weight and blood pressure were expected to be obtained primarily from the investigations database (IiPCA) but through searching the free-text, values were obtained and, for BMI and weight, over 50% of individuals had multiple values meaning a change in these values over time could be calculated.

Values that had been obtained through the free-text were checked within IiPCA to determine if the values obtained were consistent. Many of the values obtained from each source were equal. It would be important to continue to use IiPCA in the case-control study as it provides a useful check for the values that are obtained along with providing additional information.

BMI and weight as factors could have been taken though to the case-control study in one of two forms; as categorised groupings (e.g. over-weight, obese) or as specific values. Although both methods provided the 3% prevalence required, there was significantly more information obtained on values of factors compared to a grouping (16.4% for BMI/weight grouping compared to 72.9% for BMI value and 77.5% for weight value) and it would be difficult to distinguish between the groupings used for each factor since terms are used that can cover both factors (e.g. obesity). Both the groupings and the value were used within the case-control study as it would be unknown if the type of information within the controls is different to the cases.

3.5.2 Strengths and weakness of the feasibility study

The study had an extensive search of published EHR studies to obtain existing code lists. The strategy of first finding the code list through using studies that had already used healthcare databases (specifically CiPCA and CPRD) allowed a clear indication of how feasible it would actually be to obtain information on a specific factor. Many of these studies had used Read-codes to identify the factor and most of the code lists were accessible allowing for a simpler application within CiPCA for this study.

Aside from the use of Read-codes, the CiPCA database also contained free-text. This was anonymised text that has a limit of 255 characters. In certain cases the Read-code did not supply sufficient information so the free-text was searched for additional information using Stata code to identify specific words within the text that relate to the factor. This text provided additional information within the study. Initially, it was expected that for factors such as BMI and blood pressure where values can be obtained, information would only be available from the investigations database (IiPCA). However, upon investigation of the free-text within CiPCA, it provided a large amount of information on different factors that initially only had been seen in a small amount of the study population (e.g. BMI, smoking status). At first this was just used to identify possible groupings that had already been obtained but the valued factors such as BMI, weight and blood pressures appeared to be more regularly available. The free-text appeared to provide more information compared to IiPCA since only 471 of the 874 patients had a recording within IiPCA before their time of surgery since IiPCA only had available data from 2009 onward. Although the searching of the free-text did come with its own set of complications including limiting the amount of characters used within the text, it did provide additional information, allowing more factors to achieve the required prevalence of 3%. The process of using the free-text had been automated with the command used being saved, making it easier to apply in the future. The results were checked by selecting a random subset of the obtained data (n=30) and checking the information that had been obtained was correct. The code was altered if the information had

not been extracted correctly. Although the process did identify a large amount of information, there was still the possibility that the inclusion of additional search terms may have increased the amount of data obtained. Although the terms used related to the different factors (e.g. weight, kg, etc.) there was still the possibility that information may have been missed within the free text. The free text was also used by health care professionals to record ideal or target values. It was possible a specific value that was recorded within this study was an ideal measurement rather than the actual measurement within certain cases. This was taken into account when creating the Stata code to search the free text by searching for the word "ideal" and then excluding those records but the possibility remains that ideal values were unintentionally included for a specific factor. The IiPCA database was used to check certain values to provide a greater confidence that the values were correct. This in itself had its own weaknesses. The first problem identified was that the IiPCA database only had investigation records between 2009 and 2011. This meant that any patient who had a surgery prior to 2009 would not have information within IiPCA. The database did not have information for the majority of the patients within the database.

Certain code lists that were identified from the different papers provided problems of their own. Some of the code lists were incomplete. A good example of this is the previous injury code list used in CiPCA which only identified severe injury of one particular joint (patella). An attempt was made to rectify this by searching Read terms and free text for all lower extremity fractures. This identified more potentially relevant injuries in the 5 years prior to THA/TKA. However, this was still relatively rare and fell below the 3% threshold when excluding hip fractures that were most likely the reasons for THA as a sensitivity analysis. The expansions of codelists to include soft tissue injuries would be useful but was beyond the scope of the current project. However, it is clear that a 5-year retrospective period will not capture many relevant previous joint injuries since these occur typically in adolescence and young-mid adulthood (Peat et al. 2014), i.e. decades prior to THA/TKA.

3.5.3 Conclusion

In total, 13 factors were taken through for inclusion within the case-control study. A table of the factors can be seen below in table 3-7. In Chapter 4, these factors were first assessed to determine their frequency within controls and then used within a case-control analysis to determine their associations with a total knee arthroplasty or total hip arthroplasty.

Table 3-7: Factors from the systematic review that were obtainable within CiPCA and its related databases

Domain	Factor
Demographic	Age
	Gender
Body Composition/Lifestyle	Body Mass Index
	Body Mass Index change over time
	Weight
	Weight change over time
	Smoking Status
Occupation, occupational/leisure time physical activity	Area-level deprivation
Medical History	Systolic Blood Pressure
	Diastolic Blood Pressure
	Glucose test value
Comorbidities	Charlson Index Score
Previous/current non-surgical treatments	Prior use of NSAIDs

4 Association of identified and additional potential risk factors with total knee or hip arthroplasty: a case-control study

4.1 Introduction

The previous chapters have identified potential risk factors from previous studies for THR/TKR, found corresponding codelists to identify a minority of these factors in the CiPCA database, and confirmed the frequency of recording of these among primary THR/TKR cases in that database. This chapter now moves on to estimate the association between risk factors and primary THR/TKR in CiPCA. A case-control design was chosen, using the primary THR/TKR cases from CiPCA that were described in Chapter 3, and selecting a set of matched controls also from CiPCA. Since a relatively small number of risk factors emerged from the preceding chapters it was decided to also conduct a 'hypothesis-free' case-control analysis using the same cases and controls.

Case-control designs are generally understood to have several strengths: they can provide important findings in a relatively short period of time due to follow-up time being avoided and can be done with relatively little money and effort (Schulz, Grimes 2002); they are particularly suitable when investigating infectious disease outbreaks or rare diseases/outcomes; a large number of factors can be studied simultaneously making them useful for preliminary investigation before larger, more costly and time-consuming studies later. There are also a number of recognised limitations: if the frequency of the exposure is low then the case-control studies become ineffective, the choice of the control group and obtaining exposure history can affect the studies vulnerability to biases such as selection and recall bias (Schulz, Grimes 2002).

Case-control study designs have been frequently used in studies based in routine electronic healthcare databases. For example, within the Clinical Practice Research Datalink (CPRD) bibliography, there are 146 studies using a case-control design published between 1988 and 2016.

This chapter reports on a case-control study conducted within CiPCA and designed to investigate risk factors for total hip and knee arthroplasty. The cases for this study were identified and described in Chapter 3 and so this is briefly summarised before then going on to describe the process of identifying the control group. The case-control analyses fell into 3 stages: (i) investigation of the risk factors identified from the systematic review (Chapter 2) and judged to be obtainable from cases (13 factors – see table 3-7); (ii) a hypothesis-free search for additional risk factors; (iii) further analyses that was performed upon the factors that were seen as feasible to identify within the cases and controls to determine associations with the requirement for knee or hip arthroplasty.

4.2 Aims

1. To determine the frequency of recording among non-THR/TKR controls of risk factors identified in the previous chapter
2. Using a hypothesis-free approach, to identify additional potential risk factors (morbidities, investigations and prescribed medicines) with a frequency of 3% or more in either the cases or controls
3. To estimate within a primary care electronic health record database the strength and direction of age-sex-practice adjusted associations between all identified risk factors and future primary hip and knee arthroplasty
4. To explore the extent to which the above risk factors outcome associations differ by joint site of arthroplasty, prior diagnosis of OA and patient gender

4.3 Methods

4.3.1 Definition of cases

As per Chapter 3, cases were defined as incident primary hip or knee arthroplasty using the code list given in Culliford and colleagues (Culliford et al. 2015) (see appendix 3 table 9-1 for the Read-

code list used). For persons who had more than one hip or knee arthroplasty procedure, the first recorded arthroplasty that took place regardless of which joint was chosen.

4.3.2 Source of cases

The source of cases was patients in the Consultations in Primary Care Archive (CiPCA) primary care electronic health record database which covered all primary care records from 13 general practices in North Staffordshire.

4.3.3 Selection of cases

All patients with a record of primary hip or knee arthroplasty in the period 1st January 2005 to 31st December 2011 were identified. The Read-code lists from the Culliford papers were used within CiPCA to identify any arthroplasty that had taken place during this time period. Only the first recorded incidence of a knee or hip arthroplasty was recorded. Cases were removed if the patient was aged 44 or under at the time of arthroplasty or did not have 5 years' worth of registration history within CiPCA. Cases were also removed if during this 5 years prior registration history there had been a previous knee or hip arthroplasty. The date of the consultation coded for first hip or knee arthroplasty was used as the 'index date' and the 5 years prior history was calculated as 5 years prior to the index date (e.g. arthroplasty on the 1st January 2006 then prior history back to no earlier than 1st January 2001).

4.3.4 Definition of controls

Controls were defined as patients consulting in primary care but with no record of a hip or knee arthroplasty up to the date of the matched case's index date and with at least 5 years prior registration history within the database.

4.3.5 Source of controls

The same source was used to identify controls as was used to identify cases (CiPCA database).

4.3.6 Selection/sampling of controls

Within the case-control design, it is important to identify a set of controls that are comparable to the cases so that reliable conclusions about any possible associations between factors can be made (Ma et al. 2004). The 'would-were' principle is used to try and minimise the potential for selection bias, i.e. controls would have been included as cases were they to have experienced the outcome of interest. To meet this requirement, controls were sampled from CiPCA and searched for in the same time period used to identify cases. It was important to ensure also that controls had comparable length of prior electronic health records for fair ascertainment of risk factors. Therefore, like cases, controls had to have been fully registered within CiPCA for at least 5-years prior to the index date (date of record of THR/TKR) of their corresponding matched case.

4.3.6.1 Risk-set sampling

Risk-set sampling (alternatively referred to as incidence density sampling or concurrent sampling) was used to select controls. This design selects controls from the at-risk population at the time that each incident case occurred. Under this approach there is the possibility that cases identified later in the time period had already been selected as controls for an earlier case. Although it sounds counter intuitive to have a control that is also a case, this scenario mimics cohort studies where cases within a cohort will contribute to both the numerator and denominator of an estimated incidence rate (Rothman, Greenland & Lash 2008). The odds ratio calculated in case-control studies that use risk-set sampling provides an estimate of the incidence rate ratio (Pearce 1993).

4.3.6.2 Matching

Matching is one strategy used when sampling controls to minimise the influence of strong potential confounding factors. In this study, the use of risk-set sampling meant that cases and controls were matched by time. Since controls were sampled from individuals consulting during the same year as cases, confounding associated with propensity to consult was also controlled to

an extent. Individual matching was then used to control for confounding by age, gender, and practice. Age, gender and practice may be strong confounders (the latter due to difference between practices in coding and referral behaviour). These factors were also recorded in full throughout the database as they were recorded at registration for each patient. Where available, controls with exactly the same age as their case were selected. However, where necessary, age matching was allowed within a range of ±2 years. This was done as there would be the possibility that at certain ages (specifically in the very elderly) it might be difficult to find enough exact-age-matched controls. Only these three factors were used to match. This was to reduce the possibility of overmatching which can make it more difficult to find suitable controls to match to the cases (Wacholder et al. 1992).

When identifying the number of controls per cases, there has been no standard identified with the ratio of controls to cases used varying between studies. Some studies used one control to one case (e.g. Kuo and colleagues (Kuo et al. 2014)) with others using 6 controls to one case (e.g. Becker and colleagues (Becker et al. 2015)) or more. In certain situations, a higher control-to-case ratio may be desirable, specifically when there are concerns over the numbers available for a stratified analysis (Hennessy et al. 1999)). However, there will be little increase in precision of the effect sizes from increasing the ratio of controls to cases beyond four (Wacholder et al. 1992). For this study, five controls were matched to one case meaning a total of 4,370 controls were identified for the study.

4.3.7 Ascertainment of risk factors

4.3.7.1 Potential risk factors previously identified

The 13 factors that were previously seen as feasible to obtain from within the cases were searched for within the controls using the same methods as were used for the cases (see section 3.3.4, Chapter 3). Briefly, the record of the factor and date closest to the matched case's surgery time were identified. Read codes were used within CiPCA to identify morbidities, symptoms,

investigations, and processes of care, and British National Formulary (BNF) subsections were used within PiPCA to locate information on prescription data. A keyword search of the free-text entries for each individual consultation in CiPCA was also used to obtain further information regarding the risk factors as was performed for the cases. Information obtained from the free-text was checked against the information within the Investigations in Primary Care Archive (IiPCA) from 2009 onwards (when IiPCA began). For those that had available information, the results were compared and if there was information closer to the date of surgery available in IiPCA then this information was used instead.

4.3.7.2 Hypothesis-free identification of other potential risk factors

In addition to searching the Read-codes, prescriptions and the free-text for the 13 potential risk factors previously identified, the case-control design was used to undertake a hypothesis-free analysis to locate other risk factors that had either not been investigated in previous prognostic studies or had not been reported. The factors covered recorded morbidities (diagnoses and symptoms), investigations and other processes of care, and prescription medicines. However, due to the large number of codes within the Read hierarchical coding system the expected prevalence of any individual code would likely be too low to be included within any analysis and, given the hierarchical nature of the Read-code system, would include multiple codes relating to the same or similar morbidities and processes of care. Therefore, Read-codes were grouped at the third hierarchical level (meaning that the groupings would be three characters in length, e.g. N05 - Osteoarthritis and allied disorders). The Read-code version used was 5-byte version 2. Many different codes identified from the previous Read-code list used within the feasibility study (Chapter 3) had used third-level Read-codes (e.g. C10 Diabetes Mellitus). Although the use of third-level Read-codes would allow the prevalence of the expected groupings to be increased, the possibility existed that codes which had already been used in Chapter 3 to locate previous factors would also be included within these groupings. To overcome this, any codes that had previously been used within the code lists for other factors were excluded from any groupings. Prescriptions

codes were grouped using the BNF subchapters using the version updated last in February 2016. These could be split into a maximum of three subsections of a chapter it was associated with (e.g. 1.1.1 Antacids and simeticone under Chapter 1 "Gastro-Intestinal system"). Prescriptions were grouped using the lowest possible BNF level (e.g. 1.1.1). In the same way as the Read-codes, any BNF codes that had previously been used by a previous prescription list used in Chapter 3 were excluded from all groupings.

For a morbidity or prescription grouping to be carried forward to estimate its association with the outcome, the prevalence of the grouping had to be 3% or higher in either the cases or in the controls. For both the Read-code groupings and the BNF subchapter, the record of the factor nearest to the date of the case's surgery was recorded for the patients and used within future analysis. Time was split up in the same way as for the factors previously obtained in Chapter 3 (e.g. 1 year before, 1-2, 2-3, 3-4, and 4-5 years before cases received a THR/TKR).

4.3.8 Analysis

To determine the association between i) the factors from Chapter 3 and ii) other factors with a prevalence of 3% or more in either cases or controls, with knee and hip arthroplasty , conditional logistic regression was used. Conditional logistic regression is a technique that is commonly used within matched case-control studies which is able to take the matching into account when performing the analysis. The logistic regression uses the indicator of being a case or control (coded 1 and 0 respectively) as the dependent variable within the process. An independent variable is added to the model with its direction and magnitude of association with the outcome of primary knee/hip arthroplasty estimated using odds ratios, 95% confidence intervals and p-values. Since the purpose in this thesis was to identify factors as potential building blocks for future multivariable prediction models, a univariable conditional logistic regression analysis was performed on all factors. For additional factors in the hypothesis-free analyses (i.e. not identified from the systematic review and brought forward from chapter 3), in the absence of any clear

guidelines in this area, we noted those with an odds ratio above 1.33 or below 0.75 as potentially useful for future multivariable prediction models within EHR database. This approach had been taken by previous studies (Jinks et al. 2008). This was used as an alternative for dealing with possible multiple testing issues that could occur by performing a large amount of test and allowing factors with larger associations be identified for possible future analysis. This did mean though that factors did not need to be statistically significant (e.g. $p<0.05$). The analyses were initially performed for all cases and controls. They were then repeated but the analysis was adjusted for OA. This adjusted analysis was to take into consideration that a possible risk prediction model for arthroplasty would predict the risk for knee or hip arthroplasty in the future for those that have a diagnosis of OA at the time of the consultation. These results should be interpreted as the risk of an arthroplasty for that factor when the patient also has a diagnosis of OA.

Within the factors identified, the majority of the factors within the cases did not have a prevalence of recording of 100% within the database. For certain factors (such as prior use of NSAIDs) it was assumed that the absence of a record was a true negative i.e. the case or control had not presented with that specific morbidity or symptoms, received a prescription or undergone a process of care. For these variables, lack of recording was considered as not having the event. For other factors, such as BMI and smoking status where, in theory, everyone should have a status recorded, multiple imputation was used. With multiple imputation, age, gender, practice, case-control status and all other identified complete risk factors were used to impute values within the data for those factors that had missing data. For continuous variables, linear regression analysis was used and for categorical variables, an ordinal logistic regression analysis was used for the imputation process. Each of the variables that did have missing information was included within separate models so only one factor had information imputed per time. There are differing views as to the number of imputations that should be used within the study. For example, White and colleagues suggested that the number of imputations (*m*) used should be

greater than the amount of missing data in the dataset (Royston 2004) *(*e.g. 29% incomplete then *m=30*). For this analysis, due to the size of the dataset, 10 imputations were used for each factor. After the imputations had been performed and the conditional logistic regression had been conducted within each of the 10 datasets, the estimates for the odds ratios and confidence intervals were calculated using the Rubin's rule. It was assumed that the factors were missing at random, i.e. the probability the data was missing depended on the observed value but not the value of the missing value. This was considered within the discussion as it was suspected that not all factors would meet this assumption. All of the analysis was performed using Stata SE 14.

4.4 Results

4.4.1 Identified controls

By applying the above criteria, a total of 4,370 (matched 5:1 to 874 cases) were obtained within the CiPCA database. The results of the matching can be seen in table 4-1.

Table 4-1: Checks for success of matching

Matched Factors	Case	Control
Age, mean (SD)	69.4 (9.51)	68.9 (9.53)
Gender, n (%)		
Female	500 (57.2)	2500 (57.2)
Male	374 (42.8)	1870 (42.8)
Practice, n (%)		
1	67 (7.7)	355 (7.7)
2	102 (11.7)	510 (11.7)
3	51 (5.8)	255 (5.8)
4	58 (6.6)	290 (6.6)
5	29 (3.3)	145 (3.3)
6	65 (7.4)	325 (7.4)
7	150 (17.2)	750 (17.2)
8	2 (0.2)	10 (0.2)
9	95 (10.9)	475 (10.9)
10	40 (4.6)	200 (4.6)
11	78 (8.9)	390 (8.9)

The mean age for the controls were 68.9 (SD 9.54) with age ranging from 44 to 95, slightly lower than for cases (69.4). This, and the lowest age value of 44 for controls (when the minimum age criteria for cases was 45) was because age was allowed to be ±2 years that of cases to allow enough controls to be identified for the study. The distribution of the ages for controls was very

similar to cases and no further adjustment for age was made in the case-control analyses (figure 4-1).

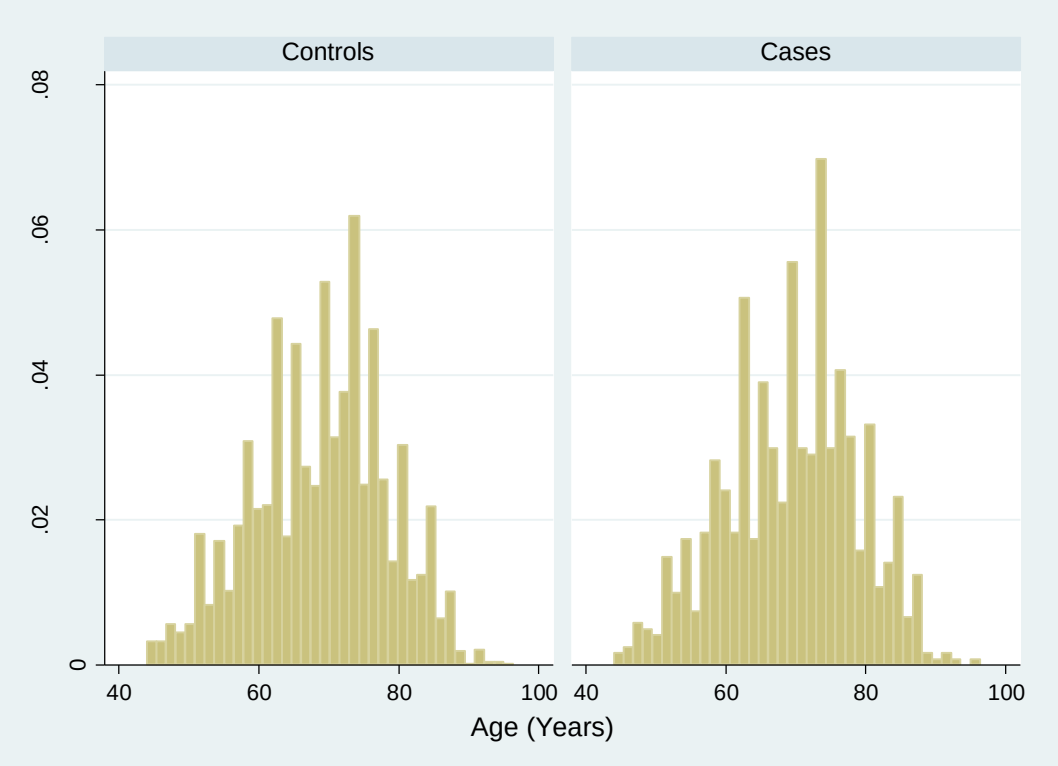

Figure 4-1: Distribution of the ages between the cases and the controls. The density represents the proportion of patients within each year of age

Within the controls, there were a total of 49 patients that were also cases within the study. The number of consultations per patient within the controls in the five years before index date ranged from 1 to 543 (median: 59; IQR 34-94). The range of the amount of consultations was smaller in the controls compared to cases (range 2-633). 81 (1.85%) controls did not receive a prescription during the five years. Of the controls that did have prescriptions, the number of prescriptions issued ranged from 1 to 2,519 (median: 115; IQR 40-254). The amount of prescriptions issued was larger in the controls compared to the cases (case range 1-1023). Since PiPCA contains both new prescriptions as well as repeat prescriptions, many patients were receiving the same prescription over a long period of time.

4.4.2 Potential risk factors previously identified

4.4.2.1 Coded information

Of the factors identified as being viable by the feasibility study (see table 4-2), age, gender and area-level deprivation all had information available for all of the controls. The overall IMD rank obtained for the controls had a median score of 12,752 (IQR 6,174-20,707), ranging from 222 up to 31,677.

Table 4-2: Number of patients with coded records of individual factors by year closest of recording before index date

	Annual Year (prior to arthroplasty)					
Factors	1	2	3	4	5	Total, n (%)
Age	-	-	-	-	-	4370 (100.0)
Gender	-	-	-	-	-	4370 (100.0)
BMI/Weight	77	38	38	24	24	201 (4.6)
Smoking status	38	24	21	20	11	114 (2.6)
Blood glucose test performed or identification of Type I/II diabetes	593	79	32	34	25	763 (17.5)
Hypertension or blood pressure	1902	399	168	116	97	2682 (61.4)
Received a prescription for an NSAID	1453	286	244	217	195	2395 (54.8)
Charlson Index	-	-	-	-	-	4370 (100.0)
Area level Deprivation	-	-	-	-	-	4370 (100.0)

BMI - Body Mass Index; NSAIDs - Non-Steroidal Anti-Inflammatory Drugs
Deprivation was calculated using the overall rank of the Index of Multiple Deprivation 2007

The Charlson index score was the fourth factor that, like for the cases, had complete data. The median score for the Charlson index was 2 (IQR 0-3) with scores ranging from 0 to 14. The overall range of the Charlson score was smaller within the controls compared to the cases (median of 2, range 0 to 17). The breakdown of how each morbidity within the Charlson index contributed to the overall score can be seen in figure 4-2. From the graph, Rheumatological disease (which does not include OA but includes rheumatoid arthritis and “rheumatism”) was seen the most within the controls with the factor being recorded within 1,678 (38.3%) of controls. The relative frequency of the morbidities within the controls was similar to that of the cases.

Of the remaining indicator variables, only the receipt of an NSAID prescription and the investigation of either hypertension or blood pressure had prevalence estimates above 50%

(54.8% and 61.6% respectively). Most patients had an NSAID prescription or blood pressure investigated in the 12 months prior to the joint arthroplasty of the matched case as 1,453 (60.7%) patients had received a NSAID and 1,902 (43.5%) patients had had a consultation where either hypertension or blood pressures were investigated in the 12 months before.

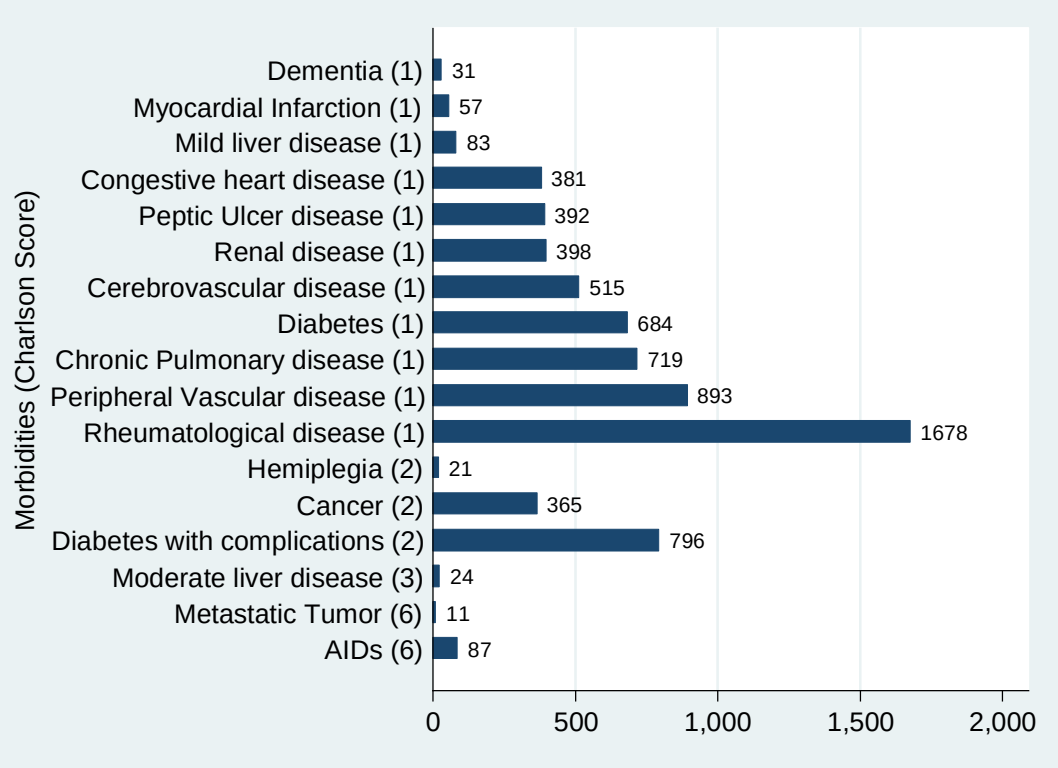

Figure 4-2: Bar graph displaying frequencies of the identified morbidities within the Charlson index and the morbidity score associated with that specific condition within the controls

Of the remaining factors identified by the code list, neither 'BMI/Weight investigated during the consultation' or 'blood glucose test performed or identification of Type I/II diabetes during the consultation' had a coded recorded prevalence above 20% with BMI/weight value or grouping being located in 209 (4.8%) controls and blood glucose record being located in 763 (17.5%) controls. However, like blood pressure and NSAIDs, both factors had the largest proportion of patients with records within the same annual year as the joint arthroplasty for the matched cases (BMI/weight=85 (40.7% of those with a recorded value) controls; blood glucose=597 (78.2%) controls).

4.4.2.2 *Information from free text*

The free-text was searched for the controls for risk factors which had been identified by a code-list. The results of the free-text search can be seen in table 4-3. From the tables, smoking status was recorded in enough patients for the prevalence to be above the required 3% with a smoking status seen within 3409 (78%) patients during at least one consultation within the free text alone. For the remaining grouped factors of BMI/weight and blood glucose, both of these factors were located in more consultations by using the free text alone compared to the use of the code-list with a BMI/weight grouping (e.g. obese) being seen in 478 (10.9%) of patients in the free-text compared to 209 (4.8%) of patients when using the Read-codes and, for blood glucose, 1,942 (44.4%) patients had a blood glucose groupings (e.g. raised blood glucose) in the free-text compared to 763 (17.5%) patients using only the Read-codes. For blood glucose, only 266 (6.1%) patients had a value for blood glucose within the text. The different groupings that were obtained for the factors can be seen in table 4-4 for BMI/weight, smoking status and blood glucose

Table 4-3: Identification of individual factors within CiPCA using a free text search. The percentage of patients with a record of the factor was identified. Identified factors recorded instance closest to the receipt of a knee/hip arthroplasty of the matched case

	Annual Year (prior to arthroplasty)					
Factors	**1**	**2**	**3**	**4**	**5**	**Total**
BMI/Weight grouping	142	109	91	65	65	472 (10.8)
BMI value(kg/m^2)	1445	617	434	264	196	2956 (67.6)
Weight value (kg)	1660	645	450	235	193	3183 (72.8)
Current Smoking Status	1442	773	562	367	235	3379 (77.3)
Blood Glucose Grouping	681	442	350	255	202	1930 (44.2)
Blood Glucose value (mmol/L)	47	61	59	48	49	264 (6.0)
SBP value (mmHg)	2198	618	335	199	132	3482 (79.7)
DBP value (mmHg)	2185	610	342	199	136	3472 (79.5)

BMI - Body Mass Index; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure
BMI/Weight groupings were groupings that had specifically been identified within the free-text without converting identified values of BMI/weight into groupings
Glucose groupings corresponds to either the results of a blood glucose test or identifying if a blood glucose test was performed

Apart from blood glucose, all factors obtained had a prevalence of a recorded value above 65% within the controls. At least one BMI value was located within 2,981 (68.2%) patients during their 5 years within the databases with 1,528 (51.3%) of these patients having at least one BMI value

recorded within the same annual year as the case's joint arthroplasty. Although a BMI value was located for over 60% of the controls, the prevalence was less than that within the cases where there was a prevalence of 72.9% of cases who had a record of at least one BMI value. Within these controls, the mean value of the BMI overall was 28.00 (SD 5.33).

