The Past, Present and Future of Total Hip and Knee Arthroplasty in the UK:
A population-based statistical analysis

by

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ABSTRACT

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THE PAST, PRESENT AND FUTURE OF TOTAL HIP AND KNEE ARTHROPLASTY IN THE UK:

A POPULATION-BASED STATISTICAL ANALYSIS

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The total replacement of the hip and knee joint has become one of the most successful surgical procedures of the late 20th century, yet in the United Kingdom little attention has been given to describing trends and exploring risk factors at a population level, with even less consideration given to future levels of activity.

This thesis has used nationally representative primary care data from the Clinical Practice Research Datalink to describe past trends, estimate the lifetime risk, explore risk factors and project future levels of total hip and knee replacement for the UK as a whole. The data comprised over 100,000 surgical procedures spanning a twenty year period, and was accompanied by demographic and clinical details for patients undergoing these procedures.

Temporal trends for hip and knee replacement between 1991 and 2006 were described by age and gender, and incidence rates were found to have increased considerably over the period. The lifetime risk of hip and knee replacement was estimated at between 5 and 10 percent for a 50-year old in the United Kingdom, which is much less than the lifetime risk of osteoarthritis, the disease for which the vast majority of these operations are performed. The time to failure of primary hip and knee replacements was found to have a small but significant association with body mass index. Finally, projections of the future rate of these replacement operations were presented, suggesting that changes in the distribution of body mass index in the UK may increase future levels of knee replacement more than hip replacement.

This thesis has presented and discussed four published articles which build upon each other to add to the descriptive epidemiological literature on the past trends, current risks and future needs of hip and knee replacement in the UK. Over the coming decades, it is important that researchers continue to analyse population-level data on hip and knee replacement in order to report on changes in risk factors, to monitor changes in the characteristics of those undergoing joint surgery and to inform policymakers and healthcare providers.
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DECLARATION OF AUTHORSHIP

I, David John Culliford, declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

The Past, Present and Future of Total Hip and Knee Arthroplasty in the UK: A population-based statistical analysis

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Parts of this work have been published as:


Signed: ............................................................................................................................................

Date: ................................................................................................................................................
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I am grateful to the patients whose records comprise the Clinical Practice Research Datalink, without whom it would not be possible to conduct the type of large-scale population-based research analysis presented in this thesis.

Thanks go to all my co-authors on the four papers presented here, but with a special mention to Andrew Judge who has always been a source of great advice on matters statistical and on the arthroplasty literature in general.

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Writing up this thesis has necessarily been an extra-curricular activity, for which my preferred setting has been a quiet corner of a pub on a Saturday lunchtime. Thanks to the Village Free House in Salisbury and the Flower Pots in Cheriton for putting up with me. They have no idea what I’ve been up to!

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Chapter 1: Introduction

1.1 Background to lower limb arthroplasty

1.1.1 Definition

Arthroplasties of the hip and knee are surgical procedures in which all or part of a joint is repaired or replaced. Total joint arthroplasty (TJA) involves the complete replacement of the articulating surfaces, and is therefore also known as total joint replacement (TJR). These procedures have for some time been acknowledged as effective both clinically and also in terms of cost benefit. (Pinedo-Villanueva et al., 2014, Jenkins et al., 2013, Daigle et al., 2012).

1.1.2 Indications

Most patients who undergo a total hip or knee arthroplasty will initially present with symptoms which include pain and/or stiffness, often resulting in some functional limitation (Crawford and Murray, 1997). In the UK, the latest available information (National Joint Registry, 2015) suggests that the primary diagnosis for 93% of all hip surgeries was osteoarthritis. For primary knee arthroplasties, the figure was 96%. Other indications include fracture and avascular necrosis (for the hip) but osteoarthritis is overwhelmingly the primary indication for TJR, especially among elective operations.

1.1.3 History of hip replacement surgery

The earliest recording of a hip arthroplasty dates back to 1891 in Germany (Knight et al., 2011), with ivory used as a surrogate femoral head. In the years immediately before and after the end of the 19th century, other early attempts were made using human and animal tissue as a cushion between the articulating surfaces.

In the mid-1920s man-made materials were starting to be employed. Mould arthroplasties of glass failed due to shattering, but stainless steel was more successful, with Smith-Petersen and Wiles using bolts and screws to fix prostheses to the femur (Smith-Petersen, 1948, Wiles, 2003).

In the early 1950s McKee developed metal-on-metal (MoM) prostheses with cobalt-chrome becoming the material of choice for the acetabular component. Although certain MoM prostheses proved to have good long-term survival (Brown et al., 2002), the effects of metal debris discovered when revision procedures were carried out eventually sounded the (temporary) death knell for MoM articulations. With hindsight, perhaps the reasons for the decline of MoM in the
Chapter 1 - Introduction

1970s could have pointed to an eventual recurrence of problems in the early 2000s, when MoM became popular once again, albeit with different physical characteristics (e.g. head size, lubrication properties). By the late 1950s, a variety of prostheses were in operation, with individual surgeons and centres employing designs which they had developed and trialled.

In 1961, John Charnley documented the development of his radical new method (Charnley, 1961), which simultaneously introduced several novelties which when taken together, changed the face of total hip arthroplasty around the world. Charnley’s prosthesis, described as a low friction arthroplasty comprised a metal stem with a head of size somewhat smaller than that which was widely used at the time. Furthermore, the prosthesis used an acetabular cup lined with polyethylene (PE). The use of acrylic cement throughout was another key factor.

By the 1970s, metal-on-polyethylene (MoP) articulations began to dominate, with other combinations of articulating surface materials being side-lined. The Exeter hip prosthesis, pioneered in the early 1970s (Fowler et al., 1988) was highly influential and remains to this day one of the most commonly used prostheses.

Another major development was the introduction of the Birmingham Hip Resurfacing (BHR) in the early 1990s (Daniel et al., 2014). This prosthesis consisted of an MoM articulation but preserved the femoral head by screwing a metal ‘cap’ onto the head without the need to excise the joint below the greater trochanter. Conserving the bone stock meant that this operation was deemed more suitable for the younger patient, allowing a total joint replacement to be carried out later in life.

A further promising extension to modern MoM articulation methods came in the mid-2000s with the large head MoM THR. Unlike the BHR, this type of prosthesis was essentially a standard THR but with MoM articulation. However, a high failure rate with these devices began to emerge (Cohen, 2011) and upon revision surgery it was commonly observed (and confirmed upon histological analysis) that nanoparticles of metal debris were found in tissue samples, with associated necrosis of the soft tissue around the joint. Metal-on-metal THR prostheses are now rarely used.

Other recent developments include ceramic articulations, cementless fixations and the introduction of cross-linked polyethylene which has given MoP articulations a new lease of life.
1.1.4 History of knee replacement surgery

The history of arthroplasty of the knee is shorter than for the hip. Furthermore, the development of knee replacement methods have not been subject to the same level of paradigm shift as seen for the hip as a result of new methods introduced by Charnley in the early 1960s.

Although the 1970s first saw knee replacements carried out in a great numbers, early attempts were seen from the mid-1800s when Verneuil was the first to suggest what is known as interposition surgery, where soft tissue or other material with similar properties is placed in between the articulating surfaces. As for the hip, all manner of materials (e.g. cellophane, nylon, pig bladder) were trialled well into the early 1930s, but with little success.

In 1940, Campbell (Campbell, 2005) proposed the use of metal in a mould arthroplasty, following on from the earlier success of Smith-Petersen using such methods in the hip (Smith-Petersen, 1948). The next major development involved the use of a hinged prosthesis (Walldius, 1960), and during the 1950s and 1960s the results obtained with this type of prosthesis were better than anything developed thus far. Nevertheless, the restriction of movement imposed by the hinge meant that surgeons continued to search for better solutions.

Developments in the early 1970s (Gunston, 1971, Coventry et al., 1973, Freeman et al., 1973) made great strides in joint arthroplasty methods, with bone cement, polyethylene and the ‘roller-in-trough’ among the innovations introduced. Some of these methods were combined with the retention of certain ligaments around the knee joint.

Further advances in the mid-1970s were made by Ranawat et al (Ranawat et al., 1976), Coventry (Coventry, 1975) and Townley (Townley, 1985), respectively providing the duocondylar, the geometric and the anatomic prostheses. More design modifications made by Walker et al (Walker et al., 1976) moved towards what is now considered to be the modern prosthesis for TKA. These changes resulted in the total condylar, tricompartmental prosthesis with advanced stability and wear characteristics.

Refinements in prosthesis design in the 1980s by Insall et al (Insall et al., 1982) further reinforced the claim that the developments introduced during the 1970s and 1980s resulted in methods which are still considered to be the foundation of modern total knee arthroplasty (Song, 2013).
1.2  Arthroplasty in the UK in recent times

By the early 2000s, both hip and knee arthroplasty had become established as almost commonplace interventions in the UK, with 38,000 primary hip and 32,000 primary knee procedures carried out in England alone by 2000 (Dixon et al., 2004). However, these operations were being carried out at a large number of different centres by many different orthopaedic surgeons at different levels of qualification and using a wide variety of prostheses and materials.

Most of the research outputs were based on a single centre, or a small number of centres and often confined to a particular type of prosthesis, fixation or articulation. As a result, it was unclear which factors might be more or less important in terms of longevity or risk of failure.

In addition to clinical considerations, it was clear that these costly procedures were now being applied to a large and growing population and that the planning of healthcare resources to accommodate these needs was becoming an issue.

This was recognised by orthopaedic surgeons and a national joint registry began collecting data on hip and knee replacement operations in 2003. This was a welcome addition and would greatly benefit clinicians and medical regulators in the years ahead, especially in providing confirmatory evidence of prosthesis-specific problems. Yet for many years afterwards there remained a paucity of research describing overall patterns, trends and projections of hip and knee arthroplasty.

In the mid-2000s, I was a relatively career-young medical statistician recently recruited within a team of rheumatologists and surgeons wishing to more fully understand where lower limb arthroplasty was heading over the next generation of the UK population. We saw that there was a need for population-level information on past trends, current associations and future predictions of arthroplasty, broken down by the important epidemiological stratifying variables of age and gender. Our aim was that the use of such information would inform those who have the responsibility of answering major public health and healthcare resource questions in the UK.
1.3 Objectives and research questions

The broad objective of this thesis is to address the lack of population-level, age-gender specific epidemiologic descriptors of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in the United Kingdom.

To expand on the stated objective, breaking it down into its constituent parts, a PICO statement (Richardson et al., 1995) is provided (Table 1.1). PICO stands for ‘Population, Intervention, Comparator and Outcome’ and although framing the research in this way is more suitable for interventions studies (e.g. randomised controlled trials), it can also be helpful for observational studies like those presented in this thesis.

Table 1.1 PICO diagram

<table>
<thead>
<tr>
<th>Paper 1</th>
<th>Paper 2</th>
<th>Paper 3</th>
<th>Paper 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>UK general population aged 18 or over</td>
<td>UK general population aged 50 and over</td>
<td>UK population aged 18 or over who have undergone a THR or TKR procedure</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Calendar year</td>
<td>Age and gender</td>
<td>BMI, age, gender</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Age-sex standardised incidence rate for primary (all-cause) THR and TKR</td>
<td>Mortality-adjusted lifetime risk for primary (all-cause) THR and TKR</td>
<td>Hazard ratio for undergoing hip or knee revision surgery (for BMI, gender and age)</td>
</tr>
</tbody>
</table>

It is proposed that the four papers presented in this thesis together have filled important gaps in the literature on the epidemiology of TJR. However, for some of the outputs (papers 2, 3 and 4) there is also novelty in the combination of existing statistical methods and/or the methods of bespoke data manipulation and data linkage. At the time of publication, these method
combinations had not been used before on population-level arthroplasty data in the UK, and in some cases have still not been replicated.

1.4 Summary

Total replacement of the hip and knee are two interventions which, in the 1970s after decades of development, finally settled down into a form which is still recognisable in the design of prostheses and their accompanying procedures in use today.

Over the last forty years, there has been a clear gap in the literature describing the incidence of these procedures within the UK population. Even as late at the early 2000s, government and policy makers in the UK had nothing in the way of reliable information at a population level describing the historical rates of joint replacement, nor did they have any idea about future growth rates.

Furthermore, clinicians and medical researchers had only small-scale studies to refer to when faced with assessing the associations of age, gender and obesity on the longevity of a hip or knee prosthesis after being implanted. A national register for joint replacements began collecting data in 2003, but had less than a complete picture for the country for several years, and even then did not include procedures performed outside of England and Wales. Even as late as 2010, the completeness of data on pre-operative obesity in the national register was only starting to approach acceptable levels.

To add to this lack of available knowledge on the descriptive epidemiology of joint replacement, even as late as 2008 clinicians in the UK had no way of assessing the lifetime risk of hip and knee replacement for subjects, although this very appealing and intuitive way of explaining risk to patients was available for osteoarthritis of the hip and knee – the disease for which primary joint replacement is indicated in the vast majority of cases.

It is against the background of this paucity of information that the research projects which comprise this thesis came into being. The broad aims of the four projects presented here were to use a nationally representative, validated and reliable data source to:

- Estimate and describe the rate of THR and TKR in the UK adult population by age and gender
- Estimate the risk of undergoing THR and TKR for a member of the UK general population aged 50 and over, by age and gender
• Estimate the associations between time from initial THR or TKR procedure until first revision procedure and age, gender and body mass index for the UK adult general population

• Provide projected counts of THR and TKR for the UK population from 2010 until 2035

1.5 Structure of thesis

The work presented in this thesis paints a descriptive epidemiological picture of the incidence and demographic structure of total hip and knee replacement in the UK over the recent past and the present, with a broad look into the future.

Chapter 2 describes the data sources, with most attention given to the Clinical Practice Research Datalink (CPRD). Other data sources which were linked to the CPRD data are also covered, but in less detail. Chapter 2 also contains the statistical methods, with brief descriptions of the linkage methods and any important programming methods which were key to producing the outputs.

Chapters 3 to 6 inclusive contain the four published articles which comprise the substantive research projects for the thesis. The content of each of the four articles is presented exactly as published, with the tables and figures as supplied to the publishing editorial team. The software used to draft the manuscripts for all four articles (including all figures and tables) was Microsoft Word®, which is the same software used to write this thesis. Consequently, the format of all figures and tables is as submitted for publication, which may appear slightly different to the format used by each article publisher’s typesetter. The articles presented in these substantive chapters will be referred to throughout the thesis as ‘Paper 1’, ‘Paper 2’, etc.

Chapter 7 contains the overarching discussion of the published articles, describing how the studies fit together, discussing the associated literature before and after the time the study was conducted. Within this chapter is a defence of the originality of the contribution to the literature represented by the articles in this thesis.
Chapter 2: Data and methods

2.1 Rationale for choice of data

To answer our research questions, we needed data (a) from which population level inferences could be made, and (b) with a long period of follow-up after surgery. Moreover the data needed to afford an opportunity for linkage to a patient’s clinical events over time.

Several datasets existed from which one could make population level inferences about the levels of TJR in the UK. These data sources had many excellent properties and some of them would have met many of the requirements of a base dataset for use in answering some of the four research questions, but none of these data sources would have been sufficient to serve as a base dataset for all four of the proposed studies.

We considered several data sources for this research:

- National Joint Registry for England and Wales
- Hospital Episode Statistics
- Health Survey for England
- GP-based electronic health records

2.1.1 Strengths and limitations of candidate datasets

The following subsections describe the reasons why most of the datasets listed above were not, on their own, suitable as the primary source of data with which to answer our research questions.

2.1.1.1 Geographical coverage

One of the key constraints imposed by the four research questions is that any chosen dataset or combination of datasets should be capable of producing population-level inferences for the whole of the United Kingdom. The Health Survey for England (HSE) and Hospital Episode Statistics (HES) were both confined to England only, and remain so at the time of writing. While both data sources have excellent coverage properties (the former is a national multi-stage stratified sample survey; the latter a national register of all episodes of secondary care carried out within the English NHS), neither covers Wales, Scotland and Northern Ireland.
Chapter 2 – Data and Methods

The National Joint Registry for England and Wales (NJR) is arguably the natural, self-selecting candidate for use as a base dataset for the research presented in this thesis, and although it contains a virtually complete register of all lower limb joint replacements in the population, it fails to cover Scotland and only very recently started to collect data from procedures carried out in Northern Ireland (National Joint Registry, 2014).

2.1.1.2 Temporal/longitudinal coverage

Two of the research questions required a long and uninterrupted period of data collection. The research work for the first of the four articles in this thesis began in late 2008. At that time, the NJR was still in its relative infancy, with only five years of data collected since its inception in 2003. In spite of the fact that the NJR was designed to contain a complete record of all hip and knee arthroplasties, the length of follow-up was insufficient to paint a long-term picture of the state of lower-limb joint replacement in the population.

Both the aforementioned data sources covering only England (HES and HSE) contained long, unbroken periods of data collection, with HES having collected national data on patient care since 1989/90 and HSE since 1991.

2.1.1.3 Subject-specific records of clinical events

In order to obtain population-level, age-gender specific epidemiologic descriptors of total joint replacement (e.g. incidence rates, prevalences, risk/hazard ratios), the data source needed to include age and gender. Subject data from NJR, HES and HSE included age, gender and other social and demographic information. However, to go further than the simple estimation of rates and prevalences as summary totals of procedure counts and population denominators (for example to assess epidemiologic associations), the data were insufficiently detailed.

Although the main candidate data sources discussed so far (NJR, HES, HSE) did include subject-level data, the data were often not provided with date-stamped events for the characteristics of interest. Within the NJR, for example, the event of interest is a surgical procedure, and only the information collected on the NJR forms completed by the surgical team are entered into the registry. While these forms (which are available for download from the NJR website, njcentre.org.uk) do contain a lot of clinically relevant data about patient characteristics (e.g. co-morbidities), these data items do not constitute a full longitudinal record of all relevant details with timing of clinically relevant events. The primary aims of maintaining a national surgical
registry are usually safety monitoring, with research use a secondary, although important, function of such data repositories.

Similarly, HES data has a given event as the unit of interest, but here it is a consultant episode rather than a surgical procedure as with the NJR. Again, data relating to the patient is collected largely for clinical relevance to a hospital episode, so a longitudinal record for the patient before and after the episode is not feasible.

The HSE also has similar shortcomings in that it is a cross-sectional survey, repeated every year with a different sample of the population, so no longitudinal linked data on clinical events is available.

2.1.2 Alternatives – Electronic Health Records

Given the geographical, temporal and content limitations presented for some of the data sources described above, a source of data which satisfied the basic requirements of the research questions needed to be identified. As with registry data, which is routinely gathered once the registry has been established, it was likely that the best candidate data source would also be a routinely collected electronic health record of some sort.

Electronic health records (EHRs) have existed since the 1970s, first seeing widespread use within the United States of America. However, these early EHRs tended to be based in individual hospitals, and only much later were these data repositories consolidated, and then often in a proprietary manner due to the mainly private funding of healthcare in the US.

Within the UK, during the 1980s, healthcare systems based within individual general practices were being introduced. Individual hospitals also had their own EHRs, largely designed for the episodes of patient care within the institution. A national system called the Secondary Uses Service was subsequently developed, aiming to provide a comprehensive single source of healthcare data nationally. These data were gathered from episodes of secondary care in hospitals, and it is directly from these data that HES is produced. Yet this national system contained no data from primary care, as is still the case.

From the early 1980s, two enterprising general practitioners (GPs) made specific developments which were to pave the way for the widespread acceptance of GP-sourced research databases in the UK. The first was the development of the Read code system (Benson, 2011) by Dr James Read, a GP based in Loughborough in England. This hierarchical coding system for clinical events gained widespread acceptance, and although coding systems existed before Read (e.g. ICD), it is the Read code system and its derivatives which gained widespread adoption within primary care.
Chapter 2 – Data and Methods

administrative computer systems in the NHS. The use of Read codes in GP-based EHRs has been mandatory within the NHS since 1999, after the UK government purchased the intellectual property for the Read code system.

The second important development was the creation of an information base by another English GP, Dr Alan Dean. He and a small team of software developers formed a venture capital company to develop and market what was then known as the VAMP database. The company was sold in the early 1990s and became the General Practice Research Database (GPRD), which is now known as the Clinical Practice Research Datalink (CPRD).

2.1.3 Why choose a general practice database for UK population-level research?

By late 2008, when this research work began, several GP-sourced databases existed which provided geographical coverage over much of the UK. Although only a subset of the UK’s general practices were submitting data, these databases were acknowledged as being broadly representative (Hollowell, 1997, Hansell et al., 1999) of the population of patients in the UK who were registered with a GP.

These databases were neither fully complete (in the way a registry is designed to include all relevant events within a population), nor were the GP practices selected by some mathematically justified sampling scheme, as is the case with the UK government surveys designed and administered by the Office for National Statistics (ONS). Nevertheless, through a combination of purposive, albeit self-selecting, sampling of practices throughout the UK, the resulting geographical coverage of these databases appeared to lead to estimates that were broadly in line with the target population of all UK general practice lists.

Crucially, these databases contained not only the clinical events recorded at GP consultations, but also laboratory test results, prescription details and secondary care events pertaining to patients, providing that the information was entered onto a practice’s computer system. Examples include consultant letters to GPs, or test results requested by the GP and returned to the practice.

The use of such databases for population-level research is only appropriate in countries like the UK which have a national practice-based primary care system, acting as the main point of entry into the healthcare system for the vast majority of the population (with a few notable exceptions such as the provision of accident and emergency services).
Why choose the CPRD?

In late 2008, at the inception of the research work presented here, the two most prominent UK general practice databases, in terms of usage and published research, were the GPRD (now CPRD) and The Health Improvement Network (THIN) database (Lewis et al., 2007).

Other candidates for a nationally representative GP research database existed in 2008, including QResearch (from the University of Nottingham) and ResearchOne (from the University of Leeds), which were perhaps the best known apart from CPRD and THIN.

All four of the databases described (CPRD, THIN, QResearch and ResearchOne) used a single proprietary coding system for clinical events. CPRD and THIN accepted data from practices running the Vision system (In Practice Systems Ltd, London, UK) using Read codes, whereas QResearch required practices running EMIS (EMIS Health, Leeds, UK) and ResearchOne took practice data from SystmOne (TPP Ltd, Leeds, UK).

It is arguable that all these databases had similar designs and that each could have answered the research questions addressed in this thesis, albeit with slightly differing estimates due to the different general practices submitting to each database. CPRD had the longest history, but due to retrospective data collection, the follow-up data available in THIN (and the other databases) also extended back to the late 1980s or early 1990s.

One factor important in our decision making was cost. The research described in this thesis was carried out as part of a National Institute for Health Research (NIHR) Programme Grant for Applied Research (PGfAR) grant (number RG-PG-0407-10064), the host institution for which was the University of Southampton. This institution houses a Medical Research Council (MRC) unit which, at the time, was entitled to conduct research using CPRD (then GPRD) data free of charge, under an agreement between the GPRD (a non-profit making organisation) and the MRC which came into effect during 2006/07. However, this agreement came with certain conditions attached, the most significant of which was that the number of subjects to be selected was 100,000 which was not sufficient for a UK population-level study on TJR over the required follow-up period.