Table 4-4: Categories for the risk factors identified from the free-text in controls

Factor	Grouping	Total, n (%)
BMI	Obesity	129 (27.0)
	Overweight	25 (5.2)
	Weight gain	43 (9.0)
	Weight lose	249 (52.1)
	Want to lose weight	26 (5.4)
Smoking Status	Never Smoked	24 (0.7)
	Non-smoker	703 (20.6)
	Ex-smoker	1550 (45.5)
	Ex-heavy smoker	54 (1.6)
	Ex-moderate smoker	104 (3.1)
	Ex-light smoker	45 (1.3)
	Smoke cessation	249 (7.3)
	Smoker	557 (16.3)
	Trivial smoker	25 (0.7)
	Light smoker	33 (1.0)
	Moderate smoker	20 (0.6)
	Heavy smoker	15 (0.4)
Blood Glucose	Fine	18 (0.9)
	Negative	1647 (84.8)
	Positive	2 (0.1)
	Abnormal	42 (2.2)
	Raised	127 (6.5)
	Tolerance test	94 (4.8)

Within the controls, 3,206 (73.4%) patients had at least one value of weight recorded during the five year period. Similarly to the BMI records, a large proportion of these patients had at least one weight record within the same annual year as the matched cases joint arthroplasty with 1,754 (54.7%) patients having the record in the same annual year. The mean for the weight was 76.65 kg (SD 16.83). For both BMI and weight, many patients had at least two records of the factor with 2,101 (48.1%) controls having at least two records of a BMI value and 2,355 (53.8%) controls having at least two records of a weight value. This allowed for the BMI change and weight change over time variables to be calculated for these controls. A graphical representation of the BMI and weight distributions can be seen in appendix 3 figure 9-1.

The remaining factors where values were obtained were systolic blood pressure (SBP) and diastolic blood pressure (DBP). Within the free-text, a similar amount of patients had a blood pressure reading for either SBP or DBP with 3,514 (80.4%) patients having at least one SBP record and 3,486 (79.8%) patients having at least one DBP record. Similarly with the other factors obtained from the free-text, a large percentage of patients had a record of blood pressure within the same annual year as the matched cases' arthroplasty with 2,276 (64.8%) patients with a SBP record and 2,261 (64.9%) patients with a DBP record having this record in the same annual year as the matched cases arthroplasty.

4.4.2.3 Comparisons of factors from CiPCA to IiPCA

A total of 2,541 (58.1%) controls had investigation data available to be reviewed. Within this investigation data, BMI, weight, SBP, DBP and smoking status were all searched to determine the amount of additional information that could be obtained for the controls. The results of this can be seen in table 4-5.

Table 4-5: Indication of where controls had information available for the different 5 different risk factors

	Body mass index	Weight	Systolic blood pressure	Diastolic blood Pressure	Smoking status
Not Identified	1052 (43.6)	1001 (41.5)	558 (23.1)	558 (23.1)	662 (28.0)
IiPCA only	477 (19.8)	396 (16.4)	610 (25.3)	621 (25.8)	818 (34.6)
CiPCA only	4 (0.2)	4 (0.2)	3 (0.1)	3 (0.1)	15 (0.6)
Identified in both	878 (36.4)	1010 (41.9)	1240 (51.4)	1229 (51.0)	871 (36.8)

CiPCA - Consultations in Primary Care Archive; IiPCA - Investigations in Primary Care Archive

From the table for each of the factors, the free-text within CiPCA had identified a large amount of information. Across all the factors a value for the factor had been identified in both CiPCA and IiPCA in over 35% of all patients. IiPCA alone did not provide a large amount of information but the values that were obtained from IiPCA were closer to the date of the matched case's arthroplasty compared to that from CiPCA ranging from a few days to a couple of months. For the four continuous factors, it was important to see how the values differed between CiPCA's free-text and IiPCA. The results of this can be seen in table 4-6.

Table 4-6: Comparison of the values for the factors obtained from CiPCA's free-text and IiPCA

	Body mass index	Weight	Systolic blood pressure	Diastolic blood pressure
Values Equal (± 1 unit)	811 (92.4)	868 (85.9)	803 (64.8)	816 (66.4)
Increased measurements from IiPCA	33 (3.8)	64 (6.3)	191 (15.4)	181 (14.7)
Increased measurements from CiPCA	34 (3.9)	78 (7.7)	246 (19.8)	232 (18.9)

CiPCA - Consultations in Primary Care Archive; IiPCA - Investigations in Primary Care Archive

From the table, it can be seen that for both BMI and weight the values obtained were roughly similar with over 60% of patients that had a record of the factor in both CiPCA and IiPCA having either similar (±1 unit) or equal values (811 (92.4%) and 868 (85.9%) respectively). Upon further investigation of the values that did differ, these differences most likely occurred since the values obtained from IiPCA had been collected more than 6 months after the identification of the CiPCA value. The SBP and DBP had more differing values between the databases with 803 (64.8%) patients with a SBP and 816 (66.4%) patients with a DBP in both CiPCA and IiPCA having equal or similar values. Upon inspection of the blood pressure values, the value identified by the CiPCA's free text was also identified within IiPCA. However, IiPCA sometimes had further values of blood pressure that appeared at a date closer to the cases time of surgery. Unlike the BMI and weight difference, the blood pressure measurements varied more within a smaller time frame (e.g. a couple of days).

4.4.3 Additional factors from electronic search

After the identification of the amount of information available for the factors obtained from the feasibility study for the controls, additional factors were searched within the Read-codes for morbidities and the BNF subchapters for the different prescriptions. Obtained Read-codes with the required prevalence for the cases or controls can be seen in Appendix 3 table 9-2 with the BNF subchapters obtained in Appendix 3 table 9-3. This resulted in 124 unique three character Read-codes and 69 unique BNF subchapters with a prevalence of 3% in either the cases or controls being obtained. The median prevalence of the Read-codes in the cases was 5.7% (IQR 4%-10.2), ranging from 2.3% (C34 - Gout) up to 76.4% (N05 - Osteoarthritis and allied disorders).

In the controls, there was a median prevalence of 4.4% (IQR 3.4%-8.2%), ranging from 0.6% (527 - plain X-ray pelvis) up to 36.5% (R06 - [D] Respiratory system and chest symptoms). Within the 69 BNF subchapters, the median prevalence within the cases was 8.9% (IQR 5.6%-14.1%), ranging from 2.4% (10.1.4 - Gout and cytotoxic induced hyperuricaemia) up to 62.0% (5.1.1 - Penicillins), with a median prevalence within the controls of 7.5% (IQR 4.7%-14.3%), ranging from 1.3% (8.1.3 - Antimetabolites) up to 59.7% (5.1.1 - Penicillins). Not all the BNF subchapter codes identified in PiPCA existed in the BNF version that was used at the time of analysis (February 2016 update) so had missing labels. These chapters are updated regularly meaning some subchapters would no longer be in use. The prescriptions within these subchapters were reassigned to combat the missing label problem by adding them to the correct groups.

N05 (Osteoarthritis and allied disorders) was not included within the main regression as this was used to adjust for OA in the later analysis. Therefore, an additional 123 three-character Read-code morbidities and 69 prescription types were taken through to the logistic regression.

4.4.4 Conditional logistic regression of risk factors identified from the systematic review

4.4.4.1 Logistic regression

The results of the logistic regression for the factors obtained from the systematic review can be seen in table 4-7 and 4-8. This analysis was performed as a complete case analysis. Only prior use of NSAIDs, deprivation score and Charlson index score had complete data and out of these factors, only the prior use of NSAIDs was statistically significant in both the knee and hip arthroplasty groups (OR 3.01 and 2.31 respectively). However, the Charlson index score was statistically significantly associated with knee arthroplasty with an increase in the score increasing the odds of receiving a arthroplasty (OR 1.07 per unit increase). The remaining factors all had incomplete data. Within the complete case analysis BMI value, weight value, DBP and the BMI

groupings had statistically significant odds ratios. All the associations had the same direction of association for the knee and hip.

Table 4-7: Conditional logistic regression results for continuous and categorical factors for primary TKA: complete case analysis

Factor	Cases	Controls	OR	95% CI	p
Age (years)	68.87 (9.4)	68.38 (9.4)	-	-	-
Female gender	53.0%	53.0%	-	-	-
Area-level deprivation					
ref 1st quintile	20.1%	20.9%	-	-	-
2nd	19.6%	21.2%	0.97	0.68-1.40	0.88
3rd	18.8%	18.7%	1.06	0.74-1.53	0.73
4th	21.6%	20.5%	1.12	0.77-1.66	0.54
5th	19.9%	18.6%	1.15	0.79-1.68	0.47
Systolic blood pressure (mmHg)	138.36 (15.8)	137.27 (15.9)	1.05	0.98 - 1.13	0.16
Diastolic blood pressure (mmHg)	78.77 (9.5)	77.89 (9.8)	1.14	1.01 - 1.29	0.03
Glucose text category					
ref: Normal	91.7%	93.8%	-	-	-
Raised	3.0%	2.5%	1.25	0.65 - 2.37	0.50
Abnormal	1.3%	1.3%	1.03	0.39 - 2.71	0.95
Tolerance test performed	4.0%	2.5%	1.66	0.93 - 2.95	0.08
Blood glucose (mmol/L)	11.57 (17.1)	8.30 (6.0)	1.06	0.92 - 1.22	0.42
Body mass index category (kg/m^2)					
ref: Normal (18.50-24.99)	11.9%	27.4%	-	-	-
Underweight (<18.50)	0.6%	1.2%	1.39	0.31 - 6.47	0.67
Overweight (25.00-29.99)	37.2%	42.2%	2.18	1.46 - 3.26	<0.01
Obese (≥30.00)	50.3%	29.3%	4.05	2.73 - 6.01	<0.01
Body mass index (kg/m^2)	30.45 (5.1)	28.01 (5.3)	1.08	1.06 - 1.11	<0.01
Weight (kg)	84.78 (16.3)	77.37 (16.8)	1.03	1.02 - 1.04	<0.01
Body mass index/time	0.31 (1.9)	-0.30 (3.7)	1.00	0.95 - 1.05	0.92
Weight/time	-0.35 (5.9)	-0.66 (7.83)	1.01	0.98 - 1.04	0.41
Current smoking status					
ref: non-smoker	23.4%	21.7%	-	-	-
Ex-smoker	54.7%	53.7%	0.96	0.70 - 1.32	0.79
Light smoker	1.5%	1.6%	0.94	0.34 - 2.61	0.91
Moderate smoker	0.3%	0.9%	0.24	0.03 - 1.95	0.18
Heavy smoker	0.3%	0.5%	0.44	0.05 - 3.65	0.45
Smoking amount NOS	19.8%	21.7%	0.85	0.57 - 1.27	0.43
Charlson Index score (0-19)	2 (1,4)	2 (0,3)	1.07	1.03 - 1.12	<0.01
NSAID prescription	77.6%	54.4%	3.01	2.33 - 3.90	<0.01

% represents proportion of patients in each group
Charlson index score displays the median and interquartile range
BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor

Table 4-8: Conditional logistic regression results for continuous and categorical factors for primary THA: complete case analysis

Factor	Cases	Controls	OR	95% CI	p
Age (years)	69.83 (9.6)	69.34 (9.6)	-	-	-
Female gender	60.7%	60.7%	-	-	-
Area-level deprivation					
ref 1st quintile	19.6%	18.4%			
2nd	19.7%	19.9%	1.08	0.77-1.51	0.66
3rd	17.2%	18.8%	0.99	0.70-1.40	0.96
4th	20.4%	21.4%	1.05	0.72-1.51	0.81
5th	24.0%	20.2%	1.31	0.93-1.85	0.12
Systolic blood pressure (mmHg)	139.11 (14.5)	137.43 (15.9)	1.06	0.99 - 1.14	0.11
Diastolic blood pressure (mmHg)	77.50 (9.18)	77.39 (9.6)	0.99	0.89 - 1.11	0.90
Glucose text category					
ref: Normal	95.6%	94.0%	-	-	-
Raised	1.3%	3.4%	0.36	0.16 - 0.84	0.02
Abnormal	1.3%	0.7%	1.85	0.69 - 4.95	0.22
Tolerance test performed	1.9%	1.9%	0.98	0.47 - 2.03	0.96
Blood glucose (mmol/L)	7.97 (3.19)	8.14 (5.4)	0.93	0.74 - 1.17	0.53
Body mass index category (kg/m^2)					
ref: Normal (18.50-24.99)	24.9%	28.6%	-	-	-
Underweight (<18.50)	1.4%	1.1%	1.48	0.53 - 4.15	0.46
Overweight (25.00-29.99)	40.0%	41.5%	1.14	0.85 - 1.53	0.38
Obese (≥30.00)	33.8%	28.8%	1.34	0.98 - 1.84	0.06
Body mass index (kg/m^2)	28.23 (4.8)	27.94 (5.1)	1.01	0.98 - 1.03	0.48
Weight (kg)	77.78 (16.0)	75.96 (16.5)	1.01	1.00 - 1.02	<0.01
Body mass index/time	0.05 (3.8)	0.02 (7.5)	1.00	0.98 - 1.02	0.74
Weight/time	-0.72 (7.4)	0.11 (17.9)	0.99	0.97 - 1.02	0.52
Current smoking status					
ref: non-smoker	23.8%	21.4%	-	-	-
Ex-smoker	54.6%	50.4%	0.92	0.68 - 1.24	0.58
Light smoker	2.1%	1.8%	0.92	0.39 - 2.13	0.83
Moderate smoker	0.5%	0.3%	2.26	0.36 - 14.04	0.38
Heavy smoker	1.1%	0.4%	2.91	0.70 - 12.02	0.14
Smoking amount NOS	17.9%	25.7%	0.61	0.42 - 0.90	0.01
Charlson Index score (0-19)	2 (1,3)	2 (1,4)	0.99	0.95 - 1.03	0.67
NSAID prescription	73.7%	55.2%	2.31	1.85 - 2.88	<0.01

% represents proportion of patients in each group
Charlson index score displays the median and interquartile range
BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor

Multiple imputation was performed on those factors that had missing data but had at least 50% worth of data already available using age, gender, practice, Charlson index, deprivation score, if the patient was a case and if the patient had received an NSAID in the imputation model. The

distributions of the imputed data were similar to that of the original data obtained. The results of the conditional logistic regression on the imputed data can be seen in table 4-9.

Table 4-9: Conditional logistic regression results for continuous and categorical factors for primary TKA/THA: imputed data analysis

Factor	Knee			Hip		
	OR	95% CI	P	OR	95% CI	P
Systolic blood pressure (mmHg)	1.05	0.98 - 1.13	0.15	1.06	0.99 - 1.13	0.11
Diastolic blood pressure (mmHg)	1.09	0.97 - 1.23	0.16	1.01	0.90 - 1.12	0.89
Body mass index category						
ref: Normal						
Underweight	1.49	0.36 - 6.12	0.58	1.62	0.55 - 4.76	0.38
Overweight	1.84	1.27 - 2.65	<0.01	1.23	0.92 - 1.66	0.16
Obese	3.36	2.37 - 4.78	<0.01	1.55	1.11 - 2.18	0.01
Body mass index (kg/m^2)	1.08	1.05 - 1.10	<0.01	1.02	1.00 - 1.04	0.05
Weight (kg)	1.01	0.97 - 1.04	0.75	1.00	0.99 - 1.02	0.68
Body mass index/time	1.03	1.02 - 1.04	<0.01	1.01	1.01 - 1.02	<0.01
Weight/time	1.00	0.98 - 1.02	0.91	0.99	0.98 - 1.01	0.48
Current smoking status						
ref: non-smoker						
Ex-smoker	0.94	0.69 - 1.29	0.72	0.93	0.71 - 1.21	0.59
Light smoker	0.91	0.37 - 2.27	0.84	0.98	0.44 - 2.22	0.96
Moderate smoker	0.37	0.05 - 2.80	0.33	1.13	0.24 - 5.29	0.88
Heavy smoker	0.48	0.05 - 4.44	0.52	1.83	0.58 - 5.83	0.30
Smoking amount NOS	0.82	0.56 - 1.19	0.29	0.61	0.42 - 0.90	0.01

BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor

From table 4-9, the direction of effect of all the odds ratios obtained from the imputed dataset was the same as that from the complete case analysis. Like the complete case analysis, only BMI value, weight value and BMI grouping were seen as significantly associated with a joint arthroplasty. In both joint groups, the direction of the odds ratio was the same with certain groupings (e.g. obese) having increased odds of requiring a joint arthroplasty compared to the baseline group (non-smokers and normal BMI). This direction of association was present in all groups apart from the heavy smokers association with knees and smoker amount not otherwise specified. Within these groups, the odds of receiving a joint arthroplasty are reduced compared to non-smokers.

4.4.4.2 *Logistic regression adjusted for osteoarthritis*

668 cases (76.4%) had a coding of osteoarthritis and 687 controls (15.7%) had a coding of osteoarthritis. Table 4-10 shows the results of the regression examining the association between OA and the different types of arthroplasty.

Table 4-10: Conditional logistic regression results of OA with primary TKA/THA

Arthroplasty type	Cases	Controls	OR	95% CI	p
TKA	78.8%	15.1%	22.23	16.18-30.54	<0.01
THA	74.4%	16.3%	17.95	13.52-23.83	<0.01
% represent the proportion of patients in each group with a coding of OA using the NO5 code					

From the tables, OA was strongly associated with the requirement for both a primary TKA and THA. Table 4-11 shows the results of the logistic regression for three coded factors, after adjustment for an OA diagnosis

Table 4-11: Conditional logistic regression results for factors obtained using a code-list with primary TKA/THA: adjusted for OA

Factor	Knee			Hip		
	OR	95% CI	P	OR	95% CI	P
Area-level deprivation (ref 1st quintile)						
2nd	0.99	0.62-1.55	0.95	1.04	0.69-1.57	0.85
3rd	1.44	0.91-2.29	0.12	0.96	0.64-1.44	0.84
4th	1.17	0.72-1.92	0.52	1.20	0.78-1.87	0.40
5th	1.23	0.77-1.99	0.38	1.70	1.12 -2.56	0.01
Charlson Index score (0-19)	1.02	0.96 - 1.07	0.57	0.95	0.90 - 1.01	0.08
NSAID prescription	1.63	1.18 - 2.26	<0.01	1.54	1.17 - 2.02	<0.01

As seen with the overall analysis, only prior use of NSAIDs was seen as statistically significant in both the knee and hip arthroplasty groups (OR 1.63 and 1.54 respectively). However, the odds-ratios were lower when the association was adjusted for OA when compared to the unadjusted results. The Charlson Index score however, was no longer seen as statistically significantly associated with either a TKA or THA.

Multiple imputation was also performed and adjusted for OA on the same factors used within the multiple imputation for the entire dataset. The results of these can be seen in table 4-12.

Table 4-12: Conditional logistic regression results for continuous and categorical factors for primary TKA/THA: imputed data analysis adjusted for OA

Factor	Knee			Hip		
	OR	95% CI	P	OR	95% CI	P
Systolic blood pressure (mmHg)	1.05	0.96 - 1.15	0.29	1.06	0.98 - 1.15	0.18
Diastolic blood pressure (mmHg)	1.17	1.01 - 1.37	0.04	1.01	0.88 - 1.15	0.94
Body mass index category (ref: Normal)						
Underweight	1.47	0.36 - 6.07	0.59	1.61	0.55 - 4.70	0.38
Overweight	1.82	1.26 - 2.64	<0.01	1.24	0.92 - 1.66	0.15
Obese	3.36	2.38 - 4.76	<0.01	1.54	1.10 - 2.17	0.01
Body mass index (kg/m^2)	1.05	1.02 - 1.08	<0.01	1.00	0.98 - 1.03	0.72
Weight (kg)	1.02	1.01 - 1.03	<0.01	1.00	0.99 - 1.01	0.42
Body mass index/time	1.01	0.95 - 1.07	0.84	1.00	0.98 - 1.03	0.72
Weight/time	1.00	0.98 - 1.02	1.00	1.00	0.98 - 1.01	0.59
Current smoking status (ref: non-smoker)						
Ex-smoker	0.92	0.60 - 1.42	0.71	0.81	0.58 - 1.13	0.22
Light smoker	0.78	0.21 - 2.90	0.71	1.18	0.44 - 3.14	0.75
Moderate smoker	0.54	0.04 - 6.77	0.63	1.95	0.27 - 14.36	0.51
Heavy smoker	0.50	0.02 - 13.01	0.67	0.88	0.22 - 3.54	0.86
Smoking amount NOS	0.86	0.51 - 1.44	0.57	0.61	0.40 - 0.93	0.02
BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor						

From the table, BMI, weight and SBP were all seen as statistically significant within the TKA group but not the THA grouping. Within the THA group, none of the factors were seen as being associated with the requirement for a THA. A graphical comparison of the odds ratios found for the entire dataset and for the OA adjusted analysis can be seen in figure 4-3. From the figure it can be seen that for the continuous factors, all of the odds ratios that were calculated were roughly equal for both TKA and THA between the adjusted and unadjusted associations. From the graph of the categorical factors, it is clearer to see that the confidence intervals obtained from the different groups were quite large for certain factors within the groupings for both OA and all patient groups. This was due to the small numbers of patients included in the analysis before imputations were performed.

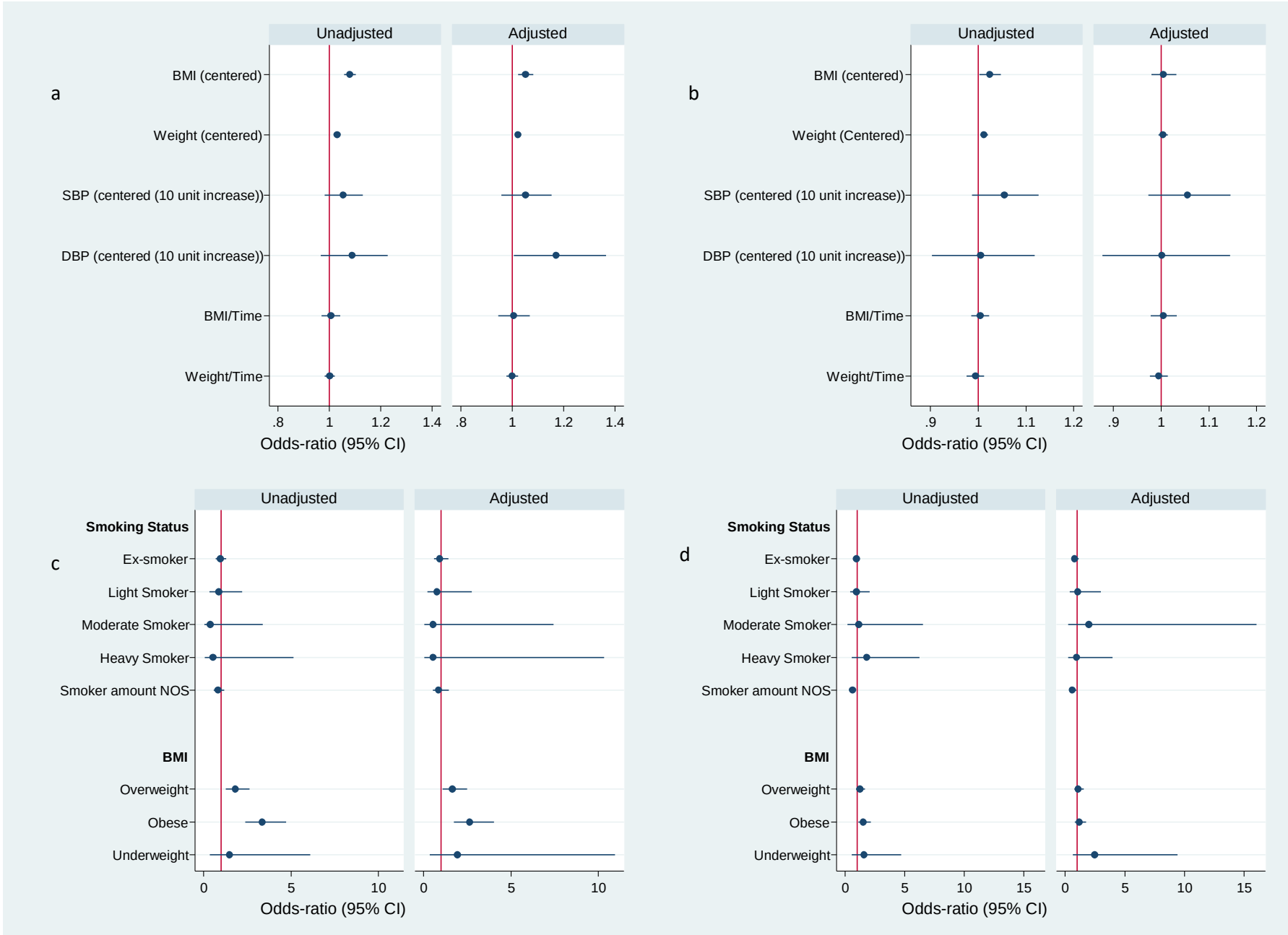

Figure 4-3: Odds ratios of the factors requiring multiple imputation comparing all cases to OA cases. A) continuous factors for a TKA, b) continuous factors for a THA, c) categorical factors for TKA d) categorical factors for THA

Logistic regression stratified by gender

Since gender was used as a factor within the matching of the controls to the cases, gender could no longer be used within the logistic regression. The data was instead stratified by gender to determine whether risk factor varied by gender. Out of the 5,239 patients within the study, 2,998 (57.2%) were female. There were 187 cases of knee arthroplasty and 187 cases of hip arthroplasty within the male population and 211 cases of knee arthroplasty and 289 cases of hip arthroplasty within the female population. Conditional logistic regression was performed for the hip and knee with the analysis being stratified by gender. It was anticipated that not all the same factors would be seen as significantly associated with a joint arthroplasty within each gender group. Results of the logistic regression on the three complete factors can be seen in table 4-13 for the knee and table 4-14 for the hip.

Table 4-13: Conditional logistic regression results for factors obtained using a code-list for primary TKA stratified by gender

Factor	Male			Female		
	OR	95% CI	P	OR	95% CI	P
Area-level deprivation (ref 1st quintile)						
2nd	1.12	0.64-1.96	0.69	0.89	0.55-1.43	0.62
3rd	1.34	0.77-2.33	0.30	0.89	0.55-1.45	0.65
4th	1.54	0.85-2.81	0.15	0.89	0.53-1.47	0.64
5th	1.86	1.07-3.24	0.03	0.73	0.43-1.24	0.24
Charlson Index score (0-19)	1.08	1.00 - 1.17	0.05	1.06	1.00 - 1.13	0.07
NSAID prescription	2.83	1.95 - 4.11	<0.01	3.18	2.23 - 4.56	<0.01

Table 4-14: Conditional logistic regression results for factors obtained using a code-list for primary THA stratified by gender

Factor	Male			Female		
	OR	95% CI	P	OR	95% CI	P
Area-level deprivation (ref 1st quintile)						
2nd	0.72	0.42-1.22	0.22	1.43	0.92-2.22	0.11
3rd	1.00	0.58-1.70	0.99	1.00	0.64-1.57	0.99
4th	0.78	0.43-1.41	0.41	1.29	0.80-2.07	0.30
5th	1.08	0.63-1.85	0.78	1.51	0.97-2.37	0.07
Charlson Index score (0-19)	0.94	0.86 - 1.03	0.18	0.99	0.93 - 1.06	0.87
NSAID prescription	1.99	1.39 - 2.84	<0.01	2.53	1.91 - 3.36	<0.01

From the tables, only prior use of NSAIDs was statistically significant for both TKA and THA within both genders. For TKA, females had a larger odds-ratio compared to males suggesting that if females had been prescribed a NSAID in the previous five years then they were more likely to have a future arthroplasty compared to men (OR (FvM) 3.18 compared to 2.83). For THA, males had a larger odds-ratio (OR (FvM) 1.99 compared to 2.53). The Charlson index score was also seen as statically significant for a knee arthroplasty. However, this association was only present for the males with the odds ratio being similar to the complete analysis (OR 1.08). Similarly to the complete sample analysis, the remaining factors were not statistically significant.

Similar to the complete case, multiple imputation was performed on the information obtained within the free-text to assess the effect these factors had on the requirement for a joint arthroplasty once stratified by gender. The results of the stratified conditional logistic regression can be seen in table 4-15 for the knee and table 4-16 for the hip.

Table 4-15: Conditional logistic regression results for continuous and categorical factors for primary TKA stratified by gender: imputed data analysis

Factor	Male			Female		
	OR	95% CI	P	OR	95% CI	P
Systolic blood pressure (mmHg)	1.01	0.91 - 1.13	0.82	1.09	0.99 - 1.19	0.08
Diastolic blood pressure (mmHg)	0.92	0.77 - 1.09	0.34	1.27	1.08 - 1.48	<0.01
Body mass index category (ref: Normal)						
Underweight	n/a	n/a	n/a	1.93	0.39 - 9.65	0.42
Overweight	1.82	1.07 - 3.09	0.03	1.86	1.08 - 3.20	0.03
Obese	2.77	1.66 - 4.60	<0.01	4.02	2.37 - 6.80	<0.01
Body mass index (kg/m^2)	1.06	1.03 - 1.10	<0.01	1.09	1.05 - 1.12	<0.01
Weight (kg)	1.01	0.95 - 1.07	0.69	1.00	0.96 - 1.04	0.93
Body mass index/time	1.02	1.01 - 1.03	<0.01	1.04	1.02 - 1.05	<0.01
Weight/time	1.01	0.98 - 1.03	0.53	0.99	0.97 - 1.02	0.61
Current smoking status (ref: non-smoker)						
Ex-smoker	0.96	0.60 - 1.53	0.85	0.92	0.59 - 1.44	0.72
Light smoker	0.44	0.06 - 3.19	0.42	1.37	0.42 - 4.40	0.60
Moderate smoker	n/a	n/a	n/a	0.55	0.06 - 4.77	0.59
Heavy smoker	0.61	0.07 - 5.28	0.65	n/a	n/a	n/a
Smoking amount NOS	1.00	0.59 - 1.70	1.00	0.67	0.38 - 1.15	0.15

BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor
n/a meant that there was not enough data for odds-ratios to be calculated

Table 4-16: Conditional logistic regression results for continuous and categorical factors for primary THA stratified by gender: imputed data analysis

Factor	Male			Female		
	OR	95% CI	P	OR	95% CI	P
Systolic blood pressure (mmHg)	1.13	1.01 - 1.27	0.03	1.01	0.93 - 1.10	0.80
Diastolic blood pressure (mmHg)	1.13	0.94 - 1.36	0.18	0.93	0.81 - 1.08	0.35
Body mass index category (ref: Normal)						
Underweight	n/a	n/a	n/a	2.16	0.73 - 6.35	0.16
Overweight	1.15	0.74 - 1.79	0.52	1.28	0.86 - 1.92	0.22
Obese	1.59	0.97 - 2.61	0.06	1.52	1.00 - 2.31	0.05
Body mass index (kg/m^2)	1.04	1.00 - 1.09	0.05	1.01	0.99 - 1.04	0.32
Weight (kg)	1.02	0.97 - 1.07	0.51	1.00	0.98 - 1.02	0.90
Body mass index/time	1.02	1.00 - 1.03	0.01	1.01	1.00 - 1.02	0.03
Weight/time	1.00	0.97 - 1.02	0.73	0.99	0.98 - 1.01	0.45
Current smoking status (ref: non-smoker)						
Ex-smoker	0.77	0.50 - 1.19	0.25	1.04	0.73 - 1.50	0.81
Light smoker	1.32	0.36 - 4.83	0.67	0.86	0.32 - 2.32	0.77
Moderate smoker	n/a	n/a	n/a	1.80	0.32 - 9.97	0.50
Heavy smoker	1.49	0.29 - 7.59	0.63	2.32	0.39 - 13.89	0.36
Smoking amount NOS	0.64	0.36 - 1.15	0.13	0.59	0.36 - 0.97	0.04

BMI, weight, SBP and DBP were all centred. BMI weight, BMI/time and weight/time's odds ratios represent a unit increase in the factor. SBP and DBP's odds ratios represent a 10 unit increase in the factor
n/a meant that there was not enough data for odds-ratios to be calculated

From table 4-15 it can be seen that, out of the continuous factors, only BMI and weight were statistically significant and associated with the requirement for a knee arthroplasty with a unit increase in either BMI or weight increasing the odds of requiring said arthroplasty in the males (odds ratio 1.06 and 1.02). In the female group, the odds ratio was larger for BMI and weight compared to the males (1.09 and 1.04 respectively) and diastolic blood pressure was also seen as being statistically significant (odds ratio 1.02). As seen in table 4-16, BMI, weight and systolic blood pressure were all statistically significantly associated with requiring a hip arthroplasty, increasing the odds of requiring a hip arthroplasty with a unit increase of each factor in the males (odds ratios 1.04, 1.02 and 1.01 respectively). Unlike for knee arthroplasty, BMI, weight and diastolic blood pressure were not statically significant within the females' hip arthroplasty. Of the categorical factors where odd-ratios could be calculated, only the obese group within the BMI grouping was statically significant within the knee, increasing the odds of requiring a joint arthroplasty if a patient was classified as being obese in both males and females (odds ratios 2.77

and 4.02 respectively). This was similar for hip arthroplasty with patients that were classified as being obese more likely to have a hip arthroplasty in both males and females (odds ratio 1.59 and 1.52 respectively). Within the smoking status, no groupings were seen as statistically significant with these either having large confidence intervals or did not have enough cases within a category for an effect size to be obtained. Figures 9-2 of appendix 3 shows the odds ratios graphically for both the continuous factors and categorical factors for both genders.