Nevertheless, the existence of the MRC agreement meant that when datasets were being considered as candidates for the research studies presented here, the wider research team had already conducted research using GPRD as a primary source and was starting to publish findings (Edwards et al., 2007). Arguably, it is this local knowledge and experience that convinced the co-applicants of the NIHR grant which funded this work of the benefits and suitability of GPRD data, and which led to it being chosen as the primary data source for our epidemiological research.
2.2 Clinical Practice Research Datalink (CPRD)

The primary data source underpinning the publications in this thesis is the Clinical Practice Research Datalink (CPRD). The CPRD, administered by the Medicines and Healthcare products Regulatory Agency (MHRA), comprises a database of routinely collected patient data from a group of general practices in the UK. The number of practices and patients within the CPRD has varied since its inception, but since the early 1990s it has been a large and representative source of population-level data for the UK population of people registered with a GP. The CPRD now contains data from over 674 practices including some 11.3 million patients, of whom approximately 4.4 million are currently active within the database. This represents a current coverage of 6.9% of the UK population.

Practices may choose to cease submitting data to the CPRD at any time, but the majority stay and most have been submitting data for most of the lifetime of the CPRD. The history of the CPRD since Dr Alan Dean’s pioneering work in the mid-1980s was covered earlier in this thesis (on page 12).

Although the practices are not selected according to any sampling scheme, the CPRD team ensure that the group of practices submitting data at any time are nationally representative (Herrett et al., 2015) in terms of certain UK population characteristics such as age, gender, ethnicity and that geographical coverage is as even as possible. Figure 2.1 has been produced by the candidate using the CPRD’s own population denominator data and shows that although the CPRD was initially based mainly in London and the South East, within a few years it was broadly balanced across the UK.
Figure 2.1  Geographical coverage of GPRD/CPRD among UK countries and English regions

The CPRD provides a complete electronic record of events pertaining to patients within practices submitting data, for the duration of a practice’s submission to the CPRD and the duration within that time of the individual patient’s registration at the practice.

An extensive range of quality control checks carried out by the CPRD team ensure that each practice is submitting data which is termed as “up to standard” (UTS). When a practice joins the CPRD and begins submitting, the data is anonymised at source and then transferred back to the CPRD secure data servers on a regular basis. Only when a practice is submitting data deemed to be of high quality is the practice data considered up to standard, although data prior to a practice’s UTS date is held within the database and can be accessed.
Chapter 2 – Data and Methods

2.2.1 Structure of CPRD data

CPRD data are derived from several sources, all of which are entered routinely onto the individual practice’s computer system. CPRD requires all its submitting practices to be running Vision software produced by InPractice Systems Ltd.

All primary care events pertaining to the patient plus all secondary care events known to the GP are entered onto the practice’s computer system in real time by practice staff. This includes doctors and practitioners recording details of consultations, diagnoses and treatments, as well as administrative staff inputting various other details. Laboratory test results, referral letters, immunisation records, outpatient visits and details of prescriptions are all routinely entered. Other data relating to the practice, such as staff roles, enable the complex structure of events reflected in the practice’s computer system to be reconstructed by the researcher using linkage methods.

A crucial element of the transfer of practice data to a set of data to be uploaded to CPRD is the anonymisation process. All patient, staff and practice IDs are randomly assigned and anonymised, with no structure within the patient numbering system other than linkage to the anonymised practice ID. The exact practice location is not identifiable and the only geographical reference for each practice is to Wales, Scotland, Northern Ireland or the English healthcare region to which it belongs.

2.2.2 Delivered format of data

CPRD delivered our study data in text file format, on multiple DVDs which were then uploaded into an SQL database in the form of rectangular tables with rows and columns. Some twenty tables were created, but not all were used for the analyses in this thesis. The most important tables were the Patient (patient details), the Clinical and Referral (all clinical events), the Additional (BMI, etc.) and the Denominator (CPRD population counts). Some of these tables were extremely large: the Clinical table, which included all clinical events for all the TJR patients and also their controls, was over 130 million rows occupying 11 gigabytes.

Each table contained variables such as patient ID, practice ID and event ID which enabled rows of data to be linked with other tables. Figure 2.2 shows some of the more common linkages.
2.2.3 Ethical approval

Although no ethical approval is required for research carried out using CPRD data, the process of acquiring the data does include what might be described as a “data ethics” approval process. Researchers who wish to use patient-level data within CPRD for research purposes must comply with the MHRA’s request for a study protocol to be submitted to their Independent Scientific Advisory Committee (ISAC). Only once the study has been approved by the ISAC can the requested data be selected from the database and sent to the researchers.
Chapter 2 – Data and Methods

The original set of CPRD data for the research presented here was approved by the ISAC in 2006 under ISAC protocol number 06_063R. The title of this protocol was ‘Patterns of care and prognosis of osteoarthritis’. This set of data was used for the research projects which resulted in papers 1 and 2.

A further set of CPRD data was acquired in 2011 which extended the temporal range of the data to twenty years and beyond (from inception of the GPRD up to mid-2010). These data were essentially an extension of the original set of CPRD data, but with certain minor additions. A new study protocol of the same title was submitted to the ISAC (protocol number 11_050) which was approved in 2011.

2.3 The study data

2.3.1 Selection criteria for the study data as supplied by CPRD

Several cohorts of patients were acquired under the ISAC protocol 06_063R described above, for a range of projects within the NIHR programme grant (RP-PG-0407-10064), but the specific cohort used for this thesis was selected according to the following specification:

“To enable the researcher to assess the incidence of knee and hip joint replacement surgery, rates of prosthesis failure and associated risk factors, GPRD will identify all patients with a medical diagnosis code for hip or knee arthroplasty in their clinical or referral record on or before 31/12/2006. Patients will be ≥ 18 years of age at index diagnosis. Person time data for patients stratified by age, gender and practice will also be provided to the researcher.”

The group defined above will be referred to as the ‘cases’, having had at least one lower limb joint replacement event within their GP records over the study period.

Furthermore, an additional set of patients were selected to form a ‘control’ group. This group were then individually matched with a random selection from all subjects of the same age, gender and general practice as the selected cases, but who had never had either a lower limb joint replacement or osteoarthritis of the hip or knee. The controls were selected according to the following specification:

“Controls will be all patients without a clinical or referral record for knee or hip arthroplasty, or knee or hip osteoarthritis ever on the database.”
Up to five controls per case were selected, subject to availability of exact matches (i.e. exactly the same age, gender and from the same practice). If an exact match were unavailable, the matching criteria (for age only) were relaxed to include those within 5 years either side of the case’s age. It should be noted that data for the controls were not required to answer the research questions in this thesis but were used for other related analyses.

### 2.3.2 Basic characteristics

When creating a base set of data for each of the papers, it was important to ensure that the events of interest took place while a practice was submitting approved data to the CPRD. For instance, all the THR and TKR events contributing to the incidence rates in paper 1 were checked to ensure that they occurred after the date at which the relevant practice was submitting what CPRD refers to as ‘up to standard’ data. Further validation checks were necessary for paper 3 to establish whether a patient had moved away from a practice before the end of the study which would affect the censoring date in survival analyses.

The age and gender characteristics for the subgroups of TJR data analysed in each of the four papers is described in tables 3.1, 4.1, 5.1 and 6.1, but a basic graphical description by age and gender is given below for the original delivery of CPRD data (1991 to 2006). The chart represents 27,113 THRs (16,969 women and 10,144 men) and 23,843 TKRs (14,121 women and 9,722 men).

![Figure 2.3 Counts of total joint replacements in CPRD data - Hip (left) and Knee (right)](image)

Figure 2.3 Counts of total joint replacements in CPRD data - Hip (left) and Knee (right)
Figure 2.3, which would have been part of paper 1 if the journal had allowed the extra figures, also demonstrates the dangers of making inferences from raw count data alone, because the population in each age-gender stratum is not included.

The geographical distribution of THR and TKR is not something which formed part of the research presented in this thesis, but the table below shows the percentage breakdown by region. Again, we should refrain from making any judgement from the percentages of raw counts and it should be noted that the research team excluded geographical analyses from the remit of the four research studies presented here.

Table 2.1  Proportion of THR and TKR counts in study data by GPRD Region, 1991-2006

<table>
<thead>
<tr>
<th>Region</th>
<th>THR</th>
<th>TKR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eastern</td>
<td>11.9%</td>
<td>11.6%</td>
</tr>
<tr>
<td>London</td>
<td>7.5%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>2.9%</td>
<td>2.1%</td>
</tr>
<tr>
<td>North West</td>
<td>10.6%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Northern and Yorkshire</td>
<td>6.1%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Scotland</td>
<td>3.8%</td>
<td>3.6%</td>
</tr>
<tr>
<td>South East</td>
<td>23.3%</td>
<td>22.6%</td>
</tr>
<tr>
<td>South West</td>
<td>11.3%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Trent</td>
<td>6.8%</td>
<td>7.3%</td>
</tr>
<tr>
<td>Wales</td>
<td>4.8%</td>
<td>5.4%</td>
</tr>
<tr>
<td>West Midlands</td>
<td>11.0%</td>
<td>10.4%</td>
</tr>
</tbody>
</table>

Other patient characteristics relevant to any of the four papers (e.g. BMI, smoking status, drinking status, number of comorbidities) are described within chapters 3 to 6 in summary tables, if appropriate for that particular study. Other variables which are sometimes presented for cohorts (e.g. ethnicity) were not expected to be relevant for any of the four research studies so therefore were not extracted from the original CPRD tables.
2.3.3 Additional data sources

Some additional data sources were required for the four papers presented, and these are described and acknowledged within each paper (chapters 3 to 6), but are briefly summarised here. Population data from the Office for National Statistics were used in paper 1 (2003 population counts), paper 2 (2006 mortality rates) and paper 4 (2010 population forecasts). Population-based BMI data from the Health Survey for England were used in paper 4 to apportion denominator populations by BMI group. Counts of THR and TKR from the Hospital Episode Statistics were used in paper 1 for comparison purposes, and similar data from the National Joint Registry.

All these data were in aggregate form and were available to the public as downloads from the website of the relevant agency, except for the HSE data for which registration was required with the Economic and Social Data Service (now incorporated within the UK Data Service). Usage of the HSE data was for academic research purposes only.

2.4 The methods

2.4.1 Preliminaries

2.4.1.1 Choice of software

The CPRD study data for the research presented here was delivered as a set of text files and required post-processing (subsetting, merging, reformatting, etc.) before the data could be meaningfully analysed.

The MHRA do not impose the use of any particular methods or software, so a research team is free to choose whichever software tools it deems appropriate. For these research projects, the software skill sets of the statistician (the candidate) and the data manager (publications co-author Joe Maskell) were heavily biased towards SAS (SAS Institute, Cary, NC) therefore this software seemed to be a natural choice.

SAS is a proprietary software environment and is excellent for handling large, complex data. It has over 40 years of development and is used extensively within the academic and commercial world. Its capabilities are evidenced by the fact that the Food and Drug Administration (FDA) in the
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United States have long accepted SAS output for the submissions of drug trial reporting data which must be approved before a pharmaceutical company can sell a drug under license.

Many research teams choose Stata (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX) for CPRD data analysis, and it too is excellent software for post-processing and analysing CPRD data. Within the academic sector in the UK, Stata is more widely used for epidemiologic analyses, largely for historical reasons but also some technical reasons (e.g. early availability of routines to perform conditional logistic regression). Nevertheless, both SAS and Stata are fully capable of effectively analysing CPRD data, and for most research teams it is largely a matter of personal choice and available experience.

The other prominent candidate was a software language called R (R Core Team. 2014. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria). The candidate was fluent in R programming but it was felt that because the data manager was a SAS programmer, it would be sensible to conduct the main data management and most of the statistical analysis in SAS. The candidate did use R for ad hoc analyses required for several of the publications, especially in the work conducted for publication 3 (the survival paper), but R was not used as a core tool, although it would have been perfectly suitable as such.

The only other software which was used, albeit it only at the early stages of this research work, was SQL Server (Microsoft Corporation). Structured Query Language (SQL) is a non-proprietary “language” which comprises a set of constructs to create and manage relational databases from a set of rectangular tables which may be linked by so-called key variables. SQL has many proprietary implementations, of which Microsoft Access (Microsoft Corporation) is arguably the best known.

For the first delivery of the TJR data from CPRD, used for paper 1 (the temporal trends paper), SQL Server was used to post-process the raw CPRD tables into a relational database which could be queried by SAS. This work was contracted to a programmer, Martin Chivers, at the University of Southampton as a one-off piece of work. For the second delivery of our TJR data from CPRD, which was used for all subsequent research work (including papers 2, 3 and 4 presented in this thesis), the raw data was directly accessed from SAS using a SAS procedure called PROC SQL. Much of this importing between software environments was carried out by the data manager, but the candidate also made extensive use of PROC SQL, writing bespoke program code to manipulate and merge the raw CPRD tables.

In addition to SAS for data manipulation and statistical analysis, the candidate also wrote extensive program code and macro routines in Stata, Excel (Microsoft Corporation) and R. All three were especially useful for graphical outputs, with R being particularly flexible in this respect.
2.4.1.2 Producing the base dataset for each paper

Although the source data was the same for all four papers, a considerable amount of reshaping work was undertaken by the candidate and his colleague, the data manager, such that different base datasets could be produced for each paper. The data manager carried out programming tasks on the data close to its source, whereas any reshaping and merging with non-CPRD sources was carried out by the candidate, as was all programming to produce tables, figures, and any inferential work to produce parameter estimates from statistical models.

Because each of the papers cover different time periods, the numbers of hip and knee replacements quoted in each paper are different, but this is purely due to the different subsets considered by each paper. Paper 1 used joint replacements between 1991 and 2006 (27,113 THRs and 23,843 TKRs), paper 2 used only those patients aged 50 and over (25,845 THRs and 23,260 TKRs), paper 3 used a different time frame (1988 to 2011) providing 63,162 THRs and 54,276 TKRs and paper 4 used only those patients with a pre-operative BMI and a TJR occurring between 1991 and 2010 (50,000 THRs and 45,609 TKRs).

For each of the four papers, the creation of a bespoke dataset took varying, but considerable amounts of time, with much of the work carried out in SAS using programs to merge the required data from each of the CPRD tables. Some of the analyses required BMI details from the CPRD’s ‘Additional Clinical Details’ table, others required data on comorbid conditions, derived from events in the CPRD’s ‘Clinical’ table. All of the four analyses required age and gender but these were present in the ‘Patient’ table. Finally, the rates required in papers 1, 2 and 4 could not have been estimated without the CPRD’s ‘Denominator’ table.

The next four subsections will describe in detail the rationale for the choice of methods, and will explain how these methods operate, expanding more fully on the analyses than was possible in the four published papers.

2.4.2 Methods specific to paper 1 (Temporal Trends)

Paper 1 is essentially about producing rates which describe the temporal background to joint replacement in the UK by age and gender, and a rate is a specific type of outcome measure with its own set of statistical methods (Fleiss et al., 2003).
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In order to estimate an event rate in its simplest form, an appropriate numerator (event counts) and denominator (persons at risk of the event) are all that is needed. Refining this basic rate further by reporting incidence rates within a given time period requires adjustment of the rate denominator such that it only includes the time during which a person is exposed to the risk of that event during the period of interest. This concept of person time is a crucial assumption in epidemiology and ensures that the rate is not an under estimate of the true risk of experiencing the event.

To meet the aims of the research question addressed in paper one, rates of primary total hip and knee replacement were estimated separately for each calendar year from 1991 to 2006 inclusive. The numerator was the number of primary total hip/knee replacement procedures identified within the entire CPRD during each calendar year. The denominator was the total person-years for all patients while alive and registered with the general practice during the same calendar year.

However, a rate calculated as described above applies to the population as a whole and does not allow for differences in the rate between genders or age groups. Therefore, different rates were calculated for each gender using the same methods, restricting numerator and denominator to men and women in turn. The resulting rates are gender specific but they do not describe the variation by age.

A further stratification of these gender specific rates by age bands produces age-gender specific rates (Figure 3.2). These rates provide information on the variability across age and gender, but we still require an overall rate which is representative of the whole population and which allows for this variation. To achieve this goal, rates which are standardised to a reference population are needed.

Directly standardised rates are those estimated such that they adjust for certain characteristics of a notional population. The most basic demographic characteristics of a human population are arguably gender and age, and these two variables were used as stratifying factors for the directly standardised rates produced in paper one (Figure 3.2).

It was decided that separate rates for hip and knee for each gender should be produced and the resultant rate is a weighted average of the individual age gender specific rates, with weights being the size of each stratum of the notional population proportion. The statistical methods and formulae used to estimate these directly standardised rates are described in detail by Breslow and Day in their classic text on statistical methods in cancer research (Breslow and Day, 1987).

Confidence intervals (95 percent) were computed assuming a Poisson model for the counts of hip and knee replacements. The Poisson model is a natural choice for count data, and the applicability
extends also to rates, where the denominator (person time) is considered fixed (*i.e.* non-stochastic) and therefore requires no distributional assumptions.

Sometimes, when the number of events is especially low, the statistical properties of the Poisson distribution affect the validity of inferences, and other distributions (*e.g.* negative binomial) are more appropriate. However, for the data examined in paper 1, the counts were more than sufficient to allow robust inferences using a Poisson model.

The interpretation of the confidence intervals for these rates is such that if many similar samples of CPRD data were drawn from a notional CPRD population under the same sampling conditions, approximately 95% of those intervals would contain the true rate (of joint replacement). We can never know the true rate, and our point estimate of the rate is merely a computed estimate from one sample out of many possible samples which could be drawn from the population of interest. These inferential definitions apply to all estimates presented within this thesis, whether rates, means, intervals, hazard ratios or whatever.

Although much of the data manipulation was performed using SAS, the estimation of incidence rates and confidence intervals was performed in Excel. Pivot tables were designed and then programmed with embedded formulae to enable the calculation of joint replacement rates with the accompanying standard errors. This flexible approach enabled point estimation and interval estimation for all required age-gender combinations. While this bespoke approach may be novel in some sense, such software applications are rarely published in their own right and a literature search found nothing of a similar nature.

Although several reference populations exist with which to compute age gender at standardised rates, it was decided to create our own reference distribution based on population totals published by the Office for National Statistics (Office for National Statistics, 2003). The year 2003 was chosen as a reference year, and the proportions of the population in each age gender group were calculated. The rationale for this approach was to ensure a reference population as close as possible to the UK population which was our inferential target. This reference distribution is available, on request, from the candidate.

2.4.3 Methods specific to paper 2 (Lifetime Risk)

The *life table* is the methodological tool which is most often used to estimate a lifetime risk for a specific event (or set of events). A life table is a set of probabilities of experiencing (or surviving) a particular event at one of a set of monotonically increasing event times. A *cohort life table* usually
includes a notional, arbitrarily chosen population count which is decremented by the event probabilities at each of the event times. The starting population is chosen to be large enough such that even very low event rates produce meaningful event counts after rounding to the nearest integer.

Often the event of interest is death, but the same methods can be applied to any event of interest, with extensions possible to incorporate recurrent events. Within the context of human populations, the rows of a life table represent time intervals, often yearly but not necessarily so. Furthermore, the intervals need not be regular, but they must be monotonically increasing.

Life tables have a long history and the first use of what we recognise as a life table was by Graunt in 1665 (Graunt, 1665). In modern times, the life table has been a staple tool of the insurance industry, and of the actuary in particular. Although in practice, the life table appears very simple, with a notional population decremented by a given amount at given intervals, the underlying justification for the method is grounded in probability theory, and carries with it certain assumptions.

The methods for paper 2 make the assumption which is commonly used, namely that the hazard of joint replacement is constant across the time interval of interest. Initially, this time interval is taken to be a single calendar year, but later the risks are aggregated across ten-year units of time. This assumption underlying the hazard rate of an event occurring is termed the force of mortality in the actuarial literature (Gerber, 1990). Sometimes, actuaries employ a method termed graduation (Gerber, 1990) to smooth estimated event rates across ages, but since here we are concerned with direct estimation of a lifetime risk at a given age, and not explicitly the estimation of the age distribution, graduation is not used.

The lifetime risk which is estimated in paper 2 is computed using a multiple decrement life table where there are two possible exit routes from the notional population count at a given age. Actuaries have a special notation (Gerber, 1990) for the components of a life table, and the population remaining at risk at a given age $x$ is written as $L_x$. In paper 2, we decrement the total $L_x$ of those exposed to the risk of experiencing a joint replacement by using the incidence rates estimated in paper 1. We then further decrement the remaining total by the estimated death rate in the general population, obtained from the Office for National Statistics (Office for National Statistics, 2003). The convention is to denote the count of deaths to be decremented at age $x$ by $d_x$, and we choose to denote the count of joint replacements to be decremented by $r_x$. This procedure is repeated for each year of age up to 100.
Unlike a typical single decrement table for mortality produced by national statistical agencies the world over, the lifetime risk results in paper 2 use a table which presents risks starting from age 50. The choice of this exact age is arbitrary but is guided by the fact that few lower limb joint replacements are carried out in the general population younger than this age. At age 40 and lower, the event counts for joint replacement become sparse (even in a large population-level data source like the CPRD) and estimates become increasingly imprecise and unreliable with decreasing age.

To produce the gender- and joint-specific lifetime risks of joint replacement at a given age \(x\), as produced for paper 2 (Table 3.1), we sum the remaining decrements up to the end of the life table, and then divide by the notional life table population at risk at the same age \(x\).

To estimate the precision of the lifetime risk estimates, a Poisson model is used, and the methods described in Schouten et al (Schouten et al., 1994) were followed to construct 95% confidence intervals using explicitly coded formulae in the life table spreadsheet created specifically for Excel. The Poisson distribution is the usual choice for data in the form of a count or a rate, so long as the count/rate is not especially low such that zeroes frequently occur. Even with the largest population-based dataset, such counts/rates will inevitably contain very low or zero counts within a given time interval at the very oldest ages, and it is acknowledged that when this occurs (e.g. at age 90 to 95 and over), the Poisson model may not be entirely appropriate for the construction of confidence intervals.

Although the results of paper 1 produced estimated replacement rates from 1991 to 2006, for the estimation of replacement risk we used the most up to date single year of data which was deemed to be reliable in the sense that there was no risk of boundary effects, which was 2005. For the ONS mortality data, we used 2006 which was the most recent year within the overall sixteen year period from which replacement rates were estimated.

Sensitivity analyses were carried out, varying the time source of both the replacement and the mortality rates. Finally, temporal trends in lifetime risk were estimated, where the mortality and replacement life table decrement counts were matched by rates applicable in the matched individual calendar year, and the results were then aggregated to provide rates over a wider time period due to the sparsity of data within single years.

All of the point and interval estimates for lifetime risk were programmed and computed in an Excel spreadsheet containing multiple linked worksheets, a small sample of which is shown in Figure 2.4 below.
Chapter 2 – Data and Methods

2.4.4 Methods specific to paper 3 (SURV)

Papers 1 and 2 were primarily concerned with estimating then making use of rates of primary TJR in the UK general population. Paper 3 has a different population and a different event as its main focus, and the methods described below must be considered in the context of this population/event combination.

Paper 3 considered two sub-populations, namely all those within the main CPRD dataset who had already experienced either a primary THR or TKR. The event of interest among those respective sub-populations was the first revision surgical procedure of the hip or knee following the primary TJR.

To estimate the risk of an event occurring over a fixed period of time within a defined population, one might consider a simple logistic regression analysis with a dichotomous outcome which indicated whether the event of interest had happened or not over the time period. Over a period of time where all subjects are exposed to the risk of the event for the whole time period under consideration, and where the occurrence/absence of the event can be reliably ascertained, then this approach is perfectly valid. However, when this is not the case, as with most medical research studies, then the results of such an analysis can be biased and hence potentially misleading.

Survival analysis, sometimes known as time-to-event analysis, is the branch of statistics which has the time to a particular event as its outcome of interest. However, survival analysis methods also deal with the situation where event times are unobserved for certain subjects because they do
not occur before the end of follow-up time. The dichotomous outcome for each subject also has a censoring indicator which shows whether the event happened at the outcome time, or whether the time represented the last known follow-up for that subject at which point the event had not occurred.

The main method of choice in estimating the risk of experiencing an event over time, in the presence of censoring, is Cox regression (Cox, 1972, Collett, 2003) which is sometimes referred to as the Cox proportional hazards model. Although the basic method for comparing risks of time in a survival context is the Kaplan-Meier estimator (Kaplan and Meier, 1958) with its characteristic plots. Cox regression allows adjustment for potential confounders which is an essential tool when using observational data such as that provided by the CPRD.

Traditionally, survival analysis methods (including the life table) were dealing with death as the event of interest. These methods have increasingly been used for non-fatal outcomes, and within the last few decades methods accommodating multiple outcome events (sometimes including death) have been essayed. However, where the main interest is in a non-fatal outcome, the competing risk of death may make the interpretation of risk estimates from Kaplan-Meier and Cox regression analyses subject to bias.

In paper 3, given that our sub-population (those already having undergone a THR or TKR) within our CPRD cohort is an elderly one, it is possible that the chosen method of analysis (Cox regression) might produce biased estimates of the risk of revision surgery due to the presence of the competing risk of death. Therefore, it was decided to use a relatively new method to tackle this potential problem, namely competing risks regression (Fine and Gray, 1999, Gray, 1988). This method explicitly takes into account the competing risk of death by adjusting the set of subjects at risk in a different way to that used in Cox regression. Where our subjects die before experiencing revision surgery on their hip or knee prosthesis, this is taken into account explicitly in the denominator of the formula for the likelihood. This is arguably better explained in texts such as that by Pintilie (Pintilie, 2011) rather than the formal mathematical proofs given in the original papers by Fine and Gray.

Whereas the result of interest in Cox regression would be a hazard ratio, which can be interpreted in a similar way to an odds ratio, a competing risks regression analysis produces a sub-hazard ratio (SHR), which although similar in interpretation to a hazard ratio, has some subtle (and almost counter-intuitive!) differences.

Paper 3 provides separate results for hip and knee revision using both competing risks regression and Cox regression, giving risk estimates adjusted for age, gender, smoking status, alcohol
consumption and the presence of comorbidities. The candidate made use of the R package `cmprsk` (author: Bob Gray) for the main analysis, also writing bespoke R program code to additionally provide analyses to create piecewise regressions using the competing risks methodology.

### 2.4.5 Methods specific to paper 4 (FP)

Paper 4 was arguably the most challenging of the four research questions in terms of method selection. Projection of past trends into the future requires inputs, either in the form of past trends from good quality data or inputs from, for example, policy makers which have been shown to have good predictive power in forecasting future trends. Unfortunately, published long-range input data for forecasts of the level of total hip/knee arthroplasty in the UK were not available in the UK, either from the government or from the National Health Service.

Researchers have therefore mainly relied on methods which project past trends of arthroplasty rates and/or counts into the future. One of the standard methods is to firstly estimate rates over a decade or two, as has been achieved in paper 1 in this thesis, and then to use a regression model with calendar time as the main predictor variable in order to predict joint replacement counts/rates over a future time period. The type of regression may be a standard linear regression (e.g. ordinary least squares), but if the outcomes are counts or rates then a Poisson model using log-linear regression is more usual and more flexible in accommodating the curvature often found with non-linear trends.

For paper 4, it was felt that such methods (log-linear models) could be improved upon. The rationale for this was twofold. Firstly, log-linear regression is modelling an exponentially increasing rate or count, and this fixed mathematical constraint can produce very high (or very low) predictions over a long range forecast. These can often seem implausible in the context of the real supply-side inputs (e.g. the population with a need for TJR) and demand-side inputs (e.g. the hospitals/surgeons performing TJR) for which we would ideally like to have data available, but do not, as previously mentioned. Secondly, log-linear regression model projections are very sensitive to the shape and goodness of fit of the past data on which the model is estimated. With exponential growth being an essential feature of this type of model, a small change in past rates could generate a substantial change in future estimated rates. Therefore, log-linear regression was used to produce the basic estimates for future THR/TKR rates in paper 4, but only as a basic starting point. The raw estimates of future TJR counts were only used as a sensitivity to demonstrate the effects of excessive curvature which can result from exponential extrapolation.
However, before any estimation could be carried out, the CPRD denominator data had to be remodelled, as one of the key objectives for paper 4 was to obtain BMI group-specific projections. As supplied, the CPRD population denominator dataset (essential for computing rates) was split by calendar year, age and gender but not by BMI group. In the absence of any available BMI group population-level proportions for the estimation time period (1990 to 2010), either from the CPRD or from elsewhere, we used unweighted data from the Health Survey for England (HSE) in order to compute proxy UK population proportions for each year-age-gender-BMI grouping. These proportions were then applied to the CPRD denominator data to arrive at the year-age-gender-BMI granularity required to estimate the log-linear model for THR and TKR rates. We used a definition derived from the standard World Health Organisation (World Health Organisation, 2006) definitions - underweight < 20 kg/m², normal 20 to 25 kg/m², overweight 25 to 30 kg/m², obese 30 to 40 kg/m², and morbidly obese > 40 kg/m².

To estimate the count of future replacement operations we needed to apply these estimated rates to forecasts of the size of the UK population. The most reliable such forecasts are produced by the Office for National Statistics and we obtained their forecasts for mid-year 2008 which were the closest to the final year of CPRD data which were available at the time (Office for National Statistics, 2010b). We produced count projections using two different population scenarios: one using changing future BMI-specific population proportions as estimated by modelling the HSE data, as described above; and one using BMI-specific proportions held constant at 2010 levels. The rationale for this was to assess whether allowing for changing BMI in this way produced any meaningful changes in projected TJR counts.

Earlier in this section, the potential shortcomings of using log-linear models for long-term projections were described, and indeed when the log-linear projection was applied to ONS population forecasts for the UK, the projected TJR counts seemed highly implausible, especially for TKR (1.2 million replacements in 2035). Consequently, it was decided that the use of fixed rates estimated for 2010 would be used and projected as if the rate had levelled off. This static rate was then applied to ONS population forecasts which, having already been supplied by age and gender groups, were further broken down by BMI group. Two scenarios were modelled: BMI group proportions held fixed at 2010 levels using our HSE data estimates, and BMI group proportions extrapolated from the linear regression estimates already obtained from HSE data.

The problem with a simple linear extrapolation of the BMI distribution was that for certain age-gender-BMI subgroups, the proportion of that subgroup in a certain BMI category (e.g. obese or underweight) was estimated to be changing so fast that the proportions would have ended up being greater than one or less than zero before the end of the projection time window in 2035,
which is clearly impossible. To counteract this effect, the candidate developed a program which
took the linearly extrapolated BMI group proportions for each age and gender combination and
smoothed them using a formula containing an inverse hyperbolic tangent function in a similar
manner to that used in the methodological supplement to a report called ‘Tackling Obesity’
(McPherson, 2008). This method is arbitrary but is a pragmatic choice in a situation where no
input data exists other than previously observed trends. The formula for the smoothing factor is
given below:

\[ 1 - \tanh^{-1} \left( (0.5 + B) \times \left( \frac{Y_f}{25} \right) \right) \]

and is applied for each calendar year projected into the future to the 2010 proportion of each
age-gender category (e.g. males aged 60 to 70) in a given BMI group. In the formula, \( Y_f \) is the
number of years projected into the future (from 1 to 25) and \( B \) is a factor which reflects the
closeness to zero or one (the limits of a proportion) of a straight line linear extrapolation of the
proportion of the age/gender-specific population occupied by a given BMI group.

For example, in the age-gender group ‘males aged 70 to 80’, the proportion of those in the BMI
group between 20 and 25 kg/m² was forecast to fall from 17% to -4% under linear extrapolation,
which is clearly not possible. The smoothing effect gradually restrained the linear growth such
that the final 25-year projected proportion of that age-gender group in the BMI 20 to 25 range
was 8%. This procedure was applied to all the data and was therefore consistent. Where the BMI
group proportions were not changing fast enough to come close to the 0 or 1 boundary, the effect
of the smoother was virtually indistinguishable from the continuation of the forecast linear
projection of the BMI group proportions. It should be stressed that this smoothing effect was only
applied to the denominator proportions which are then applied to the future official population
estimates from the ONS. The smoothing is not applied to the counts of TJRs.

In summary, four separate sets of projection estimates were produced for THR and TKR
separately: raw log-linear projection, for static and changing BMI group distribution in the
population, and 2010 rate projection, again for both BMI scenarios.

### 2.5 Summary

This chapter has described the dataset chosen for the analyses presented in the four papers in
this thesis and has justified the reasons for its selection. It has also described the process of data
refinement and manipulation needed to produce datasets which could be used to answer the
research questions posed. The statistical methods have also been described and discussed in more detail than the restricted content of a journal article allows. What follows are four chapters which present each of the papers which make up this thesis, in the order in which the research was carried out.

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3.1 Abstract

Using the General Practice Research Database, we examined the temporal changes in the rates of primary total hip (THR) and total knee (TKR) replacement, the age at operation and the female-to-male ratio between 1991 and 2006 in the United Kingdom. We identified 27,113 patients with THR and 23,843 with TKR. The rate of performance of THR and TKR had increased significantly (p < 0.0001 for both) during the 16-year period and was greater for TKR, especially in the last five years. The mean age at operation was greater for women than for men and had remained stable throughout the period of study. The female-to-male ratio was higher for THR and TKR and had remained stable. The data support the notion that the rate of joint replacement is increasing in the United Kingdom with the rate of TKR rising at the highest rate. The perception that the mean age for TKR has decreased over time is not supported.

3.2 Introduction

The increasing size of the elderly population will raise the demand on healthcare systems (Kim, 2008). In order to monitor the increase and any subsequent attempt to manage the rising demand, accurate and up-to-date information is essential. While some estimates can be made, the impact of specific diseases requires more detailed attention since no useful general model can be applied. One such specific area in musculoskeletal medicine is the treatment of osteoarthritis (OA) by joint replacement.

OA of the hip and knee has a high prevalence in the population aged over 60 years (Felson et al., 1987, Davies et al., 2002, Dagenais et al., 2009, Quintana et al., 2008) and replacement surgery in both joints is considered to be successful and cost-effective for end-stage disease. Changing indications for joint replacement surgery, along with the increasing prevalence of OA, particularly in younger patients (Ingvarsson et al., 1999b, Grotle et al., 2008), has meant that, historically, demand has usually outstripped supply. Recent waiting-list initiatives and other efforts to increase provision have partly reduced the immediate threat of unacceptably long waits for joint replacement. However, there is evidence from projection studies from the United States that the demand for total knee replacement (TKR) will double by 2015 and grow by 673% to nearly 3.5 million per annum by 2030 (Kurtz et al., 2007). For the hip, the demand is expected to grow by 174% to 572,000 joints per annum. It is notable that the requirement for TKR is set to be greater than for hips.

Data from the United States, although helpful, are not directly applicable to the United Kingdom and have other limitations. They are often incongruent with epidemiological findings from the
United Kingdom. Many studies from the Western world have used data which terminated in the year 2000. There are few data from our National Health Service (NHS) with a corresponding lack of reports on temporal trends of total hip replacement (THR) and TKR, except for the study by Dixon et al (Dixon et al., 2004).

With limited funding for health-care, it is essential to track patterns of disease in order to target resources and validate common perceptions about changes in practice. One is that since OA of the knees is considered to be more prevalent and is diagnosed more readily, TKR is being performed at an increasingly younger age. The study by Kim (Kim, 2008) substantiates this trend, as does the 2008 Annual Report from the Swedish Knee Arthroplasty Register (Swedish Knee Arthroplasty Register, 2009). If this trend is shown to be universal, new treatment algorithms will be required to manage the local provision of replacement. The ratios of incidence by gender are unclear. It has been suggested that women have more THRs than men and vice versa for TKR (Srikanth et al., 2005, Kim et al., 2008). It is necessary to clarify this, along with the most likely age at which different subgroups undergo replacement.

With this background, our aim was to describe the rates, age at operation and gender ratios of THR and TKR in the United Kingdom and to answer questions on current issues, including the reported trend for surgeons to operate on younger patients.

3.3 Patients and Methods

We obtained data from the General Practice Research Database. This comprises the entire computerised medical records of a sample of patients attending general practitioners in the United Kingdom. It covers a population of 6.5 million patients from 433 contributing practices, chosen as being representative of the wider population in the United Kingdom. General Practitioners have a key role in providing primary care and referral to specialist services. Patients are registered with one practice which stores medical information from primary care and hospital attendances.

The database is administered by the Medicines and Healthcare Products Regulatory Agency. Its records contain all clinical and referral events in primary and secondary care along with comprehensive details of prescription data, clinical events, specialist referrals, hospital admissions and their major outcomes. The data are stored using Oxford Medical Information Systems (OXMIS) and Read codes for diseases which are cross-referenced to the International Classification of Diseases ICD-9 (World Health Organisation, 2009). OXMIS and Read coding systems are commonly used in general practice for the classification of all diseases. Only those
practices which pass quality control are used in the General Practice Research Database. Deleting or encoding personal and clinic identifiers ensure confidentiality.

We identified all the patients in the database with a medical diagnosis code for THR or TKR between 1991 and the end of 2006. Read/OXMIS codes were used to identify primary THRs and TKRs. Patients were included if aged 18 years or over at operation. Those with a code for private practice were excluded as this variable has not been validated within the General Practice Research Database, therefore we could not be certain of its accuracy.

3.3.1 Statistical analysis

Age-gender standardised replacement rates for calendar years were calculated using ten-year age groups with the mid-year population estimates for 2003 as the reference standard. These estimates were published by the Office for National Statistics (Office for National Statistics, 2003), the General Register Office for Scotland and the Northern Ireland Statistics and Research Agency. We computed the 95% confidence interval (CI) using a Poisson model appropriate for directly standardised rates.

The mean age at total replacement was calculated for the hip and knee for each calendar year and 95% CIs computed. The age distribution at operation was calculated by gender for three consecutive five-year periods for the hip and knee, to investigate patterns over time.

3.4 Results

We identified 27 113 primary THRs and 23 843 primary TKRs between 1991 and 2006 (Table 3.1). Women were 67% more likely to undergo THR and 45% more likely to undergo TKR than men. They were on average almost three years older than men at THR, but this difference was halved for TKR. The female-to-male ratio (Figure 3.1) for the estimated incidence rates has remained fairly stable from 1995 onwards, varying between 1.46:1 and 1.63:1 for hips and between 1.18:1 and 1.42:1 for knees. The body mass index of patients undergoing TKR was significantly greater than that for those with THR ($p < 0.0001$) and this difference was greater for women than for men (Table 3.1).

3.4.1 Hip replacement

Between 1991 and 2006, the estimated age-standardised rates for primary THR (100 000 person years) increased from 60.3 (95% CI 53.7 to 67.0) to 144.6 (95% CI 138.1 to 151.1) for women and from 35.8 (95% CI 30.4 to 41.3) to 88.6 (95% CI 83.4 to 93.7) for men. The rise in rates for hips was
Chapter 3 - Paper 1: Temporal Trends

steady between 1993 and 2005 (Figure 3.2). When the 2006 rates for THR were applied to the mid-2006 population estimates for the United Kingdom, we obtained an estimated total number of primary THRs (excluding private practice) of 35 437 (95% CI 33 847 to 37 028) for women and 20 346 (95% CI 19 165 to 21 527) for men.

3.4.2 Total knee replacement

During the period of study, the estimated age-standardised primary TKR rates increased from 42.5 (95% CI 37.0 to 48.0) to 138.7 (95% CI 132.3 to 145.0) for women and from 28.7 (95% CI 23.9 to 33.6) to 99.4 (95% CI 93.9 to 104.8) for men. The temporal trend in rates for knees has not been as steady as that for hips, with a marked plateau from the mid-1990s, followed by a sharp rise from 2000. The estimated rates for women doubled between 2000 and 2006 (Figure 3.3). When the 2006 rates for TKR were applied to the mid-2006 population estimates for the United Kingdom, we obtained an estimated total number of primary TKRs (excluding private practice) of 33 972 (95% CI 32 413 to 35 531) for women and 22 825 (95% CI 21 575 to 24 075) for men.

3.4.3 Age at operation

In 2006, the mean age at operation for THR was 70.3 years (95% CI 69.8 to 70.8) for women and 67.6 years (95% CI 66.9 to 68.2) for men. For TKR it was 70.1 years (95% CI 69.6 to 70.5) for women and 69.2 years (95% CI 68.6 to 69.7) for men. The highest rates of THR and TKR were for women aged between 70 to 79 years (Table 3.2). The mean rate for hips in this age group was 541.8 (95% CI 501.0 to 582.5) and 555.3 (95% CI 514.1 to 596.6) for knees. The number of replacements for those aged between 60 and 79 years comprised almost two-thirds of the total for hips (64.3%) and a similar proportion for knees (66.2%), with little gender difference in both cases.

The mean age at THR was significantly greater in women than in men for all years after 1991 (Figure 3.4). For TKR (Figure 3.5) the gender difference for the mean age at primary replacement was much narrower than that for hips, to the extent that it was not significantly greater in the last two years of the study. Although the mean age at TKR and THR in men appeared to have increased with time these changes did not reach statistical significance.

In order to explore the possibility that there had been a change in the distribution of the age of patients undergoing joint replacement surgery, we examined the distribution of age in five-year age bands over three periods: 1991 to 1995, 1996 to 2000 and 2001 to 2005. The distribution of age across these time periods remained stable for both operations and genders.
The ratio of the incidence of TKR to THR was greater in men than in women (Figure 3.6). It fell initially in both genders between 1994 and 2000, but has since been increasing in both to the extent that it is 1.1:1 for men and approaching parity for women.

### 3.5 Discussion

We have shown that the rate of primary THR has more than doubled and that for TKR more than trebled during the period of study. We have also demonstrated that the mean age at THR and TKR was similar and has remained stable during this period. The female-to-male ratio for replacement was greatest for THR and has also remained stable.

In order to validate the rates obtained from the General Practice Research Database, we calculated the number of primary total THRs (finished consultant episodes) from the Hospital Episode Statistics for 2005 to 2006 (Hospital Episode Statistics). This contains data only for England and we therefore used mid-2006 population estimates to gross up to comparable figures for the United Kingdom. This method produced very similar estimates of 34,905 THRs for women and 21,008 for men and of 37,548 TKRs for women and 26,485 for men. This suggests that our data are as reliable as an estimate of joint replacement rates as the hospital episode statistics, but have the advantage of including Scotland, Wales and Northern Ireland. In order to validate our estimates further, we accessed data from the National Joint Registry (National Joint Registry, 2008), which covers England and Wales for NHS and private replacement operations. Although exact comparisons between sources were difficult, we extracted the number of hip and knee procedures at NHS hospitals and treatment centres in the financial year 2006 to 2007 as 51,956 and 54,604 respectively, after grossing-up to comparable figures for the United Kingdom using mid-2006 population estimates. These figures for THR and TKR, which included secondary procedures, were 6.9% and 3.9% less than the corresponding estimates from the General Practice Research Database. Given the various differences in the methods of data collection in these three sources along with the sampling variation within the General Practice Research Database, we are satisfied that our estimates represented the incidence of primary THR and TKR in the United Kingdom. It is accepted (Parkinson et al., 2007, Hollowell, 1997) that patients included in the General Practice Research Database are broadly representative of the population of the United Kingdom with respect to age, gender, socio-economic class and region and further examples of this validation have been given by van Staa et al (Van Staa et al., 2000, van Staa et al., 2001b).

We have shown that the increase in rates up to 2000 (Dixon et al., 2004) has continued, but that it is more marked for TKR than THR. The reasons are likely to be multifactorial. It may be that the patterns reflect maturation in the development and acceptance for each type of implant. The
older pedigree and surgical confidence with THR has been greater for longer. Conversely, TKR has a more recent documentation of reliability and has been the treatment of choice for a shorter period of time in strong contrast to the hip. A further and possibly more important reason, is the community burden of OA of the knee and hip. Radiological OA of the knee is approximately two to three times more prevalent than that of the hip in the general population (Arden and Nevitt, 2006). The number of TKRs per year is similar to that of THRs despite the much higher prevalence of OA of the knee. It is possible that the level of provision of THR is appropriate to the burden of OA of the hip whereas that for TKR is still below that required by surgeons operating on patients with lower levels of pain and disability.

One area of interest is the age of patients undergoing replacement and the perception that TKR is performed in younger patients. For the hip and knee, men are likely to undergo replacement earlier than women (Figure 3.4, Figure 3.5). The reason is unclear, but may reflect the mean life expectancy of the genders.

The mean age for both operations remained stable between 1991 and 2006. By contrast to anecdotal belief, surgeons are not operating on younger patients with increasing frequency. This finding is supported by the consistent data on age distribution for primary TKR in the periods 1990 to 1995, 1996 to 2000 and 2001 to 2005. Our study also challenges the perception that surgeons now perform TKR on increasingly younger patients, since the mean age at TKR has not changed. The perception was probably created falsely by the increase in the number of young patients undergoing TKR as part of the general increase in the overall number of TKRs.

The gender distribution of replacement is noteworthy. THR and TKR in women have consistently outnumbered those of men and the pattern has changed little over the years. It is not clear whether this indicates that hip disease is more predominant in women than in men or whether it reflects a difference in the tolerance for surgical intervention for gender, either by patient or clinician.