4.4.5 Hypothesis free identification of other potential risk factors

4.4.5.1 Logistic regression

The results of the logistic regression for factors obtained from the additional electronic search that had an odds ratio larger than 1.33 or less than 0.75 for association with knee arthroplasty can be seen in table 4-17 and for hip arthroplasty in table 4-18. A graphical representation of the odds ratios for the Read-code factors and the BNF subchapters can be seen in the appendix 3 figure 9-3 for the knee and figure 9-4 for the hip.

From these tables, 88 further factors were associated with a knee arthroplasty and 76 were associated with a hip arthroplasty. Out of these factors, 45 were seen to be associated with both a knee and a hip arthroplasty. From these 45, 25 factors had a larger odds ratio for knee arthroplasty compared to the hip.

Pain in the lower limb (Read-code 1M1) was the factor which increased the odds of requiring a knee arthroplasty the most (OR 11.04). The effect size was much smaller but was still associated with the requirement for a hip arthroplasty (OR 1.65). Plain x-ray of the pelvis (527) was the factor which increased the odds of requiring a hip arthroplasty the most (OR 13.38). However, this factor was not associated with knee arthroplasty. However there were certain factors that were highly associated with the requirement for both a knee and hip arthroplasty. Plain x-ray of the hip or leg (52A) was associated with the requirement for both a knee and hip arthroplasty (OR 10.45 for the knee and 9.58 for the hip).

Table 4-17: Results of the conditional logistic regression for factors with Odds-ratios <0.75 or >1.33 for knee arthroplasty

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
1M1	Pain in lower limb	11.04	6.70 - 18.17	<0.01
52A	Plain X-ray hip/leg	10.45	6.72 - 16.25	<0.01
7K6	Other joint operations	7.45	4.82 - 11.52	<0.01
4.7.2	Opioid analgesics	6.57	5.01 - 8.62	<0.01
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	6.17	3.75 - 10.13	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	4.87	3.64 - 6.50	<0.01
N09	Other and unspecified joint disorders	4.35	3.46 - 5.47	<0.01
9EG	Disabled driver badge report	3.99	2.27 - 7.01	<0.01
9ND	Incoming mail processing	3.93	1.77 - 8.73	<0.01
10.3.2	Rubefacients and other topical antirheumatics	3.66	2.88 - 4.65	<0.01
10.1.2	Corticosteroids	3.18	1.75 - 5.79	<0.01
2.3.2	Drugs for arrhythmias	3.11	1.75 - 5.52	<0.01
9N1	Site of encounter	2.63	1.63 - 4.25	<0.01
ZV5	[V]Specified procedures and aftercare	2.63	1.45 - 4.77	<0.01
987	FP/MS - minor surgery claim	2.57	1.52 - 4.35	<0.01
6.3.2	Glucocorticoid therapy	2.35	1.84 - 3.02	<0.01
K51	Genital prolapsed	2.25	1.25 - 4.03	<0.01
K5A	Menopausal and postmenopausal disorders	2.14	1.37 - 3.36	<0.01
8.1.3	Antimetabolites	2.12	1.10 - 4.06	0.02
7L1	Other miscellaneous operations	2.06	1.16 - 3.68	0.01
ZV6	[V]Other reasons for encounter	2.00	1.38 - 2.90	<0.01
3.9.1	Cough Suppressants	1.97	1.13 - 3.42	0.02
ZV0	[V]Persons with potential health hazards related to communicable diseases	1.96	0.85 - 4.52	0.11
1.6.4	Osmotic laxatives	1.94	1.49 - 2.53	<0.01
F34	Mononeuritis of upper limb and mononeuritis multiplex	1.94	1.08 - 3.48	0.03
1.3.6	Other Antisec Drugs+Mucosal Protectants	1.92	1.53 - 2.40	<0.01
G83	Varicose veins of the legs	1.90	1.26 - 2.87	<0.01
M03	Other cellulitis and abscess	1.86	1.13 - 3.07	0.01
8B6	Prophylactic drug therapy	1.85	1.11 - 3.10	0.02
585	Other diagnostic ultrasound	1.83	1.21 - 2.77	<0.01
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.83	1.15 - 2.91	0.01
4.7.4	Antimigraine drugs	1.72	1.04 - 2.86	0.03
8H7	Other referral	1.71	0.83 - 3.50	0.14
5.4.1	Antimalarials	1.68	1.19 - 2.39	<0.01
65E	Influenza vaccination	1.68	1.21 - 2.32	<0.01
J51	Diverticula of intestine	1.66	0.96 - 2.86	0.07
1.6.2	Stimulant laxatives	1.65	1.14 - 2.37	<0.01

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
1.7.2	Compound haemorrhoidal preparations with corticosteroids	1.64	1.10 - 2.45	0.01
9.6.4	Vitamin D	1.64	1.13 - 2.37	<0.01
4.3.1	Tricyclic and related antidepressants	1.63	1.24 - 2.15	<0.01
G84	Haemorrhoids	1.63	1.04 - 2.56	0.03
N22	Other disorders of the synovium, tendon and bursa	1.63	1.05 - 2.53	0.03
6.4.1	Female sex hormones and their modulators	1.62	0.97 - 2.69	0.06
9N4	Failed encounter	1.62	1.27 - 2.07	<0.01
12.2.3	Nasal Preparations for Infection	1.61	1.02 - 2.54	0.04
2.2.1	Thiazides and related diuretics	1.60	1.25 - 2.04	<0.01
C36	Disorders of fluid, electrolyte and acid-base balance	1.60	0.93 - 2.75	0.09
H12	Chronic pharyngitis and nasopharyngitis	1.60	0.96 - 2.67	0.07
M23	Diseases of nail	1.60	0.93 - 2.77	0.09
F4F	Lacrimal system disorders	1.59	0.97 - 2.60	0.07
M07	Other local infections of skin and subcutaneous tissue	1.58	1.01 - 2.48	0.05
N11	Spondylosis and allied disorders	1.58	1.04 - 2.39	0.03
4.1.1	Hypnotics	1.57	1.05 - 2.35	0.03
D21	Other and unspecified anaemias	1.57	0.94 - 2.61	0.09
19F	Diarrhoea symptoms	1.56	0.98 - 2.48	0.06
4.8.1	Control of the epilepsies	1.56	1.05 - 2.32	0.03
7.4.1	Drugs for urinary retention	1.55	1.00 - 2.40	0.05
9N3	Indirect encounter	1.55	1.08 - 2.23	0.02
44P	Serum cholesterol	1.54	1.04 - 2.27	0.03
G80	Phlebitis and thrombophlebitis	1.52	0.88 - 2.63	0.13
J16	Disorders of stomach function	1.51	1.08 - 2.11	0.02
2.2.4	Potassium-sparing diuretics with other diuretics	1.49	0.84 - 2.64	0.18
H1y	Other specified diseases of upper respiratory tract	1.49	0.85 - 2.60	0.16
J34	Diaphragmatic hernia	1.48	0.91 - 2.41	0.12
F59	Hearing loss	1.47	0.99 - 2.18	0.05
537	Soft tissue X-ray breast	1.46	0.62 - 3.47	0.39
A08	Ill-defined intestinal tract infections	1.46	0.94 - 2.29	0.09
K19	Other urethral and urinary tract disorders	1.46	1.10 - 1.93	<0.01
SK1	Other specified injury	1.46	1.02 - 2.08	0.04
13.10.2	Antifungal preparations	1.45	1.06 - 1.98	0.02
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.45	0.89 - 2.35	0.14
1C1	Hearing symptoms	1.44	0.72 - 2.87	0.30
2.6.2	Calcium-channel inhibitors	1.44	1.14 - 1.81	<0.01

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
9.1.1	Iron-deficiency anaemias	1.44	0.98 - 2.12	0.06
N21	Peripheral enthesopathies and allied syndromes	1.44	1.05 - 1.96	0.02
J52	Functional gastrointestinal tract disorders NEC	1.42	1.00 - 2.03	0.05
461	Urine exam. – general	1.40	1.00 - 1.96	0.05
R01	[D]Nervous and musculoskeletal symptoms	1.37	0.84 - 2.22	0.21
8B3	Drug therapy	1.36	1.02 - 1.82	0.04
5.1.5	Macrolides	1.35	1.03 - 1.78	0.03
M22	Other dermatoses	1.35	0.93 - 1.98	0.12
4.6.	Drugs used in nausea and vertigo	1.34	0.98 - 1.85	0.07
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	1.34	0.88 - 2.04	0.17
M26	Sebaceous gland diseases	0.68	0.34 - 1.37	0.28
G57	Cardiac dysrhythmias	0.65	0.39 - 1.08	0.09
2.8.2	Oral Anticoagulants	0.60	0.34 - 1.09	0.09
9.4.2	Enteral nutrition	0.59	0.30 - 1.16	0.13
685	Cervical neoplasia screening	0.48	0.28 - 0.83	<0.01

Table 4-18: Results of the conditional logistic regression for factors with Odds-ratios <0.75 or >1.33 for hip arthroplasty

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
527	Plain X-ray pelvis	13.38	6.71 - 26.68	<0.01
52A	Plain X-ray hip/leg	9.58	6.30 - 14.58	<0.01
N09	Other and unspecified joint disorders	7.72	6.13 - 9.72	<0.01
4.7.2	Opioid analgesics	5.83	4.61 - 7.36	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	5.52	4.15 - 7.34	<0.01
9ND	Incoming mail processing	5.20	2.56 - 10.59	<0.01
7K6	Other joint operations	3.29	2.10 - 5.18	<0.01
8.1.3	Antimetabolites	3.05	1.63 - 5.74	<0.01
8H7	Other referral	2.50	1.32 - 4.76	<0.01
9EG	Disabled driver badge report	2.26	1.35 - 3.81	<0.01
12.2.3	Nasal Preparations for Infection	2.04	1.34 - 3.09	<0.01
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	2.04	1.12 - 3.73	0.02
8C1	Nursing care	1.93	1.16 - 3.23	0.01
771	Colon operations and sigmoidoscopy of rectum	1.89	1.15 - 3.11	0.01
9.1.1	Iron-deficiency anaemias	1.86	1.33 - 2.62	<0.01
C36	Disorders of fluid, electrolyte and acid-base	1.84	1.14 - 2.98	0.01

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
	balance			
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.83	1.22 - 2.75	<0.01
9.6.4	Vitamin D	1.83	1.33 - 2.53	<0.01
9N1	Site of encounter	1.82	1.11 - 3.00	0.02
J52	Functional gastrointestinal tract disorders NEC	1.80	1.31 - 2.47	<0.01
5.4.1	Antimalarials	1.79	1.31 - 2.44	<0.01
N33	Other bone and cartilage disorders	1.79	1.21 - 2.64	<0.01
1.6.4	Osmotic laxatives	1.75	1.37 - 2.23	<0.01
N11	Spondylosis and allied disorders	1.75	1.22 - 2.49	<0.01
R14	[D]Nonspecific abnormal function studies	1.75	1.18 - 2.59	<0.01
2.3.2	Drugs for arrhythmias	1.69	0.82 - 3.49	0.16
D21	Other and unspecified anaemias	1.66	1.06 - 2.61	0.03
1.6.2	Stimulant laxatives	1.65	1.20 - 2.27	<0.01
12.3.1	Drugs for Oral Ulceration and Inflammation	1.65	0.95 - 2.85	0.07
1M1	Pain in lower limb	1.65	0.94 - 2.90	0.08
10.3.2	Rubefacients and other topical antirheumatics	1.63	1.31 - 2.04	<0.01
4.1.1	Hypnotics	1.59	1.10 - 2.28	0.01
PC0	Anomalies of ovaries	1.58	0.91 - 2.73	0.10
5.1.13	Urinary tract infections	1.56	1.02 - 2.38	0.04
44P	Serum cholesterol	1.55	1.02 - 2.33	0.04
4.3.1	Tricyclic and related antidepressants	1.50	1.16 - 1.94	<0.01
1.6.1	Bulk forming laxatives	1.49	1.08 - 2.06	0.02
M07	Other local infections of skin and subcutaneous tissue	1.49	0.99 - 2.25	0.06
8B3	Drug therapy	1.46	1.12 - 1.90	<0.01
1.7.2	Compound haemorrhoidal preparations with corticosteroids	1.45	0.97 - 2.17	0.07
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	1.45	1.00 - 2.10	0.05
N14	Other and unspecified back disorders	1.43	1.15 - 1.77	<0.01
A53	Measles	1.41	0.90 - 2.22	0.14
F34	Mononeuritis of upper limb and mononeuritis multiplex	1.41	0.72 - 2.77	0.31
M15	Erythematous conditions	1.41	0.84 - 2.37	0.20
5.1.2	Cephalosporins, carbapenems and other betalactams	1.39	1.09 - 1.78	<0.01
9.1.2	Drugs used in megaloblastic anaemias	1.39	0.86 - 2.26	0.18
R09	[D]Other abdominal and pelvic symptoms	1.39	1.08 - 1.79	<0.01
1.3.6	Other Antisec	1.38	1.12 - 1.69	<0.01

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
	Drugs+Mucosal Protectants			
G80	Phlebitis and thrombophlebitis	1.38	0.80 - 2.37	0.25
685	Cervical neoplasia screening	1.37	0.83 - 2.28	0.22
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.37	0.87 - 2.16	0.18
2.2.1	Thiazides and related diuretics	1.36	1.09 - 1.69	<0.01
7L1	Other miscellaneous operations	1.36	0.74 - 2.48	0.32
8BA	Other misc. Therapy	1.36	0.85 - 2.16	0.20
G84	Haemorrhoids	1.36	0.88 - 2.10	0.17
1C1	Hearing symptoms	1.35	0.77 - 2.35	0.29
525	Plain X-ray spine	1.35	0.72 - 2.52	0.35
9N3	Indirect encounter	1.35	0.97 - 1.89	0.08
657	Other bacterial vaccinations	1.34	0.96 - 1.86	0.08
H1y	Other specified diseases of upper respiratory tract	1.34	0.78 - 2.32	0.29
6.1.2	Anti-Diabetic drugs	0.71	0.48 - 1.04	0.08
12.2.1	Drugs used in Nasal Allergy	0.69	0.51 - 0.93	0.02
H05	Other acute upper respiratory infections	0.69	0.49 - 0.96	0.03
730	External ear and external auditory canal operations	0.68	0.40 - 1.17	0.17
B76	Benign neoplasm of skin	0.68	0.38 - 1.19	0.18
68N	Immunisation status screen	0.67	0.31 - 1.41	0.29
535	Standard chest X-ray	0.66	0.42 - 1.04	0.07
F59	Hearing loss	0.66	0.43 - 1.01	0.06
G33	Angina pectoris	0.66	0.38 - 1.14	0.14
H01	Acute sinusitis	0.66	0.42 - 1.04	0.07
6C2	Primary prevention of cardiovascular disease	0.63	0.30 - 1.31	0.21
68A	Neurolog./special sense screen	0.52	0.27 - 1.02	0.06
H12	Chronic pharyngitis and nasopharyngitis	0.52	0.28 - 0.98	0.04
10.1.4	Gout and cytotoxic induced hyperuricaemia	0.50	0.24 - 1.06	0.07
C34	Gout	0.46	0.22 - 0.96	0.04

The prescriptions drugs that were most strongly associated with knee and hip arthroplasty were Opioid analgesics (BNF 4.7.2) but the association was larger for knee arthroplasty compared to the hip (OR 6.57 compared to 5.83).

4.4.5.2 Logistic regression adjusted for osteoarthritis

The conditional logistic regression for the factors obtained from the electronic search was also adjusted for OA. The results of this can be seen in table 4-19 for TKA and table 4-20 for THA. A graphical representation of the odds ratios for the Read-code factors and the BNF subchapters can be seen in the appendix 3 figure 9-5 for the knee and figure 9-6 for the hip.

From the tables, 102 factors for TKA and 82 factors for THA now had an OR>1.33 or <0.75 of which 56 had an association with both a knee and hip arthroplasty. From the unadjusted factors that were associated, 6 factors for TKA and 17 for THA no longer fell within the required range.

Having a plain x-ray in either the hip or leg (Read-code 52A) was the factor which increased the odds of requiring a knee arthroplasty the most (OR 11.73). The effect size was larger in the hip arthroplasty group for this factor (OR 13.43). Plain x-ray of the pelvis (527) was the factor which increased the odds of requiring a hip arthroplasty the most and had a larger effect size compared to the complete sample analysis (OR 16.21 compared to 13.38). This factor was also seen to be associated with a knee arthroplasty but the effect size was smaller than for hip arthroplasty (OR 1.36). The prescription drugs that increased the odds the most in the knee were Opioid analgesics (4.7.2). The effect of this prescription was slightly lower once adjusted for OA compared to the unadjusted results (OR 6.53 compared to 6.57). However, the effect of this prescription was larger within the knee group compared to the hip group (OR 5.52).

Table 4-19: Results of the conditional logistic regression for factors with Odds-ratios <0.75 or >1.33 for knee arthroplasty: adjusted for OA.

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
52A	Plain X-ray hip/leg	11.73	7.11 - 19.36	<0.01
1M1	Pain in lower limb	10.11	5.86 - 17.44	<0.01
7K6	Other joint operations	6.65	4.10 - 10.79	<0.01
4.7.2	Opioid analgesics	6.53	4.81 - 8.86	<0.01
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	6.06	3.54 - 10.39	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	5.80	4.13 - 8.16	<0.01
N09	Other and unspecified joint disorders	4.21	3.25 - 5.44	<0.01
10.3.2	Rubefacients and other topical antirheumatics	4.17	3.16 - 5.50	<0.01
9EG	Disabled driver badge report	3.85	2.04 - 7.24	<0.01
9ND	Incoming mail processing	3.49	1.55 - 7.89	<0.01
2.3.2	Drugs for arrhythmias	3.41	1.77 - 6.57	<0.01
10.1.2	Corticosteroids	3.32	1.64 - 6.74	<0.01
987	FP/MS - minor surgery claim	2.67	1.52 - 4.69	<0.01
6.3.2	Glucocorticoid therapy	2.34	1.78 - 3.07	<0.01
K5A	Menopausal and postmenopausal disorders	2.27	1.39 - 3.73	<0.01
M03	Other cellulitis and abscess	2.27	1.29 - 4.01	<0.01
9N1	Site of encounter	2.24	1.33 - 3.77	<0.01
537	Soft tissue X-ray breast	2.14	0.84 - 5.47	0.11
1.3.6	Other Antisec Drugs+Mucosal Protectants	2.06	1.60 - 2.65	<0.01
ZV5	[V]Specified procedures and aftercare	2.03	1.03 - 4.02	0.04
5.4.1	Antimalarials	2.02	1.38 - 2.96	<0.01
3.9.1	Cough Suppressants	2.00	1.05 - 3.82	0.04
ZV0	[V]Persons with potential health hazards related to communicable diseases	1.99	0.84 - 4.73	0.12
12.2.3	Nasal Preparations for Infection	1.95	1.17 - 3.26	0.01
K51	Genital prolapse	1.95	1.02 - 3.74	0.04
1.6.4	Osmotic laxatives	1.93	1.43 - 2.59	<0.01
H12	Chronic pharyngitis and nasopharyngitis	1.93	1.10 - 3.41	0.02
7L1	Other miscellaneous operations	1.90	0.94 - 3.85	0.08
N11	Spondylosis and allied disorders	1.89	1.22 - 2.94	<0.01
J51	Diverticula of intestine	1.85	1.01 - 3.40	0.05
ZV6	[V]Other reasons for encounter	1.84	1.21 - 2.79	<0.01

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
4.7.4	Antimigraine drugs	1.81	1.02 - 3.21	0.04
8H7	Other referral	1.78	0.62 - 5.15	0.29
4.8.1	Control of the epilepsies	1.77	1.14 - 2.74	0.01
4.3.1	Tricyclic and related antidepressants	1.75	1.29 - 2.38	<0.01
F4F	Lacrimal system disorders	1.75	1.04 - 2.97	0.04
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.74	1.01 - 3.00	0.05
F34	Mononeuritis of upper limb and mononeuritis multiplex	1.74	0.92 - 3.30	0.09
H1y	Other specified diseases of upper respiratory tract	1.73	0.92 - 3.25	0.09
9N4	Failed encounter	1.72	1.30 - 2.28	<0.01
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.69	0.99 - 2.87	0.05
9N3	Indirect encounter	1.68	1.12 - 2.51	0.01
2.2.1	Thiazides and related diuretics	1.67	1.28 - 2.19	<0.01
D21	Other and unspecified anaemias	1.67	0.94 - 2.98	0.08
M07	Other local infections of skin and subcutaneous tissue	1.66	1.01 - 2.71	0.04
1.7.2	Compound haemorrhoidal preparations with corticosteroids	1.62	1.05 - 2.51	0.03
8.1.3	Antimetabolites	1.61	0.72 - 3.60	0.24
19F	Diarrhoea symptoms	1.59	0.93 - 2.70	0.09
M23	Diseases of nail	1.59	0.85 - 2.98	0.15
G83	Varicose veins of the legs	1.58	0.98 - 2.54	0.06
1.6.2	Stimulant laxatives	1.57	1.04 - 2.37	0.03
771	Colon operations and sigmoidoscopy of rectum	1.57	0.88 - 2.78	0.13
585	Other diagnostic ultrasound	1.56	0.98 - 2.49	0.06
8B3	Drug therapy	1.56	1.12 - 2.17	<0.01
J16	Disorders of stomach function	1.56	1.07 - 2.26	0.02
C36	Disorders of fluid, electrolyte and acid-base balance	1.55	0.86 - 2.78	0.15
G84	Haemorrhoids	1.55	0.92 - 2.60	0.10
9.6.4	Vitamin D	1.54	1.00 - 2.35	0.05
M15	Erythematous conditions	1.54	0.88 - 2.71	0.13
G80	Phlebitis and thrombophlebitis	1.53	0.82 - 2.84	0.18
65E	Influenza vaccination	1.52	1.05 - 2.20	0.03
9.1.1	Iron-deficiency anaemias	1.50	0.98 - 2.31	0.07
F59	Hearing loss	1.50	0.97 - 2.31	0.07
6.4.1	Female sex hormones and their modulators	1.49	0.84 - 2.67	0.17
J34	Diaphragmatic hernia	1.49	0.86 - 2.56	0.15

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
67E	Foreign travel advice	1.47	0.97 - 2.22	0.07
N22	Other disorders of the synovium, tendon and bursa	1.47	0.89 - 2.43	0.13
1B1	General nervous symptoms	1.46	0.78 - 2.74	0.24
13.10.2	Antifungal preparations	1.45	1.02 - 2.08	0.04
4.1.1	Hypnotics	1.45	0.92 - 2.31	0.11
7.4.1	Drugs for urinary retention	1.45	0.89 - 2.36	0.13
8B6	Prophylactic drug therapy	1.45	0.80 - 2.65	0.22
1C1	Hearing symptoms	1.44	0.60 - 3.44	0.42
461	Urine exam. - general	1.44	1.00 - 2.09	0.05
M22	Other dermatoses	1.44	0.94 - 2.22	0.09
2.2.4	Potassium-sparing diuretics with other diuretics	1.42	0.75 - 2.68	0.29
4.6.	Drugs used in nausea and vertigo	1.41	0.99 - 2.02	0.06
SK1	Other specified injury	1.41	0.94 - 2.12	0.10
2.6.2	Calcium-channel inhibitors	1.39	1.07 - 1.80	0.01
7E2	Ovary and broad ligament operations	1.39	0.59 - 3.30	0.45
H01	Acute sinusitis	1.39	0.88 - 2.20	0.16
M08	Cutaneous cellulitis	1.39	0.74 - 2.60	0.30
N13	Other cervical disorders	1.39	0.94 - 2.06	0.10
J52	Functional gastrointestinal tract disorders NEC	1.38	0.93 - 2.04	0.11
R08	[D]Urinary system symptoms	1.38	0.95 - 2.01	0.09
1.3.1	H2-receptor antagonists	1.37	0.91 - 2.06	0.13
525	Plain X-ray spine	1.37	0.70 - 2.69	0.35
527	Plain X-ray pelvis	1.36	0.38 - 4.89	0.63
N21	Peripheral enthesopathies and allied syndromes	1.36	0.96 - 1.93	0.09
F48	Visual disturbances	1.35	0.68 - 2.67	0.39
K15	Cystitis	1.35	0.70 - 2.62	0.37
K19	Other urethral and urinary tract disorders	1.34	0.97 - 1.84	0.08
R02	[D]Symptoms affecting skin and other integumentary tissue	1.34	1.02 - 1.76	0.04
ZV4	[V]Persons with a condition influencing their health status	0.72	0.43 - 1.22	0.22
M18	Pruritus and related conditions	0.69	0.38 - 1.25	0.22
2.8.2	Oral Anticoagulants	0.64	0.33 - 1.26	0.20
H17	Allergic rhinitis	0.62	0.25 - 1.58	0.32
M26	Sebaceous gland diseases	0.62	0.26 - 1.46	0.27
685	Cervical neoplasia screening	0.56	0.30 - 1.03	0.06
9OX	Influenza vacc.	0.56	0.22 - 1.43	0.23

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
	administratn.			
6C2	Primary prevention of cardiovascular disease	0.54	0.23 - 1.28	0.16
9.4.2	Enteral nutrition	0.51	0.23 - 1.14	0.10

Table 4-20: Results of the conditional logistic regression for factors with Odds-ratios <0.75 or >1.33 for hip arthroplasty: adjusted for OA

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
527	Plain X-ray pelvis	16.21	7.35 - 35.74	<0.01
52A	Plain X-ray hip/leg	13.43	7.99 - 22.56	<0.01
N09	Other and unspecified joint disorders	7.80	5.95 - 10.23	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	7.50	5.19 - 10.83	<0.01
4.7.2	Opioid analgesics	7.01	5.29 - 9.30	<0.01
9ND	Incoming mail processing	5.01	2.45 - 10.24	<0.01
7K6	Other joint operations	2.90	1.71 - 4.92	<0.01
12.2.3	Nasal Preparations for Infection	2.32	1.47 - 3.69	<0.01
9EG	Disabled driver badge report	2.28	1.24 - 4.21	<0.01
8H7	Other referral	2.14	0.81 - 5.65	0.13
8.1.3	Antimetabolites	2.09	0.86 - 5.11	0.11
9.1.1	Iron-deficiency anaemias	2.09	1.42 - 3.07	<0.01
9N1	Site of encounter	2.07	1.14 - 3.75	0.02
771	Colon operations and sigmoidoscopy of rectum	2.01	1.17 - 3.45	0.01
J52	Functional gastrointestinal tract disorders NEC	1.95	1.38 - 2.77	<0.01
8C1	Nursing care	1.92	1.08 - 3.41	0.03
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	1.91	0.93 - 3.91	0.08
C36	Disorders of fluid, electrolyte and acid-base balance	1.90	1.10 - 3.29	0.02
4.1.1	Hypnotics	1.85	1.21 - 2.81	<0.01
H1y	Other specified diseases of upper respiratory tract	1.82	1.03 - 3.21	0.04
9.6.4	Vitamin D	1.81	1.25 - 2.62	<0.01
PC0	Anomalies of ovaries	1.81	0.96 - 3.39	0.07
1M1	Pain in lower limb	1.79	0.92 - 3.47	0.08
D21	Other and unspecified anaemias	1.75	1.06 - 2.89	0.03
10.3.2	Rubefacients and other topical antirheumatics	1.72	1.33 - 2.22	<0.01
N33	Other bone and cartilage disorders	1.72	1.09 - 2.71	0.02

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
1.6.4	Osmotic laxatives	1.71	1.30 - 2.27	<0.01
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.71	1.09 - 2.69	0.02
A53	Measles	1.71	1.03 - 2.85	0.04
5.4.1	Antimalarials	1.70	1.18 - 2.46	<0.01
5.1.13	Urinary tract infections	1.63	0.98 - 2.72	0.06
N11	Spondylosis and allied disorders	1.63	1.09 - 2.45	0.02
10.1.2	Corticosteroids	1.62	0.70 - 3.78	0.26
ZV5	[V]Specified procedures and aftercare	1.62	0.76 - 3.45	0.21
7L1	Other miscellaneous operations	1.59	0.75 - 3.37	0.23
1.6.1	Bulk forming laxatives	1.58	1.10 - 2.26	0.01
G80	Phlebitis and thrombophlebitis	1.58	0.88 - 2.84	0.13
G84	Haemorrhoids	1.57	0.96 - 2.58	0.07
4.3.1	Tricyclic and related antidepressants	1.55	1.15 - 2.07	<0.01
1.6.2	Stimulant laxatives	1.54	1.06 - 2.22	0.02
J57	Other disorders of intestine	1.51	0.95 - 2.41	0.08
M2y	Other specified diseases of skin or subcutaneous tissue	1.51	0.86 - 2.65	0.15
9OX	Influenza vacc. administratn.	1.50	0.81 - 2.77	0.19
R14	[D]Nonspecific abnormal function studies	1.49	0.92 - 2.40	0.10
1.4.2	Antimotility drugs	1.48	0.95 - 2.31	0.08
2.3.2	Drugs for arrhythmias	1.48	0.63 - 3.47	0.37
537	Soft tissue X-ray breast	1.48	0.67 - 3.25	0.33
F34	Mononeuritis of upper limb and mononeuritis multiplex	1.48	0.67 - 3.26	0.33
F4F	Lacrimal system disorders	1.48	0.91 - 2.41	0.12
ZV0	[V]Persons with potential health hazards related to communicable diseases	1.48	0.71 - 3.07	0.29
R09	[D]Other abdominal and pelvic symptoms	1.47	1.10 - 1.97	<0.01
7E2	Ovary and broad ligament operations	1.45	0.65 - 3.23	0.36
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	1.44	0.94 - 2.21	0.10
8B3	Drug therapy	1.42	1.04 - 1.94	0.03
2.2.1	Thiazides and related diuretics	1.41	1.10 - 1.82	<0.01
12.1.1	Otitis Externa	1.40	0.96 - 2.02	0.08
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.40	0.84 - 2.33	0.20
K51	Genital prolapse	1.40	0.72 - 2.73	0.32
F4K	Other eye disorders	1.39	0.76 - 2.55	0.28

Read-code/BNF subchapter	Read Term/ BNF Label	OR	95% CI	P-Value
M07	Other local infections of skin and subcutaneous tissue	1.39	0.87 - 2.23	0.17
1.3.6	Other Antisec Drugs+Mucosal Protectants	1.38	1.09 - 1.74	<0.01
41D	Sample obtained	1.36	0.71 - 2.58	0.35
N14	Other and unspecified back disorders	1.35	1.05 - 1.74	0.02
3.4.1	Antihistamines	1.34	1.01 - 1.78	0.05
1.3.1	H2-receptor antagonists	0.74	0.47 - 1.16	0.19
4.7.4	Antimigraine drugs	0.74	0.35 - 1.55	0.42
12.2.1	Drugs used in Nasal Allergy	0.73	0.52 - 1.03	0.07
19F	Diarrhoea symptoms	0.73	0.39 - 1.36	0.32
J34	Diaphragmatic hernia	0.72	0.38 - 1.38	0.33
M03	Other cellulitis and abscess	0.72	0.38 - 1.38	0.33
H05	Other acute upper respiratory infections	0.69	0.46 - 1.02	0.06
9.4.2	Enteral nutrition	0.66	0.34 - 1.28	0.22
1B8	Eye symptoms	0.65	0.32 - 1.32	0.23
730	External ear and external auditory canal operations	0.65	0.35 - 1.20	0.17
H12	Chronic pharyngitis and nasopharyngitis	0.63	0.32 - 1.23	0.17
3.1.2	Antimuscarinic bronchodilators	0.62	0.35 - 1.10	0.10
6.1.2	Anti-Diabetic drugs	0.62	0.39 - 0.98	0.04
10.1.4	Gout and cytotoxic induced hyperuricaemia	0.59	0.26 - 1.31	0.19
6C2	Primary prevention of cardiovascular disease	0.58	0.24 - 1.40	0.22
68A	Neurolog./special sense screen	0.56	0.26 - 1.18	0.13
F59	Hearing loss	0.56	0.33 - 0.92	0.02
C34	Gout	0.55	0.25 - 1.23	0.15

In addition to the adjusted analysis, the data was also stratified by gender. The results of this can be seen in table 9-5 and table 9-6 of appendix 3.