The strengths of our study are that the dataset includes practices from the whole of the United Kingdom with a follow-up of up to 20 years. The dataset has been validated and audited and only the practices providing good quality data are admitted. A limitation of the General Practice Research Database is that it does not provide exact details of the indication for any procedure. However, provisional data suggest that the same trends are observed, as in the National Joint Registry in which around 90% to 95% of all THRs and TKRs are performed for OA.

Our study has shown that General Practice Research Database can provide useful data to describe trends in replacement practice in the United Kingdom. It confirms that the rate of replacement is
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increasing, with TKR showing the greater change. The perception that the mean age for TKR has
decreased is not supported.

We gratefully acknowledge all the general practitioners and their patients who have consented to
give information to the General Practitioner Research database. This study is based in part on
data from the full feature General Practice Research Database obtained under licence from the
UK Medicines and Healthcare Products Regulatory Agency. However, the interpretation and
conclusions contained in this study are those of the authors alone. We also acknowledge the
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from a commercial party related directly or indirectly to the subject of this article.
### 3.6 Tables and Figures for Paper 1

Table 3.1  Demographic characteristics of GPRD subjects undergoing primary total hip or knee arthroplasty, 1991 to 2006

<table>
<thead>
<tr>
<th></th>
<th>Hip</th>
<th>Knee</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Age (at replacement) (mean, range, N)</td>
<td>70.4 (85)</td>
<td>67.5 (81)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>62.6</td>
<td>37.4</td>
</tr>
<tr>
<td>BMI (most recent) (median, IQR, N)</td>
<td>26.3</td>
<td>27.1</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>11.4</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>16033</td>
<td>9616</td>
</tr>
</tbody>
</table>
Table 3.2  Number and rate (per 100,000 person years) of primary procedures for total hip and knee replacements in the GPRD, by age group and gender, 2006

<table>
<thead>
<tr>
<th>Age group</th>
<th>Female Hips</th>
<th>Female Knees</th>
<th>Male Hips</th>
<th>Male Knees</th>
</tr>
</thead>
<tbody>
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1911 1142 1827 1283
Figure 3.1  Gender ratio for number of replacements by type of procedure

Chapter 3 - Paper 1: Temporal Trends
Figure 3.2  Trends in primary total joint replacement rates with 95% confidence intervals 1991 to 2006 - Total Hip Replacement

Figure 3.3  Trends in primary total joint replacement rates with 95% confidence intervals 1991 to 2006 - Total Knee Replacement
Figure 3.4  Mean age at primary joint replacement with 95% confidence intervals 1991 to 2006 - Total hip replacement

Figure 3.5  Mean age at primary joint replacement with 95% confidence intervals 1991 to 2006 - Total knee replacement
Figure 3.6  Ratio of incidence rates for total knee: hip replacements for men and women between 1991 and 2006
3.7 Reference List for Paper 1


Chapter 3 - Paper 1: Temporal Trends


3.8 Declaration of authorship for Paper 1

David Culliford: Reviewed the literature; Responsible for study design and choice of methodology; Conducted some of the data manipulation programming; Conducted all the statistical programming; Conducted all statistical analyses; Drafted all versions of the manuscript (except for parts of the introduction and discussion in the first draft only); Held overall responsibility for manuscript submission and all associated administration

Joe Maskell: Restructured the raw CPRD data; Provided SAS programming support and advice; Provided Excel support and advice; Commented on later versions of the manuscript

David Beard: Wrote majority of sections for the initial draft of the introduction and discussion; Contributed to the literature search; Commented on subsequent drafts of the manuscript

David Murray: Commented on later drafts of the manuscript

Andrew Price: Commented on later drafts of the manuscript

Nigel Arden: Principal Investigator for the grant; Secured grant funding; Provided ongoing guidance and supervision to candidate; Commented on all drafts of the manuscript; Held overall responsibility for the research as PI and as corresponding author

All co-authors below confirm the accuracy of the declaration of authorship for paper 1:

Signature                        Date

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Chapter 4: Paper 2 – The Lifetime Risk of Total Hip and Knee Arthroplasty: Results from the General Practice Research Database

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Chapter 4 - Paper 2: Lifetime Risk

4.1 Summary

Objective: To estimate the lifetime risk of undergoing primary total hip (THR) or knee (TKR) replacement in the UK.

Method: A Population-based cohort study of 25,845 patients who had undergone a THR and 23,260 patients who had undergone a TKR between 1991 and 2006, using data from the UK General Practice Research Database.

Results: The estimated mortality-adjusted lifetime risk of THR at age 50 for the year 2005 was 11.6% (95% CI: 11.1, 12.1) for women and 7.1% (95% CI: 6.7, 7.5) for men. For TKR the risks were 10.8% (95% CI: 10.3, 11.3) for women and 8.1% (95% CI: 7.6, 8.5) for men. Between 1991 and 2006, the lifetime risk of THR at age 50 rose from 4.0% (95% CI: 3.5, 4.4) to 11.1% (95% CI: 10.6, 11.6) for women and for men from 2.2% (95% CI: 1.8, 2.5) to 6.6% (95% CI: 6.2, 7.0). Over the same period, for TKR the risk for women increased from 2.9% (95% CI: 2.6, 3.3) to 10.6% (95% CI: 10.1, 11.1) and for men from 1.8% (95% CI: 1.5, 2.2) to 7.7% (95% CI: 7.3, 8.2).

Conclusion: The lifetime risk of undergoing THR or TKR is estimated to be substantially less than the risk of developing symptomatic hip or knee osteoarthritis. For the knee, the difference between these risk estimates is particularly wide. The reasons for the size of these differences are not clear, and further work is needed to quantify the extent of latent demand for these cost-effective and established interventions among the population with symptomatic osteoarthritis of the hip or knee.

4.1.1 What is already known on this topic

Total hip (THR) and knee (TKR) replacements are among the most successful and reliable orthopaedic procedures for joint pain relief in patients with advanced osteoarthritis.

The lifetime risk of developing knee and hip osteoarthritis has already been estimated at 45% and 25% respectively.

Register data and published incidence rates from the UK show an increasing trend in hip and knee replacement but there is no corresponding data on lifetime risk.

4.1.2 What this study adds

The lifetime risk of undergoing a THR or TKR in the UK is estimated at between 5 and 10 percent, which is substantially less than the risk of hip or knee osteoarthritis. Between 1991 and 2006 there is an upward trend in risk.
The lifetime risk of hip or knee osteoarthritis is greater than that for total hip or knee replacement.

4.2 Introduction

The lifetime risk of developing knee osteoarthritis has been estimated at 45% (Murphy et al., 2008), with the corresponding figure for osteoarthritis of the hip at 25% (Murphy et al., 2010). The magnitude of these risks is not surprising given that hip and knee osteoarthritis has such a high prevalence among elderly people (Felson et al., 1987, Quintana et al., 2008) and the average life expectancy in the UK population is over 75 years. Joint replacement surgery for both hip and knee is an efficacious and cost-effective treatment for end stage joint disease (Liang et al., 1986) and the number of primary total joint replacements being performed per annum in the UK is currently rising and has been predicted to continue to increase by as much as 50% by 2026 (Birrell et al., 1999).

Historically total hip and knee replacements have been amongst the most successful and reliable orthopaedic interventions for pain relief and improvement in quality of life, with greater than 90% prosthesis survival at 10 years (Segal and Bellamy, 1988).

Given that osteoarthritis is now the most frequent indication for total hip or knee arthroplasty in the UK (Culliford et al., 2010) (over 90% for hips and over 95% for knees), it might be expected that the lifetime risk of undergoing this form of surgery is substantial, yet we are unaware of any existing population-based estimates for this risk. Although demand for such surgery has usually outstripped supply, the number of operations performed is still considerable, with over 160,000 hip and knee replacements carried out in England and Wales in the 12 months to April 2010 (National Joint Registry, 2010).

Lifetime risk is a concept which is easily interpretable by patients, clinicians and policymakers, arguably providing a more patient-centred measure of risk for the onset of disease or the occurrence of a specific event (Sasieni and Adams, 1999). For most lay persons, it is easier to understand a lifetime risk percentage than an age-specific incidence rate. A lifetime risk estimate can be made more informative by additionally calculating interval risks (e.g., 10 years) at different ages to establish the periods of greatest risk during the lifetime.

The primary aim of this study was to use data from the General Practice Research Database (GPRD), combined with national Office for National Statistics (ONS) mortality data to provide simple estimates for the lifetime risk of undergoing a primary THR or TKR replacement in the UK.
A secondary aim was to describe temporal changes in these estimated risks between 1991 and 2006.

4.3 Method

4.3.1 Participants

We used data obtained from the GPRD. The GPRD comprises the entire computerized medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from 433 contributing practices chosen to be representative of the wider UK population (Parkinson et al., 2007). GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD is administered by the Medicines and Healthcare products Regulatory Agency (MHRA).

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read and OXMIS codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. Complex survey methods were not required for this analysis because the GPRD comprises entire general practice populations rather than probability-based samples of patients.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from 1991 until the end of 2006. Read/OXMIS codes were used to identify primary THRs and TKRs. Patients were included in the analysis if aged 50 years or over at the time of the replacement. Participant demographics including age, gender, body mass index (BMI) and smoking status were collated. We also obtained gender-specific all-cause mortality data from the ONS (Office for National Statistics, 2010a) for the time period 1991-2006.
4.3.2 Analysis

The GPRD data was aggregated into single-year age intervals. The age label was defined as age at last birthday at the end of a calendar year, starting at age 50. Consistent definitions were applied to the death data and exposed to risk. Incidence rates for joint replacement were computed by dividing the count of primary THRs and TKRs in the GPRD data by the corresponding amount of person time spent by those in the entire GPRD population who matched the age band, gender and time interval of interest. We computed the lifetime risk of replacement at 50 years of age separately for hip and knee. This was achieved by a life table method similar to that used by van Staa and colleagues (van Staa et al., 2001a), applying the incidence rates for replacement and the rates for all-cause mortality as multiple decrements at 1-year age intervals. The resulting counts of THR and TKR for the hypothetical life table population were then summed and divided by the life table population base to produce estimates of lifetime risk from age 50. Confidence intervals at the 95% level were estimated under a Poisson model (Schouten et al., 1994), which is the standard assumption for count data. Risks were estimated separately for gender and hip/knee. This procedure was repeated with 60, 70 and 80 years of age as the starting point for the risk of replacement. Additionally, we computed 10-year risk percentages from age 50 up to age 80. Estimates were tabulated using 2005 replacement and mortality data due to the possibility of boundary effects with the GPRD data for 2006, although we additionally calculated risk percentages based on the replacement counts and person-time for the entire study period 1991-2006. All estimates for single calendar years used mortality data matched to the same calendar year, but for the estimates based on the entire study period we used 2006 mortality rates, which were the most recent rates available falling within that period, but a sensitivity analysis using 1991 mortality rates was also carried out. Finally, lifetime risks of THR and TKR stratified by gender for individual calendar years, were estimated in order to compare temporal trends.

All statistical analyses were performed in Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA), SAS version 9.1.3 (SAS Institute Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria).

4.4 Results

4.4.1 Participant demographics

We identified 49,105 patients from the database who had undergone a THR (N=25,845) or TKR (N=23,260) during the study period. The average age at replacement was similar in both THR and
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TKR cohorts but the proportion of women was greater for both THR and TKR (Table 4.1). For those with a recorded pre-operative BMI, the proportion of obese (BMI > 30) subjects was 25% for THR and 37% for TKR.

4.4.2 Lifetime risks

Using rates from 2005, we estimated that the mortality-adjusted lifetime risk of THR at age 50 was 11.6% for women and 7.1% for men (see Table 4.2). For TKR the risk was estimated at 10.8% for women and 8.1% for men. The lifetime risk decreases with increasing age for both THR and TKR in men and women. At age 80 the gender gap in risk of THR has reduced to 40% higher for women than men (22% higher for TKR). Estimated risk percentages at ages 50, 60, 70 and 80 are presented in Table 4.2.

For the aggregated data over the period 1991 and 2006, the mortality-adjusted lifetime risk of THR at age 50 was estimated at 8.3% for women and 5.2% for men. For TKR the risk was estimated at 7.0% for women and 5.2% for men. The gender gap in the estimates obtained for the whole study period was similar to those for the 2005 estimates. Mortality data from 2006 was used for the whole study period estimates. As a sensitivity analysis, these estimates were recalculated using 1991 mortality data, but this only resulted in a small reduction in the lifetime risk estimates of between 0.6 and 0.8 percentage points at age 50 and a reduction of 0.2-0.3 at age 80. These reductions were seen for both THR and TKR and for men and women.

Between 1991 and 2006, the lifetime risk of THR at age 50 rose from 4.0% (95% CI: 3.0, 5.0) to 11.1% (95% CI: 9.9, 12.2) for women and for men from 2.2% (95% CI: 1.4, 3.0) to 6.6% (95% CI: 5.7, 7.5). Over the same period, for TKR the risk for women increased from 2.9% (95% CI: 2.1, 3.8) to 10.6% (95% CI: 9.5, 11.7) and for men from 1.8% (95% CI: 1.1, 2.6) to 7.7% (95% CI: 6.8, 8.7). Lifetime risks at age 50 for each year of the study period are presented in Figure 4.1.

When shortening the time horizon to 10 years rather than the remainder of life, it can be seen (Table 4.3) that in 2005 the risk of a 50-year old female undergoing a THR by age 60 is low (1.1%, 95% CI: 0.8, 1.4) compared with the 10-year risk for an 80-year old (3.5%, 95% CI: 2.7, 4.3). Ten-year TKR risks are slightly higher than THR risks for men aged 60 and over, but for women they are more similar. Figure 4.2 shows the temporal trend in 10-year risk of THR for women. Single-year estimates of 10-year risk at ages 50, 60, 70 and 80 are presented between 1991 and 2006 at five-yearly intervals. Figure 2 also shows that among these four starting ages, the 10-year risk of undergoing THR is consistently highest for 70-year old women and lowest for 50-year old women between 1991 and 2006. This was also true for 10-year THR risks for men and for 10-year TKR risks for both women and men.
4.5 Discussion

4.5.1 Summary of results

This study presents population-based estimates for the lifetime risk of undergoing total hip and knee arthroplasty in the United Kingdom for those aged 50 and over. The lifetime risk estimates for arthroplasties are substantially less than the corresponding lifetime risks for clinical osteoarthritis. Temporal trends in lifetime risk of THR and TKR between 1991 and 2006 show a steady rise, with rates for women being consistently higher than for men.

The estimation of lifetime risks for major diseases and events is well established, including coronary heart disease (CHD) (Lloyd-Jones et al., 1999), cancer (Feuer et al., 1993), and fracture (van Staa et al., 2001a, Johnell and Kanis, 2005). Although published incidence rates exist for hip and knee replacement in the UK (Culliford et al., 2010, Dixon et al., 2004) and internationally (Birrell et al., 1999, Merx et al., 2003, Kurtz et al., 2011, Kurtz et al., 2005), we are unaware of any lifetime risk estimates available in the literature for undergoing these surgical procedures. The estimates presented here suggest a lifetime risk of THR or TKR for women or men aged 50 living in the UK of 10-11% and 6-7% respectively, based on GPRD data from 2005. These estimates are considerably less than the lifetime risks for osteoarthritis of the hip (HOA) and knee (KOA) which in the United States have been estimated at 25% (Murphy et al., 2010) and 45% (Murphy et al., 2008) respectively, based on a symptomatic and radiographic (Kellgren/Lawrence >= 2) diagnosis of osteoarthritis. Osteoarthritis is by far the most common primary indication for THR and TKR, accounting for 93% and 97% respectively of all such operations in England and Wales in 2009 (National Joint Registry, 2010), with similar figures of 90% for THR and TKR reported in the United States (Singh et al., 2010).

The mismatch between the lifetime risks of such an established intervention (THR/TKR) and its main indication (HOA/KOA) is interesting, especially so for the knee given the much larger difference in risks. There are a number of potential explanations for the differences between these estimates, and we address each of these in turn. A major part of the difference between risks estimates for osteoarthritis and joint replacement may be related to the lack of consensus on the severity of symptoms required for an indication for surgery (Gossec et al., 2011), coupled with the variability of the natural history of osteoarthritis. Indications for surgery include end-stage joint arthritis (typically a K/L grade of 3 or 4), a degree of mobility affected by symptoms and persistent severe pain which has failed to be relieved by non-surgical treatment (Dieppe et al., 2011, Dreinhofer et al., 2006). An earlier population-based study of TKR by Juni et al (Juni et al., 2010) in the south west of England used an assessment of need based on the New Zealand Score...
Chapter 4 - Paper 2: Lifetime Risk

(Hadorn and Holmes, 1997), suggesting that differences in the perception of disease severity may account for some of the underprovision reported by the study team.

At least some of the disparity between the estimated risks of knee osteoarthritis and TKR might be because not all of those with radiographic and symptomatic OA require TKR surgery. There is a considerable disparity between the presence and severity of radiographic OA and symptoms: data from the Framingham Osteoarthritis demonstrated that only 59% of those with definite radiographic knee OA (K/L grade >= 2) reported knee pain on most days in the previous month (Felson et al., 1987). Furthermore, there is now increasing data to suggest that OA does not necessarily progress over time such that many patients may never require surgery: data from the Chingford study have demonstrated that 61% of patients with radiographic OA do not progress radiographically over a period of 15 years (White et al., 2010); that self-reported knee pain may resolve over a similar time period in 30% of patients (Soni et al., 2010) and that in a cross sectional survey of patients diagnosed with clinical knee OA 29% did not report clinically important symptoms (Jordan et al., 2004).

A further possibility is that some of this differential may be related to unmet need for THR and TKR. Judge et al have estimated the mismatch between need and provision of hip and knee replacement surgery in the UK (Judge et al., 2009a, Judge et al., 2009b) and attempts have been made to explain such differences in terms of geographical and sociodemographic characteristics (Judge et al., 2010). A study based on UK data from the late 1990s (Dieppe et al., 2008) found that although there was little mismatch for THR, there was a large mismatch between estimated need and provision for TKR. The aforementioned paper by Juni et al (Juni et al., 2003) adds further support to this evidence. Although our GPRD data does not extend further than 2006, data from the National Joint Registry (National Joint Registry, 2010) show that for England and Wales, the years 2007-2010 have seen a much slower growth in provision than was seen in the period from 1995 to 2005 (Culliford et al., 2010). This suggests that the perceived gap between need and provision is unlikely to have been substantially narrowed in the time since the end 2006, the year on which our most recent estimates of lifetime risk are based. This would depend on there having been no change in the risk of developing osteoarthritis over the same period.

Notwithstanding the explanations already offered for the disparity between lifetime risk estimates for OA and THR/TKR, there is also the issue of patient choice in whether to accept a surgical intervention, if it is offered. Research by Hawker and colleagues in Canada (Hawker et al., 2004) examined OA patients’ perceptions of total joint arthroplasty as an intervention, finding that willingness to undergo surgery was associated with misperceptions about its appropriateness. Another study by the same team found low rates of willingness to undergo
surgery among those with disabling arthritis (Hawker et al., 2001). Studies in the UK have also shown that a substantial proportion of those for whom THR/TKR is a suitable intervention may not be willing to have surgery, with women less willing than men (Juni et al., 2010) and willingness to undergo TKR less than that for THR (Dieppe et al., 2008). One study (Juni et al., 2003) reported that 32% of those considered for TKR were unwilling, for a variety of reasons, to consider surgery as an option.

Finally, our lifetime risk estimates for THR and TKR are based on data from the United Kingdom, yet we are making comparisons to lifetime risks for osteoarthritis based on cohort data from the United States. It is accepted that we are comparing data from different countries and with different study designs, but the osteoarthritis risks estimated by Murphy et al. (Murphy et al., 2008, Murphy et al., 2010) are the only reliable, large-scale estimates available for a developed population.

4.5.2 Strengths and potential limitations of the study

One of the strengths of this study is the data on which it was based. The usefulness of registers and databases is highly dependent on the quality of the data collection. The data imported into the UK GPRD is in an extremely detailed, descriptive and well-structured format which permits accurate interpretation. It is accepted (Parkinson et al., 2007, Hollowell, 1997) that the data subjects included in the GPRD are broadly representative of the UK population as a whole with respect to age, sex, socio-economic class and UK region. Further examples of GPRD validation are given by van Staa and colleagues (van Staa et al., 2001a, Van Staa et al., 2005, van Staa et al., 2001b).

The life table method of estimating lifetime risk is a standard and straightforward method which permits multiple decrements to cater for competing risks. It can provide accurate estimates of risk, particularly where the time interval between successive decrements is small. However, it does not have the flexibility in dealing with predictor variables afforded by more sophisticated model-based methods.

We chose to stratify only by age and gender, and the only competing risk we considered was all cause mortality. Although mortality for those with OA has been reported to be elevated compared with the general population (Nuesch et al., 2011), we used mortality for the general population as our lifetime risks are estimated for such a population and not specifically for the OA population. The quoted lifetime risks of 25% and 45% for hip and knee osteoarthritis are based on age 18 whereas our estimates of risk for THR and TKR are from age 50. However, very few primary THR/TKR operations are performed on those under the age of 50, and the majority of these are
indicated by trauma rather than osteoarthritis. To examine the sensitivity of our estimates to survival bias, we computed lifetime risks at ages 20, 30 and 40, finding virtually no difference between risks estimates at those ages (approximately 0.05 of one percentage point) and risks at age 50. There is no specific code for THR/TKR performed in private practice as opposed to the NHS setting and we cannot be certain that some operations may not have been recorded. Our rates however are consistent with those from the NJR which did record private operations.

Obesity was not used as a stratifying factor in our analysis. BMI data is only available for the cohort who underwent THR or TKR (respectively 25% and 37% obese), and is not available for the GPRD population which comprise the denominator in the THR/TKR incidence rates from which our lifetime risk estimates are derived. Furthermore, BMI data is not collected systematically for GPRD data, and as a consequence is not available for approximately 15% of subjects. Hence direct statistical comparisons with the baseline obesity proportion for the Johnston County cohort (25%) in the osteoarthritis risk papers by Murphy et al (Murphy et al., 2008, Murphy et al., 2010) are not possible.

Care should be exercised in generalising these lifetime risk results to countries and sub-populations where the patterns of access to medical care are different from those in the UK. Within the United States, for example, differing levels of health insurance coverage may result in variability in the lifetime risk of THR/TKR.

The data we have used does not extend beyond the end of 2006, and therefore one should be wary of generalising the results to current patterns of THR/TKR utilisation. In particular, TKR rates are now considerably higher than those for THR, but here we have chosen to concentrate on the difference between the risks of disease and intervention rather than any estimated differences between THR and TKR.