4.5 Discussion

4.5.1 Overview

Within this chapter, all the risk factors identified from the literature review that were seen as feasibly obtainable within the cases were also seen as obtainable within the controls. In addition to these risk factors, an additional 123 three character length Read-codes and 69 BNF subchapters were identified within the study. 92 factors were associated with the requirement for a knee arthroplasty and 79 factors were associated with the requirement for a hip arthroplasty. When analysis was adjusted for OA, 106 risk factors for the knee and 83 risk factors for the hip were associated with the requirement for a joint arthroplasty which included different comorbidities, lifestyle and body composition factors identified by both the systematic review and the search for additional Read-codes/BNF subchapters. Factors that were found to be associated highly with both a knee and a hip arthroplasty were x-rays of the specific joints (with plain x-ray of the hip or leg being highly associated) and opioid analgesics. Both of these factors remained highly associated when adjusting for OA.

4.5.2 Study strengths and weaknesses

The study contains a number of strengths which helped to improve the way in which the data was collected and analysed. The use of the matched case control design allowed comparison between separate at risk groups to be made. The controls were at risk of a joint arthroplasty for a similar amount of time as the cases they were matched to since, like the cases, the controls had to have 5 years' worth of prior consultation history before the case's arthroplasty coding. By matching to the date of a joint arthroplasty allowed individuals to be considered as cases later in the study even if they were controls for a prior case. This was representative of the fact that the patients were still at risk of requiring a possible joint arthroplasty throughout their time in the healthcare

databases. The matched design also allowed for the reduction of possible selection bias that may have occurred since they were all chosen from the same population of subjects. The study removed the risk of recall bias since the electronic health care record is updated for each consultation that occurs.

The case control study had been used to not only assess the availability of the factors obtained from the systematic review but also allowed for the identification of additional potential risk factors. This approach was used to assess first what factors were commonly recorded within either the cases or controls and then to determine their relationship with the requirement for a joint arthroplasty. The identification of further potential risk factors allowed different relationships with arthroplasty to be identified which would otherwise have been missed if only the factors obtained from the systematic review had been used. Some of these factors were specific comorbidities (e.g. gout) whilst others signalled management or investigations before deciding to advise a joint arthroplasty (e.g. x-ray of the lower limb).

The conditional logistic regression took into account the two separate joints of interest within the study and therefore the analysis was split between those cases that had a knee arthroplasty and those that had a hip arthroplasty. Analysing the joints separately allowed the effect of specific risk factors to be compared between the separate joints.

Although the study did have its strengths, there were also certain weaknesses to the study. One of the problems came from the matching aspect of the study design. Although matching allowed the controls to have similar characteristics to the cases they were being matched to, it also prevented age and gender from being assessed to determine their association with a knee or hip arthroplasty. While stratification did provide insight as whether risk factors varied by gender, it would be of interest to see the direct affect age and gender have on the requirement for a joint arthroplasty within the health care records.

The purely statistical approach of the study also presented its own problems. This problem could be seen predominantly within the identification of the additional factors using the Read-codes and BNF subchapters with a prevalence of 3% or more in either the cases or controls. Although the approach allowed additional risk factors to be obtained, the approach did not take into consideration the clinical aspects of certain factors. Many factors did provide some insight with the process in which an arthroplasty is decided upon (e.g. use of x-rays) whereas other factors would be representative of the potential influence of comorbidity (e.g. Gout). However, potential risk factors were identified that would be difficult to interpret. Examples of this include code 7K6 (other joint operations) which could be an alternative approach to recording TKA/THA and N09 (other and unspecified joint disorders) which could be an indicator for OA. Both of these factors were seen as statistically significant within the study for both primary TKA and THA but neither were specific in detail as to what disorders were being investigated or what joints were being looked into. For more detail on these factors, 4^{th} or 5^{th} level codes would need to be looked at. A way to improve how the risk factors are interpreted would be to include a health care professional within the process to gain clinical significance for the different factors.

The use of the multiple imputation within the study can be considered as both a strength of the study as well as a weakness. As a strength, the imputation allowed all patients to have values for those risk factors which were expected to be identified in all patients. When the estimates for the values observed were compared to the distribution of the data that had been imputed, the imputed data was similar to that data. A weakness of the multiple imputation approach is the assumption that the data was missing at random. Missing at random assumes that the probability that the data was missing can be explained by the observed data. For example, with blood pressure, older individuals were more likely to have blood pressure recorded but recording does not depend on the blood pressure value. Certain data that was imputed was expected to be missing not at random as a record most likely depends on the actual value for example, GPs may be more likely to investigate BMI if the patient looked overweight). Although the estimates of the

logistic regression in the complete case were similar to those obtained by the use of the multiple imputation, it would be of importance to use caution with the imputed data.

The multiple testing issue was an additional limitation within the analysis during the hypothesis free approach. Although this approach allowed for many additional potential risk factors to be investigated, the large amount of tests being performed could risk false associations being identified. The false positive is also described as a type I error which corresponds to the incorrect rejection of null hypothesis which in this case is there being no association with either a knee or hip replacement. To try and combat this, instead of using p-values, a required range for the odds-ratio was used. Although this identified factors that had a larger association with the requirement for a joint arthroplasty, not all of their odds ratios were statistically significant. An option to handle multiple testing is by using the Bonferroni correction. This divides the p-value by the amount of tests being performed and uses that as the new significance level. However, within this study, nearly 200 tests were performed meaning a p-value of 0.00025 would be needed to be statistically significant which only a small amount of factors would obtain. In this situation it would still be expected that at least 10 by chance would be significantly associated that shows that even if steps are taken to try and compensate for possible false positives they can still occur. Within the analysis however, roughly 50 were significant for the knee and hip suggesting that some of the variables have potential in a possible risk prediction model.

All of the odds-ratios obtained were unadjusted. For future analysis, these factors can be used within an adjusted multivariable model to determine how independent associations of factors affect the risk arthroplasty.

4.5.3 Comparison to previous literature

A number of the factors identified within the case-control study that had been seen within previous literature as having an association with the requirement of joint arthroplasty were supported within this study. Wang and colleagues (Wang et al. 2009) supported the association

for BMI with the requirement for a knee arthroplasty (odds ratio 1.88 (1.76, 2.00)). Unlike other studies however, within the knee the case-control study did not identify differences in assocation of BMI with arthroplasty when stratified by gender. Manninen and colleagues (Manninen et al. 2001) identified an association within the female but not within males (odds-ratios of 1.11 (1.06, 1.18) and 1.09 (0.98, 1.21) respectively). Although the effect sizes were similar within our study (1.09 and 1.06 respectively), BMI for males and females were associated with the requirement for a knee arthroplasty in the case-control study.

Unlike previous literature, the BMI and weight change over time were not seen as being associated with the requirement for a joint arthroplasty of either the knee or hip. Nicholls at el. (Nicholls et al. 2012) saw a positive association with the requirement for a joint arthroplasty (odds-ratio 1.09 (1.00, 1.12)). Within the case-control study, BMI change over time was not seen as statistically significant within either the knee or the hip (1.01 (0.95, 1.05) and 0.99 (0.97, 1.02) respectively). Within the Nicholls study where the association was seen as significant, a set time period of 5 year difference had been determined whereas the BMI change over time in the case-control study was calculated using the values furthest and closest to the index date meaning the time difference would vary between patients. If a set time difference had been used within CiPCA then a similar result may have been identified.

The prior use of NSAIDs was associated with the requirement for a joint arthroplasty of both the knee and hip. This supports the results that were seen within the study by Gossec at el. (Gossec et al. 2005). They obtained a positive association with the requirement for a hip arthroplasty in the presence of osteoarthritis (logistic regression p-value=0.003). Within the case-control study, prior use of NSAIDs when adjusted for OA saw a strong relationship with the requirement for a hip arthroplasty (odds-ratio 14.24 (6.28, 32.3). However this would be part of the management process.

4.5.4 Implications

All of the factors that were seen as statistically significant with the requirement for a joint arthroplasty provided useful insights. The case-control study supports most of the findings seen in the systematic review with the direction of associations for the requirement for a joint arthroplasty. The search for additional risk factors using three character length Read-codes and BNF subchapters for prescriptions allowed additional associations that would have otherwise been missed to be investigated.

Before any of the factors from the Read-code and BNF subchapter search are included in any further analysis, it would be of use to consult a clinician to determine which factors can be seen to have clinical significance. Although many factors were obtained, not all factors will be of clinical importance whilst others can be difficult to interpret. There will also be factors that can be combined therefore reducing the amount of factors (e.g. C34 – Gout and 10.1.4 - Gout and cytotoxic induced hyperuricaemia). By gaining the clinical insight, the risk factors would be more interpretable within any future models.

The factors could then be used to assess the risk of a patient with OA requiring future knee or hip arthroplasty using a risk prediction model within the electronic healthcare records. By combining the factors into one model, the number of factors seen as significant would reduce whilst providing a possible model that could be used by GPs to assess the risk of a patient entering a practice with OA requiring a joint arthroplasty in the future. They could then provide possible measures which would reduce the risk of a arthroplasty in the future (e.g. a weight loss program) or if the risk is great, recommend them for a joint arthroplasty.

5 Discussion

5.1 Overview of the thesis

The overall aim of the thesis was to identify a set of risk factors associated with the requirement for either a total knee arthroplasty or total hip arthroplasty within routinely collected primary care consultation data. To achieve this, a systematic review was first performed to identify from previous literature a set of risk factors that were associated with the need for a total knee or hip arthroplasty within patients with a previous diagnosis of osteoarthritis. After this, a feasibility study was performed to determine which of these factors could be obtained from the electronic healthcare database. This was done by identifying previous studies that had used electronic healthcare records in order to obtain Read-code or prescription lists for these factors and obtain a prevalence of recording for each risk factor. A case-control study was then performed to assess the strength of the association with knee/hip arthroplasty of the identified factors and to obtain additional factors associated with the requirement for a knee/hip arthroplasty.

A set of 42 possible factors were first identified from within the systematic review as being either associated with the requirement for either a knee or hip arthroplasty or had inconclusive evidence in regards to an association. Out of these factors, a total of 13 factors had a Read-code list or prescription list that was obtainable from previously published literature that had used electronic health care records (such as CiPCA). Out of these 13, 12 factors (13 after splitting blood pressure) had the required prevalence of recording once a free-text search had been performed within patients who had had a knee or hip arthroplasty recorded. These factors were also seen as feasible to obtain within the controls that had no arthroplasty recorded. 123 further factors based on third level Read-codes and 69 prescription groups had a prevalence above 3% and so were analysed further using conditional logistic regression to assess their association with arthroplasty. 92 risk factors were associated with the requirement for a knee arthroplasty and 79

risk factors were associated with the requirement for a hip arthroplasty in the case-control study. When restricted to patients with diagnosed OA, 106 risk factors for the knee and 83 risk factors for the hip were associated with the requirement for a joint arthroplasty which included different comorbidities, lifestyle and body composition factors identified by both the systematic review and by the search for additional Read-codes/BNF subchapters.

5.2 Interpretation

Many of the factors that were seen as having an association with arthroplasty identified within the systematic review also had an association identified within the case-control analysis. However, specific factors such as blood pressure and smoking status were not seen as having an association even though the systematic review finding suggested these factors had an association.

Higher BMI was identified as being associated with the requirement for both a knee and hip arthroplasty, supporting the results obtained from the systematic review. However, once BMI had been categorised only the obese category was seen as associated with the requirement for a joint arthroplasty. BMI change over time was also not associated with the requirement for a joint arthroplasty. This factor was calculated using the difference in the values of BMI closest to the surgery and the BMI furthest from the surgery. Studies within the systematic review used the difference in BMI between the end of the study and 5 years prior.

With smoking status, there was no consistent association found in the analyses between this factor and the risk of a TKA/THA. This was not an unexpected finding given that the evidence from the systemic review was inconclusive for both types of joint arthroplasty.

Many additional factors were identified from the search of the Read-codes and BNF subchapters. For some of these observed associations an argument for their relationship with TKA/THA can be made relatively easily. The factors that appeared to have the higher associations were x-ray factors of the specific joint. Although it is not used in all cases of arthroplasty, the x-ray of the

affected joint allows the clinician to see the current condition of the joint (e.g. severity of structural changes). Other obtained factors that were seen with an association may be related to other factors. An example of this is the Read-code 9EG (disable driver badge report) which had an association with both knee and hip arthroplasty. It does not specify the specific disability that has caused the need for the driver badge but provides possible relationships to other conditions (e.g. osteoarthritis). The change in the risk and prognostic factors that were seen as being associated with the requirement for a knee or hip arthroplasty when the analysis was restricted to cases that had osteoarthritis was expected. Many of the factors more strongly associated with joint arthroplasty were still present but those that were only just significant either gained a stronger association or were no longer consider as statistically significant. The prior use of NSAIDs was one of the factors whose association increased. This factor make clinical sense since patients will be offered pharmacological treatments before any surgery is offered. Certain factors that had an association with arthroplasty would not be of clinical significance and could have been identified by chance. An example of this is hearing loss. This was statistically significant but from a clinical standpoint, it would not make sense that this affects the risk of requiring a knee or hip arthroplasty.

5.3 Strengths and weaknesses of the thesis

The reasons for seeking to explore the routine primary care EHR as the sole source of information on risk factors for primary total hip and knee arthroplasty were laid out in Chapter 1. A finding of the thesis was that most of the risk factors for primary TKR/THR investigated in previously published studies are not easily obtainable from the primary care EHR. Given this starting point, critical consideration of the strengths and weaknesses of this thesis focus on the design, conduct, and interpretation of the studies and analyses undertaken.

All analyses in this thesis were undertaken in the Consultations in Primary Care Archive (CiPCA) database. This had the major advantage of being available at no cost. However, compared with

other UK primary care databases (e.g. CPRD, THIN) CiPCA is relatively small (approximately 100,000 annual registered population) and recent (data was available from 2000 onwards). Both CPRD and THIN contained more data in terms of population size (e.g. CPRD covered over 11.3 million patients in the UK) which would have allowed the possibility for more cases of TKA or THA to be identified and since the time interval available would be larger (e.g. CPRD has anonymised general practice records since 1987) changes in specific factors could be obtained. Comparison between different areas in the UK could also be investigated which CiPCA was unable to do. However, these databases would have had the same fundamental problems in terms of the identification of the risk factors from the systematic review in that not all would be recorded. It would be likely that the same factors identified in CiPCA would be the only ones obtained within these larger databases. These databases would also still suffer from missing data like CiPCA meaning that although national comparisons could be made, the results obtained will be subject to these similar problems.

The use of the electronic healthcare database in general provided certain advantages. One of the main advantages of the electronic records was the amount of information that was available for the study. The Read-codes were useful in that they allowed the individual factors to be identified within the population and simplified finding suitable cases for the study along with the controls. Along with the Read-code, additional information was available within the free text. This free text provided a lot of information as many factors where an actual value was recorded (e.g. BMI) had the value recorded within the free text. However, the ability to routinely use this information in future in an EHR-based prediction model may still be limited.

The electronic healthcare database also allowed for additional factors to be investigated during the thesis. These additional factors could be electronically searched within the database to obtain their relative frequency as well as determine which were associated with the requirement for a

joint arthroplasty. It would be of importance to obtain clinical input into which factors have clinical significance.

A problem with the electronic health records however would be the possibility of the factors being miscoded. This miscoding can result in a patient being diagnosed with something different compared to what they actually had at that time of the consultation. If this miscoding was consistent over the cases and the controls then the issue would not affect the results greatly compared to if miscoding was present more within one group (e.g. cases). The nature of the miscoding was unknown so it was unknown whether miscoding did affect any of the results within the study.

A potential additional disadvantage of the health records would be the presence of potential treatment bias. Treatment bias or confounding by indication are sometimes concerns within research studies relying on data from electronic health records. These, however, are concerns when seeking to infer causality from observed associations between exposures and outcome. In this study, we were interested only in their predictive value.

A problem with the matching process would provide an issue within the thesis. Although the matching reduced the possibility of selection bias from occurring, it also meant that certain factors could no longer be directly investigated to determine their association with a joint arthroplasty. These factors were age and gender. Both of these factors were seen as significantly associated within the requirement for a knee or hip arthroplasty within the systematic review. However, since these factors (along with practice and consultation in the same annual year) had been used as matching factors, these could no longer be used within any logistic regression analysis to determine their associations in CiPCA. It was possible to stratify the analysis by the age and gender to determine an indirect effect that these factors had on the requirement for a joint arthroplasty but could not be investigated directly.

A possible further issue was the use of the 5 year period prior to surgery. For certain factors this allowed changes in the factors over the time to be calculated that were seen as having a possible association within the systematic review (e.g. change in BMI over time). For factors that were recorded more commonly (e.g. BMI, blood pressure) the use of the five years was enough to identify a change for the patients. However, for other factors that occur less regularly within the population, the five year time period may not be enough, for example the previous history of fracture. Although the five years proved useful in identifying the most recent previous fractures, there was still the possibility that, had the option been there to look further back, more fractures may have been identified within the patients. This would be a similar case with previous injury (which was not investigated). Had a larger time period been available then a previous injury from further back that was associated with the requirement for a joint arthroplasty may have been identified. However, using a longer time before the surgery to identify risk factors would reduce the time period available to obtain cases, thus reducing the number of cases. There would also be the possibility that fewer patients had the required time within the database to be included within the study which would have also reduced the population size.

A further issue that occurred within the analysis was the presence of missing data. This data could have been missing due to multiple reasons. In certain situations, the presence of missing data would represent the patient of interest not having that specific factor (e.g. previous fracture, prior use of NSAIDs). These sort of missing factors were easily overcome by using the assumption that the data was missing meant that the patient did not have that particular condition/factor. However, within other factors it was expected that a value for the factor should be available for all patients (e.g. BMI value, smoking status). The effect of the missing data is that it reduces the statistical power of the overall study meaning that the probability that the test performed correctly rejects the null hypothesis (in this case, not associated with knee/hip arthroplasty) will be reduced. The effect of possible power loss was addressed by using multiple imputation. This approach works for data that is expected to be missing at random (e.g. blood pressure) but there

will be other factors within the dataset where the data will be missing not at random meaning the data is missing because it still depends on the unseen values. An example of this would be BMI, as it was expected the GPs would measure BMI in those patients that are seen as overweight or at risk of other conditions relating to high BMI (e.g. diabetes). This data would not be missing at random so even though multiple imputation was performed, it would be worth being cautious with the results that were obtained.

A final problem that may occur will be the validity of the outcome definition. Within the study, the outcome was defined as the first occurrence of a knee or hip arthroplasty within CiPCA with 5 years prior history within the database. The arthroplasties were identified by using the Read-code list devised by Culliford and colleagues. It is possible there were further arthroplasties of the knee or hip that were not identified by these codes. There may be codes for arthroplasties which were missing from the list or, more likely, the arthroplasty had been recorded within a less obvious code (e.g. 7K6 - Other joint operations). An additional problem is that the arthroplasty that was identified may not be the first instance of a knee/hip arthroplasty for that individual. There exists the possibility that although the arthroplasty that occurred for the case was the first within the 5 year time period, the patients may have had an arthroplasty further back which was not identified in this study. This prior surgery could affect the requirement for surgery as it would be more likely someone who has had a surgery on a particular joint may require a revision surgery on the same joint. However, as explained before, increasing the time frame would reduce the number of incidence cases identified due to the reduced time period in which they can be obtained. The third issue that can occur from the definition of the outcome was the source of the outcome. The arthroplasty would not take place in a primary care setting and the GP would only add the record of a joint arthroplasty taking place if the practice had received notes from the secondary care or there was a related consultation either prior to or after the surgery. This also means that the date obtained from the joint arthroplasty may not be completely accurate. However, this inaccuracy

with the date may only be within a short time frame meaning that this dating issue should not have affected the results obtained.

5.4 Implications of the results

5.4.1 Implication on further research in this field

The thesis provides a number of potential risk factors that can be used as "building blocks" for a possible future multivariable risk prediction model. There are many possible routes that can be used to develop this model.

The first would be to assess the associations of the identified factors within a second database. Although the factors were seen as significant in CiPCA, this does not mean that within a different population the results would be the same. If the aim was to create a risk prediction within the electronic health care records, then it would be important to assess the factors within other electronic health care databases also. Alternative EHR databases exist that can be used which include the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN) database. Both of these databases contain consultation data from a larger population compared to CiPCA as the CPRD covers 674 practices in the UK covering over 11.3 million patients (Herrett et al. 2015) and THIN contain data collected from 562 general practices within the UK. Both of these databases are on a UK wide scale compared to the localised CiPCA area.

The second approach would be to develop the model within CiPCA itself. Within the risk model, the risk of requiring a knee or hip arthroplasty in a set time frame (say 5 years) will be of interest. Two models can be created to assess the risk of a knee arthroplasty or a hip arthroplasty separately since there were factor identified within the thesis that were associated with a joint arthroplasty in the knee but not the hip (e.g. R01 – Nervous and musculoskeletal symptoms) and vice-versa (e.g. C34 - Gout). Within the thesis, individual, unadjusted associations were identified within the dataset. By using the multivariable risk models, not all of the factors would be

associated with the requirement for a joint arthroplasty. In the creation of a risk prediction model it would be worth considering both the statistical significance of the particular risk factor, along with the clinical significance. There may be factors of clinical interest that are not of statistical importance but should be included within a model. Therefore, clinical advice should be used in conjunction with statistical methods to keep factors which clinicians see as important whilst also retaining the statistical power of the model. An example of a factor that could be excluded, even though it was seen as statically significant is hearing loss (F59). This appears unlikely to be truly associated with either knee or hip arthroplasty so it would be highly unlikely that this factor would be seen as clinically significant.

Regardless of how the model is developed, it would be of importance to externally validate the model within a separate electronic healthcare database. This will be used to determine how good the model actually is. With external validation, it will be of importance not to create a separate model within the new database using the existing factors but to assess the current model (Collins et al. 2015). If the model has been constructed correctly then it should be able to calculate the risk accurately outside of the population it was created within. These steps will show the model can be used on a larger scale. Both CPRD and THIN can be used to assess the validity of the model along with other electronic healthcare records databases.

5.4.2 Implication for clinicians

This thesis describes developmental work useful to underpin future multivariable prediction model for primary hip and knee arthroplasty. As such, the findings are unlikely to have immediate clinical applications. However, there are risk factors the clinician can use to idenfy patient at risk of arthroplasty. Certain factors identified within the thesis were potentially modifiable factors (e.g. BMI). To the extent that these are causal, steps can be taken to modify the value of the factor which may affect the future risk of joint arthroplasty. The clinician could take steps with reducing the patients risk by providing treatments that would help with a specific condition or

provide advice which the patients can use themselves. Within the BMI case, if the patient has a higher BMI value then weight loss programs can be suggested by the GP. Of the factors that could not be changed by this sort of advice (e.g. the Charlson Index scores) the GP can monitor the patients more closely.

Finally, it should be acknowledged that even well-performing multivariable prediction models may not be superior to clinical judgement (Sanders, Doust & Glasziou 2015) or may not be taken up and used routinely in practice (Wyatt, Altman 1995).

5.5 Conclusion

Overall, the thesis was able to complete its main aim of identifying a set of risk factors associated with the requirement for a knee or hip arthroplasty using electronic health care records. These include risk factors identified from previous studies and a set of additional potential risk factors with no prior evidence. Additional evidence would need to be obtained to assess the true strength of association of these factors with knee and hip arthroplasty from both a statistical and clinical standpoint. The set of risk factors can then be used within future studies to derive a risk prediction model to assess the risk of patients presenting with OA needing a knee/hip arthroplasty in the future.

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7 Appendix 1: Systematic review additional tables and figures

Table 7-1: Search Strategy used for searching Medline using the OVIDsp search engine

Order	Search Term Used	Order	Search Term Used
1	Exp Osteoarthritis	27	course.mp.
2	Osteoarthritis .ti,ab.	28	long-term.mp.
3	OA .ti,ab.	29	progress*.mp.
4	Arthrosis.mp	30	modif*.mp.
5	(degenerative adj (arthritis or joint or joints)) .ti,ab.	31	preval*.mp.
6	or/ 1-5	32	inciden*.mp.
7	(knee adj3 (pain or painful)) .ti,ab.	33	epidemiol*.mp.
8	(hip adj3 (pain or painful)) .ti,ab.	34	epidemiology.fs.
9	(joint* adj3 (pain or painful)) .ti,ab.	35	etiology.fs.
10	or/ 7-9	36	or/ 19-35
11	6 AND 10	37	exp EPIDEMIOLOGIC STUDIES/
12	Exp Arthroplasty	38	cohort*.mp.
13	Total knee replace* .ti,ab.	39	follow-up.mp.
14	Total hip replace* .ti,ab.	40	("case control" or "case controlled").mp.
15	TKR .ti,ab.	41	retrospective*.mp.
16	THR .ti,ab.	42	prospective*.mp.
17	Replace* .ti,ab.	43	((patient* or medical) adj3 (record* or review* or histor*)).mp.
18	or/ 12-17	44	longitudinal*.mp.
19	exp EPIDEMIOLOGY/	45	inception.mp.
20	exp PROGNOSIS/	46	observation*.mp.
21	exp DISEASE PROGRESSION/	47	time series.mp.
22	predict*.mp.	48	Prognos* .ti,ab.
23	factor*.mp.	49	or/ 37-48
24	risk*.mp.	50	36 and 49
25	model*.mp.	51	11 AND 18 AND 50
26	indicator*.mp.		

Table 7-2: Example of the data extraction form used for studies used within the systematic review

General Information	
Study Number:	
Article Title:	
Lead Author:	
Journal of Publication (Date):	
Country:	
Population	
Original Sample (yes/no):	
If no an original sample, what sample was used?	
Sample Size:	
Age (mean, standard deviation):	
Inclusion Criteria:	
Exclusion Criteria:	
Study Characteristics	
Study design:	
Study Setting:	
Aims/objectives:	
Recruitment Procedure:	

Outcome Measured:	
Length of follow-up (where applicable):	
Condition of interest	
Joint investigated:	
Definition of OA:	
Analysis	
Prognostic factors investigated:	
Factors for the knee (effect sizes):	
Factors for the hip (effect sizes):	
Type of analysis performed:	
Prognostic model identified (where applicable):	
Additional Information	

Table 7-3: Full list of factors obtained for the systematic review for the knee which could possibly be associated with total knee arthroplasty

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
Socio-demographic	Age*	Cicuttini at el. (2004)	High	Logistic	Odd-Ratio	1	0.9 (0.7, 1.3)	No Association	No Association
		Manninen at el. (2001)	High	Logistic	Odds-Ratio	2	men: 1.01 (0.43, 1.04) women: 1.07 (1.03, 1.10)	Men: No Association Women: Positive	
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.95 (0.94, 0.96)	Positive	
	Sex (F v M)*	Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	9.9 (1.5, 65.4)	Positive	Positive
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	1.27 (1.16, 1.39)	Positive	
Body Composition	BMI*	Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	0.9 (0.8, 1.1)	No Association	Positive
		Franklin at el. (2009)	High	Logistic	Odds-Ratio	4	Men BMI >30: 5.3 (2.8, 10.1) Women BMI >30: 4.0 (2.6, 6.1)	Positive	
		Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	30+: 2.47 (2.25, 2.71)	Positive	
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 4.6 (2.9, 7.1)	Positive	
		Manninen at el. (2001)	High	Logistic	Odds-Ratio	2	men: 1.09 (0.98, 1.21) women: 1.11 (1.06, 1.18)	Men: No Association Women: Positive	
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	5	35+: 3.72 (3.03, 4.57)	Positive	

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
		Wang at el. (2013)	Moderate	Cox PH	Hazard-Ratio	12	Men Middle Age BMI 30+: 1.02 (3.00, 5.39) Women Middle Age BMI 30+: 4.81 (3.94, 5.88)	Positive	
		Leung at el. (2015)	Moderate	Cox PH	Hazard-Ratio	13	17-18: 0.66 (0.34, 1.29) 23-24: 2.73 (1.97, 3.79)	Inconclusive	
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.88 (1.76, 2.00)	Positive	
	Weight*	Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	65-69: 1.51 (1.35, 1.69) 70-74: 1.92 (1.73, 2.14)	Positive	Positive
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd quartile: 3.0 (2.0, 4.4)	Positive	
		Wang at el. (2013)	Moderate	Cox PH	Hazard-Ratio	16	Men Middle Aged 73-80: 1.21 (0.86, 1.68) 80-87: 1.32 (0.93, 1.86) Women Middle Aged 60-66: 2.23 (1.66, 2.99) 66-75:3.30 (2.50, 4.35)	inconclusive	
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.58 (1.51, 1.65)	Positive	
	Height*	Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	165-169: 1.64 (1.50, 1.79)	Positive	Positive
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 1.5 (1.2, 2.0)	Positive	
	Waist/Hip Ratio*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 1.6 (1.2, 2.2)	Positive	Positive
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.43 (1.29, 1.58)	Positive	
	Body Fat*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 2.2 (1.6, 3.1)	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	2.84 (2.47, 3.26)	Positive	
	Waist Circumference*	Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.62 (1.53, 1.72)	Positive	Positive
		EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	4.5 (3.0-6.8)	Positive	
	Waist Size*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 3.6 (2.4, 5.5)	Positive	Positive
	Fat mass*	Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.88 (1.76, 2.00)	Positive	Positive
	BMI Change (over time)*	Nicholls at el. (2012)	Moderate	Logistic	Odds-Ratio	2	5 years' time: 1.086 (1.003, 1.175)	Positive	Positive
	Weight Change (over time)	Manninen at el. (2004)	Low	Logistic	Odds-Ratio	6	Overweight all the time: 2.37 (1.21, 4.62)	Positive	Positive
Lifestyle	Physical Activity (General)*	Ageberg at el. (2012)	High	Cox PH	Relative-Risk	3	Moderate-high: 1.36 (1.04, 1.77)	No Association	No Association
		Manninen at el. (2001)	High	Logistic	Odds-Ratio	8	Men Low Cumulative: 0.76 (0.29, 1.97) Women Low Cumulative: 0.55 (0.29, 1.03)	No Association	
		Wang at el. (2011)	High	Cox PH	Hazard-Ratio	13	Moderate : 1.13 (0.87, 1.46)	No Association	
	Smoking Status*	Leung at el.(2014)	High	Cox PH	Hazard-Ratio	21	Current Smoker: 0.49 (0.40, 0.60)	Negative	Negative
		Manninen at el. (2001)	High	Logistic	Odds-Ratio	4	Men ex or current: 0.84 (0.42, 1.68) Women ex or current: 0.59 (0.35, 0.99)	No Association	
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.59 (0.48, 0.73)	Negative	
	No of competitive skiing races*	Michaëlsson at el.	High	Cox PH	Hazard-	1	1.09 (1.02, 1.16)	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
		(2011)			Ratio				
	Time completed skiing races*	Michaëlsson at el. (2011)	High	Cox PH	Hazard-Ratio	1	1.10 (0.96, 1.26)	No Association	No Association
	Occupation*	Franklin at el. (2010)	High	Logistic	Odds-Ratio	14	Technicians and Clerks >Men: 2.0 (0.71, 5.7) Farmers >Men: 5.1 (2.1, 12.4)	Inconclusive	Inconclusive
	Seifa Score*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	1.00 (0.99, 1.00	Inconclusive	Inconclusive
	Physical work stress	Manninen at el. (2001)	High	Logistic	Odds-Ratio	6	Heavy: 0.61 (0.29, 1.27)	No Association	No Association
	Previous Knee Injury	Manninen at el. (2001)	High	Logistic	Odds-Ratio	4	Yes: 2.90 (1.48, 5.66)	Positive	Positive
	Meat Consumption*	Wang at el. (2011)	Moderate	Cox PH	Hazard-Ratio	4	Processed Meat: 1.00 (0.95, 1.05)	No Association	No Association
Biomarkers (imaging, biochemical)	Radiological Grade/Progression*	Bruyere at el. (2013)	High	Logistic	Odds-Ratio	2	new definition: 3.92 (1.44-10.67)	Positive	Inconclusive
		Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	1.8 (0.6, 6.1)	No Association	
	HFE Genotype group*	Wang at el. (2012)	High	Cox PH	Hazard-Ratio	9	Recessive 2 copies: 0.50 (0.16, 1.55)	No Association	No Association
	Tibial Bone Area	Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	1.2 (1.0, 1.4)	Positive	Positive
	Cartilage loss	Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	1.2 (1.1, 1.3)	Positive	Positive
	Trabecular bone texture	Podsiadlo at el. (2014)	Moderate	Logistic	Odds-Ratio	2	Medial Compartment >FDH T2: 0.28 (0.09, 0.83)	Negative	Negative
	Bone Marrow Lessions	Tanamas at el. (2010)	Moderate	Linear Regression	Odds-Ratio	3	Total tibiofemoral BMLs: 1.55 (1.04, 2.29)	Positive	Positive
	Subchondral bone abnormality	Tanamas at el. (2010)	Moderate	Logistic	Odds-Ratio	2	Laterial TF compartment: 0.95 (0.48, 1.88)	No Association	No Association
	C-Reactive Protein*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	2	(1-3 v <1mg/L): 1.4 (0.8-2.2)	No Association	No Association

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
Clinical	WOMAC (Pain score)	Cicuttini at el. (2004)	High	Logistic	Odds-Ratio	1	1.5 (1.1, 2.0)	Positive	Positive
	Carlson Index*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.70 (0.63, 0.77)	Negative	Negative
	SBP*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.99 (0.99, 0.99)	Inconclusive	Inconclusive
	Metabolic Syndrome*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	2.3 (1.5-3.5)	Positive	Positive
	High-density lipoprotein cholestrol *	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.0 (0.6-1.6)	No Association	No Association
	Hypertriglyceridemia*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.4 (0.9-2.2)	No Association	No Association
	Hypertension*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.7 (0.9-3.4)	No Association	No Association
	Hyperglycemia*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	2.3 (1.5-3.7)	Positive	Positive
Other	2D:4D index to finger ratio*	Hussain at el. (2014)	High	Cox PH	Hazard-Ratio	3	Left 2D:4D : 0.93 (0.86, 1.01)	No Association	No Association
		Sigurjonsdottir at el. (2010)	Low	Logistic	Odds-Ratio	1	1.65 (1.24, 2.2)	Positive	
*** - Factors identified for both the knee and the hip**									

Table 7-4: Full list of factors obtained for the systematic review for the hip which could possibly be associated with total hip arthroplasty

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
Socio-demographic	Age*	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.65 (1.06,	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
							2.56)		
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.97 (0.96, 0.98)	Negative	
		Rubak at el. (2013)	High	Logistic	Odds-Ratio	2	Women: 1.11 (1.11, 1.11) Men: 1.09 (1.09, 1.09)	Positive	
		Vinciguerra at el. (1995)	Low	Cox PH	Relative-Risk	1	3.15 (1.18, 4.48)	Positive	
		Karlson at el. (2003)	Low	Logistic	Odds-Ratio	5	65-69: 9.1 (5.9-14.0)	Positive	
		Gossec at el. (2005)	High	Logistic	P-Value	1	0.09	No Association	
	Sex (F v M)*	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.71 (1.11, 2.62)	Positive	Inconclusive
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	1.34 (1.21, 1.49)	Positive	
		Gossec at el. (2005)	High	Logistic	P-Value	1	0.53	No Association	
Body Composition	BMI*	Flugsrud at el. (2002)	High	Cox PH	Relative-Risk	8	Men 23.5-25.2: 1.3 (0.9, 1.9) 27.4 +: 2.0 (1.4, 2.9) Women 22.3-24.2: 1.3 (0.9, 1.8) 27.1+: 3.0 (2.1, 4.1)	Inconclusive	Positive
		Franklin at el. (2009)	High	Logistic	Odds-Ratio	4	Men BMI >30: 1.7 (1.0, 2.9) Women BMI >30: 1.0 (0.6, 1.5)	Inconclusive	
		Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	30+: 10.51	Positive	

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
							(9.52, 11.62)		
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 2.1 (1.6, 2.8)	Positive	
		Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	4	35+: 1.57 (1.17, 2.09)	Positive	
		Vinciguerra at el. (1995)	Low	Cox PH	Relative-Risk	1	2.26 (1.23, 3.99)	Positive	
		Cooper at el. (1998)	Low	Logistic	Odds-Ratio	3	24.6-27.9: 1.2 (0.9, 1.6) 28.0+: 1.7 (1.3, 2.4)	Inconclusive	
		Flugsrud at el. (2006)	High	Cox PH	Relative-Risk	20	Men 32.0+: 3.4 (2.9, 4.0) Women 32.0+: 2.3 (2.1, 2.4)	Positive	
		Karlson at el. (2003)	Low	Logistic	Odds_ratio	5	35+: 2.6 (1.9, 3.6)	Positive	
		Gossec at el. (2005)	High	Logistic	P-Value	1	0.55	No Association	
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.26 (1.15, 1.38)	Positive	
	Weight*	Flugsrud at el. (2002)	High	Cox PH	Relative-Risk	8	Men 85.1+: 2.1 (1.4, 3.2) Women 72.1+:3.4 (2.4, 4.9)	Positive	Positive
		Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	70-74: 4.27 (3.63, 5.02)	Positive	
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 2.1 (1.6, 2.8)	Positive	
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.22 (1.15, 1.30)	Positive	

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
	Height*	Liu at el.(2007)	Moderate	Cox PH	Relative-Risk	5	55-159: 1.04 (0.91, 1.19) 170+: 1.55 (1.32, 1.80)	Inconclusive	Positive
		Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 1.8 (1.4, 2.4)	Positive	
		Flugsrud at el. (2006)	High	Cox PH	Relative-Risk	10	Men 181+: 1.3 (1.2, 1.4) Women 168+: 1.9 (1.9, 2.0)	Positive	
	Waist/Hip ratio*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 1.1 (0.9, 1.4)	No Association	No Association
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.01 (0.85, 1.19)	No Association	
	Body Fat*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Qurtile: 1.3 (1.0, 1.7)	Positive	Positive
		Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.37 (1.19, 1.57)	Positive	
	Waist Circumference*	Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.10 (1.01, 1.38)	Positive	Positive
		EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.8 (1.2-2.7)	Positive	
	Fat Mass*	Wang at el. (2009)	High	Cox PH	Hazard-Ratio	1	1.29 (1.18, 1.41)	Positive	Positive
	Waist Size*	Lohmander at el. (2009).	Moderate	Cox PH	Relative-Risk	4	3rd Quartile: 1.9 (1.4, 2.6)	Positive	Positive
	BMI Change (over time)*	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	14	Men change 10-42: 2.16 (1.25, 3.70) Women Change 10-42: 2.46 (1.47, 4.13)	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
Lifestyle	Occupation*	Franklin at el. (2010)	High	Logistic	Odds-Ratio	14	Technicians and Clerks >Men: 1.6 (0.85, 3.0) Farmers >Men: 3.6 (2.1, 6.2)	Inconclusive	Inconclusive
		Rubak at el. (2013)	High	Logistic	Odds-Ratio	10	Men top managers (upper level): 0.63 (0.58, 0.68) Women Employees (intermediate level): 0.91 (0.82, 1.02)	Inconclusive	
	Smoking Status*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.72 (0.58, 0.90)	Negative	No Association
		Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	8	Men Pack years 20-40: 0.84 (0.64, 1.09) Women Pack years 20-40: 0.92 (0.70, 1.21)	No Association	
		Cooper at el. (1998)	Low	Logistic	Odds-Ratio	3	Previous: 0.9 (0.7, 1.2) Current: 0.8 (0.5, 1.3)	No Association	
		Karlson at el. (2003)	Low	Logistic	Odds-Ratio	5	Current (per day) 0-14: 0.9 (0.6, 1.5)	No Association	

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
							15-24: 0.8 (0.5, 1.3)		
	Physical Activity (General)*	Ageberg at el. (2012)	High	Cox PH	Relative-Risk	3	moderate-high: 0.91 (0.72 ,1.16)	No Association	No Association
		Wang at el. (2011)	High	Cox PH	Hazard-Ratio	13	Moderate (3-4): 0.89 (0.67, 1.16)	No Association	
		Karlson at el. (2003)	Low	Logistic	Odds-Ratio	5	Hours per week 4-6.9: 0.9 (0.7, 1.3)	No Association	
	Physical Activity (at leisure)	Flugsrud at el. (2002)	High	Cox PH	Relative-Risk	8	Men Intermediate: 0.9 (0.7, 1.4) Women Intermediate: 0.9 (0.6, 1.2)	No Association	No Association
	Physical Activity (at work)	Flugsrud at el. (2002)	High	Cox PH	Relative-Risk	8	Men Intermediate: 1.7 (1.1, 2.4) Women Intermediate: 1.4 (0.9, 2.0)	Inconclusive	Inconclusive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
	Physical Workload	Rubak at el. (2013)	High	Logistic	Odds-Ratio	2	Women Worked in industry 5-point year increments: 1.00 (0.99, 1.01) Men Worked in industry 5-point year increments:1.02 (1.02, 1.03)	No Association	No Association
	Occupational mechanical exposures	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	18	Men ton years 10-20: 0.89 (0.67, 1.17) Women ton years 10-20: 0.81 (0.61, 1.09)	No Association	No Association
	Seifa Score*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	1.00 (0.99, 1.00)	Inconclusive	Inconclusive
	Endurance Sport	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	2	Men: 1.14 (0.93, 1.40) Women: 1.25 (1.01, 1.54)	No Association	No Association
	Contact Sport	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	2	Men: 1.46 (1.20, 1.77) Women: 1.19 (0.94, 1.52)	Inconclusive	Inconclusive
	No of competitive skiing races*	Michaëlsson at el. (2011)	High	Cox PH	Hazard-Ratio	1	1.08 (1.03, 1.14)	Positive	Positive
	Time completed skiing races*	Michaëlsson at el. (2011)	High	Cox PH	Hazard-Ratio	1	1.10 (0.96, 1.26)	No Association	No Association

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
	Alcohol Consumption	Cooper at el. (1998)	Low	Logistic	Odds-Ratio	1	1.1 (0.9, 1.5)	No Association	No Association
		Karlson at el. (2003)	Low	Logistic	Odds-Ratio	5	G/D 10-14: 1.4 (0.9, 2.4)	No Association	
	Meat Consumption*	Wang at el. (2011)	Moderate	Cox PH	Hazard-Ratio	5	Processed Meat: 0.96 (0.91, 1.02)	No Association	No Association
Biomarkers (imaging, biochemical)	HFE genotype group*	Wang at el. (2012)	High	Cox PH	Hazard-Ratio	9	Codominant 1 Copy: 1.06 (0.87, 1.29)	No Association	No Association
	Radiological Grade/Progression*	Vinciguerra at el. (1995)	Low	Cox PH	Relative-Risk	1	2.97 (1.66, 5.32)	Positive	Positive
		Gossec at el. (2005)	High	Logistic	P-Value	1	<0.0001	Association†	
	K-L	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.89 (1.21, 2.96)	Positive	Positive
	Heberden nodes	Cooper at el. (1998)	Low	Logistic	Odds-Ratio	3	Possible: 1.3 (0.9, 1.8)	No Association	No Association
	Lequesne index	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	2.59 (1.73, 3.88)	Positive	Positive
	C-Reactive Protein*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	2	1-3 v <1mg/L: 1.4 (0.9-2.2)	No Association	No Association
Clinical	Carlson Index*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.79 (0.71, 0.88)	Negative	Negative
	SBP*	Mnatzaganian at el. (2013)	Moderate	Cox PH	Hazard-Ratio	1	0.99 (0.99, 0.99)	Negative	Negative
	JSW	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.85 (1.18, 2.90)	Positive	Positive
	Pain	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.86 (1.23, 2.83)	Positive	Positive
	Previous Fracture	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	2	Men: 1.52 (1.19, 1.94) Women: 1.55 (1.28, 2.03)	Positive	Positive

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
	Previous Hip Injury	Cooper at el. (1998)	Low	Logistic	Odds-Ratio	1	4.3 (2.2, 8.4)	Positive	Positive
	Superolateral migration of femoral head	Dougados at el. (1999)	Low	Cox PH	Relative-Risk	1	1.96 (1.27, 3.02)	Positive	Positive
	Oral Contraception Use	Karlson at el. (2003)	Low	Logistic	Odds-Ratio	1	1.0 (0.8, 1.2)	No Association	No Association
	Postmenopausal hormone use	Karlson at el. (2003)	Low	Logistic	Odds-Ratio	3	Current: 1.0 (0.8, 1.2)	No Association	No Association
	Location of hip OA	Gossec at el. (2005)	High	Logistic	P-Value	3	Global: 0.53	No Association	No Association
	Duration of symptoms (years)	Gossec at el. (2005)	High	Logistic	P-Value	1	0.28	No Association	No Association
	OA in contralateral hip	Gossec at el. (2005)	High	Logistic	P-Value	1	0.27	No Association	No Association
	Previous Treatment	Gossec at el. (2005)	High	Logistic	P-Value	2	NSAIDs: 0.003 Hip intra-articular injections: 0.81	NSAIDs: Association Hip intra-articular injections: No Association	Inconclusive
	Baseline Pain	Gossec at el. (2005)	High	Logistic	P-Value	1	0.03	Association†	Association
	Baseline WOMAC (Pain Score)	Gossec at el. (2005)	High	Logistic	P-Value	1	0.17	No Association†	No Association
	Baseline patient global assessment	Gossec at el. (2005)	High	Logistic	P-Value	1	0.006	Association†	Association
	Mean pain over first 6 months >42	Gossec at el. (2005)	High	Logistic	P-Value	1	<0.0001	Association†	Association
	Mean WOMAC function score over first 6 months >26	Gossec at el. (2005)	High	Logistic	P-Value	1	0.001	Association†	Association
	Mean patient global assessment over the first 6 months >47	Gossec at el. (2005)	High	Logistic	P-Value	1	<0.0001	Association†	Association
	Metabolic Syndrome*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.0 (0.6-1.5)	No Association	No Association

Type of Factor	Prognostic Factor	Studies	Quality of Study	Type of Analysis	Type of Effect Size	No. of Categories	Effect Size (certain categories)	Association	Overall Association
	High-density lipoprotein cholestrol *	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	0.8 (0.5-1.1)	No Association	No Association
	Hypertriglyceridemia*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	0.9 (0.6-1.4)	No Association	No Association
	Hypertension*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	1.4 (0.8-2.4)	No Association	No Association
	Hyperglycemia*	EngStrom et al (2009)	Moderate	Cox PH	Relative-Risk	1	0.8 (0.5-1.4)	No Association	No Association
Other	Familial predisposition	Rubak at el. (2014)	Moderate	Logistic	Odds-Ratio	2	Men: 1.86 (1.24, 2.80) Women: 1.87 (1.26, 2.79)	Positive	Positive
	Parity	Karlson at el. (2003)	Low	Logistic	Odds-Ratio	5	4+: 1.0 (0.7, 1.4)	No Association	No Association
	2D:4D index to finger ratio*	Hussain at el. (2014)	High	Cox PH	Hazard-Ratio	3	Average 2D:4D : 0.97 (0.89, 1.06)	No Association	No Association
		Sigurjonsdottir at el. (2010)	Low	Logistic	Odds-Ratio	1	1.14 (0.9, 1.44)	No Association	

*** - Factors identified for both the knee and the hip**

† - Factors specific to the particular study and are not comparable to other studies. Only the p-values are assigned, therefore preventing the direction of the association being obtained.

Table 7-5: Individual quality levels assigned for the six different aspects considered by the QUIPs tool for each study. L=Low Bias, M=Moderate Bias, H=High Bias

Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis and Reporting
Vinciguerra at el. (1995)	M	H	L	L	H	H
Cooper at el. (1998)	M	H	H	M	H	M
Dougados at el. (2002)	M	M	M	L	H	H
Michaëlsson at el. (2011)	L	M	L	L	M	L
Karlson at el. (2003)	L	M	H	H	H	M
Chan at el. (2010)	M	L	L	M	M	M
Sigurjonsdottir at el. (2010)	M	H	L	L	H	H
Nicholls at el. (2012)	M	H	M	L	L	M
Wang at el. (2009	L	M	L	L	L	M
Wang at el. (2011)	L	M	M	L	L	M
Wang at el. (2011)	L	M	M	L	L	L
Wang at el. (2012)	L	M	L	L	L	M
Wang at el. (2013)	L	M	M	L	L	M
Hussain at el. (2014)	M	M	L	L	L	L
Lohmander at el. (2009).	M	M	L	L	L	M
EngStrom et al (2009)	M	M	L	L	M	L
Ageberg at el. (2012)	L	M	L	L	L	M
Leung at el.(2014)	L	L	M	L	M	L
Leung at el. (2015)	L	H	L	L	M	M
Cicuttini at el. (2004)	M	H	L	L	L	L
Podsiadlo at el. (2014)	M	M	L	M	M	M
Franklin at el. (2009)	L	M	L	L	L	M
Franklin at el. (2010)	L	M	L	L	L	L
Manninen at el. (2001)	L	L	L	L	M	L
Manninen at el. (2004)	M	H	H	L	M	M
Rubak at el. (2013)	L	M	L	L	M	L
Rubak at el. (2014)	L	M	L	L	H	M
Tanamas at el. (2010)	M	H	M	L	M	M
Tanamas at el. (2010)	M	H	M	L	M	M
Flugsrud at el. (2002)	L	H	L	L	L	L
Liu at el.(2007)	M	H	M	L	L	M
Flugsrud at el. (2006)	L	M	M	L	L	L
Mnatzaganian at el. (2013)	L	M	M	L	M	M
Bruyere at el. (2013)	M	H	L	L	L	L
Gossec at el. (2005)	L	L	L	M	M	L

8 Appendix 2: Feasibility study additional tables and figures

Table 8-1: Read-codes used the identify the case of knee or hip arthroplasty within CiPCA

Read-code	Read-Term
Knee Arthroplasty	
X606O	Total knee arthroplasty
XE08w	Total prosthetic arthroplasty of knee using cement
XE08y	Total prosthetic arthroplasty of knee joint not using cement
XE090	Other total prosthetic arthroplasty of knee joint
XE091	Primary hybrid total knee arthroplasty NEC
7K300	Primary cemented total knee arthroplasty
7K30y	Total prosthetic arthroplasty of knee joint using cement OS
7K30z	Total prosthetic arthroplasty of knee joint using cement NOS
7K310	Primary uncemented total knee arthroplasty
7K31y	Total prosthetic arthroplasty knee joint not using cement OS
7K31z	Total prosthetic arthroplasty knee joint not using cement NOS
7K32y	Other total prosthetic arthroplasty of knee joint OS
7K32z	Other total prosthetic arthroplasty of knee joint NOS
Hip Arthroplasty	
XE2n7	Primary total prosthetic arthroplasty of hip joint NEC
XaF7k	Primary hybrid total arthroplasty of hip joint NEC
XE08o	Other total prosthetic arthroplasty of hip joint
XE08j	Total prosthetic arthroplasty of hip joint using cement
XaF7j	Primary hybrid total arthroplasty of hip joint
XE08k	Primary cemented total hip arthroplasty
7K22y	Other specified total prosthetic arthroplasty of hip joint
XaF7l	Prosthetic hybrid total arthroplasty of hip joint
X606J	Total hip arthroplasty
XE08m	Total prosthetic arthroplasty of hip joint not using cement
7K21y	Other specified total prosthetic arthroplasty of hip joint not using cement
7K20y	Other specified total prosthetic arthroplasty of hip joint using cement
7K210	Primary uncemented total hip arthroplasty
7K21z	Total prosthetic arthroplasty of hip joint not using cement NOS
7K20z	Total prosthetic arthroplasty of hip joint using cement NOS
7K22z	Total prosthetic arthroplasty of hip joint NOS

Table 8-2: Read code lists obtained from previous electronic healthcare studies

Read Code/BNF subchapter	Read term/BNF subchapter title
Body weight / BMI (obtained from Monk et al. (2013))	
1624	Abnormal weight gain
1625	Abnormal weight loss
6878	Obesity screen
13AC	Diabetic weight reducing diet
1D1A	Complaining of weight loss
22A	O/E - weight

Read Code/BNF subchapter	Read term/BNF subchapter title
22K	Body mass index - observation
22N7	Waist/hip ratio
66C1	Initial obesity assessment
66C2	Follow-up obesity assessment
66C6	Treatment of obesity started
66C7	Treatment of obesity stopped
66C9	Target weight discussed
66CA	Ideal weight discussed
66CB	Ideal body weight
66CC	Wants to lose weight
66CF	Target weight
66CG	Weight management programme offered
66CH	Weight management programme started
66CJ	Weight management programme completed
66CK	Target weight reached
66CZ	Obesity monitoring NOS
8IAH	Body weight measurement declined
C380	Obesity
C38z0	Simple obesity NOS
R031	(D) Abnormal weight gain
R032	(D) Abnormal loss of weight
ZV778	Screening for obesity
Blood pressure (obtained from Monk et al. (2013))	
246	O/E - blood pressure reading
6627	Good hypertension control
6628	Poor hypertension control
14A2	H/O: Hypertension
315B	Ambulatory blood pressure recording
662c	Hypertension six month review
662d	Hypertension annual review
662L	24 hr blood pressure monitoring
662P	Hypertension monitoring
662V	Blood pressure monitoring
68B1	Hypertension screening
6A2	Coronary heart disease annual review
6N4L	24 hr blood pressure monitoring
8I3Y	Blood pressure procedure refused
9N03	Seen in hypertension clinic
9OD	Hypertension screening administration
9OI	Hypertension monitoring admin.
G2	Hypertensice disease
G87	Hypertension
R1y2	(D) Raised blood pressure reading
R1y3	(D) Low blood pressure reading
ZV70B	(V) Examination of blood pressure
ZV7B1	Screening for hypertension
Glucose (obtained from Monk et al. (2013))	
466	Urine test for glucose
6872	Diabetes mllitus screening
1I0	Diabetes mellitus excluded

Read Code/BNF subchapter	Read term/BNF subchapter title
44f	Serum glucose level
44g	Plasma glucose level
44j	Glucose load test
44T	Blood glucose method
44TJ	Blood glucose level
44TK	Fasting blood glucose level
44U	Blood glucose result
44V1	Glucose tolerance test normal
44V2	Glucose tolerance test impaired
44V3	Glucose tolerance test diabetic
44V4	GTT=renal glycosuria
44V6	Extended glucose tolerance test
44VZ	Glucose tolerance test NOS
46S4	Urine glucose: chem. titre
46Z0	Urine screening test for diabetes
4I39	Fluid sample glucose
4Q83	Estimated average glucose level
66An	Diabetes type I review
66Ao	Diabetes type II review
68K1	Urine screen for glucose
7P172	Glucose tolerance test
9Oy	Diabetes screening administration
9m9	Impaired glucose tolerance monitoring administration
C10	Diabetes
C10E	Type 1 diabetes mellitus
C10F	Type 2 diabetes mellitus
C11y2	Impaired glucose tolerance
R102	(D) Glucose tolerance test abnormal
R1057	[D]Glucose, blood level abnormal
R10D0	Impaired fasting glycaemia
R10E	(D) Impaired glucose tolerance
ZV771	(V0 Screening for diabetes mellitus
Smoking (obtained from Monk et al. (2013))	
137	Tobacco consumption
6791	Health education - smoking
13p	Smoking cessation milestones
13p4	Smoking free weeks
745H	Smoking cessation therapy
8CAL	Smoking cessation advice
8HTK	Referral to stop-smoking clinic
8IAj	Smoking cessation advice declined
9km	Ex-smoker annual review
9kn	Non-smoker annual review
9ko	Current smoker annual review
Fracture (obtained from Wood et al. (2011))	
PE413	Congenital dislocation of patella
PF644	Congenital dislocation of patella
S32	Fracture of patella
S320	Closed fracture of patella
S3200	Closed fracture of patella, transverse

Read Code/BNF subchapter	Read term/BNF subchapter title
S3201	Closed fracture of patella, proximal pole
S3202	Closed fracture of patella, distal pole
S3203	Closed fracture of patella, vertical
S3204	Closed fracture of patella, comminuted (stellate)
S321	Open fracture of patella
S3210	Open fracture of patella, transverse
S3211	Open fracture of patella, proximal pole
S3212	Open fracture of patella, distal pole
S3213	Open fracture of patella, vertical
S3214	Open fracture of patella, comminuted (stellate)
S32z	Fracture of patella, NOS
S4F4	Closed fracture dislocation, patellofemoral joint
S4F5	Open fracture dislocation, patellofemoral joint
S4F6	Closed fracture subluxation, patellofemoral joint
S4F7	Open fracture subluxation, patellofemoral joint
NSAID (obtained from Bedson et al. (2013))	
10.1.1	Non-steroidal anti-inflammatory drugs

Table 8-3: Charlson Index Read codes and the corresponding score used

Read code	Read term	Charlson Index Score
AIDs		
A78	Other viral or chlamydial diseases	6
Cancer		
141	H/O: infectious disease	2
142	H/O: malignant neoplasm (*)	2
143	H/O: endocrine disorder	2
144	H/O: metabolic disorder	2
145	H/O: blood disorder	2
146	H/O: psychiatric disorder	2
147	H/O: CNS disorder	2
148	H/O: eye disorder	2
149	H/O: ear disorder	2
151	Menstrual data	2
152	Parity status	2
153	Gravida status	2
154	Past pregnancy outcome	2
155	H/O: infant feeding method	2
156	Contraceptive history	2
157	H/O: menstrual disorder	2
158	H/O: abnormal uterine bleeding	2
159	H/O:gynaecological problem NOS	2
161	Appetite symptom	2
162	Weight symptom	2
163	Feeding problem symptom	2
171	Cough	2
172	Blood in sputum - haemoptysis	2