4.6 Conclusion

The lifetime risk of undergoing total hip or knee arthroplasty is estimated to be substantially less than the risk of developing hip or knee osteoarthritis, which is by far the most common indication for such surgical interventions. The reasons for such a gap, which is particularly wide in the case of total knee replacement, are not yet clear, and further work is needed to establish the extent of any latent demand for these cost-effective and established interventions among the population with symptomatic osteoarthritis of the hip or knee.
Author contributions

David Culliford: Conception and design, Analysis and interpretation of the data, Drafting of the article, Statistical expertise, Final approval of the article, Responsibility for integrity of the work as a whole

Joe Maskell: Assembly, design, post-processing and restructuring of data, Final approval of the article

Amit Kiran: Conception and design, Statistical expertise, Final approval of the article

Andy Judge: Conception and design, Statistical expertise, Final approval of the article

Kassim Javaid: Conception and design, Critical revision of the article for important intellectual content, Final approval of the article

Cyrus Cooper: Conception and design, Critical revision of the article for important intellectual content, Final approval of the article

Nigel K Arden: Obtaining of funding, Conception and design, Provision of study materials, Final approval of the article, Responsibility for integrity of the work as a whole

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Ethical approval

No ethical approval was required for this study.

Conflict of interest

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements

We gratefully acknowledge all the general practitioners and their patients who have consented to give information to the GPRD along with the MRC support in providing access to the database.
### Table 4.1 Clinical and Demographic characteristics – for subjects aged 50 and over

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<td></td>
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<td>Male</td>
</tr>
<tr>
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<td>9544</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
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<td>69.1 (9.1)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>67.1</td>
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</tr>
<tr>
<td>BMI\textsuperscript{a} (mean, SD)</td>
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<td>27.5 (4.3)</td>
</tr>
<tr>
<td>No. of comorbid conditions (%)</td>
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<td>2+</td>
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<td>Indications for surgery\textsuperscript{b} (%)</td>
<td>Rheumatoid arthritis</td>
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<td>Osteoarthritis</td>
<td>93.4%</td>
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<tr>
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<td>Others</td>
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</tr>
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</table>

\textsuperscript{a}BMI only used if within one year pre-surgery - available for 85% of subjects

\textsuperscript{b}For those subjects where an indication could be reliably ascertained
Table 4.2 Estimated lifetime risk (percentage with 95% confidence intervals) of undergoing primary total hip or knee replacement surgery based on age and gender-specific incidence rates from GPRD data in 2005, adjusted for mortality

<table>
<thead>
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<th>Current age (years)</th>
<th>Risk of Primary Total Hip Replacement (%)</th>
<th>Risk of Primary Total Knee Replacement (%)</th>
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<td>6.7 (5.8,7.7)</td>
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</tbody>
</table>

Table 4.3 Estimated ten-year risk (percentage with 95% confidence intervals) of undergoing primary total hip or knee replacement surgery based on age and gender-specific incidence rates from GPRD data in 2005, adjusted for mortality

<table>
<thead>
<tr>
<th>Current age (years)</th>
<th>Risk of Primary Total Hip Replacement (%)</th>
<th>Risk of Primary Total Knee Replacement (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>50</td>
<td>1.1 (0.8,1.4)</td>
<td>0.8 (0.5,1.0)</td>
</tr>
<tr>
<td>60</td>
<td>3.5 (2.8,4.1)</td>
<td>2.2 (1.7,2.7)</td>
</tr>
<tr>
<td>70</td>
<td>5.2 (4.4,6.1)</td>
<td>3.5 (2.8,4.3)</td>
</tr>
<tr>
<td>80</td>
<td>3.5 (2.7,4.3)</td>
<td>2.4 (1.5,3.2)</td>
</tr>
</tbody>
</table>
Figure 4.1  Temporal trends in the estimated lifetime risk at age 50 of undergoing primary total hip or knee replacement surgery based on age and gender-specific incidence rates from GPRD data, adjusted for mortality
Figure 4.2  Temporal trends in the estimated 10-year risk for women of undergoing primary total hip replacement surgery at current age 50, 60, 70 and 80 based on age and gender-specific incidence rates from GPRD data, adjusted for mortality
Chapter 4 - Paper 2: Lifetime Risk

4.8 Reference List for Paper 2


Chapter 4 - Paper 2: Lifetime Risk


4.9 Declaration of authorship for Paper 2

David Culliford: Reviewed the literature; Responsible for study design, choice of methodology, implementation in software; Conducted all data manipulation programming (from the restructured CPRD data); Conducted all statistical programming; Conducted all statistical analyses; Drafted all versions of the manuscript; Held overall responsibility for manuscript submission and all associated administration

Joe Maskell: Restructured the raw CPRD data; Advised on advanced elements of SAS programming; Provided Excel advice; Commented on later versions of the manuscript

Amit Kiran: Advised on actuarial methods (life table analysis); Reviewed methodological design and software implementation; Reviewed drafts of the manuscript

Andrew Judge: Provided statistical mentoring for candidate; Reviewed methodological design; Reviewed drafts of the manuscript

Kassim Javaid: Reviewed drafts of the manuscript

Cyrus Cooper: Reviewed drafts of the manuscript

Nigel Arden: Principal Investigator for the grant; Secured grant funding; Provided on-going guidance and supervision to candidate; Commented on all drafts of the manuscript; Held overall responsibility for the research as PI and as corresponding author

All co-authors below confirm the accuracy of the declaration of authorship for paper 2:

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
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<tbody>
<tr>
<td>Joe Maskell</td>
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<td>Amit Kiran</td>
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<td>Andrew Judge</td>
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<tr>
<td>Cyrus Cooper</td>
<td></td>
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<td>Nigel Arden</td>
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</table>
Chapter 5: Paper 3 – A population-based survival analysis describing the association of body mass index on time to revision for total hip and knee replacements: Results from the General Practice Research Database

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5.1 Abstract

Objectives: Against a backdrop of rising levels of obesity, we describe and estimate associations of body mass index (BMI), age and gender with time to revision for participants undergoing primary total hip (THR) or knee (TKR) replacement in the UK.


Setting: Routinely collected primary care data from a representative sample of general practices, including linked data on all secondary care events.


Primary and secondary outcomes: Risk of THR and TKR revision associated with BMI, age and gender, after adjusting for the competing risk of death.

Results: The 5-year cumulative incidence rate for THR was 2.2% for men and 1.8% for women (TKR 2.3% for men, 1.6% for women). The adjusted overall subhazard ratio (SHR) for patients with THR undergoing subsequent hip revision surgery, with a competing risk of death, were estimated at 1.020 (95% CI 1.009 to 1.032) per additional unit (kg/m²) of BMI, 1.23 (95% CI 1.10 to 1.38) for men compared with women and 0.970 (95% CI 0.967 to 0.973) per additional year of age. For patients with TKR, the equivalent estimates were 1.015 (95% CI 1.002 to 1.028) for BMI; 1.51 (95% CI 1.32 to 1.73) for gender and 0.957 (95% CI 0.951 to 0.962) for age. Morbidly obese patients with THR had a 65.5% increase (95% CI 15.4% to 137.3%, p=0.006) in the subhazard of revision versus the normal BMI group (18.5–25). The effect for TKR was smaller (a 43.9% increase) and weaker (95% CI 2.6% to 103.9%, p=0.040).

Conclusions: BMI is estimated to have a small but statistically significant association with the risk of hip and knee revision, but absolute numbers are small. Further studies are needed in order to distinguish between effects for specific revision surgery indications.

Strengths and limitations of this study strengths and limitations of this study

The large sample size of the General Practice Research Database (GPRD; over 5% of the UK general practice population) enables population level inferences to be made.

The statistical methods explicitly account for the competing risk of death which has a much higher event rate than the event of interest (total hip or knee replacement) in this patient group.
GPRD data do not have directly linked information detailing the reasons for being referred for surgery, so we were unable to establish an exact indication.

5.2 Introduction

Total joint replacement of the hip and knee are well established as interventions for those suffering with end-stage osteoarthritis (OA) of the lower limb, with OA being the most frequent indication for total hip (THR) or knee replacement (TKR) in the UK (National Joint Registry, 2012) (over 90% for hips and over 95% for knees). Yet hip and knee prostheses do not necessarily continue to function effectively for the lifetime of the patient (National Joint Registry, 2012, Kurtz et al., 2005). Many traditional metal-on-polyethylene implants are likely to require revision surgery due to wear after 20 years of use due to wear characteristics and peri-prosthetic loosening. As a consequence, elective THR and TKR procedures have until relatively recently been indicated mainly in older patients, but even prostheses which make use of the latest technological developments (e.g. unicondylar knee prostheses) are not yet routinely recommended for use in younger patients.

A further dimension is added by the increasing prevalence of obesity in western populations, with clinicians in some cases considering patients too obese to undergo surgery (Sturmer et al., 2005, Santaguida et al., 2008), partly due to the perceived increase in risk of both perioperative and postoperative complications. There have also been examples of obese and/or morbidly obese patients experiencing restricted access to hip replacement surgery in some parts of the UK (NHS Warwickshire, 2011, NHS Yorkshire and the Humber, 2011, Peninsula Commissioning Priorities Group, 2011) where local healthcare planners have had similar concerns.

Revision procedures involve a surgical intervention to correct a prosthesis which is not functioning properly. Such operations are more costly than the original replacement procedure (Maradit Kremers et al., 2013, Vanhegan et al., 2012) and are often more complex, with a higher level of risk to the patient. Population-based estimates of the time from primary surgery to a revision procedure are of importance to orthopaedic surgeons, rheumatologists, healthcare providers, policymakers and patients. Registry data, both in the UK (National Joint Registry, 2012) and internationally (International Society of Arthroplasty Registers, Serra-Sutton et al., 2009), have been used extensively to estimate time to revision (Kurtz et al., 2011). Such data have been used previously to model prosthesis survival time in order to assess which specific demographic, clinical and prosthesis-specific factors are associated with time to failure (Jameson et al., 2012, Havelin et al., 2011).
Chapter 5 - Paper 3: Survival

Over the 12 months to April 2011, there were over 178 000 THR and TKR operations recorded in the National Joint Registry (NJR) for England and Wales (National Joint Registry, 2012). The NJR began recording data in 2003, and although it now contains virtually all replacements carried out in England and Wales, the maximum follow-up is currently less than 10 years. The registry contains complete data on many variables, including age and gender, but body mass index (BMI) is recorded in approximately 61% of participants undergoing hip replacement (62% for knee). We chose to use data from a primary care database with long follow-up and UK-wide coverage.

The primary aim of this study was to use data from the General Practice Research Database (GPRD) to produce population-based estimates for the association of BMI, age and gender with the time to revision surgery in the long term following THR or TKR.

5.3 Method

5.3.1 Participants

We used data from the GPRD. The GPRD comprises the entire computerised medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from over 600 contributing practices chosen to be representative of the wider UK population (Parkinson et al., 2007). GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The GPRD has recently become part of the new Clinical Practice Research Datalink which is administered by the Medicines and Healthcare products Regulatory Agency.

The GPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data and hospital admissions. Data are stored using read codes for diseases that are cross-referenced to the International Classification of Diseases-9. Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the GPRD database. Deleting or encoding personal and clinical identifiers ensures the confidentiality of information in the GPRD. The GPRD comprises entire general practice populations rather than probability-based samples of patients.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from the beginning of 1988 until August 2011. We then identified any secondary (revision) hip or
knee operations for these patients which occurred subsequent to the primary operation. The list of Read codes used to identify the primary and revision operations were independently reviewed by different clinicians and a consensus list agreed between them. Deaths recorded within the GPRD were also identified. The date of the first incidence of a patient’s hip or knee replacement was used as the start time. The event of interest in all time-to-event models was the first recorded revision operation. Censoring events were the end of study date (11 August 2011) or the transfer of a patient out of the GPRD for any reason other than death. Death from any cause was treated as a competing risk in the primary analysis. Patients were included in the analysis if aged 18 years or over at the time of the replacement operation. Participant demographics including age, gender, preoperative BMI, smoking and drinking status were collated, in addition to information on comorbid conditions.

5.3.2 Analysis

We used the competing risks regression methods of Fine and Gray (Fine and Gray, 1999) to estimate the effects of a participant’s BMI, age and gender on the time to revision of a prosthesis implanted during THR or TKR operation. The substantive event of interest was the first incidence of revision surgery, with all-cause mortality separately identified as a competing risk. The rationale for using competing risks regression is that methods which treat death as just another censoring event may overestimate risk for an event of interest, especially in an older population (Berry et al., 2010). We adjusted for a range of important covariates and potential confounders: smoking status, alcohol consumption and the number of comorbid conditions (which include diabetes, hypertension, stroke, cardiovascular disease and anaemia). All covariates were treated as fixed at baseline. Analyses for hips and knees were performed separately, with prosthesis survival at the end of follow-up being of primary interest. Proportionality of hazards assumptions was assessed by examining complementary log-log plots of the cumulative incidence. As a sensitivity analysis we modelled the same data using standard methods which do not cater for competing risks (i.e. Cox regression analysis with death as a censoring event). We also calculated stand-alone estimates for the cumulative incidence of revision surgery at 1, 5, 10 and 15 years, and plotted estimates of the age-specific, gender-specific and BMI-specific cumulative incidence curves for the whole cohort.

All tests of significance were at the 5% level and two-sided. Interval estimates were based on 95% CIs. The main statistical analysis was carried out using R (R Core Team, 2012. R Foundation for Statistical Computing, Vienna, Austria), SAS V.9.2 (SAS Institute Inc., Cary, North Carolina, USA) and Stata (StataCorp. 2011; Stata Statistical Software: Release 12. College Station, Texas, USA).
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5.4 Results

5.4.1 Participant demographics

Over the study period the database contained 63,162 patients undergoing THR and 54,276 patients undergoing TKR. The average age at replacement was similar in both the THR and the TKR groups but the proportion of women was greater for both THR and TKR (Table 5.1).

For those with a recorded preoperative BMI, the proportion of obese patients (BMI (>=30 kg/m²) was 26.2% for THR and 39.8% for TKR and the proportion of morbidly obese patients (which we define as having BMI >=40 kg/m²) was 1.6% for THR and 3.6% for TKR. Eighty per cent of preoperative BMI values used were recorded within 5 years of the primary operation. Table 5.1 describes the baseline characteristics of the cohort, including summary statistics and missing data percentages for all explanatory variables where complete data were not observed.

5.4.2 Survival analysis

The estimated cumulative incidence of revision at 5 years was 2.0% (95% CI 1.8% to 2.1%) for THR and 1.9% (95% CI 1.8% to 2.1%) for TKR. For women, cumulative incidence at 5 years was 1.8% (95% CI 1.7% to 2%) for THR and 1.6% (95% CI 1.5% to 1.8%) for TKR, and for men 2.2% (95% CI 2% to 2.4%) and 2.3% (95% CI 2.1% to 2.6%), respectively. Table 5.2 provides gender-specific estimates of cumulative incidence with point-wise CIs for a range of times (1, 3, 5, 10 and 15 years after THR/TKR). Figures 5.1/5.2 and 5.3/5.4 provide a further breakdown of the cumulative incidence of revision for the whole THR and TKR cohorts, respectively, with separate incidence curves for categorised BMI (Figure 5.1 and Figure 5.2) and categorised age (Figure 5.3 and Figure 5.4). Gray’s test was used to examine whether there were differences in the overall cumulative incidence of revision by gender, categorised age (<55, 55–64, 65–74, 75–84 >85 years) and categorised BMI (<18.5, 18.5–24.9, 25–29.9, 30–39.9 and >40 kg/m²). All three variables showed statistically significant differences in cumulative incidence for both hip (Gray’s test statistic: gender, age, BMI, p<0.001 for all) and knee (Gray’s test statistic: gender, age, BMI, p<0.001 for all).

In a single predictor (univariable) survival model allowing for the competing risk of death over the entire period of follow-up, we estimated that THR participants had a 3% increase in the subhazard of revision (SHR 1.030, 95% CI 1.020 to 1.041, p<0.001) for each extra unit (kg/m²) of BMI, with TKR participants showing a 2.6% increase per unit (SHR 1.026, 95% CI 1.013 to 1.038, p<0.001). The SHR was significantly greater for men compared with women for both THR (subhazard ratio (SHR)): 1.35, 95% CI 1.23 to 1.48, p<0.001) and TKR (SHR 1.54, 95% CI 1.37% to 1.72%, p<0.001).
Age at total joint replacement was also a significant univariable predictor of revision for both hip and knee, with THR participants estimated to have a 3% reduction in the SHR (0.970, 95% CI 0.967 to 0.973, p<0.001) for each extra year of age, with TKR participants showing a 4.3% reduction (SHR 0.957, 95% CI 0.952% to 0.961%, p<0.001).

The effects for all three variables (gender, age and BMI) were then estimated in multivariable competing risks regression models after adjusting for smoking status, drinking status and the number of comorbid conditions, again over the entire period of follow-up. For age, the estimates for the SHR were almost exactly the same as those from the univariable model for both hip and knee, but for gender (SHR 1.23 for hip; 1.51 for knee) and BMI (SHR 1.020 for hip; 1.015 for knee) the estimates were smaller. Nevertheless, all three variables remained statistically significant for both hip and knee in the presence of adjustment. For a 5-unit and 10-unit increase in BMI, this represents an increase in THR revision risk of 10.4% and 21.9%, respectively (7.7% and 16.1% for TKR). Testing for two-way interactions between age, gender and BMI did not produce any significant effects. All subhazard estimates (with 95% CIs and p-values) from the univariable and multivariable models are given in Table 5.3 and Table 5.4.

To further explore the effect estimates for BMI we ran the same adjusted age-gender-BMI model described above, but used categorical BMI instead of continuous. For morbidly obese TKR participants (BMI 40+) there was a 43.9% increase (95% CI 2.6% to 103.9%, p=0.040) in the SHR compared with those with a normal BMI (18.5–25), but the effect for THR was larger (a 65.5% increase) and stronger (95% CI 15.4% to 137.3%, p=0.006). The effect sizes were similar to those obtained when using the adjusted sub-HR estimate of continuous BMI for a participant with a BMI of 45 relative to one with a BMI of 22 (increase of 57.7% for THR; 40.8% for TKR). For obese patients in the range 30–40 kg/m² versus those with a normal BMI, the estimated sub-HR for revision was weakly significant for THR (15.7% increase, 95% CI 0.2% to 33.7%, p=0.048) but not for TKR (17.9% increase, 95% CI –1.9% to 41.6%, p=0.079).

As a sensitivity analysis, we also performed standard Cox regressions with revision surgery as the event of interest and where no distinction was made between death and other censoring events. Univariable models for age, gender and BMI gave very similar results to the competing risks analysis, as did the multivariable models which adjusted for the same factors as in the competing risks regression. Results from the Cox regression models are given in Table 5.5 and Table 5.6. In addition, we calculated that it would take 175 patients with TKR to reduce their baseline BMI from obese to normal in order to prevent one revision operation after 5 years. For patients with THR this number reduces to 152.
Finally, we assessed whether the higher incidence of hip revision surgery during the first year following THR (Figure 5.1 and Figure 5.2) might compromise the proportionality assumption and therefore suggest the inclusion of time-dependent effects. Separate univariable piecewise competing risk models for hip revision were fitted for gender, age (≤65 years vs >65) and BMI (>40 vs ≤40). A single change point at 1 year was used to simultaneously estimate two sub-HR\textquotesingle s for revision (before and after 1 year following THR). The only model which provided some evidence for a different sub-HR during the first year was with BMI (>40 vs ≤40) as the predictor (SHR 2.619, 95% CI 1.502 to 4.560, \(p=0.001\)), but this was not matched with a statistically significant estimate for revision after the first year (SHR 0.575, 95% CI 0.238 to 1.170, \(p=0.130\)).

5.5 Discussion

This study presents population-based estimates for the risk of revision following total joint replacement of the hip and knee using methods from survival analysis. Cumulative incidence rates of revision were higher for men than for women and higher for hips than knees. Age, gender and BMI were estimated to be significant predictors of time to revision in an adjusted model allowing for the competing risk of death. Severely obese patients undergoing THR were observed to have a higher risk of revision surgery during the first year following replacement, but the same effect was not observed for knee replacement.

The literature on obesity as a risk factor for hip and knee arthroplasty concentrates mainly on the risk for primary replacement rather than for revision procedures, and most use rate differences to estimate relative risk, rather than using time-to-event methods. Many published studies are small and do not have sufficient power to detect rare outcomes. Often these studies are locally based and the generalisability to population level is questionable. Mostly results are presented for categorised BMI, which is often dichotomised at 30 kg/m\(^2\), and where results for the morbidly obese are reported, the sample size is small.

One of the largest studies examining primary replacement followed up a cohort of over 490 000 middle-aged women over an average of 2.9 years and found increased incidence of hip and knee replacement in obese participants (Liu et al., 2007) Of the studies which consider the effect of obesity on outcomes after primary joint replacement, several focus mainly on events such as complications arising from surgery (Lubbeke et al., 2007b) or subsequent admission to an intensive care unit (AbdelSalam et al., 2012), rather than the time to revision surgery. Among studies of other non-revision outcomes, Andrew et al (Andrew et al., 2008) looked at the change in Oxford Hip Score 5 years after THR and found no difference between non-obese, obese and
morbidly obese patients, but in a smaller study (Lubbeke et al., 2007a) using Harris Hip Score (HHS) with the same length of follow-up, an increase in BMI was associated with a small but significant reduction in HHS.

An editorial on obesity and joint replacement in 2006 (Horan, 2006) suggested that it is those with BMI of greater than 40 units (rather than 30) who are at risk of worse outcomes, yet several subsequent studies have used a BMI cut-point of 30 kg/m². A recent Australian study of 2026 patients with THR and 535 with TKR found no difference in mid-term survival rates between the obese (BMI > 30 kg/m²) and non-obese (Yeung et al., 2011). Another study from Switzerland used Cox regression to estimate the risk of revision in 2495 THRs using the same cut-point for BMI, estimating a non-significant adjusted HR for revision of 2.2 (95% CI 0.9 to 5.3) for obese versus non-obese patients (Lubbeke et al., 2007b). However, a recent Canadian study of 3290 THRs did categorise BMI to include a morbidly obese group (BMI>40 kg/m²) and although the authors found no difference in time to revision between BMI categories in an unadjusted analysis, there was a marginally significant difference for septic revisions (McCalden et al., 2011).

Our results suggest that there may be a 1.5–2% rise in the risk of knee and hip revision, respectively, for each extra unit of BMI. However, there is some variation in risk across the entire range of observed BMI values. For hips, there appears to be very little difference in BMI-related risk between the normal weight and overweight categories. However, Figure 5.1 shows that for hips there may be a revision rate of approximately 6% for the morbidly obese after 10 years, against a 3% rate for the normal and overweight. For knees, Figure 5.2 shows a more even distribution across the BMI categories up to about 7 years after TKR, but with higher risk for the morbidly obese between 7 and 10 years after TKR.

Although recommendations (Fennema and Lubsen, 2010, Ranstam et al., 2011) to consider the use of the cumulative incidence function for analysing prosthesis survival are gaining acceptance (Gillam et al., 2010), the use of competing risks regression to model associated risk factors is still not widely observed. The justification for using competing risks methods in our primary analysis is that hip and knee prostheses are mainly implanted in older patients for whom mortality is a substantial competing risk which may be several times greater than the risk of revision. What is perhaps surprising is that our results show little difference between the HR and sub-HR estimates from the Cox and the competing risks regression models, respectively, although the former has a cause-specific interpretation with no distinction between death and censoring whereas the latter directly models the cumulative incidence of revision.
Strengths and potential limitations of the study

The strengths of the study data more than make up for its limitations. GPRD data have individual date-stamped records of patient event data in primary and secondary care settings, including data on many potential confounders, including comorbidities, BMI, smoking and drinking. The GPRD practice network covers all of the UK, and approximately 5% of all practices are covered by the GPRD. The high degree of generalisability afforded by this very large sample enables population-level inferences to be made. Follow-up is long, with several hundred prostheses in the dataset having over 20 years of follow-up without being revised. The choice of the statistical methods used to allow for the competing risk of death adds a further degree of robustness to the study. The regression estimates of the HR for BMI as a factor associated with revision benefit from a precision which is not usually achievable outside of national registers, especially for the group of morbidly obese patients within which event rates in the literature are low.

There are several limitations to this work. The revision rate estimates hip and knee at 5 years are close to, but slightly less than those reported by the NJR, but the GPRD data used in this study include prostheses implanted from the late 1980s. Also our data do not have directly linked information on the indication for surgery, which would have been enabled a sub-analysis by reason for revision. Although certain indications for revision are more common than others depending on follow-up time (e.g., infection occurring early), any inferences about indication-specific risks before or after a given follow-up time would not have been reliable.

5.6 Conclusion

This study has presented estimates of rates and risk factors for revision surgery on hip and knee prostheses using one of the largest available population-based sets of joint replacement data outside of national arthroplasty registries. Our estimates suggest that BMI is positively associated with the risk of hip and knee revision, but studies of register data linked with sources of demographic and clinical data are needed in order to distinguish between effects for specific indications for revision surgery.
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Collaborators

The following people are members of the COAST Study group: Cyrus Cooper, Mark Mullee, James Raftery, Andrew Carr, Andrew Price, Kassim Javaid, David Beard, Douglas Altman, Nicholas Clarke, Jeremy Latham, Sion Glyn-Jones and David Barrett.

Contributors

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

NKA had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DC, AJ and NKA participated in study conception and design.

NKA participated in acquisition of the data.

DC, JM, AJ and NKA participated in analysis and interpretation of the data.

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Competing interests

NKA has received consultancy payments, honoraria and consortium research grants, respectively, from: Flexion (PharmaNet), Lilly, Merck Sharp and Dohme, Q-Med, Roche; Amgen, GSK, NiCox and Smith & Nephew; Novartis, Pfizer, Schering-Plough and Servier.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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## 5.7 Tables and Figures for Paper 3

Table 5.1 Clinical and Demographic characteristics – all subjects undergoing Total Hip or Knee Replacement

<table>
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<tr>
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<th>Total Hip Replacement (N=63,162)</th>
<th>Total Knee Replacement (N=54,276)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Female (N=39,292)</td>
<td>Male (N=23,870)</td>
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<td>Age (mean, SD)</td>
<td>70.5 (11.1)</td>
<td>67.7 (11.0)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>62.2</td>
<td>37.8</td>
</tr>
<tr>
<td>BMI (mean, SD)</td>
<td>27.2 (5.1)</td>
<td>27.7 (4.3)</td>
</tr>
<tr>
<td>Missing BMI (%)</td>
<td>19.1</td>
<td>19.3</td>
</tr>
<tr>
<td>Revisions (N, %)</td>
<td>1000 (2.55)</td>
<td>811 (3.40)</td>
</tr>
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<td>6615 (16.8)</td>
<td>4201 (17.6)</td>
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<td>Number of comorbid</td>
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Table 5.2  Cumulative incidence rates for revision surgery at selected times following THR and TKR

<table>
<thead>
<tr>
<th>Years since total joint replacement</th>
<th>Hip</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>Cumulative incidence of revision (%)</td>
<td>95% Confidence Interval</td>
<td>Cumulative incidence of revision (%)</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.6 (0.5, 0.6)</td>
<td>0.7 (0.6, 0.8)</td>
<td>0.3 (0.2, 0.4)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.2 (1.1, 1.3)</td>
<td>1.4 (1.3, 1.6)</td>
<td>1.1 (1.0, 1.2)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.8 (1.7, 2.0)</td>
<td>2.2 (2.0, 2.4)</td>
<td>1.6 (1.5, 1.8)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>3.4 (3.1, 3.6)</td>
<td>4.6 (4.3, 5.0)</td>
<td>2.8 (2.5, 3.1)</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>6.0 (5.5, 6.6)</td>
<td>8.3 (7.6, 9.1)</td>
<td>4.4 (3.9, 5.0)</td>
</tr>
</tbody>
</table>
Table 5.3 Estimated subhazard of revision for Total Hip Replacement – Competing risks analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariable</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td><strong>BMI</strong>&lt;sup&gt;b&lt;/sup&gt; (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.030</td>
<td>(1.020, 1.041)</td>
</tr>
<tr>
<td>(per additional unit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female (ref)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.35</td>
</tr>
<tr>
<td><strong>Age</strong> (years at THR)</td>
<td>(per additional year)</td>
<td>0.970</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for smoking (yes/no/ex), drinking (yes/no/ex), number of comorbid conditions.

<sup>b</sup>BMI available in 86.1% of patients.
Table 5.4  Estimated subhazard of revision for Total Knee Replacement – Competing risks analysis

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;b&lt;/sup&gt; (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.026 (1.013, 1.038)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(per additional unit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.54 (1.37, 1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years at TKR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per additional year)</td>
<td>0.957 (0.952, 0.961)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for smoking (yes/no/ex), drinking (yes/no/ex), number of comorbid conditions.

<sup>b</sup>BMI available in 80.9% of patients.
Table 5.5  Estimated hazard of revision for THR—Univariable and adjusted Cox regression analysis with death as a censoring event

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th></th>
<th>Adjusted&lt;sup&gt;a&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% Confidence Interval</td>
<td>p-value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>BMI&lt;sup&gt;b&lt;/sup&gt; (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.029 (1.017, 1.040)</td>
<td>&lt;0.001</td>
<td>1.019 (1.008, 1.031)</td>
<td>0.001</td>
</tr>
<tr>
<td>(per additional unit)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (ref)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.36 (1.24, 1.29)</td>
<td>&lt;0.001</td>
<td>1.26 (1.13, 1.41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years at THR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per additional year)</td>
<td>0.978 (0.974, 0.983)</td>
<td>&lt;0.001</td>
<td>0.977 (0.972, 0.982)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for smoking (yes/no/ex), drinking (yes/no/ex), number of comorbid conditions.

<sup>b</sup>BMI available in 86.1% of patients.
Table 5.6  Estimated hazard of revision for TKR– Univariable and adjusted Cox regression analysis with death as a censoring event

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th></th>
<th>Adjusted^a</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio</td>
<td>95% Confidence Interval</td>
<td>p-value</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>BMI^b (kg/m^2)</td>
<td>(per additional unit)</td>
<td>1.024 (1.012, 1.037)</td>
<td>&lt;0.001</td>
<td>1.015 (1.003, 1.028)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female (reference)</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1.58 (1.41, 1.77)</td>
<td>&lt;0.001</td>
<td>1.55 (1.36, 1.77)</td>
</tr>
<tr>
<td>Age (years at THR)</td>
<td>(per additional year)</td>
<td>0.962 (0.956, 0.967)</td>
<td>&lt;0.001</td>
<td>0.961 (0.955, 0.968)</td>
</tr>
</tbody>
</table>

^aAdjusted for smoking (yes/no/ex), drinking (yes/no/ex), number of comorbid conditions.

^bBMI available in 80.9% of patients.
Figure 5.1  Cumulative incidence estimate for revision of THR by body mass index

Figure 5.2  Cumulative incidence estimate for revision of TKR by body mass index
Figure 5.3  Cumulative incidence estimate for revision of THR by age

Figure 5.4  Cumulative incidence estimate for revision of TKR by age
5.8 Reference List for Paper 3


5.9 Declaration of authorship for Paper 3

David Culliford: Reviewed the literature; Responsible for study design, choice of methodology, implementation in software; Conducted all data manipulation programming (from the restructured CPRD data); Conducted all statistical programming; Conducted all statistical analyses; Drafted all versions of the manuscript; Held overall responsibility for manuscript submission and all associated administration

Joe Maskell: Restructured the raw CPRD data; Commented on later versions of the manuscript

Andrew Judge: Reviewed methodological design; Reviewed drafts of the manuscript

Nigel Arden: Principal Investigator for the grant; Secured grant funding; Provided on-going guidance and supervision to candidate; Commented on all drafts of the manuscript; Held overall responsibility for the research as PI and as corresponding author

All co-authors below confirm the accuracy of the declaration of authorship for paper 3:

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joe Maskell</td>
<td></td>
</tr>
<tr>
<td>Andrew Judge</td>
<td></td>
</tr>
<tr>
<td>Nigel Arden</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 6: Paper 4 - Future Projections of Total Hip and Knee Arthroplasty in the UK: Results from the Clinical Practice Research Datalink

Osteoarthritis and Cartilage 2015; 23; 594-600

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N. K. Arden, NIHR Musculoskeletal Biomedical Research Unit, University of Oxford and MRC Lifecourse Epidemiology Unit, University of Southampton

On behalf of the COAST Study Group
6.1 Summary

Objective: To estimate the future rate of primary total hip (THR) or knee (TKR) replacement in the UK to 2035 allowing for changes in population demographics and obesity.

Design: Using age/gender/body mass index (BMI)-specific incidence rates from a population-based cohort study of 50,000 THR and 45,609 TKR patients from the UK Clinical Practice Research Datalink (CPRD) between 1991 and 2010, we projected future numbers of THR and TKR using two models: a static, estimated rate from 2010 applied to population growth forecasts to 2035, and a log-linear rate extrapolation over the same period. Both scenarios used population forecast data from the UK Office for National Statistics (ONS).

Results: Assuming rates of THR and TKR for 2010, and given projected population changes in age, gender and BMI, the number of THRs and TKRs performed in the UK in 2035 is estimated to be, respectively: 95,877 and 118,666. By comparison, an exponential extrapolation of historical rates using a log-linear model produces much higher estimates of THR and TKR counts in 2035 at 439,097 and 1,219,362 respectively. Projected counts were higher for women than men. Assuming a changing (rather than fixed) future BMI distribution increases TKRs by 2035 but not THRs.

Conclusions: Using historical rates and population forecasts we have projected the number of THR/TKR operations in the UK up to 2035. This study will inform policymakers requiring estimates of future demand for surgery. Incorporating future forecasts for BMI into projections of joint replacement may be more relevant for TKR rather than THR.

6.1.1 What is already known on this topic

Register data and published incidence rates from the UK show an increasing trend in annual rates of total hip (THR) and knee (TKR) replacement. The most recently published projections of UK future rates covered England only, and were based on a 10-year period of hospital episode data from 1991 to 2001 and did not account for changes in BMI or other important risk factors for arthroplasty.

6.1.2 What this study adds

Using population-based data over a 20-year period to 2010, two methods of projection show widely different estimates for the level of hip and knee replacement in 2035.
Estimates of future incidence rates resulting from log-linear models can be particularly sensitive to the choice of time period used for estimation.

Based on changing population demographics (age, gender, obesity) and a static rate of replacement at 2010 levels, approximately 96,000 THRs and 119,000 TKRs could be carried out in the year 2035.

The Poisson (log-linear) method produces long-term estimates for future levels of replacement which are arguably neither plausible nor sustainable in terms of NHS capacity and funding levels.

6.2 Introduction

Joint replacement surgery for both hip and knee is one of the most common elective surgical procedures carried out in the UK (Judge et al., 2006). It is well established as a cost-effective intervention for end stage lower-limb joint disease (Jenkins et al., 2013). The annual incidence rates of primary total joint replacements have been growing steadily throughout the 1990s and have continued to rise since the year 2000 (Culliford et al., 2010). Recent data from the National Joint Registry for England, Wales and Northern Ireland (NJR) show that the number of primary total joint replacement operations is still climbing with 75,366 hip and 76,497 knee procedures performed in the 12 months to April 2012 (National Joint Registry, 2012). The cost burden to the National Health Service (NHS) is considerable, and although each primary THR and TKR procedure is estimated to cost in excess of £7000 (Jenkins et al., 2013), recent work using a cost-effectiveness model for THR shows that when primary care costs are incorporated then the discounted cost is higher (Pinedo-Villanueva et al., 2014). Policymakers require estimates of future demand for these procedures but providing accurate medium to long-term forecasts is difficult given that provision of the majority of surgical capacity is determined by governments which necessarily have limits on their planning horizons.

Given the lack of availability of accurate predictions for the more relevant inputs to forecasting models, often researchers make use of more pragmatic methods. Occasionally there are rare exceptions where a more sophisticated modelling approach is employed (Holt et al., 2011), but this usually requires access to at least one population-based cohort or survey dataset with long-term follow-up. A more common approach is to base future projections on a fitted model for observed temporal trends derived from a set of high-quality research data, and then to extrapolate into the future using an appropriate linear or log-linear model. Sometimes these projections may incorporate published long-term population projections from national statistical
organisations. In the field of lower limb joint replacement, there have been few published articles over the past 20 years describing future projections. At a national level, the literature is concentrated around the United States (Kurtz et al., 2007, Kurtz et al., 2006), the Nordic countries (Pedersen et al., 2005), the United Kingdom (Birrell et al., 1999, Dixon et al., 2004), the Netherlands (Otten et al., 2010) and Germany (Lohmann et al., 2007).

The aim of this study was to use data from the Clinical Practice Research Datalink (CPRD), combined with national population forecasts from the Office for National Statistics (ONS) to calculate age-gender specific forecasts for the number of primary total hip (THR) and knee (TKR) replacements in the UK between 2010 and 2035. A secondary, and novel, aim was to produce forecasts which reflect the changing distribution of body mass index (BMI).

6.3 Method

6.3.1 Participants

We used data obtained from the Clinical Practice Research Datalink (CPRD). The CPRD comprises the entire computerized medical records of a sample of patients attending general practitioners (GPs) in the UK covering a population of 6.5 million patients from over 630 contributing practices chosen to be representative of the wider UK population. GPs in the UK play a key role in the delivery of healthcare by providing primary care and referral to specialist hospital services. Patients are registered with one practice that stores medical information from primary care and hospital attendances. The CPRD is administered by the Medicines and Healthcare products Regulatory Agency (MHRA).

The CPRD records contain all clinical and referral events in both primary and secondary care in addition to comprehensive demographic information, prescription data, and hospital admissions. Data is stored using Read and OXMIS codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). Read codes are used as the standard clinical terminology system within UK primary care. Only practices that pass quality control are used as part of the CPRD database. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the CPRD.

We identified all patients in the database with a diagnosis code for total hip or knee arthroplasty from 1991 until the end of 2010. Read codes were used to identify primary THRs and TKRs (see appendix A, page 153). Patients were included in the analysis if aged 18 years or over at the time
of the replacement. Participant demographics including age, gender and BMI were collated. The BMI used was the nearest pre-operative measurement to the THR/TKR date. We also acquired data from the Health Survey for England (HSE) for the purposes of constructing a denominator to estimate BMI specific rates. Lastly, we obtained gender specific population projections for the UK from the ONS covering the period 2011 to 2035 (Office for National Statistics, 2010b), upon which to project the estimated THR and TKR rates.

6.3.2 Analysis

Estimation

Firstly the CPRD data was used to estimate annual incidence rates for THR and TKR for the years 1991-2010 inclusive. We used standard log-linear regression models to produce calendar year, age and gender specific rates. These methods were used in our previously published research article on temporal trends in THR/TKR (Culliford et al., 2010), but our aim was to extend this to include rates additionally specific to BMI.

The CPRD is supplied with person-time denominator for its practice population which enables the construction of annual incidence rates by age and gender, but not by BMI group. In order to further apportion the CPRD-supplied person-time denominator by BMI categories, we used data from the HSE covering the period 1991 to 2010 as a proxy for the change in the distribution of BMI in the UK population (Figure 6.1). Unweighted HSE data was used, since we only required approximate relative proportions among BMI groups in order to estimate the linear trend in these proportions. The CPRD person-time denominator data was then re-modelled by calendar year, age, gender and BMI, using the year-age-gender specific BMI proportions obtained from the HSE data. Age was grouped into those aged 18 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79 and 80 years and above. Categories for BMI (in kg/m²) were less than 20, 20 to 24.9, 25 to 29.9, 30 to 39.9 and 40 and above. Rates for hips and knees were estimated separately.

Before applying the estimated incidence rates to the ONS population forecasts, we used the BMI data obtained from the HSE data to split the ONS age-gender specific forecasts by BMI group. Two methods were used to split the ONS forecasts: BMI proportions fixed at 2010 levels, and BMI proportions increasing linearly based on ordinary least squares regression estimates derived from the HSE BMI data from 1991 to 2010. The second of these methods produced group proportion estimates which, over the 25-year forecasting timeframe, would have resulted in proportions greater than one or less than zero for some of the age-gender-BMI categories. We therefore employed a pragmatic method of smoothing the BMI group proportions over the forecasting
Chapter 6 - Paper 4: Future Projections

timeframe by using a hyperbolic tangent function similar to the method used in the Foresight report entitled ‘Tackling Obesity’ (McPherson, 2008).

**Projection**

Separately, for hips and then knees, we used two different projection methods on each of the two future UK population scenarios, described as follows. The first projection method used THR/TKR incidence rate estimates held at 2010 levels, applied to each of the two population scenarios, while the second method used an exponential extrapolation directly from the log-linear model estimated rates for THR/TKR. The exponential extrapolation method is included for comparison purposes. The two population forecast datasets to which these rates were applied both contained exactly the same population growth estimates by age and gender over time, as forecast by the ONS. The difference between the two population scenarios was that one population dataset assumed a static BMI distribution, held fixed at 2010 levels as estimated from the HSE data, whereas the other reflected our HSE- and CPRD-based estimates of forecast BMI distribution change in the UK population. Thus the population forecast totals for each of the two datasets were the same, the only difference being in the BMI proportions used to split the forecast counts into age-gender-BMI specific totals for each year up to 2035.

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC), with PROC GENMOD used for both log-linear and linear regression model estimation.

### 6.4 Results

Within the CPRD data there were 50,000 patients undergoing THR and 45,609 patients undergoing TKR between 1991 and 2010 for whom age, gender and BMI were recorded. The average age at replacement was similar in both the THR and the TKR groups but the proportion of women was greater for both THR and TKR (Table 6.1). Pre-operative BMI was slightly higher for TKR than THR.

The HSE data used to estimate the future BMI distribution covered the period 1991 to 2010 and comprised 186,174 subjects with BMI measured. A breakdown of this total by age, gender and BMI group is given in Table 6.2. The ONS population forecast data for the UK (Office for National Statistics, 2010b) to which our estimated incidence rates were applied are based on 2010 estimates for the following 25 years, suggesting that the UK adult population will grow from 49.0 million in 2010 to approximately 58.5 million by 2035.
Under the static rate projection method, with the BMI distribution held fixed at levels estimated for 2010, the annual number of THRs is forecast to grow to 95,877 by 2035, with TKRs growing to 118,666. Under the same projection method, but with the BMI distribution changing according to our HSE-based forecast, THRs grow to 97,536 and TKRs to 110,306.

Under the log-linear projection method, with the BMI distribution held fixed at levels estimated for 2010, the annual number of THRs is forecast to grow to 437,708 by 2035, with TKRs growing to 439,097. With a changing BMI distribution THRs grow to 1,070,790 and TKRs to 1,219,362.

Table 6.3 and Table 6.4 show five-yearly projections for all four forecasting scenarios up to the year 2035.

For all results that follow, we present counts split by gender, BMI and age which are only estimated using the static rate projection method. Table 6.5 and Table 6.6 show projected TJR counts by gender for hip and knee respectively. For THR, when we compare projection with fixed or varying future estimates of BMI category distribution, there is little gender specific difference in counts at 2035. However, for knees differences between methods exist, especially for women whose TKR count at 2035 is estimated to be 9% higher when using varying BMI distribution as opposed to fixed.

Figure 6.2 and Figure 6.3 show projected THR counts for each calendar year, split by BMI group, under the two assumptions for future BMI distribution. Clear differences in the relative contribution of the major BMI categories are apparent, with the overweight and obese groups having a greater proportion of the total THR count when we allow the BMI distribution to change going forward. Figure 6.4 and Figure 6.5 show the same for projected TKR counts. Figure 6.6 and Figure 6.7 show the projected counts for THR and TKR respectively, for each calendar year, split by age group in decades (i.e., subject in his/her 40s, 50s, 60s, etc.)

### 6.5 Discussion

With this study we have combined data from three different sources (CPRD, ONS and HSE) to estimate the future projected count of THR and TKR operations in the UK up to the year 2035. The estimates extend the methods of Kurtz and colleagues (Kurtz et al., 2007) to add BMI to age and gender to construct replacement incidence rate estimates which are specific to these three variables.
Apart from the work of Kurtz, there are few major large population-level studies describing how future THR and/or TKR incidence might change in future years. Over the past 20 years, some examples exist outside the UK and US at national (Pedersen et al., 2005, Otten et al., 2010, Robertsson et al., 2000, Ingvarsson et al., 1999a) and at regional (Overgaard et al., 1992) level but arguably the best examples within the UK are the studies by Dixon et al (Dixon et al., 2004) in which data from HES was used to estimate THR and TKR counts which were projected linearly over a 10 year period, and by Birrell et al (Birrell et al., 1999) who used Swedish THR rates imposed onto ONS population forecasts to project THR counts to the year 2026. The Kurtz paper used Poisson regression, combining forecasts from the US census bureau to estimate counts in age-gender-race domains.

The main criticisms of such data-driven projections, including our own, is that: (1) they do not involve any estimates of future need from government or other planning authorities, and (2) they do not incorporate supply-side constraints (e.g., availability of surgeons; hospital units) into the modelling process. This is not due to difficulties with the statistical technicalities of introducing such information into the model, but is due to the lack of availability of reliable data on future need or supply. Information on future demand is hard to elicit and even if available, may be based on opinions of a relatively small group of medical experts rather than specialists in the forecasting of service provision. Supply-side data is more predictable, at least in the short-term, but in the longer term the unpredictability of the direction of healthcare policy introduces more uncertainty. All the projection estimates presented here are only a guideline to the possible future direction of THR/TKR counts, having been constructed using three different sources of data, each with their own degree of imprecision, and any interval estimate about these counts is likely to be wide. This lack of precision about prediction is a common limitation of all such studies estimating future projections.

A further limitation is that we only had available data from England with which to estimate the BMI distribution for the UK over the study period. Even though England accounts for almost 85% of the UK population, our estimated BMI distribution is likely overall to be little different to that of the UK. Comparisons between countries show that Scotland does have a slightly higher obesity prevalence than England, but for Wales and Northern Ireland the prevalence is lower than in England (Public Health England, 2013).