Read code	Read term	Charlson Index Score
173	Breathlessness	2
174	Hiccough	2
181	Palpitations	2
182	Chest pain	2
183	Oedema	2
184	Prominent veins	2
185	Impaired exercise tolerance	2
186	C/O cold extremities	2
187	Frequency of angina	2
188	Ankle flare	2
189	Worsening exercise tolerance	2
191	Tooth symptoms	2
192	Mouth symptoms	2
193	Chewing symptoms	2
194	Swallowing symptoms	2
195	Indigestion symptoms	2
196	Type of GIT pain	2
199	Vomiting	2
B00	Malignant neoplasm of lip	2
B01	Malignant neoplasm of tongue	2
B02	Malignant neoplasm of major salivary glands	2
B03	Malignant neoplasm of gum	2
B04	Malignant neoplasm of floor of mouth	2
B05	Malignant neoplasm of other and unspecified parts of mouth	2
B06	Malignant neoplasm of oropharynx	2
B07	Malignant neoplasm of nasopharynx	2
B08	Malignant neoplasm of hypopharynx	2
B0z	Malignant neoplasm of other and ill-defined sites within the lip, oral cavity and pharynx	2
B10	Malignant neoplasm of oesophagus	2
B11	Malignant neoplasm of stomach	2
B12	Malignant neoplasm of small intestine and duodenum	2
B13	Malignant neoplasm of colon	2
B14	Malignant neoplasm of rectum, rectosigmoid junction and anus	2
B15	Malignant neoplasm of liver and intrahepatic bile ducts	2
B16	Malignant neoplasm of gallbladder and extrahepatic bile ducts	2
B17	Malignant neoplasm of pancreas	2
B18	Malignant neoplasm of retroperitoneum and peritoneum	2
B1z	Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum	2
B20	Malignant neoplasm of nasal cavities, middle ear and accessory sinuses	2
B21	Malignant neoplasm of larynx	2
B22	Malignant neoplasm of trachea, bronchus and lung	2
B23	Malignant neoplasm of pleura	2
B24	Malignant neoplasm of thymus, heart and mediastinum	2
B25	Malignant neoplasm, overlapping lesion of heart, mediastinum and pleura	2
B26	Malignant neoplasm, overlapping lesion of respiratory and intrathoracic organs	2
B2z	Malignant neoplasm of other and ill-defined sites within the respiratory and intrathoracic organs	2
B30	Malignant neoplasm of bone and articular cartilage	2

Read code	Read term	Charlson Index Score
B31	Malignant neoplasm of connective and other soft tissue	2
B32	Malignant melanoma of skin	2
B33	Other malignant neoplasm of skin	2
B34	Malignant neoplasm of female breast	2
B35	Malignant neoplasm of male breast	2
B3y	Malignant neoplasm of bone, connective tissue, skin and breast otherwise specified	2
B3z	Malignant neoplasm of bone, connective tissue, skin and breast NOS	2
B40	Malignant neoplasm of uterus, part unspecified	2
B41	Malignant neoplasm of cervix uteri	2
B42	Malignant neoplasm of placenta	2
B43	Malignant neoplasm of body of uterus	2
B44	Malignant neoplasm of ovary and other uterine adnexa	2
B45	Malignant neoplasm of other and unspecified female genital organs	2
B46	Malignant neoplasm of prostate	2
B47	Malignant neoplasm of testis	2
B48	Malignant neoplasm of penis and other male genital organs	2
B49	Malignant neoplasm of urinary bladder	2
B4A	Malignant neoplasm of kidney and other unspecified urinary organs	2
B4y	Malignant neoplasm of genitourinary organ otherwise specified	2
B4z	Malignant neoplasm of genitourinary organ NOS	2
B50	Malignant neoplasm of eye	2
B51	Malignant neoplasm of brain	2
B52	Malignant neoplasm of other and unspecified parts of nervous system	2
B53	Malignant neoplasm of thyroid gland	2
B54	Malignant neoplasm of other endocrine glands and related structures	2
B55	Malignant neoplasm of other and ill-defined sites	2
B59	Malignant neoplasm of unspecified site	2
B60	Lymphosarcoma and reticulosarcoma	2
B61	Hodgkin's disease	2
B62	Other malignant neoplasm of lymphoid and histiocytic tissue	2
B63	Multiple myeloma and immunoproliferative neoplasms	2
B64	Lymphoid leukaemia	2
B65	Myeloid leukaemia	2
B66	Monocytic leukaemia	2
B67	Other specified leukaemia	2
B68	Leukaemia of unspecified cell type	2
B69	Myelomonocytic leukaemia	2
B6y	Malignant neoplasm of lymphatic or haematopoietic tissue otherwise specified	2
B6z	Malignant neoplasm lymphatic or haematopoietic tissue NOS	2
Byu	[X]Additional neoplasm classification terms	2
ZV1	[V]Potential health hazards related to personal history (PH) and family history (FH)	2
Chronic pulmary disease		
114	Full History Taken	1
14B	H/O: respiratory disease	1
173	Breathlessness	1
176	C/O - catarrh	1
178	Asthma trigger	1
1O2	Asthma confirmed	1
466	Urine test for glucose	1

Read code	Read term	Charlson Index Score
491	Semen examination - general	1
492	Semen sample volume	1
493	Sperm number/cc	1
515	Progress of radiotherapy	1
516	Dual energy X-ray photon absorptiometry scan requested	1
663	Respiratory disease monitoring	1
66Y	Other respiratory disease monitoring	1
691	Special examination - general	1
783	Pancreas operations	1
8H2	Emergency hospital admission	1
9OJ	Asthma monitoring admin.	1
H30	Bronchitis unspecified	1
H31	Chronic bronchitis	1
H32	Emphysema	1
H33	Asthma	1
H34	Bronchiectasis	1
H35	Extrinsic allergic alveolitis	1
H3z	Chronic obstructive airways disease NOS	1
H40	Coal workers' pneumoconiosis	1
H41	Asbestosis	1
H42	Silica and silicate pneumoconiosis	1
H43	Pneumoconiosis due to other inorganic dust	1
H44	Pneumopathy due to inhalation of other dust	1
H45	Pneumoconiosis NOS	1
H46	Respiratory disease due to chemical fumes and vapours	1
H47	Pneumonitis due to inhalation of solids or liquids	1
H4y	Other specified lung diseases due to external agent	1
H4z	Lung disease due to external agents NOS	1
H57	Lung involvement in diseases EC	1
H58	Other diseases of lung	1
Hyu	[X]Additional respiratory disease classification terms	1
L51	Maternal care for other known or suspected fetal problems	1
SK0	Early trauma complications	1
Cerebrovascular diease		
147	H/O: CNS disorder	1
14A	H/O: cardiovascular disease	1
431	ABO blood grouping	1
435	Transfusion centre ref. no.	1
436	Rhesus antibody titre	1
438	Syphilis infectious titre test	1
662	Cardiac disease monitoring	1
700	Brain tissue operations	1
F11	Other cerebral degenerations	1
G60	Subarachnoid haemorrhage	1
G61	Intracerebral haemorrhage	1
G62	Other and unspecified intracranial haemorrhage	1
G63	Precerebral arterial occlusion	1
G64	Cerebral arterial occlusion	1
G65	Transient cerebral ischaemia	1

Read code	Read term	Charlson Index Score
G66	Stroke and cerebrovascular accident unspecified	1
G67	Other cerebrovascular disease	1
G68	Late effects of cerebrovascular disease	1
G6y	Other specified cerebrovascular disease	1
G6z	Cerebrovascular disease NOS	1
Gyu	[X]Additional circulatory system disease classification terms	1
S62	Cerebral haemorrhage following injury	1
Dementia		
146	H/O: psychiatric disorder	1
293	O/E - muscle mass	1
299	O/E - gait	1
E04	Other chronic organic psychoses	1
Eu0	[X]Organic, including symptomatic, mental disorders	1
Cognetive heart disease		
14A	H/O: cardiovascular disease	1
1O1	Heart failure confirmed	1
425	Haematocrit - PCV	1
427	Colour index	1
662	Cardiac disease monitoring	1
782	Bile duct operations	1
8B2	Therapeutic prescription	1
8CL	Discussion about disorder	1
8H2	Emergency hospital admission	1
G23	Hypertensive heart and renal disease	1
G55	Cardiomyopathy	1
G58	Heart failure	1
SP1	Body system complications NEC	1
Diabetes		
143	H/O: endocrine disorder	1
66A	Diabetic monitoring	1
8A1	Metabolic monitoring	1
8BL	Patient on maximum tolerated dose	1
8H2	Emergency hospital admission	1
C10	Diabetes mellitus	1
Cyu	[X]Additional endocrine, nutritional, metabolic and immunity disease classification terms	1
G73	Other peripheral vascular disease	1
L18	Other medical condition during pregnancy, childbirth and the puerperium	1
Diabetes with complication		
2BB	O/E - retinal inspection	2
F37	Inflammatory and toxic neuropathy	2
F38	Myoneural disorders	2
F3y	Other specified disorders of peripheral nervous system	2
F42	Other retinal disorders	2
F46	Cataract	2
K01	Nephrotic syndrome	2
Hemilegia		
283	O/E - paralysis	2
436	Rhesus antibody titre	2
438	Syphilis infectious titre test	2

Read code	Read term	Charlson Index Score
F14	Spinocerebellar disease	2
F22	Hemiplegia	2
F23	Congenital cerebral palsy	2
F24	Other paralytic syndromes	2
Metastatic tumor		
196	Type of GIT pain	6
197	Site of GIT pain	6
198	Nausea	6
199	Vomiting	6
B15	Malignant neoplasm of liver and intrahepatic bile ducts	6
B56	Secondary and unspecified malignant neoplasm of lymph nodes	6
B57	Secondary malignant neoplasm of respiratory and digestive systems	6
B58	Secondary malignant neoplasm of other specified sites	6
B59	Malignant neoplasm of unspecified site	6
B5y	Malignant neoplasm of other and unspecified site otherwise specified	6
B5z	Malignant neoplasm of other and unspecified site NOS	6
Byu	[X]Additional neoplasm classification terms	6
Mild liver disease		
571	Isotope uptake/excret studies	1
573	Isotope distribut.static scan	1
C31	Disorders of carbohydrate transport and metabolism	1
C35	Disorders of mineral metabolism	1
J60	Acute and subacute liver necrosis	1
J61	Cirrhosis and chronic liver disease	1
J63	Other liver disorders	1
Jyu	[X]Additional digestive system disease classification terms	1
Moderate liver disease		
571	Isotope uptake/excret studies	3
573	Isotope distribut.static scan	3
760	Oesophagus (including hiatus hernia) operations	3
A70	Viral hepatitis	3
G85	Other varicose veins	3
Gyu	[X]Additional circulatory system disease classification terms	3
J62	Liver abscess and sequelae of chronic liver disease	3
Myocardial infarction		
14A	H/O: cardiovascular disease	1
429	Mean corpusc. Hb. conc. (MCHC)	1
G30	Acute myocardial infarction	1
G32	Old myocardial infarction	1
Peptic ulcer disease		
195	Indigestion symptoms	1
531	Soft tissue X-ray - general	1
532	Soft tissue X-ray face	1
533	Soft tissue X-ray neck	1
534	Soft tissue X-ray mouth	1
761	Stomach and pylorus operations	1
762	Duodenum operations	1
J10	Diseases of oesophagus	1
J11	Gastric ulcer - (GU)	1

Read code	Read term	Charlson Index Score
J12	Duodenal ulcer - (DU)	1
J13	Peptic ulcer - (PU) site unspecified	1
J14	Gastrojejunal ulcer (GJU)	1
K42	Cervical, vaginal and vulval inflammatory diseases	1
ZV1	[V]Potential health hazards related to personal history (PH) and family history (FH)	1
Peripheral vascular disease		
14A	H/O: cardiovascular disease	1
14N	H/O: surgery	1
2I1	O/E - general sign	1
441	Blood chemistry - general	1
443	Gonadotrophin levels	1
445	Serum pregnancy test (B-HCG)	1
7A1	Aorta operations	1
C10	Diabetes mellitus	1
G73	Other peripheral vascular disease	1
Gyu	[X]Additional circulatory system disease classification terms	1
R05	[D]Cardiovascular system symptoms	1
Renal disease		
14D	H/O: urinary disease	2
1Z1	Chronic renal impairment	2
582	Infrared radiation in diagn.	2
583	Laser radiation in diagn.	2
593	Fast-electron therapy	2
K00	Acute glomerulonephritis	2
K01	Nephrotic syndrome	2
K02	Chronic glomerulonephritis	2
K03	Nephritis and nephropathy unspecified	2
K04	Acute renal failure	2
K05	Chronic renal failure	2
K06	Renal failure unspecified	2
K08	Impaired renal function disorder	2
K0A	Glomerular disease	2
K10	Infections of kidney	2
Kyu	[X]Additional genitourinary disease classification terms	2
Rheumatological disease		
2A4	O/E - ankle reflex	1
695	Travel examinations	1
712	Other endocrine gland operations	1
F37	Inflammatory and toxic neuropathy	1
F39	Muscular dystrophies and other myopathies	1
G5y	Other specified heart disease	1
H57	Lung involvement in diseases EC	1
K01	Nephrotic syndrome	1
N00	Diffuse diseases of connective tissue	1
N04	Rheumatoid arthritis and other inflammatory polyarthropathies	1
N06	Other and unspecified arthroplasties	1
N20	Polymyalgia rheumatica	1
N23	Muscle, ligament and fascia disorders	1
N24	Other soft tissue disorders	1

Read code	Read term	Charlson Index Score
N2y	Other specified nonarticular rheumatism	1
N2z	Nonarticular rheumatism NOS	1
Nyu	[X]Additional musculoskeletal and connective tissue disease classification terms	1

Table 8-4: List of terms used to identify values within the free-text for factors identified within the systematic review and seen as feasible to obtain from Electronic Health Care Records

Factor within the Free text	Terms used within the free text
Body Mass Index (value or grouping)	"BMI", "bmi", "b.m.i", "B.M.I", "body mass index", "Body mass index"
Weight (value or grouping)	"wei", "Wei", "Wt", "wt", "Kg", "kg"
Smoking Status	"smok", "Smok"
Blood Pressure value	"bp", "BP", "Bp", "b.p", "B.P", "B.p"
Blood glucose test	"suga", "Suga", "gluc", "Gluc", "mmol"
Any Previous Fracture*	"Frac", "frac"
*Previous fracture was searched for within the Read code terms instead of the free text	

9 Appendix 3: Case-control study additional tables and graphs

Table 9-1: Read-codes used the identify the case of knee or hip arthroplasty within CiPCA

Read-code	Read-Term
Knee Arthroplasty	
X606O	Total knee arthroplasty
XE08w	Total prosthetic arthroplasty of knee using cement
XE08y	Total prosthetic arthroplasty of knee joint not using cement
XE090	Other total prosthetic arthroplasty of knee joint
XE091	Primary hybrid total knee arthroplasty NEC
7K300	Primary cemented total knee arthroplasty
7K30y	Total prosthetic arthroplasty of knee joint using cement OS
7K30z	Total prosthetic arthroplasty of knee joint using cement NOS
7K310	Primary uncemented total knee arthroplasty
7K31y	Total prosthetic arthroplasty knee joint not using cement OS
7K31z	Total prosthetic arthroplasty knee joint not using cement NOS
7K32y	Other total prosthetic arthroplasty of knee joint OS
7K32z	Other total prosthetic arthroplasty of knee joint NOS
Hip Arthroplasty	
XE2n7	Primary total prosthetic arthroplasty of hip joint NEC
XaF7k	Primary hybrid total arthroplasty of hip joint NEC
XE08o	Other total prosthetic arthroplasty of hip joint
XE08j	Total prosthetic arthroplasty of hip joint using cement
XaF7j	Primary hybrid total arthroplasty of hip joint
XE08k	Primary cemented total hip arthroplasty
7K22y	Other specified total prosthetic arthroplasty of hip joint
XaF7l	Prosthetic hybrid total arthroplasty of hip joint
X606J	Total hip arthroplasty
XE08m	Total prosthetic arthroplasty of hip joint not using cement
7K21y	Other specified total prosthetic arthroplasty of hip joint not using cement
7K20y	Other specified total prosthetic arthroplasty of hip joint using cement
7K210	Primary uncemented total hip arthroplasty
7K21z	Total prosthetic arthroplasty of hip joint not using cement NOS
7K20z	Total prosthetic arthroplasty of hip joint using cement NOS
7K22z	Total prosthetic arthroplasty of hip joint NOS

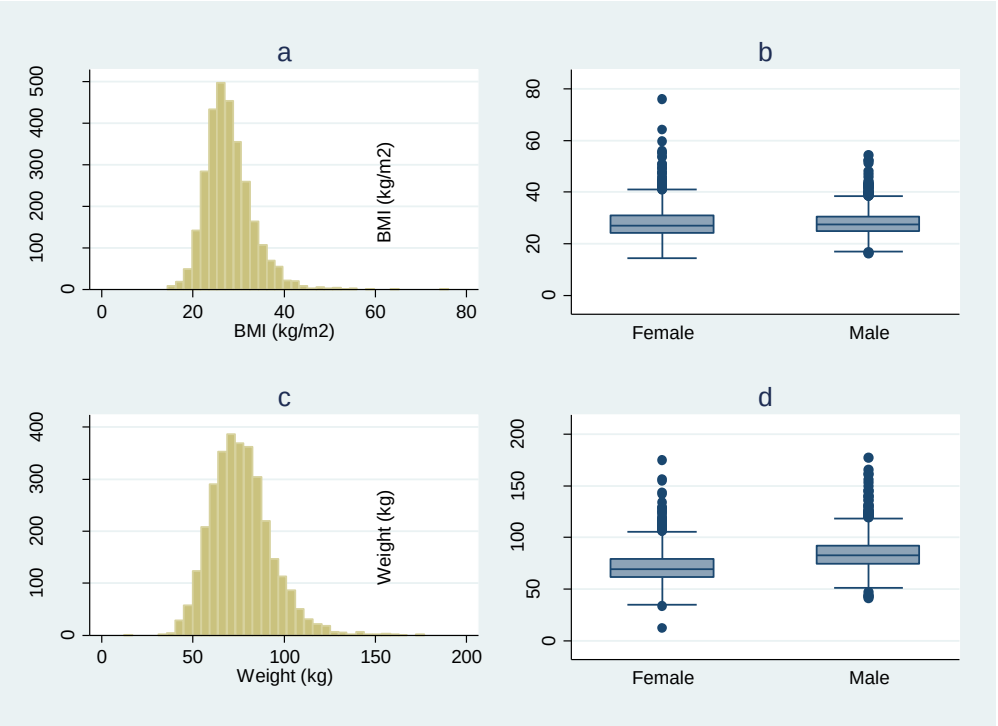

Figure 9-1:(a) distribution of the BMI values obtained from the free-text for the controls; (b) boxplot for the obtained BMI values for the males and females within the controls; (c) distribution of the weights obtained from the free-text for the controls; (d) boxplot for the obtained weight values for the males and females within the controls

Table 9-2: Identified three character Read-codes within CiPCA with frequencies of which annual year each code was first identified within for cases and controls

Read-Code	Code-meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
19F	Diarrhoea symptoms	12	13	9	8	2	44	5.0%	52	49	41	32	28	202	4.6%
1B1	General nervous symptoms	3	10	0	8	13	34	3.9%	54	36	30	28	21	169	3.9%
1B8	Eye symptoms	9	9	4	7	3	32	3.7%	45	41	27	36	22	171	3.9%
1C1	Hearing symptoms	5	5	8	6	5	29	3.3%	34	20	19	18	17	108	2.5%
1J4	Suspected UTI	14	8	4	5	3	34	3.9%	64	27	28	12	19	150	3.4%
1M1	Pain in lower limb	42	6	7	11	7	73	8.4%	29	23	12	14	13	91	2.1%
321	ECG - general	17	16	22	10	8	73	8.4%	92	95	82	64	61	394	9.0%
41D	Sample obtained	9	6	5	4	4	28	3.2%	27	32	26	20	17	122	2.8%
44P	Serum cholesterol	24	19	28	10	12	93	10.6%	84	70	73	63	57	347	7.9%
461	Urine exam. - general	30	30	17	16	15	108	12.4%	169	107	88	68	55	487	11.1%
525	Plain X-ray spine	6	9	4	6	2	27	3.1%	22	31	20	16	14	103	2.4%
527	Plain X-ray pelvis	22	4	4	2	2	34	3.9%	7	5	4	6	5	27	0.6%
52A	Plain X-ray hip/leg	89	26	18	12	7	152	17.4%	37	34	28	18	15	132	3.0%
535	Standard chest X-ray	16	14	17	8	7	62	7.1%	116	74	75	51	40	356	8.1%
537	Soft tissue X-ray breast	10	13	7	8	4	42	4.8%	63	49	41	11	23	187	4.3%
585	Other diagnostic ultrasound	21	16	8	8	8	61	7.0%	76	47	47	38	28	236	5.4%
657	Other bacterial vaccinations	22	32	33	22	25	134	15.3%	119	138	149	112	86	604	13.8%
65E	Influenza vaccination	202	42	28	17	19	308	35.2%	849	268	88	110	92	1407	32.2%
67E	Foreign travel advice	15	11	18	13	11	68	7.8%	86	68	68	52	46	320	7.3%
685	Cervical neoplasia screening	12	12	18	7	10	59	6.8%	58	56	72	62	81	329	7.5%
68A	Neurolog./special sense screen	21	5	1	0	0	27	3.1%	94	39	21	9	6	169	3.9%
68N	Immunisation status screen	16	6	1	4	3	30	3.4%	101	22	10	11	15	159	3.6%
6C2	Primary prevention of cardiovascular disease	9	6	6	1	0	22	2.5%	75	41	22	2	0	140	3.2%
730	External ear and external auditory canal operations	9	6	7	9	4	35	4.0%	32	41	47	49	42	211	4.8%
771	Colon operations and sigmoidoscopy of rectum	13	10	5	8	3	39	4.5%	32	29	33	22	9	125	2.9%
7E2	Ovary and broad ligament operations	6	3	10	8	14	41	4.7%	40	32	41	32	45	190	4.3%
7K6	Other joint operations	39	29	1	9	11	89	10.2%	24	19	24	21	14	102	2.3%
7L1	Other miscellaneous operations	19	8	5	1	1	34	3.9%	43	39	13	10	3	108	2.5%
8B3	Drug therapy	139	32	30	16	19	236	27.0%	479	187	141	87	82	976	22.3%

Read-Code	Code-meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
8B6	Prophylactic drug therapy	12	10	5	8	7	42	4.8%	43	23	21	33	36	156	3.6%
8BA	Other misc. therapy	7	6	8	11	12	44	5.0%	62	37	36	23	24	182	4.2%
8BI	Other medication review	9	6	5	6	3	29	3.3%	35	36	33	18	9	131	3.0%
8C1	Nursing care	44	17	14	9	7	91	10.4%	185	75	58	28	38	384	8.8%
8H7	Other referral	10	11	6	4	6	37	4.2%	30	20	18	25	21	114	2.6%
987	FP/MS - minor surgery claim	13	6	9	3	5	36	4.1%	32	30	20	19	15	116	2.7%
9EG	Disabled driver badge report	20	11	6	5	6	48	5.5%	23	20	22	18	11	94	2.2%
9N1	Site of encounter	52	7	4	3	2	68	7.8%	117	44	18	10	9	198	4.5%
9N2	Provider of encounter	64	23	19	12	11	129	14.8%	277	154	86	56	34	607	13.9%
9N3	Indirect encounter	91	27	18	5	4	145	16.6%	315	139	72	45	20	591	13.5%
9N4	Failed encounter	113	57	37	43	19	269	30.8%	360	248	212	149	110	1079	24.7%
9ND	Incoming mail processing	24	11	8	5	5	53	6.1%	35	25	21	21	19	121	2.8%
9OX	Influenza vacc. administratn.	5	9	8	2	4	28	3.2%	41	37	17	20	15	130	3.0%
A08	Ill-defined intestinal tract infections	16	10	13	11	8	58	6.6%	55	53	44	44	35	231	5.3%
A53	Measles	10	7	14	5	10	46	5.3%	41	27	23	41	40	172	3.9%
AB0	Dermatophytosis including tinea or ringworm	26	12	10	15	9	72	8.2%	73	67	50	67	55	312	7.1%
AB2	Candidiasis	12	3	6	12	6	39	4.5%	51	48	31	36	40	206	4.7%
B76	Benign neoplasm of skin	3	8	9	6	6	32	3.7%	32	45	36	41	23	177	4.1%
C04	Acquired hypothyroidism	24	12	9	5	2	52	5.9%	145	58	34	20	19	276	6.3%
C32	Disorders of lipoid metabolism	45	29	19	19	11	123	14.1%	258	134	89	64	60	605	13.8%
C34	Gout	6	5	3	0	6	20	2.3%	54	36	23	23	15	151	3.5%
C36	Disorders of fluid, electrolyte and acid-base balance	17	13	5	4	4	43	4.9%	42	32	19	23	12	128	2.9%
D21	Other and unspecified anaemias	24	9	6	5	3	47	5.4%	54	38	28	20	9	149	3.4%
E20	Neurotic disorders	39	16	17	14	13	99	11.3%	172	102	83	86	68	511	11.7%
E22	Sexual deviations or disorders	4	6	7	4	10	31	3.5%	37	37	28	30	16	148	3.4%
E2B	Depressive disorder NEC	16	7	5	4	2	34	3.9%	52	31	30	26	25	164	3.8%
Eu3	[X]Mood - affective disorders	24	15	10	10	3	62	7.1%	99	66	42	30	32	269	6.2%
F34	Mononeuritis of upper limb and mononeuritis multiplex	6	7	6	6	2	27	3.1%	30	13	12	17	9	81	1.9%
F45	Glaucoma	15	8	7	3	0	33	3.8%	81	34	19	12	4	150	3.4%
F48	Visual disturbances	7	5	13	8	2	35	4.0%	41	18	30	30	23	142	3.2%

Read-Code	Code-meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
F4C	Disorders of conjunctiva	19	17	11	14	16	77	8.8%	86	72	87	84	68	397	9.1%
F4D	Inflammation of eyelids	11	5	4	3	5	28	3.2%	29	26	31	23	27	136	3.1%
F4F	Lacrimal system disorders	12	9	9	7	10	47	5.4%	52	33	33	26	23	167	3.8%
F4K	Other eye disorders	7	3	8	5	6	29	3.3%	35	33	29	24	15	136	3.1%
F50	Disorders of external ear	59	44	34	23	17	177	20.3%	322	207	158	138	108	933	21.4%
F58	Other ear disorders	15	16	13	14	7	65	7.4%	79	68	55	63	54	319	7.3%
F59	Hearing loss	17	12	12	10	11	62	7.1%	84	78	55	58	41	316	7.2%
G33	Angina pectoris	13	5	4	8	3	33	3.8%	67	42	27	29	24	189	4.3%
G57	Cardiac dysrhythmias	27	8	4	4	1	44	5.0%	141	50	37	31	20	279	6.4%
G80	Phlebitis and thrombophlebitis	10	5	5	6	9	35	4.0%	42	19	25	19	18	123	2.8%
G83	Varicose veins of the legs	17	8	12	12	11	60	6.9%	60	61	33	30	41	225	5.1%
G84	Haemorrhoids	18	10	5	11	10	54	6.2%	47	38	32	39	30	186	4.3%
H01	Acute sinusitis	10	13	7	13	7	50	5.7%	86	60	64	35	43	288	6.6%
H02	Acute pharyngitis	26	9	16	14	12	77	8.8%	72	71	84	56	64	347	7.9%
H05	Other acute upper respiratory infections	33	19	19	19	14	104	11.9%	148	115	122	108	86	579	13.2%
H06	Acute bronchitis and bronchiolitis	83	51	34	39	35	242	27.7%	351	231	205	158	141	1086	24.9%
H0z	Acute respiratory infection NOS	7	6	15	4	3	35	4.0%	53	42	40	22	22	179	4.1%
H12	Chronic pharyngitis and nasopharyngitis	7	9	5	6	5	32	3.7%	50	38	26	26	31	171	3.9%
H17	Allergic rhinitis	5	4	7	6	3	25	2.9%	41	29	32	12	18	132	3.0%
H1y	Other specified diseases of upper respiratory tract	12	10	5	4	3	34	3.9%	27	32	22	23	18	122	2.8%
J16	Disorders of stomach function	24	17	16	18	15	90	10.3%	97	97	79	60	47	380	8.7%
J34	Diaphragmatic hernia	13	10	6	6	8	43	4.9%	51	33	38	30	14	166	3.8%
J51	Diverticula of intestine	15	9	7	7	3	41	4.7%	61	37	24	20	17	159	3.6%
J52	Functional gastrointestinal tract disorders NEC	41	24	14	13	14	106	12.1%	122	71	56	57	44	350	8.0%
J57	Other disorders of intestine	9	10	12	8	4	43	4.9%	51	46	42	31	42	212	4.9%
K15	Cystitis	8	4	11	7	3	33	3.8%	28	26	26	25	32	137	3.1%
K19	Other urethral and urinary tract disorders	88	31	25	23	15	182	20.8%	264	137	118	103	87	709	16.2%
K20	Benign prostatic hypertrophy	12	9	5	4	8	38	4.3%	65	30	20	30	19	164	3.8%
K31	Other breast disorders	6	4	6	12	11	39	4.5%	37	41	35	36	24	173	4.0%
K51	Genital prolapse	9	7	9	4	3	32	3.7%	44	19	11	11	14	99	2.3%
K5A	Menopausal and postmenopausal disorders	9	15	16	15	7	62	7.1%	64	55	48	44	53	264	6.0%