A limitation of approaches which extrapolate rates from log-linear models is that rates are implicitly assumed to continue exponentially increasing into the future, and the most recent data from the NJR suggests that for the UK rates may be levelling off after a period of prior expansion in capacity through, for example, the introduction of specialist treatment centres. It has been
suggested that, once adjusted for patient willingness and fitness for surgery, the balance between provision of and need for TJR may be closer than the true burden of disease might suggest (Carr et al., 2012). For healthcare planners, the static rate assumption is arguably a sensible one, and places the focus on addressing any additional capacity demands as a result of changing demographics. This is especially true if we accept that current rates are affordable.

One of the most striking differences in the results is that when we use the full extrapolation scenario from the log-linear incidence model gives estimated projected counts in 2035 for TKR of 1.2 million and for THR of 400,000. With the latest figures from the National Joint Registry for England and Wales showing the annual number of THRs and TKRs both in the mid-70,000s, and growing slower over the past 5 years than the 5 years prior, it is hard to see how future demand and supply will rise to meet these estimates. What we can say is that the log-linear extrapolation-based estimates are much more sensitive to differences in the trajectory of past incidence rates than to the other two sources of data (ONS population forecasts and HSE-based BMI distribution). Any log-linear model will produce exponential growth (or shrinkage) and over such a long timeframe this has the potential to produce projections which are widely different from what might anecdotally be deemed ‘sensible’.

Nevertheless, although we feel that our alternative scenario (THR and TKR incidence rates to remain at 2010 levels, as estimated by log-linear model) yields projected counts that are perhaps more plausible (TKR of 119,000 and for THR of 96,000 by 2035), these could be seen as underestimates, especially so in the case of THR. Although this static rates model is unlikely to be accurate, the log-linear rates model is even less likely to be either accurate or sustainable and the answer is likely to lie between the two approaches.

The other key finding is that for THR, there is virtually no difference in projected counts whether we fix our future estimates of BMI category distribution at HSE-estimated 2010 levels, or vary them in line with a linear extrapolation of our 20-year HSE-derived BMI estimates. However, for TKR there is a difference, with the latter method estimating over 8000 more TKRs at 2035 than the former. Initially this difference of 7% for TKRs may appear striking, as it is solely due to the estimated change in BMI distribution moving forwards towards 2035. However, there is evidence that the link between BMI and knee osteoarthritis is stronger than that for the hip (Lohmander et al., 2009, Jiang et al., 2011, Jiang et al., 2012). The evidence for BMI as a risk factor for hip osteoarthritis is more mixed (Cooper et al., 1998, Reijman et al., 2007), and the fact that THR projection is insensitive to changing BMI distribution (whereas TKR is not) may be partly driven by the 2010 baseline BMI profile, given that it appears to be the proportion of obese subjects which is the important factor for higher projections (Figure 6.4, Figure 6.5, Figure 6.6 and Figure 6.7).
6.6 Conclusion

This study combines comprehensive data sources to project future counts of THR and TKR procedures in the UK and is the first to model BMI to show an effect on future rates of TKR. It is hoped that the principle of integrating BMI into models for future demand of healthcare resources may be of use to healthcare planners where such resources are sensitive to the distribution of BMI in the population.

Declaration of contributions

Conception and design (DJC, AJ, NKA)

Analysis and interpretation of the data (DJC)

Drafting of the article (DJC, JM, AJ, CC, DPA, NKA)

Critical revision of the article for important intellectual content

(DJC, JM, AJ, CC, DPA, NKA)

Final approval of the article (DJC, JM, AJ, CC, DPA, NKA)

Statistical expertise (DJC, AJ)

Obtaining of funding (NKA)

Ethical approval

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Competing interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2014.12.022.
Table 6.1  Demographic characteristics - CPRD subjects used to construct incidence rates

<table>
<thead>
<tr>
<th></th>
<th>Total Hip Replacement (N=50,000)</th>
<th>Total Knee Replacement (N=45,609)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (N=31,148)</td>
<td>Male (N=18,852)</td>
</tr>
<tr>
<td></td>
<td>Female (N=26,623)</td>
<td>Male (N=18,986)</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>69.9 (10.9)</td>
<td>67.8 (10.7)</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>62.2</td>
<td>37.8</td>
</tr>
<tr>
<td>BMI (mean, SD)</td>
<td>27.2 (5.1)</td>
<td>27.7 (4.2)</td>
</tr>
<tr>
<td></td>
<td>29.6(5.4)</td>
<td>28.8(4.4)</td>
</tr>
</tbody>
</table>
Table 6.2  Health Survey for England 1991 to 2010: Number of subjects by gender, age, BMI

<table>
<thead>
<tr>
<th>Total subjects</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>186,174</td>
<td>100,576 (54.0%)</td>
<td>85,598 (46.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 39</td>
<td>37664</td>
<td>37.4%</td>
<td>32527</td>
<td>38.0%</td>
</tr>
<tr>
<td>40 to 49</td>
<td>18503</td>
<td>18.4%</td>
<td>15704</td>
<td>18.3%</td>
</tr>
<tr>
<td>50 to 59</td>
<td>15620</td>
<td>15.5%</td>
<td>13640</td>
<td>15.9%</td>
</tr>
<tr>
<td>60 to 69</td>
<td>13813</td>
<td>13.7%</td>
<td>12433</td>
<td>14.5%</td>
</tr>
<tr>
<td>70 to 79</td>
<td>10430</td>
<td>10.4%</td>
<td>8504</td>
<td>9.9%</td>
</tr>
<tr>
<td>80 and over</td>
<td>4546</td>
<td>4.5%</td>
<td>2790</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BMI group (kg.m²)</th>
<th>N</th>
<th>%</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 20</td>
<td>6117</td>
<td>6.1%</td>
<td>2933</td>
<td>3.4%</td>
</tr>
<tr>
<td>20 to 25</td>
<td>39261</td>
<td>39.0%</td>
<td>27347</td>
<td>31.9%</td>
</tr>
<tr>
<td>25 to 30</td>
<td>33361</td>
<td>33.2%</td>
<td>38681</td>
<td>45.2%</td>
</tr>
<tr>
<td>30 to 40</td>
<td>19688</td>
<td>19.6%</td>
<td>16216</td>
<td>18.9%</td>
</tr>
<tr>
<td>40 and over</td>
<td>2149</td>
<td>2.1%</td>
<td>421</td>
<td>0.5%</td>
</tr>
</tbody>
</table>
Table 6.3  Projected UK counts for total hip replacement in adults to the year 2035

<table>
<thead>
<tr>
<th>Year</th>
<th>Estimated THR incidence rates fixed at 2010 level</th>
<th>Estimated THR incidence rates increasing log-linearly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI category proportions fixed at 2010 estimates</td>
<td>BMI category proportions changing over time</td>
</tr>
<tr>
<td>2015</td>
<td>72762</td>
<td>72418</td>
</tr>
<tr>
<td>2020</td>
<td>79716</td>
<td>79048</td>
</tr>
<tr>
<td>2025</td>
<td>85988</td>
<td>85026</td>
</tr>
<tr>
<td>2030</td>
<td>91496</td>
<td>90202</td>
</tr>
<tr>
<td>2035</td>
<td>97516</td>
<td>95877</td>
</tr>
</tbody>
</table>
Table 6.4 Projected UK counts for total knee replacement in adults to the year 2035

<table>
<thead>
<tr>
<th>Projection scenario</th>
<th>Estimated TKR incidence rates fixed at 2010 level</th>
<th>Estimated TKR incidence rates increasing log-linearly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI category proportions fixed at 2010 estimates</td>
<td>BMI category proportions changing over time</td>
</tr>
<tr>
<td></td>
<td>BMI category proportions changing over time</td>
<td>BMI category proportions fixed at 2010 estimates</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2020</th>
<th>2025</th>
<th>2030</th>
<th>2035</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>82610</td>
<td>85019</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2020</td>
<td>90555</td>
<td>94783</td>
<td>128944</td>
<td>221653</td>
<td>234244</td>
</tr>
<tr>
<td>2025</td>
<td>97780</td>
<td>103657</td>
<td>376384</td>
<td>407400</td>
<td></td>
</tr>
<tr>
<td>2030</td>
<td>103810</td>
<td>111015</td>
<td>632257</td>
<td>701052</td>
<td></td>
</tr>
<tr>
<td>2035</td>
<td>110306</td>
<td>118666</td>
<td>1071790</td>
<td>1219362</td>
<td></td>
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</tbody>
</table>
Table 6.5  Projected UK counts for total hip replacement by gender to the year 2035 with estimated THR incidence rates fixed at 2010 level

<table>
<thead>
<tr>
<th>Year</th>
<th>Women BMI category proportions fixed at 2010 estimates</th>
<th>Men BMI category proportions fixed at 2010 estimates</th>
<th>Women BMI category proportions changing over time</th>
<th>Men BMI category proportions changing over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>45143</td>
<td>27618</td>
<td>44905</td>
<td>27513</td>
</tr>
<tr>
<td>2020</td>
<td>49207</td>
<td>30509</td>
<td>48752</td>
<td>30296</td>
</tr>
<tr>
<td>2025</td>
<td>52949</td>
<td>33039</td>
<td>52307</td>
<td>32719</td>
</tr>
<tr>
<td>2030</td>
<td>56255</td>
<td>35241</td>
<td>55426</td>
<td>34776</td>
</tr>
<tr>
<td>2035</td>
<td>59909</td>
<td>37607</td>
<td>58850</td>
<td>37026</td>
</tr>
</tbody>
</table>

Table 6.6  Projected UK counts for total knee replacement by gender to the year 2035 with estimated TKR incidence rates fixed at 2010 level

<table>
<thead>
<tr>
<th>Year</th>
<th>Women BMI category proportions fixed at 2010 estimates</th>
<th>Men BMI category proportions fixed at 2010 estimates</th>
<th>Women BMI category proportions changing over time</th>
<th>Men BMI category proportions changing over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>47703</td>
<td>34908</td>
<td>49207</td>
<td>35812</td>
</tr>
<tr>
<td>2020</td>
<td>51931</td>
<td>38624</td>
<td>54638</td>
<td>40145</td>
</tr>
<tr>
<td>2025</td>
<td>55785</td>
<td>41995</td>
<td>59604</td>
<td>44054</td>
</tr>
<tr>
<td>2030</td>
<td>58919</td>
<td>44891</td>
<td>63665</td>
<td>47350</td>
</tr>
<tr>
<td>2035</td>
<td>62493</td>
<td>47813</td>
<td>68082</td>
<td>50584</td>
</tr>
</tbody>
</table>
Figure 6.1   Health Survey for England 1991 to 2010 – Proportion of respondents by BMI group
Chapter 6 - Paper 4: Future Projections

Figure 6.2  Projected UK counts for total hip replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level – by BMI group with BMI category proportions fixed at 2010 estimates

Figure 6.3  Projected UK counts for total hip replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level – by BMI group with BMI category proportions changing over time
Figure 6.4  Projected UK counts for total knee replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level – by BMI group with BMI category proportions fixed at 2010 estimates

Figure 6.5  Projected UK counts for total knee replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level – by BMI group with BMI category proportions changing over time
Figure 6.6 Projected UK counts for total joint replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level, with BMI category proportions changing over time – by age group (Hip)

Figure 6.7 Projected UK counts for total joint replacement to the year 2035 with estimated THR incidence rates fixed at 2010 level, with BMI category proportions changing over time – by age group (Knee)
6.8 Reference List for Paper 4


Chapter 6 - Paper 4: Future Projections


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6.9 Declaration of authorship for Paper 4

**David Culliford**: Reviewed the literature; Responsible for study design, choice of methodology, implementation in software; Conducted all data manipulation programming (from the restructured CPRD data); Conducted all statistical programming; Conducted all statistical analyses; Drafted all versions of the manuscript; Held overall responsibility for manuscript submission and all associated administration

**Joe Maskell**: Restructured the raw CPRD data; Provided Excel advice; Commented on manuscripts

**Andrew Judge**: Provided statistical mentoring for candidate; Reviewed methodological design; Reviewed drafts of the manuscript

**Cyrus Cooper**: Reviewed drafts of the manuscript

**Daniel Prieto-Alhambra**: Reviewed drafts of the manuscript

**Nigel Arden**: Principal Investigator for the grant; Secured grant funding; Provided on-going guidance and supervision to candidate; Commented on all drafts of the manuscript; Held overall responsibility for the research as PI and as corresponding author

All co-authors below confirm the accuracy of the declaration of authorship for paper 4:

<table>
<thead>
<tr>
<th>Signature</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joe Maskell</td>
<td></td>
</tr>
<tr>
<td>Andrew Judge</td>
<td></td>
</tr>
<tr>
<td>Cyrus Cooper</td>
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</table>
Chapter 6 - Paper 4: Future Projections

<table>
<thead>
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<tbody>
<tr>
<td>Daniel Prieto-Alhambra</td>
<td></td>
</tr>
<tr>
<td>Nigel Arden</td>
<td></td>
</tr>
</tbody>
</table>
7.1 Summary of main findings

When setting out on the programme of work which has culminated in the papers presented in this thesis, there was very little high quality, population-level, epidemiologically descriptive evidence available by which policymakers, planners and clinicians could arrive at an informed understanding of the immediate past, the present and the future direction for lower limb total joint arthroplasty in the United Kingdom.

This thesis has presented four papers which sought to address this knowledge gap by describing the temporal trends and estimating the lifetime risk, the time to failure and the future level of activity for one of the most clinically and cost-effective major surgical interventions of the late 20th and early 21st century which is now not only common, but viewed as almost commonplace among populations in all but the most underdeveloped countries of the world.

Paper 1 put down a marker in the sand by describing age and gender specific incidence rates of THR and TKR for the UK as a whole over the period 1991 to 2006. Direct standardisation for age was used to produce summary rates of TJR for the UK population as a whole, for hip and knee separately, and for each gender. Also produced were population-level estimates of the ratio between hip and knee procedures and of that between the genders. Descriptions of the distribution of age at replacement were also presented. Paper 1 therefore led logically into the question posed in paper 2, i.e. “what proportion of the population at a given age end up undergoing a THR or TKR during their subsequent lifetime?”

Paper 2 estimated the risk of undergoing a THR or TKR in the remaining lifetime conditional upon reaching a certain age (50 and upwards). The incidence rates produced in paper 1 were used in conjunction with life table methods to produce lifetime risks at different ages. These risk rates were then compared, and found to be much greater than the lifetime risks of hip and knee osteoarthritis at the same ages, albeit in a different population (in the United States). Given that the lifetime risk of undergoing a THR for a 50-year old woman in the UK was estimated at 12%, the next logical question to pose is “how long might a typical hip prosthesis function properly before some form of surgical revision is deemed necessary, and what factors affect long-term success?”

Around the early-to-mid 2000s, some surgeons were imposing targets on patients for them to achieve an “ideal” pre-operative BMI. Therefore, paper 3 estimated the association of obesity, as
measured by BMI, with the time to failure of a prosthesis implanted in a THR or TKR procedure. Although numerous studies of time to revision had been conducted in the UK, a large-scale population-based study with near complete data on BMI had yet to be carried out. This paper also addressed recently voiced concerns over the use of the \textit{de facto} methods of survival analysis (proportional hazards model) in orthopaedic surgery studies of time to prosthesis failure where there is the substantial competing risk of death in older populations. Having considered past trends, lifetime risks and post-intervention prospects for total joint replacement, the final piece of the jigsaw was to make future predictions of the need for these surgical procedures.

Paper 4 built on the estimation of incidence rates in paper 1 to provide projections for future rates of THR and TKR. Continuing with the focus on how obesity is associated with arthroplasty addressed in paper 3, the last paper in this series of four added stratification at BMI group level to the established age-gender specific estimation, re-estimating incidence in order to then use the changing age-gender-BMI distribution to project onto national forecasts for UK population levels. The culmination of this work has coincided with international interest in future arthroplasty rates and the methods by which they are forecast.

7.2 Discussion of individual papers

Each paper will now be discussed separately to assess the results within the context of the existing literature at the time of publication. It should be noted that five years elapsed between the publication date of the first paper (early 2010) and the fourth paper (early 2015), and it is important to evaluate the relevance of each paper’s results conditional upon the state of the literature at the time.

7.2.1 Paper 1 – Temporal Trends

Paper 1 presented incidence rates for THR and TKR for the whole of the UK over a 16-year period, as estimated from data supplied from the GPRD. Paper 1 also described, for the same period, changes in the average age at operation and the gender ratio for these types of surgical procedure.

In summary, the findings were that:
Chapter 7 - Discussion

1. The rates of THR and TKR rose gradually throughout the 1990s and 2000s, with TKR showing a more acute rise in the late 1990s.
2. The rates of TKR were higher than for THR.
3. Rates for women were higher than for men.
4. Women underwent TKR three years later than men, but age at THR was similar for men and women.
5. The TKR:THR ratio fell for both men and women in the late 1990s, but increased to around parity in the early 2000s.

At the time when the research for paper 1 was planned and carried out (early 2008 to late 2009), there had been very little published on population-level UK trends for THR or TKR. The fledgling National Joint Registry had barely been collecting data for five years, and only for England and Wales. The NJR’s annual reports, which were based on financial year periods, provided excellent summary information on current usage of orthopaedic surgery, but had not been in existence for long enough to describe long-term trends. Furthermore, the levels of compliance in submitting returns were not high in the early years of the NJR (between 85% and 90%), but this was progressively rectified and by the time the 7th annual report was published in 2010, the overall percentage of hip and knee replacements in England and Wales which were submitted to NJR for the financial year 2008/09 was up to 92.5%. Other than within the NJR’s own annual reports, no other research groups were yet using NJR data to answer research questions on descriptive epidemiology, and certainly not to specifically describe trends of surgical events at a population level.

Similarly, very little had been published using the other major source of data for surgical events – Hospital Episode Statistics. Data from HES was available from the financial year 1989/90, and although HES data continues to be collected to this day, it is confined to hospitals located in England. The only significant article in the literature giving a comprehensive description of the temporal trends for THR and TKR for a large sub-population of the UK (England) was published in 2004 by Professor Paul Dieppe’s research group (Dixon et al., 2004). This article used HES data for the period 1991 to 2001 and used the same method of age standardisation (direct; specific to gender; estimating rates separately for THR and TKR) as that used in paper 1, although the reference population used for standardisation was different (mid-year population estimates from 1996 rather than 2003). The Dixon paper, in an extended report format, provided detailed information on age-specific rates at five-year intervals, and included rates for not only primary but revision operations. Indeed, had the Dixon paper (a) covered more recent trends, and (b) for a longer period, and (c) also provided geographical coverage for all of the UK, then the novelty of paper 1 would have been reduced to the use of a different data source. One slight difference
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between these two papers is that the Dixon paper examined all primary replacements and a primary is not necessarily the same as a total replacement. Most primaries will indeed be total replacements of the joint, but not all. The focus of paper 1 was total joint replacement for which the terminology (and the coding) is well defined.

The motivation for wanting to answer the research questions addressed by paper 1 were two-fold: firstly, the gap in the literature highlighted above and secondly, the need for recent historical descriptive epidemiological information on THR/TKR to use as a base from which to answer more forward-looking research questions.

The novelty which is implicit in addressing an important knowledge gap is, of course, a necessary condition for conducting research, but the use of the results from paper 1 as the building blocks for later stages of work within a funded programme of research was the main motivation. Paper 1 was an essential pre-requisite in order to provide the lifetime risk estimates and future projections as presented in papers 2 and 4.

Since paper 1 was published in early 2010, very little else has been published describing historical temporal trends of THR/TKR in the UK. The NJR annual reports have continued to provide excellent descriptive information on each successive year’s THR/TKR activity for almost the entire population of England and Wales. In 2014, Northern Ireland began to submit data to the NJR, but at the time of writing Scotland does not submit to the NJR, having its own mechanism for reporting on arthroplasty activity (Scottish Arthroplasty Project, 2014).

Now that the NJR has achieved near full compliance in submissions from all hospitals in England, Wales and Northern Ireland it is doubtful whether the same strength of justification could be used for performing an analysis to estimate rates using a general practice database. The follow-up in the NJR is now over 13 years and the potential for a detailed regional breakdown is possible, which is something that databases such as CPRD can only offer at a regional level dictated by the former NHS Strategic Health Authority boundaries. Although the benefit of the extended temporal range of the NJR has been a natural corollary of the passing of time since paper 1 was published, there were no data collected into the registry for the period before 2003. Paper 1 remains the only research output to have estimated UK-wide rates for the 1990s and beyond.

Within the UK, the only comprehensive report of estimated rates at a regional level (apart from Dixon’s analysis of hip and knee replacement rates (Dixon et al., 2006) at English region level using the same data as in her 2004 paper) is an article by Ibrahim et al (Ibrahim et al., 2010) describing in detail the temporal trends of THR and TKR in the Trent region of England between 1991 and 2004, a paper published a few months after paper 1. Historical counts and rates of operations by
age and gender were reported, with more detail on changes in the age distribution over the study period. The data were collected from individual hospital registers completed by surgeons within the Trent region and to date provides the only significant register-style analysis for a large subset of the UK population for the period before the NJR started collecting data.

Interestingly, I developed some regional THR/TKR incidence rates from the same data used for paper 1 and found similar levels of incidence for the Trent region when compared to Ibrahim’s rates for the early 2000s. This work was presented to the annual meeting of the British Society of Rheumatology (Culliford et al., 2008). The rates for women were more similar than for men, with our CPRD-based data somewhat underestimating the rates produced by Ibrahim, although exact period comparisons were not available. Our regional work was also useful in comparing rates between regions of the UK with a very different age profile (e.g. London vs. South-West). For this we used the same method of age-gender standardisation employed in paper 1. The regional rate estimates were not reported temporally for individual calendar years due to a lack of precision, and we make no further comment here on regional (sub-national) rates since their estimation was not one of the objectives of paper 1.

In terms of statistical methodology for paper 1, the techniques used were well established. The only possibly novel technique was the creation of bespoke pivot tables within a Microsoft Excel spreadsheet in which to embed the direct standardisation into the estimation of the individual rates and computation of confidence limits. This provided a flexible platform for displaying graphs and tables in order to show the results by subsets and combinations of age range, gender, calendar year range and operation type (hip or knee).

The results from paper 1 provide some ideas for policy makers within the NHS and the government who may wish to review the provision of services for hip and knee replacement in the 1990s and 2000s, especially with respect to age and gender. The rise in rates from the mid-1990s onwards could be evaluated alongside historical data for waiting times for THR/TKR which may be available internally within the UK government’s Department of Health.