Read-Code	Code-meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
M03	Other cellulitis and abscess	9	9	6	9	6	39	4.5%	49	37	35	19	25	165	3.8%
M07	Other local infections of skin and subcutaneous tissue	16	8	15	7	12	58	6.6%	47	42	47	26	32	194	4.4%
M08	Cutaneous cellulitis	13	11	3	1	4	32	3.7%	46	36	23	17	21	143	3.3%
M12	Contact dermatitis and other eczemas	26	15	17	15	9	82	9.4%	94	75	65	69	64	367	8.4%
M15	Erythematous conditions	13	4	10	5	5	37	4.2%	53	32	24	18	21	148	3.4%
M18	Pruritus and related conditions	18	11	9	4	5	47	5.4%	69	51	36	43	35	234	5.4%
M22	Other dermatoses	22	19	11	15	9	76	8.7%	111	62	80	49	48	350	8.0%
M23	Diseases of nail	7	8	8	2	5	30	3.4%	21	27	22	21	21	112	2.6%
M26	Sebaceous gland diseases	4	5	6	5	6	26	3.0%	26	31	21	26	28	132	3.0%
M2y	Other specified diseases of skin or subcutaneous tissue	13	8	5	6	5	37	4.2%	40	46	27	28	16	157	3.6%
M2z	Other skin and subcutaneous tissue disease NOS	22	7	10	8	10	57	6.5%	95	91	53	41	42	322	7.4%
N05	Osteoarthritis and allied disorders	596	36	14	12	10	668	76.4%	252	166	86	96	87	687	15.7%
N09	Other and unspecified joint disorders	352	102	58	31	27	570	65.2%	338	235	186	155	160	1074	24.6%
N11	Spondylosis and allied disorders	24	17	10	16	10	77	8.8%	72	45	54	43	26	240	5.5%
N13	Other cervical disorders	14	21	26	17	18	96	11.0%	109	75	78	67	64	393	9.0%
N14	Other and unspecified back disorders	89	69	48	28	44	278	31.8%	343	226	232	192	146	1139	26.1%
N21	Peripheral enthesopathies and allied syndromes	29	26	24	20	11	110	12.6%	99	116	104	72	83	474	10.8%
N22	Other disorders of the synovium, tendon and bursa	15	12	5	12	5	49	5.6%	47	33	28	33	28	169	3.9%
N33	Other bone and cartilage disorders	24	12	13	4	5	58	6.6%	83	42	41	26	24	216	4.9%
PC0	Anomalies of ovaries	11	8	9	5	4	37	4.2%	64	46	19	16	7	152	3.5%
R00	[D]General symptoms	77	59	37	29	33	235	26.9%	374	268	171	150	142	1105	25.3%
R01	[D]Nervous and musculoskeletal symptoms	13	5	9	7	4	38	4.3%	42	29	31	39	26	167	3.8%
R02	[D]Symptoms affecting skin and other integumentary tissue	92	65	36	37	31	261	29.9%	392	279	200	166	130	1167	26.7%
R04	[D]Head and neck symptoms	21	26	24	12	22	105	12.0%	156	116	109	89	85	555	12.7%
R06	[D]Respiratory system and chest symptoms	111	82	48	42	41	324	37.1%	595	353	266	202	181	1597	36.5%
R07	[D]Digestive system symptoms	29	32	17	11	13	102	11.7%	141	128	92	73	64	498	11.4%
R08	[D]Urinary system symptoms	33	21	23	14	10	101	11.6%	120	102	78	66	48	414	9.5%
R09	[D]Other abdominal and pelvic symptoms	67	37	31	24	22	181	20.7%	225	156	143	102	88	714	16.3%

Read-Code	Code-meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
R14	[D]Nonspecific abnormal function studies	24	10	6	9	9	58	6.6%	65	53	26	28	21	193	4.4%
SK1	Other specified injury	19	23	13	17	13	85	9.7%	99	76	78	71	72	396	9.1%
ZV0	[V]Persons with potential health hazards related to communicable diseases	63	6	2	1	2	74	8.5%	266	48	16	6	5	341	7.8%
ZV4	[V]Persons with a condition influencing their health status	11	16	13	10	13	63	7.2%	92	85	60	52	44	333	7.6%
ZV5	[V]Specified procedures and aftercare	9	8	2	5	3	27	3.1%	25	19	14	12	8	78	1.8%
ZV6	[V]Other reasons for encounter	32	18	10	12	17	89	10.2%	98	82	58	55	36	329	7.5%

Table 9-3: Identified BNF subchapters within PiPCA with frequencies of which annual year each code was first identified within for cases and controls

BNF Subchapter	Meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
1.1.2	Compound Alginates and proprietary indigestion preparation	44	21	14	4	15	98	11.2%	233	57	52	44	53	439	10.0%
1.3.1	H2-receptor antagonists	44	4	9	10	10	77	8.8%	150	47	47	54	53	351	8.0%
1.3.6	Other Antisec Drugs+Mucosal Protectants	300	28	24	20	11	383	43.8%	1012	163	118	74	77	1444	33.0%
1.4.2	Antimotility drugs	25	6	6	8	7	52	5.9%	79	36	42	33	54	244	5.6%
1.6.1	Bulk forming laxatives	43	21	12	7	12	95	10.9%	174	54	52	43	35	358	8.2%
1.6.2	Stimulant laxatives	65	16	5	10	5	101	11.6%	151	51	46	44	33	325	7.4%
1.6.4	Osmotic laxatives	150	34	15	14	10	223	25.5%	397	119	85	55	54	710	16.2%
1.7.2	Compound haemorrhoidal preparations with corticosteroids	27	10	11	10	9	67	7.7%	68	41	36	46	31	222	5.1%
2.2.1	Thiazides and related diuretics	134	57	52	23	11	277	31.7%	532	192	176	99	75	1074	24.6%
2.2.2	Loop diuretics	62	13	20	7	5	107	12.2%	280	98	99	34	26	537	12.3%
2.2.4	Potassium-sparing diuretics with other diuretics	12	5	9	5	3	34	3.9%	62	26	16	22	13	139	3.2%
2.3.2	Drugs for arrhythmias	15	4	4	2	4	29	3.3%	30	8	7	7	9	61	1.4%

BNF Subchapter	Meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
2.5.4	Alpha-adrenoreceptor blocking drugs	54	10	5	7	1	77	8.8%	218	21	21	28	22	310	7.1%
2.5.5	Drugs affecting the renin-angiotensin system	317	11	12	5	3	348	39.8%	1554	44	42	25	17	1682	38.5%
2.6.1	Nitrates	81	15	8	11	9	124	14.2%	410	66	55	47	43	621	14.2%
2.6.2	Calcium-channel inhibitors	258	32	11	7	10	318	36.4%	1037	88	71	49	55	1300	29.7%
2.8.2	Oral Anticoagulants	34	1	0	1	1	37	4.2%	202	13	9	8	6	238	5.4%
3.1.1	Adrenoreceptor agonists	137	20	16	7	17	197	22.5%	726	110	63	58	41	998	22.8%
3.1.2	Antimuscarinic bronchodilators	40	2	3	2	0	47	5.4%	200	12	16	9	12	249	5.7%
3.4.1	Antihistamines	69	30	23	32	14	168	19.2%	323	151	122	89	91	776	17.8%
3.9.1	Cough Suppressants	3	8	3	10	12	36	4.1%	19	22	24	26	39	130	3.0%
4.1.1	Hypnotics	39	10	8	10	8	75	8.6%	109	42	36	26	32	245	5.6%
4.1.2	Anxiolytics	67	26	13	22	17	145	16.6%	294	96	82	78	77	627	14.3%
4.3.1	Tricyclic and related antidepressants	91	37	17	15	20	180	20.6%	319	87	75	78	70	629	14.4%
4.3.3	Selective serotonin re-uptake inhibitors	83	21	19	14	12	149	17.0%	421	76	74	75	64	710	16.2%
4.3.4	Other antidepressant drugs	20	6	4	7	5	42	4.8%	92	26	16	17	22	173	4.0%
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	27	6	7	6	6	52	5.9%	34	14	9	5	10	72	1.6%
4.6.	Drugs used in nausea and vertigo	42	23	14	17	19	115	13.2%	161	115	83	85	77	521	11.9%
4.7.1	Non-opioid analgesics and compound analgesic preparations	532	101	59	28	17	737	84.3%	1224	387	341	245	169	2366	54.1%
4.7.2	Opioid analgesics	521	46	20	9	7	603	69.0%	967	207	102	43	43	1362	31.2%
4.7.4	Antimigraine drugs	14	9	4	6	4	37	4.2%	71	16	24	20	27	158	3.6%
4.8.1	Control of the epilepsies	41	8	5	4	6	64	7.3%	181	20	19	10	8	238	5.4%
5.1.1	Penicillins	270	107	72	49	44	542	62.0%	1208	558	396	242	205	2609	59.7%
5.1.2	Cephalosporins, carbapenems and other betalactams	42	43	37	44	42	208	23.8%	167	155	177	189	159	847	19.4%
5.1.3	Tetracyclines	52	27	20	13	11	123	14.1%	255	149	93	72	69	638	14.6%
5.1.5	Macrolides	56	37	29	30	24	176	20.1%	275	180	124	103	103	785	18.0%
5.1.12	Quinolones	18	21	21	8	10	78	8.9%	81	61	71	74	64	351	8.0%
5.1.13	Urinary tract infections	31	11	10	2	2	56	6.4%	102	48	33	23	8	214	4.9%

BNF Subchapter	Meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
5.4.1	Antimalarials	55	17	19	8	8	107	12.2%	178	51	38	20	38	325	7.4%
5.4.4	Antigiardial drugs	8	11	5	9	11	44	5.0%	49	43	39	34	33	198	4.5%
6.1.2	Anti-Diabetic drugs	60	3	1	1	1	66	7.6%	400	6	8	5	3	422	9.7%
6.2.1	Thyroid hormones	63	1	0	0	0	64	7.3%	334	1	1	0	1	337	7.7%
6.3.2	Glucocorticoid therapy	116	39	34	12	23	224	25.6%	346	147	104	82	68	747	17.1%
6.4.1	Female sex hormones and their modulators	18	7	11	6	7	49	5.6%	60	24	34	45	46	209	4.8%
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	58	5	8	2	0	73	8.4%	231	14	9	9	9	272	6.2%
7.2.1	Preparations for vaginal and vulval changes	20	9	7	7	7	50	5.7%	90	46	35	26	40	237	5.4%
7.2.2	Vaginal and vulval infections	20	5	7	11	6	49	5.6%	64	53	37	43	28	225	5.1%
7.4.1	Drugs for urinary retention	39	4	4	4	4	55	6.3%	167	15	12	13	13	220	5.0%
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	32	10	7	7	4	60	6.9%	92	25	15	22	17	171	3.9%
8.1.3	Antimetabolites	17	3	3	3	3	29	3.3%	32	13	8	3	2	58	1.3%
9.1.1	Iron-deficiency anaemias	59	10	8	7	5	89	10.2%	131	48	39	30	35	283	6.5%
9.1.2	Drugs used in megaloblastic anaemias	32	2	1	3	1	39	4.5%	119	17	12	8	7	163	3.7%
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	17	14	7	5	5	48	5.5%	52	44	27	25	27	175	4.0%
9.4.2	Enteral nutrition	15	1	6	2	3	27	3.1%	99	28	27	10	17	181	4.1%
9.6.4	Vitamin D	86	10	4	5	0	105	12.0%	273	19	13	10	13	328	7.5%
10.1.2	Corticosteroids	4	6	5	6	7	28	3.2%	9	14	11	14	20	68	1.6%
10.1.4	Gout and cytotoxic induced hyperuricaemia	17	2	1	0	1	21	2.4%	105	12	6	7	9	139	3.2%
10.3.2	Rubefacients and other topical antirheumatics	211	64	31	28	20	354	40.5%	533	177	130	99	86	1025	23.5%
11.3.1	Antibacterials	29	22	16	29	20	116	13.3%	149	112	111	119	95	586	13.4%
11.8.1	Tear deficiency, ocular lubricants and astringents	70	10	6	9	4	99	11.3%	305	51	48	38	27	469	10.7%
12.1.1	Otitis Externa	28	19	13	13	13	86	9.8%	127	67	71	69	66	400	9.2%
12.1.3	Removal of Ear Wax	30	20	9	12	8	79	9.0%	117	92	78	71	57	415	9.5%

BNF Subchapter	Meaning	Case							Control						
		1	2	3	4	5	Total	%	1	2	3	4	5	Total	%
12.2.1	Drugs used in Nasal Allergy	49	20	16	16	7	108	12.4%	318	114	97	77	69	675	15.4%
12.2.3	Nasal Preparations for Infection	29	12	5	6	6	58	6.6%	45	39	29	26	24	163	3.7%
12.3.1	Drugs for Oral Ulceration and Inflammation	15	8	5	3	3	34	3.9%	33	32	19	22	19	125	2.9%
12.3.2	Oropharyngeal anti-infective Drugs	13	3	8	8	7	39	4.5%	62	39	22	26	29	178	4.1%
13.2.1	Emollients	69	21	13	15	5	123	14.1%	295	127	62	58	40	582	13.3%
13.10.1	Antibacterial preparations	28	22	11	15	20	96	11.0%	135	88	84	65	69	441	10.1%
13.10.2	Antifungal preparations	50	12	15	18	10	105	12.0%	149	105	90	89	60	493	11.3%

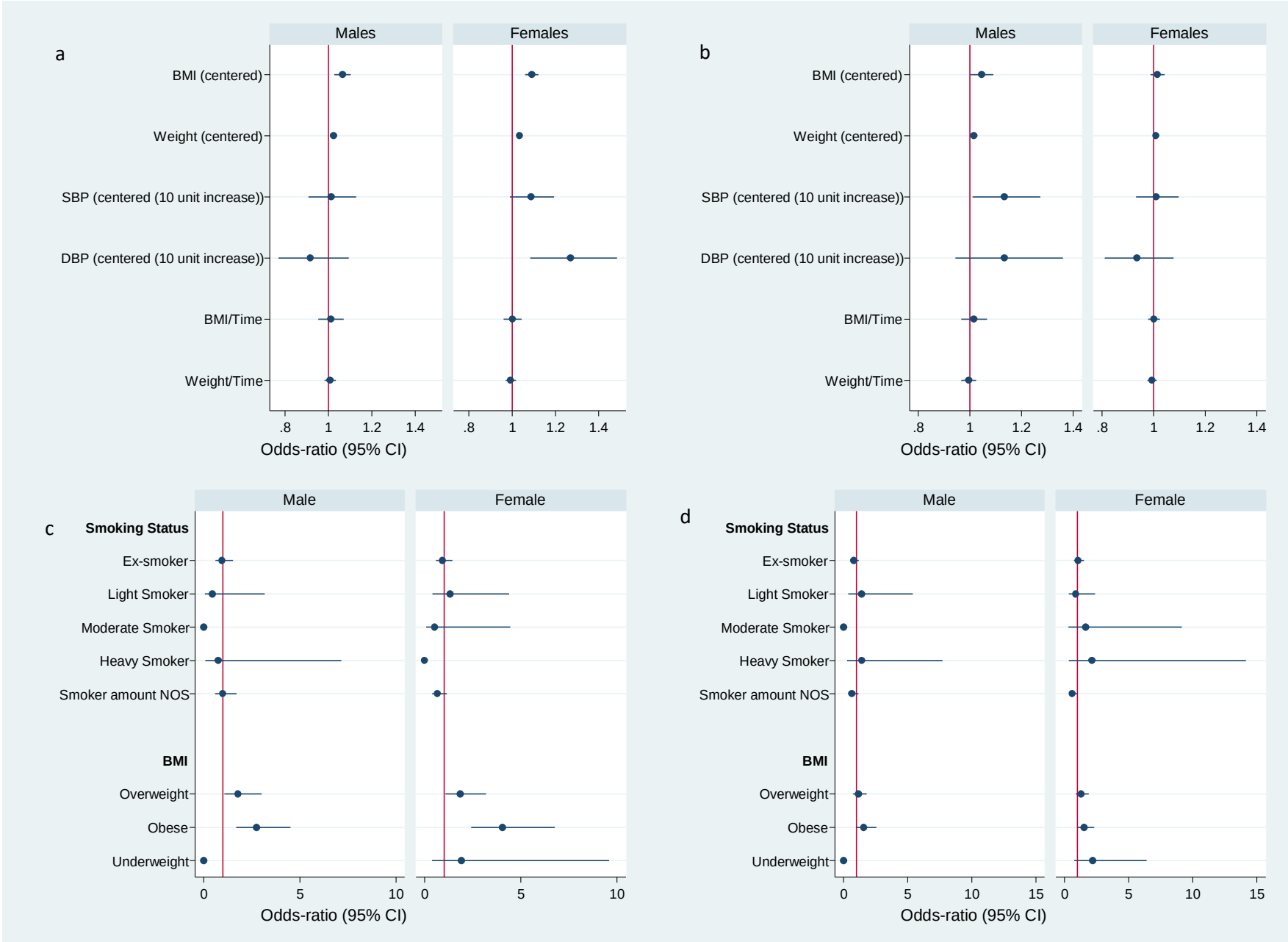

Figure 9-2: Odds ratios of the stratified conditional logistic regression for factors requiring multiple imputation by gender. A) continuous factors for a TKA, b) continuous factors for a THA, c) categorical factors for TKA d) categorical factors for THA

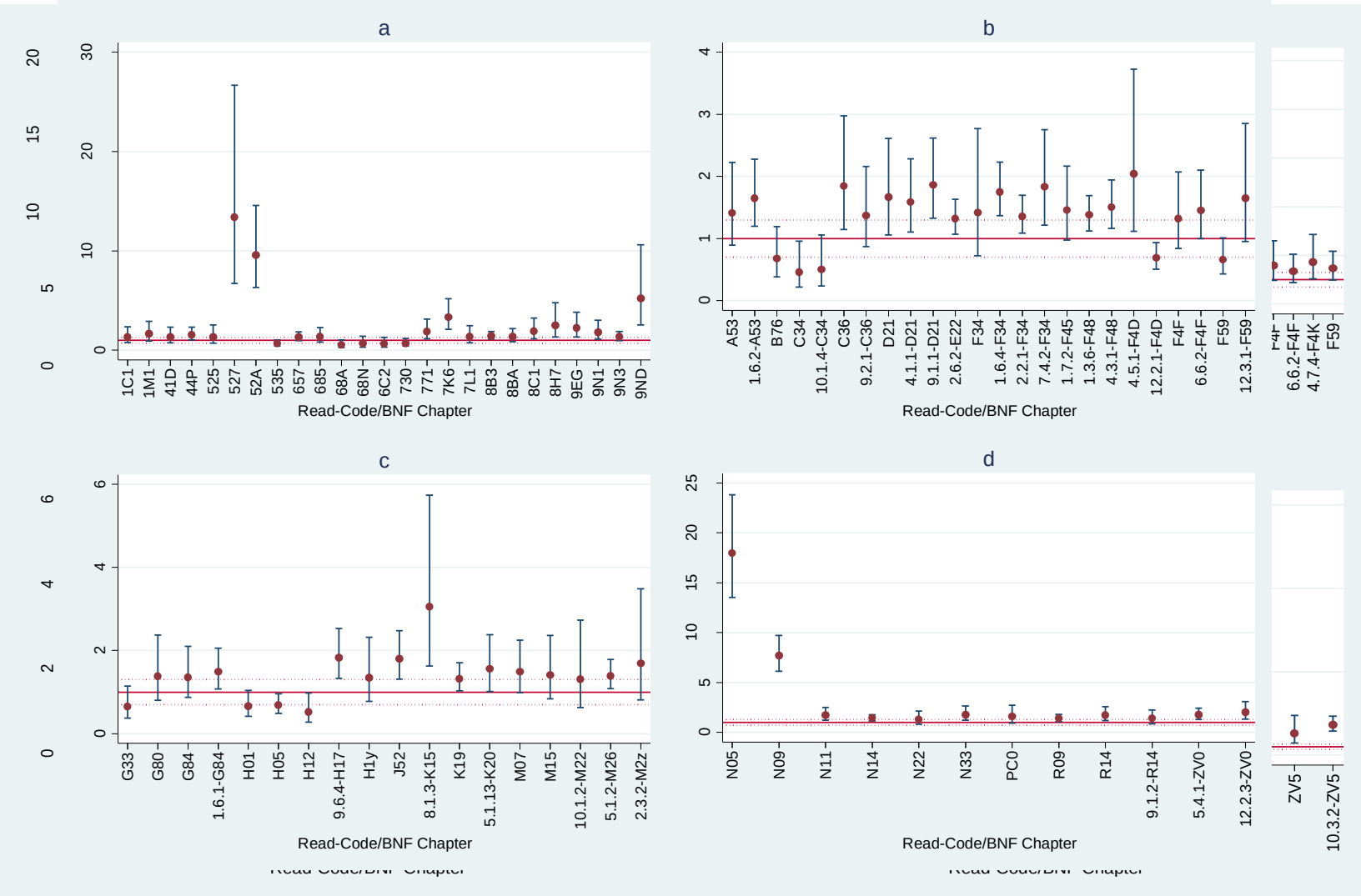

Figure 9-3: Odds ratios of Read-code and BNF subchapter factors for TKA with odds ratios <0.7 or >1.3

Figure 9-4: Odds ratios of Read-code and BNF subchapter factors for THA with odds ratios <0.7 or >1.3

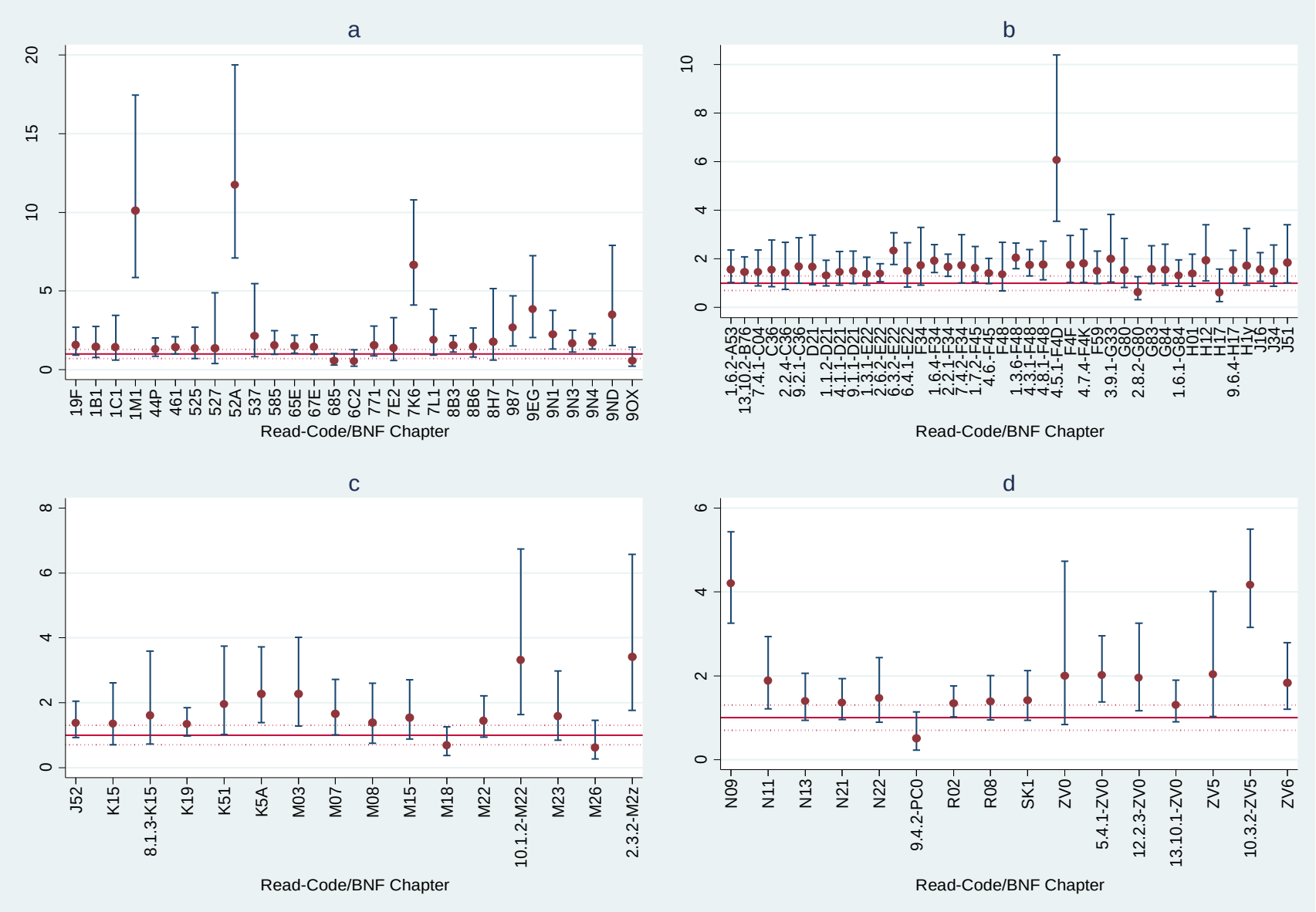

Figure 9-5 : Odds ratios of Read-code and BNF subchapter factors for TKA with odds ratios <0.7 or >1.3 adjusted for OA

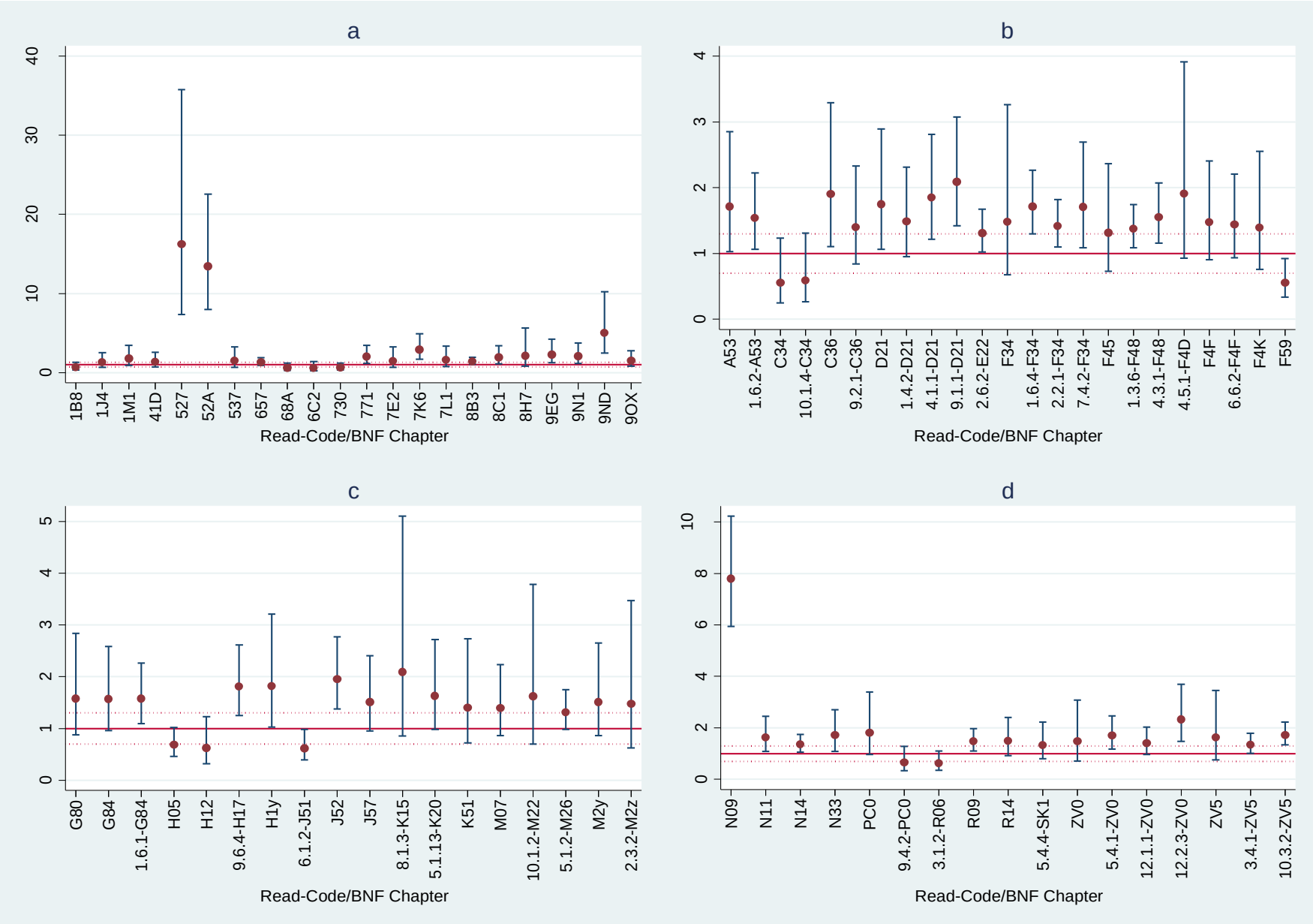

Figure 9-6: Odds ratios of Read-code and BNF subchapter factors for THA with odds ratios <0.7 or >1.3 adjusted for OA

Table 9-4: Conditional logistic regression results for TKA stratified by gender: displaying odds ratios for the males if they are either <0.75 or >1.33

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
52A	Plain X-ray hip/leg	12.04	5.84 - 24.83	<0.01	9.55	5.46 - 16.71	<0.01
1M1	Pain in lower limb	10.19	5.26 - 19.73	<0.01	12.23	5.70 - 26.24	<0.01
7K6	Other joint operations	9.33	4.68 - 18.63	<0.01	6.36	3.61 - 11.20	<0.01
4.7.2	Opioid analgesics	6.77	4.59 - 9.97	<0.01	6.39	4.38 - 9.32	<0.01
N09	Other and unspecified joint disorders	5.61	4.01 - 7.84	<0.01	3.45	2.53 - 4.71	<0.01
9EG	Disabled driver badge report	5.14	2.43 - 10.85	<0.01	2.81	1.15 - 6.83	0.02
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	5.00	2.08 - 12.01	<0.01	6.81	3.72 - 12.46	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	4.96	3.32 - 7.40	<0.01	4.77	3.14 - 7.24	<0.01
9N1	Site of encounter	4.47	1.97 - 10.18	<0.01	1.95	1.06 - 3.59	0.03
10.3.2	Rubefacients and other topical antirheumatics	3.99	2.80 - 5.70	<0.01	3.40	2.46 - 4.69	<0.01
ZV5	[V]Specified procedures and aftercare	3.74	1.74 - 8.03	<0.01	1.56	0.57 - 4.27	0.38
9ND	Incoming mail processing	3.66	1.29 - 10.38	0.01	4.34	1.23 - 15.24	0.02
7L1	Other miscellaneous operations	3.29	1.56 - 6.95	<0.01	1.09	0.42 - 2.84	0.87
2.3.2	Drugs for arrhythmias	3.21	1.44 - 7.17	<0.01	3.00	1.31 - 6.86	<0.01
987	FP/MS - minor surgery claim	3.18	1.46 - 6.92	<0.01	2.16	1.06 - 4.43	0.04
1.6.2	Stimulant laxatives	3.02	1.70 - 5.35	<0.01	1.13	0.70 - 1.84	0.61
J51	Diverticula of intestine	2.70	1.14 - 6.38	0.02	1.24	0.60 - 2.54	0.56
N22	Other disorders of the synovium, tendon and bursa	2.70	1.39 - 5.25	<0.01	1.15	0.63 - 2.10	0.64
8B6	Prophylactic drug therapy	2.50	0.63 - 10.00	0.20	1.77	1.02 - 3.07	0.04
6.3.2	Glucocorticoid therapy	2.49	1.72 - 3.60	<0.01	2.25	1.61 - 3.14	<0.01
10.1.2	Corticosteroids	2.45	1.03 - 5.81	0.04	4.12	1.78 - 9.55	<0.01

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
M03	Other cellulitis and abscess	2.29	1.01 - 5.23	0.05	1.66	0.88 - 3.12	0.12
C36	Disorders of fluid, electrolyte and acid-base balance	2.26	1.05 - 4.87	0.04	1.18	0.54 - 2.57	0.68
1.6.4	Osmotic laxatives	2.09	1.38 - 3.14	<0.01	1.85	1.31 - 2.61	<0.01
M07	Other local infections of skin and subcutaneous tissue	2.05	1.09 - 3.88	0.03	1.25	0.66 - 2.37	0.49
SK1	Other specified injury	2.04	1.22 - 3.41	<0.01	1.10	0.67 - 1.82	0.71
4.1.1	Hypnotics	2.03	1.10 - 3.74	0.02	1.31	0.76 - 2.25	0.32
M22	Other dermatoses	1.99	1.21 - 3.26	<0.01	0.84	0.46 - 1.55	0.59
9N3	Indirect encounter	1.98	1.18 - 3.33	<0.01	1.23	0.74 - 2.06	0.42
G83	Varicose veins of the legs	1.92	0.97 - 3.78	0.06	1.89	1.12 - 3.18	0.02
19F	Diarrhoea symptoms	1.89	0.93 - 3.82	0.08	1.36	0.73 - 2.52	0.34
1.3.6	Other Antisec Drugs+Mucosal Protectants	1.87	1.34 - 2.61	<0.01	1.96	1.45 - 2.65	<0.01
R01	[D]Nervous and musculoskeletal symptoms	1.85	0.92 - 3.70	0.08	1.04	0.52 - 2.10	0.90
3.1.2	Antimuscarinic bronchodilators	1.84	0.99 - 3.39	0.05	0.75	0.37 - 1.54	0.43
65E	Influenza vaccination	1.82	1.14 - 2.90	0.01	1.56	0.99 - 2.45	0.05
8H7	Other referral	1.78	0.55 - 5.72	0.33	1.66	0.67 - 4.13	0.27
8.1.3	Antimetabolites	1.76	0.70 - 4.48	0.23	2.56	1.02 - 6.45	0.05
9N4	Failed encounter	1.75	1.22 - 2.50	<0.01	1.52	1.09 - 2.13	0.01
4.3.4	Other antidepressant drugs	1.74	0.77 - 3.92	0.18	1.09	0.54 - 2.20	0.81
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.72	0.75 - 3.95	0.20	1.88	1.07 - 3.30	0.03
H1y	Other specified diseases of upper respiratory tract	1.72	0.75 - 3.95	0.20	1.33	0.63 - 2.82	0.46
4.3.1	Tricyclic and related antidepressants	1.71	1.09 - 2.67	0.02	1.59	1.13 - 2.25	<0.01
44P	Serum cholesterol	1.71	0.94 - 3.09	0.08	1.42	0.84 - 2.38	0.19
5.1.5	Macrolides	1.70	1.13 - 2.56	0.01	1.14	0.79 - 1.65	0.47

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
4.8.1	Control of the epilepsies	1.69	0.97 - 2.96	0.06	1.44	0.82 - 2.54	0.21
F58	Other ear disorders	1.67	0.96 - 2.90	0.07	0.52	0.26 - 1.06	0.07
N11	Spondylosis and allied disorders	1.66	0.87 - 3.16	0.12	1.52	0.88 - 2.62	0.13
13.10.2	Antifungal preparations	1.65	1.05 - 2.60	0.03	1.29	0.84 - 2.00	0.24
1.3.1	H2-receptor antagonists	1.64	0.98 - 2.76	0.06	1.06	0.63 - 1.79	0.82
5.4.1	Antimalarials	1.62	0.93 - 2.82	0.09	1.73	1.10 - 2.70	0.02
730	External ear and external auditory canal operations	1.62	0.86 - 3.08	0.14	0.40	0.14 - 1.14	0.09
525	Plain X-ray spine	1.61	0.57 - 4.60	0.37	1.20	0.56 - 2.59	0.63
68N	Immunisation status screen	1.61	0.61 - 4.26	0.34	0.89	0.27 - 2.90	0.84
7.4.1	Drugs for urinary retention	1.60	1.03 - 2.49	0.04			
585	Other diagnostic ultrasound	1.59	0.84 - 2.99	0.15	2.04	1.18 - 3.54	0.01
ZV6	[V]Other reasons for encounter	1.59	0.90 - 2.82	0.11	2.40	1.47 - 3.92	<0.01
Eu3	[X]Mood - affective disorders	1.58	0.84 - 2.95	0.15	1.14	0.64 - 2.01	0.65
2.2.1	Thiazides and related diuretics	1.56	1.08 - 2.25	0.02	1.63	1.17 - 2.26	<0.01
F34	Mononeuritis of upper limb and mononeuritis multiplex	1.56	0.50 - 4.86	0.45	2.11	1.06 - 4.18	0.03
461	Urine exam. - general	1.55	0.91 - 2.66	0.11	1.32	0.86 - 2.02	0.21
M23	Diseases of nail	1.54	0.70 - 3.40	0.29	1.67	0.78 - 3.57	0.19
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	1.54	0.50 - 4.72	0.45	1.31	0.84 - 2.07	0.24
N21	Peripheral enthesopathies and allied syndromes	1.51	0.97 - 2.33	0.06	1.37	0.88 - 2.12	0.16
1C1	Hearing symptoms	1.50	0.54 - 4.15	0.44	1.39	0.55 - 3.55	0.49
M2y	Other specified diseases of skin or subcutaneous tissue	1.49	0.70 - 3.14	0.30	0.85	0.35 - 2.07	0.72
1.7.2	Compound haemorrhoidal preparations with corticosteroids	1.48	0.80 - 2.72	0.21	1.79	1.05 - 3.04	0.03
J34	Diaphragmatic	1.47	0.63 - 3.43	0.38	1.48	0.81 - 2.69	0.20

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	hernia						
F48	Visual disturbances	1.47	0.62 - 3.49	0.38	1.00	0.44 - 2.30	1.00
2.2.4	Potassium-sparing diuretics with other diuretics	1.46	0.46 - 4.57	0.52	1.50	0.77 - 2.92	0.23
AB0	Dermatophytosis including tinea or ringworm	1.44	0.86 - 2.38	0.16	1.17	0.63 - 2.18	0.62
M2z	Other skin and subcutaneous tissue disease NOS	1.44	0.76 - 2.71	0.27	0.82	0.44 - 1.53	0.54
H12	Chronic pharyngitis and nasopharyngitis	1.43	0.67 - 3.08	0.35	1.76	0.88 - 3.52	0.11
F4K	Other eye disorders	1.42	0.60 - 3.37	0.43	0.64	0.25 - 1.67	0.37
H02	Acute pharyngitis	1.42	0.75 - 2.71	0.28	1.13	0.71 - 1.81	0.60
G84	Haemorrhoids	1.41	0.70 - 2.82	0.34	1.83	1.01 - 3.30	0.04
1B8	Eye symptoms	1.39	0.65 - 2.97	0.40	0.66	0.29 - 1.51	0.33
4.6.	Drugs used in nausea and vertigo	1.39	0.80 - 2.43	0.24	1.32	0.90 - 1.94	0.16
K31	Other breast disorders	1.39	0.29 - 6.70	0.68	1.25	0.72 - 2.19	0.43
J16	Disorders of stomach function	1.37	0.83 - 2.26	0.22	1.64	1.05 - 2.58	0.03
ZV0	[V]Persons with potential health hazards related to communicable diseases	1.37	0.41 - 4.59	0.61	2.67	0.85 - 8.42	0.09
535	Standard chest X-ray	1.37	0.76 - 2.46	0.29	0.81	0.44 - 1.48	0.49
F4F	Lacrimal system disorders	1.35	0.63 - 2.88	0.44	1.81	0.94 - 3.47	0.07
5.1.2	Cephalosporins, carbapenems and other betalactams	1.35	0.86 - 2.13	0.19	1.26	0.89 - 1.79	0.20
3.9.1	Cough Suppressants	1.34	0.52 - 3.46	0.55	2.47	1.24 - 4.91	0.01
8BI	Other medication review	0.72	0.24 - 2.14	0.56	1.75	0.82 - 3.72	0.15
3.4.1	Antihistamines	0.72	0.44 - 1.17	0.18	1.06	0.74 - 1.51	0.74
12.3.1	Drugs for Oral Ulceration and Inflammation	0.71	0.21 - 2.40	0.58	1.38	0.73 - 2.62	0.32
2.8.2	Oral Anticoagulants	0.69	0.32 - 1.47	0.33	0.51	0.20 - 1.29	0.16
321	ECG - general	0.68	0.36 - 1.30	0.24	1.07	0.66 - 1.74	0.78
1.4.2	Antimotility drugs	0.65	0.27 - 1.55	0.33	1.23	0.68 - 2.22	0.50

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
M26	Sebaceous gland diseases	0.55	0.17 - 1.83	0.33	0.76	0.32 - 1.82	0.54
M18	Pruritus and related conditions	0.52	0.20 - 1.32	0.17	0.92	0.49 - 1.71	0.79
M15	Erythematous conditions	0.50	0.15 - 1.63	0.25	1.62	0.86 - 3.06	0.13
N33	Other bone and cartilage disorders	0.45	0.06 - 3.52	0.45	1.04	0.60 - 1.78	0.90
5.1.13	Urinary tract infections	0.36	0.05 - 2.72	0.32	1.30	0.80 - 2.13	0.29
9.4.2	Enteral nutrition	0.13	0.02 - 0.97	0.05	0.95	0.46 - 2.00	0.90
12.2.3	Nasal Preparations for Infection	0.76	0.32 - 1.82	0.54	2.44	1.39 - 4.29	<0.01
K51	Genital prolapse				2.25	1.25 - 4.03	<0.01
K5A	Menopausal and postmenopausal disorders				2.14	1.37 - 3.36	<0.01
A08	Ill-defined intestinal tract infections	0.83	0.37 - 1.84	0.64	2.05	1.18 - 3.54	0.01
4.7.4	Antimigraine drugs	0.94	0.27 - 3.25	0.92	2.01	1.15 - 3.53	0.02
G80	Phlebitis and thrombophlebitis	0.91	0.31 - 2.67	0.86	1.90	1.00 - 3.64	0.05
F59	Hearing loss	1.20	0.70 - 2.06	0.51	1.89	1.06 - 3.36	0.03
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.08	0.50 - 2.31	0.84	1.81	0.96 - 3.39	0.07
2.6.2	Calcium-channel inhibitors	1.12	0.79 - 1.57	0.52	1.80	1.31 - 2.47	<0.01
9.6.4	Vitamin D	1.05	0.35 - 3.13	0.93	1.75	1.18 - 2.61	<0.01
D21	Other and unspecified anaemias	1.32	0.56 - 3.13	0.53	1.73	0.91 - 3.27	0.09
771	Colon operations and sigmoidoscopy of rectum	0.97	0.43 - 2.22	0.94	1.72	0.82 - 3.60	0.15
H0z	Acute respiratory infection NOS	0.89	0.34 - 2.33	0.81	1.72	0.72 - 4.07	0.22
527	Plain X-ray pelvis				1.67	0.45 - 6.16	0.44
8B3	Drug therapy	1.05	0.67 - 1.64	0.85	1.65	1.13 - 2.42	0.01
6.4.1	Female sex hormones and their modulators				1.62	0.97 - 2.69	0.06
K19	Other urethral and urinary tract disorders	1.18	0.71 - 1.98	0.52	1.60	1.14 - 2.25	<0.01
10.1.4	Gout and cytotoxic induced	0.86	0.40 - 1.87	0.70	1.60	0.57 - 4.48	0.37

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	hyperuricaemia						
2.5.4	Alpha-adrenoreceptor blocking drugs	1.11	0.64 - 1.93	0.71	1.58	0.93 - 2.67	0.09
8C1	Nursing care	0.95	0.44 - 2.05	0.90	1.55	0.69 - 3.50	0.29
A53	Measles	1.09	0.54 - 2.20	0.81	1.53	0.78 - 3.03	0.22
PC0	Anomalies of ovaries				1.51	0.59 - 3.90	0.39
9.1.1	Iron-deficiency anaemias	1.33	0.68 - 2.60	0.40	1.50	0.93 - 2.40	0.09
J52	Functional gastrointestinal tract disorders NEC	1.30	0.72 - 2.37	0.38	1.50	0.96 - 2.33	0.07
R08	[D]Urinary system symptoms	1.15	0.69 - 1.93	0.59	1.50	0.96 - 2.35	0.08
C34	Gout	0.78	0.38 - 1.60	0.50	1.50	0.41 - 5.45	0.54
4.3.3	Selective serotonin re-uptake inhibitors	0.99	0.62 - 1.57	0.96	1.46	1.02 - 2.07	0.04
537	Soft tissue X-ray breast				1.46	0.62 - 3.47	0.39
R14	[D]Nonspecific abnormal function studies	1.12	0.54 - 2.35	0.76	1.42	0.75 - 2.70	0.28
R00	[D]General symptoms	1.11	0.76 - 1.62	0.59	1.41	1.01 - 1.95	0.04
R09	[D]Other abdominal and pelvic symptoms	1.16	0.76 - 1.77	0.48	1.40	0.97 - 2.00	0.07
2.5.5	Drugs affecting the renin-angiotensin system	1.09	0.79 - 1.50	0.61	1.37	1.01 - 1.87	0.04
5.4.4	Antigiardial drugs				1.37	0.79 - 2.35	0.26
N14	Other and unspecified back disorders	1.05	0.73 - 1.51	0.80	1.35	0.99 - 1.84	0.05
2.6.1	Nitrates	0.93	0.59 - 1.44	0.73	1.34	0.87 - 2.06	0.19
H17	Allergic rhinitis	0.89	0.34 - 2.31	0.82	0.74	0.26 - 2.12	0.57
6C2	Primary prevention of cardiovascular disease	0.92	0.42 - 2.03	0.83	0.64	0.14 - 2.98	0.57
12.2.1	Drugs used in Nasal Allergy	1.27	0.84 - 1.94	0.26	0.59	0.37 - 0.96	0.03
ZV4	[V]Persons with a condition influencing their health status	0.98	0.53 - 1.82	0.95	0.59	0.31 - 1.14	0.12
F50	Disorders of external ear	1.30	0.91 - 1.87	0.15	0.58	0.37 - 0.90	0.01

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
G57	Cardiac dysrhythmias	0.83	0.42 - 1.63	0.59	0.48	0.21 - 1.07	0.07
685	Cervical neoplasia screening				0.48	0.28 - 0.83	<0.01

Table 9-5: Conditional logistic regression results for THA stratified by gender: displaying odds ratios for the males if they are either <0.75 or >1.33

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
527	Plain X-ray pelvis	27.50	6.10 - 124.07	<0.01	10.27	4.66 - 22.67	<0.01
52A	Plain X-ray hip/leg	12.99	6.51 - 25.90	<0.01	7.86	4.62 - 13.36	<0.01
8.1.3	Antimetabolites	10.00	3.05 - 32.80	<0.01	1.67	0.71 - 3.92	0.24
9ND	Incoming mail processing	8.80	2.41 - 32.13	<0.01	3.95	1.68 - 9.28	<0.01
N09	Other and unspecified joint disorders	8.51	5.82 - 12.43	<0.01	7.27	5.44 - 9.73	<0.01
4.7.1	Non-opioid analgesics and compound analgesic preparations	5.76	3.69 - 9.01	<0.01	5.36	3.71 - 7.74	<0.01
4.7.2	Opioid analgesics	5.55	3.86 - 7.98	<0.01	6.03	4.44 - 8.19	<0.01
8H7	Other referral	4.93	1.87 - 12.98	<0.01	1.36	0.54 - 3.42	0.51
7K6	Other joint operations	3.67	1.83 - 7.36	<0.01	3.05	1.68 - 5.53	<0.01
9EG	Disabled driver badge report	3.46	1.41 - 8.51	<0.01	1.85	0.98 - 3.51	0.06
9N1	Site of encounter	2.63	1.25 - 5.51	0.01	1.35	0.68 - 2.69	0.39
8C1	Nursing care	2.51	1.14 - 5.56	0.02	1.60	0.82 - 3.12	0.16
10.3.2	Rubefacients and other topical antirheumatics	2.43	1.72 - 3.45	<0.01	1.26	0.95 - 1.68	0.11
9.1.2	Drugs used in megaloblastic anaemias	2.36	1.18 - 4.75	0.02	0.92	0.46 - 1.84	0.82
G80	Phlebitis and thrombophlebitis	2.33	0.95 - 5.72	0.06	1.07	0.53 - 2.12	0.86
1M1	Pain in lower limb	2.27	0.91 - 5.68	0.08	1.38	0.67 - 2.83	0.39
2.3.2	Drugs for	2.19	0.74 - 6.48	0.16	1.39	0.52 - 3.74	0.52

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	arrhythmias						
N22	Other disorders of the synovium, tendon and bursa	2.15	0.96 - 4.85	0.06	1.02	0.54 - 1.91	0.96
4.5.1	Anti-obesity drugs acting on the gastro-intestinal tract	2.14	0.55 - 8.29	0.27	2.02	1.03 - 3.95	0.04
9.6.4	Vitamin D	2.14	1.05 - 4.35	0.04	1.76	1.23 - 2.53	<0.01
987	FP/MS - minor surgery claim	2.14	0.65 - 7.01	0.21	0.67	0.29 - 1.54	0.35
1C1	Hearing symptoms	2.08	0.99 - 4.39	0.05	0.83	0.35 - 1.98	0.67
F4K	Other eye disorders	2.06	0.82 - 5.19	0.12	0.91	0.46 - 1.80	0.78
M07	Other local infections of skin and subcutaneous tissue	2.04	0.97 - 4.31	0.06	1.31	0.80 - 2.15	0.28
F34	Mononeuritis of upper limb and mononeuritis multiplex	2.00	0.63 - 6.38	0.24	1.21	0.53 - 2.78	0.65
1.6.2	Stimulant laxatives	1.95	1.17 - 3.26	0.01	1.49	0.99 - 2.25	0.06
N11	Spondylosis and allied disorders	1.94	1.04 - 3.62	0.04	1.66	1.08 - 2.56	0.02
5.4.1	Antimalarials	1.89	1.13 - 3.17	0.02	1.73	1.17 - 2.56	<0.01
8BA	Other misc. therapy	1.86	0.94 - 3.68	0.08	1.06	0.55 - 2.02	0.87
ZV0	[V]Persons with potential health hazards related to communicable diseases	1.86	0.48 - 7.25	0.37	0.95	0.43 - 2.09	0.89
1.6.4	Osmotic laxatives	1.85	1.22 - 2.81	<0.01	1.70	1.26 - 2.29	<0.01
7.4.2	Drugs for urinary frequency, enuresis, and incontinence	1.70	0.79 - 3.69	0.18	1.88	1.16 - 3.04	0.01
1.6.1	Bulk forming laxatives	1.65	0.95 - 2.87	0.08	1.41	0.95 - 2.11	0.09
R14	[D]Nonspecific abnormal function studies	1.64	0.90 - 3.00	0.11	1.83	1.10 - 3.06	0.02

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
9.2.1	Oral Prepn for Fluid & Electrolyte Imb	1.63	0.68 - 3.91	0.27	1.29	0.75 - 2.20	0.36
9.1.1	Iron-deficiency anaemias	1.62	0.89 - 2.94	0.11	2.00	1.32 - 3.02	<0.01
657	Other bacterial vaccinations	1.62	0.97 - 2.72	0.07	1.17	0.77 - 1.80	0.46
PC0	Anomalies of ovaries	1.60	0.64 - 4.05	0.32	1.56	0.79 - 3.09	0.20
F4C	Disorders of conjunctiva	1.58	0.93 - 2.70	0.09	0.67	0.41 - 1.10	0.12
G84	Haemorrhoids	1.54	0.75 - 3.19	0.24	1.27	0.73 - 2.19	0.40
8B3	Drug therapy	1.52	1.00 - 2.30	0.05	1.42	1.01 - 1.99	0.04
12.1.1	Otitis Externa	1.51	0.92 - 2.46	0.10	0.97	0.61 - 1.52	0.88
12.2.3	Nasal Preparations for Infection	1.48	0.69 - 3.16	0.32	2.38	1.44 - 3.92	<0.01
F45	Glaucoma	1.46	0.69 - 3.11	0.32	0.83	0.40 - 1.69	0.60
12.1.3	Removal of Ear Wax	1.42	0.85 - 2.36	0.18	0.74	0.47 - 1.18	0.21
4.3.1	Tricyclic and related antidepressants	1.40	0.88 - 2.24	0.16	1.55	1.14 - 2.11	<0.01
771	Colon operations and sigmoidoscopy of rectum	1.36	0.58 - 3.20	0.48	2.29	1.24 - 4.24	<0.01
9N3	Indirect encounter	1.36	0.78 - 2.38	0.28	1.35	0.89 - 2.05	0.16
N14	Other and unspecified back disorders	1.36	0.96 - 1.94	0.09	1.47	1.12 - 1.94	<0.01
M18	Pruritus and related conditions	1.35	0.61 - 3.01	0.46	1.23	0.74 - 2.03	0.42
G33	Angina pectoris	0.74	0.30 - 1.78	0.50	0.61	0.30 - 1.25	0.18
ZV5	[V]Specified procedures and aftercare	0.74	0.22 - 2.54	0.64	1.40	0.61 - 3.24	0.43
M2z	Other skin and subcutaneous tissue disease NOS	0.73	0.39 - 1.35	0.31	0.77	0.45 - 1.31	0.33
321	ECG - general	0.72	0.37 - 1.40	0.33	1.07	0.68 - 1.68	0.78
C32	Disorders of lipoid metabolism	0.69	0.38 - 1.25	0.22	1.04	0.71 - 1.51	0.85
13.2.1	Emollients	0.67	0.39 - 1.15	0.15	1.37	0.97 - 1.93	0.07
M12	Contact dermatitis and other eczemas	0.67	0.35 - 1.29	0.23	1.36	0.92 - 2.01	0.12
1.1.2	Compound	0.66	0.36 - 1.22	0.18	1.36	0.94 - 1.99	0.11

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	Alginates and proprietary indigestion preparation						
4.3.3	Selective serotonin re-uptake inhibitors	0.66	0.37 - 1.15	0.14	1.02	0.74 - 1.40	0.89
R06	[D]Respiratory system and chest symptoms	0.66	0.46 - 0.94	0.02	1.04	0.80 - 1.36	0.75
AB2	Candidiasis	0.65	0.22 - 1.90	0.43	1.20	0.72 - 2.02	0.48
K31	Other breast disorders	0.63	0.08 - 5.00	0.66	1.07	0.64 - 1.80	0.79
68N	Immunisation status screen	0.62	0.19 - 2.01	0.42	0.70	0.26 - 1.88	0.48
10.1.4	Gout and cytotoxic induced hyperuricaemia	0.60	0.27 - 1.36	0.22	0.23	0.03 - 1.75	0.16
F48	Visual disturbances	0.60	0.21 - 1.71	0.34	1.79	1.00 - 3.19	0.05
6.2.1	Thyroid hormones	0.60	0.18 - 1.99	0.40	0.99	0.67 - 1.46	0.95
12.3.2	Oropharyngeal anti-infective Drugs	0.59	0.23 - 1.53	0.28	1.64	0.97 - 2.78	0.07
H0z	Acute respiratory infection NOS	0.59	0.21 - 1.60	0.30	0.97	0.54 - 1.76	0.92
E20	Neurotic disorders	0.58	0.29 - 1.16	0.13	0.97	0.67 - 1.39	0.85
G83	Varicose veins of the legs	0.58	0.23 - 1.50	0.26	1.19	0.73 - 1.95	0.48
12.2.1	Drugs used in Nasal Allergy	0.57	0.34 - 0.97	0.04	0.76	0.52 - 1.10	0.15
1.3.1	H2-receptor antagonists	0.56	0.27 - 1.14	0.11	1.22	0.78 - 1.89	0.38
3.1.1	Adrenoreceptor agonists	0.56	0.36 - 0.88	0.01	1.05	0.79 - 1.42	0.72
3.9.1	Cough Suppressants	0.55	0.16 - 1.83	0.33	1.36	0.75 - 2.49	0.31
68A	Neurolog./special sense screen	0.50	0.19 - 1.30	0.15	0.55	0.21 - 1.41	0.21
C04	Acquired hypothyroidism	0.47	0.11 - 2.03	0.31	0.96	0.63 - 1.47	0.86
H12	Chronic pharyngitis and nasopharyngiti	0.46	0.14 - 1.52	0.20	0.55	0.26 - 1.15	0.11

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	s						
19F	Diarrhoea symptoms	0.45	0.14 - 1.47	0.19	0.91	0.52 - 1.60	0.74
4.3.4	Other antidepressant drugs	0.42	0.13 - 1.37	0.15	1.55	0.94 - 2.55	0.09
3.1.2	Antimuscarinic bronchodilators	0.42	0.18 - 0.98	0.05	1.07	0.61 - 1.87	0.81
1J4	Suspected UTI	0.41	0.05 - 3.19	0.39	1.45	0.83 - 2.54	0.20
535	Standard chest X-ray	0.39	0.17 - 0.93	0.03	0.84	0.49 - 1.45	0.54
C34	Gout	0.37	0.15 - 0.93	0.04	0.75	0.22 - 2.53	0.64
5.4.4	Antigiardial drugs	0.35	0.08 - 1.47	0.15	1.55	0.96 - 2.50	0.07
10.1.2	Corticosteroids	0.32	0.04 - 2.48	0.28	2.04	0.89 - 4.68	0.09
5.1.13	Urinary tract infections	0.31	0.04 - 2.34	0.25	1.83	1.17 - 2.86	<0.01
2.2.4	Potassium-sparing diuretics with other diuretics	0.30	0.04 - 2.31	0.25	1.29	0.73 - 2.27	0.38
1B8	Eye symptoms	0.20	0.03 - 1.49	0.12	1.21	0.67 - 2.17	0.53
C36	Disorders of fluid, electrolyte and acid-base balance	1.14	0.43 - 3.03	0.79	2.22	1.27 - 3.88	<0.01
J52	Functional gastrointestinal tract disorders NEC	1.26	0.71 - 2.26	0.43	2.14	1.45 - 3.14	<0.01
7.4.1	Drugs for urinary retention	1.02	0.62 - 1.68	0.94	2.00	0.39 - 10.31	0.41
12.3.1	Drugs for Oral Ulceration and Inflammation	1.14	0.42 - 3.09	0.79	1.98	1.02 - 3.84	0.04
D21	Other and unspecified anaemias	1.21	0.53 - 2.80	0.65	1.93	1.12 - 3.32	0.02
N33	Other bone and cartilage disorders	0.83	0.18 - 3.78	0.81	1.92	1.27 - 2.89	<0.01
1.7.2	Compound haemorrhoidal preparations with corticosteroids	1.00	0.48 - 2.09	1.00	1.75	1.08 - 2.82	0.02
4.1.1	Hypnotics	1.25	0.60 - 2.61	0.55	1.73	1.13 - 2.63	0.01
44P	Serum cholesterol	1.31	0.66 - 2.58	0.44	1.71	1.02 - 2.87	0.04
M15	Erythematous conditions	0.82	0.27 - 2.47	0.72	1.71	0.94 - 3.09	0.08

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
525	Plain X-ray spine	0.88	0.26 - 3.01	0.84	1.62	0.77 - 3.41	0.20
H1y	Other specified diseases of upper respiratory tract	0.78	0.23 - 2.70	0.70	1.58	0.86 - 2.93	0.14
A53	Measles	1.23	0.58 - 2.57	0.59	1.55	0.87 - 2.75	0.14
5.1.2	Cephalosporins, carbapenems and other betalactams	1.10	0.68 - 1.77	0.71	1.53	1.14 - 2.05	<0.01
R09	[D]Other abdominal and pelvic symptoms	1.18	0.76 - 1.83	0.47	1.52	1.12 - 2.06	<0.01
6.6.2	Bisphosphonates and other drugs affecting bone metabolism	1.14	0.43 - 3.03	0.79	1.51	1.01 - 2.27	0.04
K19	Other urethral and urinary tract disorders	0.87	0.49 - 1.54	0.64	1.49	1.12 - 1.98	<0.01
2.2.1	Thiazides and related diuretics	1.15	0.78 - 1.69	0.48	1.48	1.12 - 1.94	<0.01
9OX	Influenza vacc. administratn.	1.04	0.42 - 2.55	0.94	1.47	0.72 - 3.00	0.30
7L1	Other miscellaneous operations	1.19	0.43 - 3.28	0.73	1.46	0.68 - 3.12	0.33
3.4.1	Antihistamines	0.95	0.59 - 1.53	0.84	1.44	1.07 - 1.92	0.01
F4F	Lacrimal system disorders	0.95	0.32 - 2.82	0.93	1.43	0.87 - 2.35	0.16
1.3.6	Other Antisec Drugs+Mucosal Protectants	1.33	0.96 - 1.84	0.08	1.41	1.08 - 1.83	0.01
2.6.2	Calcium-channel inhibitors	1.21	0.86 - 1.70	0.27	1.40	1.06 - 1.84	0.02
41D	Sample obtained	1.22	0.48 - 3.07	0.68	1.39	0.68 - 2.85	0.36
4.8.1	Control of the epilepsies	0.93	0.43 - 2.01	0.85	1.37	0.82 - 2.28	0.23
685	Cervical neoplasia screening				1.37	0.83 - 2.28	0.22
M03	Other cellulitis and abscess	0.87	0.38 - 1.98	0.74	0.74	0.36 - 1.51	0.41
67E	Foreign travel	1.15	0.63 - 2.10	0.65	0.72	0.40 - 1.30	0.27

Read-code/BNF subchapter	Read Term/ BNF Label	Male OR	Male 95% CI	Male P-Value	Female OR	Female 95% CI	Female P-Value
	advice						
R04	[D]Head and neck symptoms	1.02	0.61 - 1.70	0.93	0.72	0.48 - 1.08	0.11
11.3.1	Antibacterials	1.28	0.80 - 2.05	0.31	0.71	0.47 - 1.05	0.09
6.1.2	Anti-Diabetic drugs	0.81	0.47 - 1.40	0.46	0.63	0.37 - 1.07	0.09
B76	Benign neoplasm of skin	0.83	0.32 - 2.16	0.70	0.61	0.30 - 1.24	0.17
H01	Acute sinusitis	0.79	0.37 - 1.70	0.55	0.61	0.35 - 1.06	0.08
730	External ear and external auditory canal operations	0.79	0.38 - 1.64	0.53	0.58	0.26 - 1.30	0.19
H05	Other acute upper respiratory infections	1.09	0.65 - 1.82	0.75	0.52	0.34 - 0.81	<0.01
F59	Hearing loss	0.97	0.55 - 1.71	0.92	0.42	0.21 - 0.84	0.01
6C2	Primary prevention of cardiovascular disease	0.82	0.34 - 1.98	0.67	0.34	0.07 - 1.52	0.16