**Strengths**

One of the main strengths of this paper is that the results are based on a UK-wide sample of general practices which are broadly representative of the UK population registered with a general practice. The CPRD has recently been validated by Herrett and colleagues (Herrett et al., 2015) who, in particular, provided a detailed and robust analysis of the suitability of CPRD data for estimating age and gender specific properties and characteristics of the UK population. This was achieved by comparing the age distribution of the UK population recorded at the 2011 census
with a one million patient sample from the CPRD population at the same time. The age profile of the CPRD shows that infants and those in their mid-twenties are under-represented in CPRD data, but that those at older ages are almost exactly matched with the UK population distribution, with a slight oversampling effect in the 40 to 60 age range. Crucially, the vast majority of the population who undergo lower limb arthroplasty are aged 60 and above, which lends validity to the use of this data source for the estimation of age-specific and age-standardised rates for THR and TKR.

The fact that paper 1 relies on data from a sample rather than a register might be considered as a limitation in the sense of lack of completeness, but a well-designed sample can both minimise bias and also properly allow for imprecision by supplying confidence intervals for estimates. The practices contributing data to CPRD are not selected at random from a sampling frame of all UK practices. The sample is self-selecting and has grown since the late 1980s to number over 600 practices and the CPRD has an open invitation for practices to join and submit data. However, the geographical balance of practices within the CPRD is monitored to ensure that the geographical balance in terms of population coverage is broadly in line with current population estimates. However, CPRD is not a multi-stage sample. The selection of practices is the only level of sampling, albeit purposive and not randomised. Once each practice is selected, data for the entire patient population of that practice becomes part of the database, after anonymisation and quality-control.

One particular strength of CPRD data is its population denominator data. The CPRD population is defined by general practice lists, and population denominator data is supplied by calendar year, age, gender and deprivation quintile. Furthermore, the recording of practice registration dates and transfer out dates for each patient enables the creation of accurate person-time denominators within the CPRD so that the rate denominator does not include time when the patient is not exposed to risk. For example, if a patient is not registered with a practice for a full calendar year, then any rates estimated by assuming that all patients are at risk for that full year will be an underestimate of the true rate, since events cannot be seen within the data if the patient is not contributing data. Empirical estimates by the candidate on the supplied CPRD data suggest that this underestimation could be in the order of 5%. Hence CPRD data is ideal for the estimation of incidence rates at a fine level of stratification. Rates analyses based on register data need to rely on (a) data completeness / submission compliance and (b) accurate UK population estimates as denominators, with further assumptions for person-time adjustment.

Another strength relates to the construction of confidence intervals for the incidence rates produced in paper 1. It is notable that neither of the papers by Dixon and Ibrahim provided
confidence intervals for the rates, although some interval estimation was performed for incidence rate ratios. Perhaps the absence of confidence intervals is because the data used in each paper were not considered to be a sample but a complete register of the population of interest (HES data for England; Trent joint register for the Trent region). With CPRD data, we do have a sample of practices and a target population of all general practices in the UK, so it is appropriate and helpful to provide confidence intervals to quantify the amount of uncertainty in our temporal rate estimates.

The comparison of THR to TKR ratios temporally by gender within the UK has not been presented before. The decrease in this ratio over the mid-to-late 1990s reflects the more acute increase in the rate of TKR than THR over this period. Also for the first time, paper 1 showed the temporal trend of the gender ratio for total joint replacements, with women consistently undergoing over than a third more TKRs than men, and just under two-thirds more THRs.

Limitations

Since the main statistical methods used for estimating standardised incidence rates are based on long-standing statistical theory (Breslow and Day, 1987), the potential limitations of paper 1 mainly relate to the suitability of the data source.

It cannot be claimed that the CPRD is a randomly chosen sample, with a designed sampling scheme (e.g. simple random sample, stratified sample, multi-stage sample) plus the associated mathematical justification and sampling weights with which to identify the probability of each practice’s selection. The 6.9% sample (Herrett et al., 2015) is representative of the UK only in broad terms although as discussed earlier, at a national level the age-gender distribution is close to that of the UK population. However, coverage properties of other demographic characteristics such as ethnicity are not so clear in the 1990s and early 2000s, but there is some evidence (Mathur et al., 2014) that the distribution of ethnicity in CPRD since 2006 is in line with the 2011 UK census.

A further limitation of the rates described in paper 1 is that when attempting to validate the CPRD-sourced rates against the NJR counts for England and Wales observed in the financial year 2006/07, the NJR totals were 6.9% and 3.9% less than estimated totals respectively for THR and TKR using the rates from paper 1 applied to ONS population estimates. Given that paper 1 produced rates by calendar year, and that CPRD data for early 2007 was not available as part of the study data, it is unlikely that a precise match would have been possible. Nevertheless, it is possible that CPRD practices were very slightly over-represented in terms of THR/TKR events in the UK population for some of the study period.
Another potential limitation which is more general within general practice databases is the issue of accurate coding of events, in particular the event of interest. For total hip and knee replacements, there is a risk that GPs may code a total replacement as simply a replacement, and conversely may sometimes code a non-total replacement as total. For this study, the lists of Read codes which were used to select an event as a THR (appendix A.1) or TKR (appendix A.2) were carefully drawn up and validated by rheumatologists and surgeons within the study team. However, the CPRD comprises real-life data, entered by busy, time-constrained GPs and the Read code entered by the GP is that which is seen by the researcher. The Vision general practice computer system (used for data entry by all CPRD-contributing practices) presents a hierarchical drop-down menu of Read code descriptions to GPs, who then select the most appropriate code. Although it is likely that some events are miscoded, the fact that the CPRD-derived replacement counts are not too far away from the NJR counts suggest that the level of miscoding is in fact minimal.

Early in the analysis for paper 1, it was hoped to distinguish between replacements carried out within the NHS and those funded privately. In spite of there being a flag within the CPRD Clinical table supposedly denoting “... whether the event occurred as part of a private healthcare service ...”, this flag was only switched on for 1% of all replacement operations. This does not mean that CPRD does not include privately funded operations, but is more likely that the flag is not used routinely by GPs within their practice’s Vision system to flag up a private operation. If a patient registered within a practice elects to undergo a THR or TKR outside of the NHS, the GP will still receive a letter confirming that the operation has taken place and this is recorded as a Read coded event within the practice. Therefore, whereas HES data only records NHS-funded THR/TKR operations, CPRD in theory records all THR/TKRs including privately funded operations, but the NJR is the only source which can distinguish between NHS and privately funded operations.

7.2.2 Paper 2 – Lifetime risk

Paper 2 presented residual lifetime risks at age 50 for THR and TKR in the UK population based on the same GPRD data used to estimate incidence rates over a 16-year period in paper 1. The headline rates were based on data from 2005 which was the most recent calendar year for which reliable full-year data was available. Lifetime risks for each calendar year between 1991 and 2006 were estimated and the temporal change in lifetime risks was reported.

In summary, the findings were that:
1. The lifetime risks of TKR were 11.1% for women and 8.1% for men
2. The lifetime risks of THR were 10.8% for women and 7.1% for men
3. The disparities between these risk estimates and the only previously published lifetime risks of hip and knee osteoarthritis (25% and 45% respectively) were surprisingly large

At the time when the research for paper 2 was carried out (2009 to 2011), there were no estimates of lifetime risk of THR or TKR, either in the UK or elsewhere in the world. Estimates of point prevalence were readily available (or calculable) from national joint registries around the world, but outside of registry reports these were rarely the focus of original research articles, with one notable exception (Singh, 2011) which systematically reviewed the literature for any articles reporting national incidence or prevalence estimates of TJR throughout the world. Singh found a report on lifetime prevalence of hip or knee replacement among the over-60s in the UK, estimated to be 6% and 5% for men and women respectively (Steel et al., 2006), but this was not an estimation of lifetime risk in the sense of prospective, remainder of lifetime, risk of an event.

Lifetime risk estimates for musculoskeletal diseases were almost unheard of until a few years ago, let alone such estimates for interventions for those diseases. The most notable exceptions, published shortly before and during the time when the research for paper 2 was carried out, were two important papers (Murphy et al., 2008, Murphy et al., 2010) from the research group in Chapel Hill, North Carolina, which estimated the lifetime risks of developing hip and knee osteoarthritis. These estimates, derived from the population-based Johnston County cohort, put the lifetime risk of hip and knee osteoarthritis at 25% and 45% respectively. At the time of writing this thesis, no further estimates of the lifetime risk of OA have been published, either in the USA or elsewhere.

Considering the complete lack of literature on lifetime risk of TJR when paper 2 was published, a comparison within the literature in terms of methods and coverage is not possible. However, it is reasonable to discuss the methods of Murphy et al used to estimate the lifetime risk of OA and to justify why such methods were not employed in paper 2. The two papers by Murphy used entirely appropriate methods considering the disease under consideration, the cohort design and the structure of the data available. Also, the authors stratified by factors other than age and gender. Unlike with the GPRD data used for paper 2, the Johnston County cohort data available to Murphy and colleagues was at two time points only (baseline and first follow-up), meaning that their use of logistic regression with generalized estimating equations (GEE) was arguably the most suitable.
The paper by Holt et al (Holt et al., 2011) used a state transition model for forecasting the prevalence of OA among an elderly population in the USA. These approaches define a minimal number of states (e.g. alive without OA, alive with OA, dead) and estimate the probability of moving between them. Like the Murphy papers, the approach adopted by Holt was appropriate partly because the data used was available at two time points several years apart. The CPRD data is available with continuous follow-up over a long period, without the restriction of only having two time points at which different states can be observed. Furthermore, state transition models require meaningful data which is known to be associated with the different states, and in Holt’s study, such data (e.g. Kellgren and Lawrence grade) were available within the NHANES surveys used to feed the model. Although our data benefitted from the continuous patient record over time, we lacked the detailed clinical data on disease progression which is available as an option when a cohort is recruited for a particular set of purposes. It is hard to say whether a life table method is better or worse than other methods. Life tables are simpler to interpret, but are limited to a few variables, whereas the models described above are more flexible in terms of explanatory variables, but less granular with respect to age/time. Often the benefits and/or the shortcomings of data sources partly inform the choice of methods, and paper 2 as much as the others discussed here, demonstrate the ‘real world’ effects of this.

One particular strength of paper 2 was that it used life table methods to estimate lifetime risk. Life tables require estimates of the probability of experiencing an event of interest between two ages or age bands, and can be as fine or as coarse in terms of age granularity as the data allow. Life tables are simple to construct and to explain to patients and carry few assumptions. Since the GPRD data used for paper 2 provides exact dates for an event within a fully recorded timeline for each patient while registered at a general practice, a life table approach at a fine level of granularity is possible without the need for a longitudinal, baseline/follow-up analysis.

The motivation for addressing the research questions of paper 2 was the absence of any lifetime risks of THR or TKR in the literature. The analysis employed in paper 1 to calculate incidence rates was used directly in the analysis for paper 2. Whereas incidence rates may be useful for policy makers, lifetime risks for the general population are of interest to clinicians who can communicate these facts to patients, and this also motivated paper 2.

The headline results tell us about lifetime risks of THR and TKR for a man or woman in the UK general population aged 50 years and older, but do not have any predictive capability in terms of other stratifying variables, whether clinical (e.g. obesity, presence/severity of OA) or demographic (e.g. ethnicity, social class). Before the analysis was undertaken, the candidate and his co-authors had no real idea of what the size of these estimates (around 10 to 11% for women and 7
to 8% for men) might be, and the range of guesses among the team ranged anywhere from 2% to 20%, with the higher guesses largely predicated on the Murphy risk estimates for OA.

The lifetime risk estimates seem to be broadly in line with the results from paper 1, when comparing THR to TJR and male to female, as expected since the same joint replacement rates are being used, although mortality rates are now incorporated. Table 4.2 and Table 4.3 provide more detailed information on the chances of undergoing TJR across the age ranges. Simple age-specific counts from registry data do not allow for differing mortality rates, so it is interesting to note from Table 4.3 that at age 60 the ten-year risk of undergoing a THR or TKR is about the same as at age 80. Also, we see from table 4.2 the sharp reduction in lifetime risk caused by mortality for those in their 70s and especially in their 80s, even though many operations are performed in patients in that age range.

Turning our attention to what has been published in the literature since paper 2 went to print in 2012, the only new estimates for lifetime risk of both THR and TKR at the time of writing this thesis were published by a research team in the state of Victoria, Australia in 2014 (Bohensky et al., 2014a, Bohensky et al., 2014b). The team used hospital admissions data to identify THR/TKR operations and population data from the Australian Bureau of Statistics. Life table methods were then used to estimate lifetime risks using 2008 data. Over 45,000 THRs and 43,000 TKRs were identified between 1998 and 2009. The lifetime risks of TKR using 2008 data were estimated at 10.3% for women and 9.9% for men. For THR the risks were 11.9% for women and 10.4% for men. It is however difficult to compare these estimates with ours since these risks were for those aged 20 to 29 years, compared with the 50 year starting point for the headline risks from paper 2.

Even though the Bohensky group used the same estimation methods as in paper 2 (but with ten-year bands rather than individual years of age) it is reassuring that the estimated risks were similar to the paper 2 results, albeit a little higher for TKR and for men. Even though the healthcare system in Australia has some similarities with that in the UK, it is almost surprising how close the estimates are, given that they are different populations. As reported in the discussion of paper 2, lifetime risks from the GPRD data at age 20, 30 and 40 were found to be similar to those at age 50 (within a few tenths of a percentage point), so one might think that it is unlikely that the life table starting age would make a very large difference to the Victoria rates. However, both of the Bohensky papers show lifetime risks at a given age decreasing more rapidly as age increases, than is the case for risks estimated in paper 2. For example, the lifetime risk of THR for men aged 70 to 79 in Victoria is 1.2% whereas in paper 2, the rate for a 70-year old is 5.3% and for an 80-year old is 2.7%. This can only be partly explained by the use of age banding used in the rates for Victoria. Differences between the two populations other than age and sex are likely to be
influential here, and Bohensky describes some potential factors such as socio-economic group and health service initiatives in Australia, but these are related more to temporal changes than to differences in lifetime risk across the age range.

Apart from the results from Australia for both THR and TKR, the only other published research is from the USA for TKR only (Weinstein et al., 2013). This analysis used the same simulation methods, data (NHANES) and state transition model as for the paper modelling the future risk of OA (Holt et al., 2011) conducted by the same research team. The lifetime risk of TKR in the USA was estimated to be 9.5% for women and 7.0% for men based on a starting age of 25 years. The team went further to estimate that over half of all adults with osteoarthritis in the USA would subsequently have a TKR. Again, the overall risk estimates for TKR are similar to those from paper 2 of 11.1% and 8.1% for women and men respectively, even though the USA and UK have quite different healthcare systems with the USA because of the differential access to healthcare between subgroups of the population.

The statistical methodology used in paper 2 was not standard, being based on life tables and with confidence interval methods based on standard Poisson assumptions (Schouten et al., 1994). The creation of a bespoke multi-sheet Excel workbook linked to embedded ONS death rates and estimated incidence rates (from paper 1) was innovative, with complex coding of functions such as VLOOKUP with which to cross reference the correct age/gender rates from the relevant calendar year. This constituted a large amount of work and although the workbook was developed \textit{ab initio} by the candidate, it was not of particular methodological interest but more a means of obtaining the end result (lifetime risks, confidence intervals) within a single, flexible programming environment.

The results from paper 2 have some implications for policy making. If we accept that levels of lifetime risk for hip and knee OA are not greatly different from those estimated by Murphy and colleagues in the USA, then there appears to be a large, unexplained difference between lifetime risk of lower limb, large joint OA and of undergoing its main intervention, a total joint replacement. Possible reasons such as lack of provision, willingness to undergo surgery, patient perception of disease severity, etc., as researched variously by Judge, Dieppe, Hawker, Juni and others have already been mentioned in the discussion section of paper 2, and these themes reappear in the literature in the work of Murphy and Bohensky discussed earlier. While there is general acceptance that these factors do play a part, it would be helpful for policy makers to know with greater certainty the components of the OA/TJR lifetime risk gap. If in future that gap were to narrow, for whatever reason, then it could have serious implications for the provision and cost of replacement surgery within the UK.
Strengths

It is worth briefly repeating that one the main strengths in all four papers within this thesis is the fine detail and representative coverage of the UK population offered by CPRD data (see ‘Strengths’ in section 7.1). For paper 2 in particular, one of the key strengths of the data is that it is a longitudinal and continuous temporal profile of patient lifecourses as viewed from the perspective of a general practitioner, and is therefore fine enough to estimate life table probabilities at the level of a single year of age, for each calendar year. In fact, it would have been possible to estimate at an even finer level of age (e.g. half-years), but this would not provide any more meaningful detail – the temporal profile would be smoother, but confidence intervals would become wider, especially at older age/gender subgroups where even the CPRD (with its large overall sample size) cannot provide precise estimates.

Although the risks presented in paper 2 are not lifetime risks for the whole of life from birth, this matters little since the risk of both life table events (TJR and death) is very small in the first few decades of life. In the lifetime risk literature previously discussed (articles by Bohensky et al, Weinstein et al, Murphy et al) the starting age was 25 to 30 years younger than the 50 years used in paper 2. The sensitivity analysis carried out in paper 2 showed that the risks at 30 and 40 years of age were almost identical to the risks estimated for a 50-year old. Bohensky found larger differences in risks between younger age groups. For example, THR risks in Victoria for those in their 30s were some two percentage points higher than in their 50s, but with our UK rates the corresponding differences were around 0.1 to 0.2%. It is unclear why the UK should not exhibit a similar risk profile across the age range. Very few TJRs are carried out on patients in the UK before the age of 50, so this suggests that rates of TJR among younger patients are higher in Victoria than in the UK.

The choice of life table methods for paper 2 is a further strength. Lifetime risks can be estimated in a number of ways, using models to estimate the probability of transitioning from one state to another. The use of TJR incidence rates and mortality rates, both applicable to the general population, mean that an individual can easily envisage a worked example where at a given age the mortality rates and TJR incidence rates are applied to each single year of age to a notional population, reducing the population at risk of both events and also accumulating the number of TJRs undergone by the notional population throughout life, or to a given age in later life. The approach does not rely on linearity or consistency in risk across the age range, and a worked example would show fluctuations in risk over the age range under consideration.

Limitations
There are several limitations of the results in paper 2. The first is that the lifetime risks only apply by age and gender, as opposed to accommodating further stratification variables. One such variable is obesity, and it is clear that this extra level of detail would be of use to clinicians advising patients. If, for instance, the lifetime risk of TJR was markedly higher for obese patients in the general population then this might guide clinicians to recommend, and patients to accept, interventions to reduce that risk. The reason for not including BMI-specific lifetime risks was the lack of population denominator data within the CPRD with which to calculate BMI-specific incidence rates for THR/TKR. Precision would also have been an issue, but only for sparse age-BMI subgroups such as the young who are underweight or morbidly obese.

As will be seen later in this discussion, the problem of a lack of BMI-specific population denominator data was partly solved for paper 4 by using other sources of data (Health Survey for England) to break down the age-gender denominator data by BMI group, but at the time of paper 1 this approach was not considered. In any case, the lifetime risks of OA produced by Murphy estimated overall lifetime risk by BMI group. Lifetime risks of knee OA were higher for the obese (60%) than the underweight/normal group (30%) but the risks for hip OA were in the 23 to 31% range for all BMI groups. It is unclear whether BMI-specific lifetime risks for the UK would show large differences between BMI groups, but given that the magnitude of the risks are much smaller than for OA, the chance of finding meaningful percentage point differences would be less, even if the risks for replacement were in proportion to the risks for OA across BMI groups. The results in paper 3 shed some light on whether BMI is associated with the time to TJR, but that analysis uses methods which are different from life tables and the estimates produced should not be considered as substitutes for BMI-specific lifetime risks.

One of the limitations of the life table method is that it cannot accommodate other explanatory factors in the same way that a regression modelling approach can. Paper 2 already stratifies the data by gender, and although it would be technically possible to stratify further (e.g. by BMI group), it would be necessary to sub-divide the data again and again, meaning the life table decrements would have smaller counts and the associated risks could only be estimated with a steadily decreasing precision. Murphy’s papers estimated lifetime risk of OA by other clinical and demographic factors such as race, education and history of hip/knee injury. However, it should be noted that those estimates are actually model-predicted prevalences, which carry assumptions about the distribution, whereas life table estimates, although limited in scope, do not make the same assumptions.

At the time when this study was conceived, the NJR may have been an option as a data source, but with only six or seven years of register data available at that time, it was not likely to be
enough to provide temporal changes in the lifetime risk of TJR over a long enough period. In theory, it would have been possible to use a life table with the latest available NJR counts to compute incidence rates using ONS population data as a denominator. Therefore, headline lifetime risks could have been estimated using NJR data, with greater precision for risks based on a single year than the CPRD data could provide. Nevertheless, CPRD data were selected because they best addressed the need of all four elements of the research (as detailed in papers 1 to 4), and not just the estimation of lifetime risk.

One criticism of the lifetime risks of paper 2 might be that they do not apply specifically to a population with disease. If such risks were available for a population of newly-diagnosed osteoarthritis patients then clearly they would be of considerably more use to clinicians than risks for the general population. This is undoubtedly true, but such data would be hard to obtain in sufficient numbers to estimate lifetime risks at single years of age. Also, the data would need to contain accurate data on disease severity. Murphy addressed this point thoroughly when using OA as the endpoint for her studies using a composite endpoint taking into account radiographic and symptomatic OA, but the recording of such detailed data by GPs within a primary care database would be extremely uncommon. The candidate did present some exploratory analysis at the OARSI conference in 2014 (Culliford et al., 2014) using the same CPRD data as used in this thesis, but with a sub-cohort representing all patients diagnosed with hip or knee OA who also underwent a subsequent THR or TKR respectively. This sub-cohort was approximately a third of the size of the overall TJR cohort in the CPRD data, with median time from OA diagnosis to eventual TJR estimated at 15 months for hip and 38 months for knee. Given that these median times are short and that the proportion of OA diagnoses in TJR patients is so low, especially in such a comprehensive database with long follow-up, the difficulties of estimating lifetime risk in a well-defined OA cohort are apparent.

Having defined the UK rates of THR and TKR and estimated lifetime risks, we next wanted to explore the risk of failure of these primary operations.

7.2.3 Paper 3 – Prosthesis survival

Paper 3 presented the age, gender and BMI-specific risks for THR and TKR patients of undergoing a subsequent revision arthroplasty. The paper used CPRD data as for the previous papers, but inferences were applicable only to adults in the UK population who had undergone a THR or TKR operation. This survival analysis estimated the risk of undergoing a revision at a given time following the original THR or TKR, and also compared relative risks between the genders, and by
increasing age and BMI. The use of appropriate methods to allow for the competing risk of death was a key feature of this work.

In summary, the findings were that:

1. The cumulative incidence rate of revision was 2.0% for THR and 1.9% for TKR at 5 years
2. These rates were higher for men than for women at 1, 3, 5, 10 and 15 years
3. The excess risk of revision for each extra unit of BMI was 2.0% for THR and 1.5% for TKR
4. The decreased risk of revision for an extra year of age was 3.0% for THR and 4.2% for TKR
5. The increased risk of revision for being male was 23% for THR and 51% for TKR
6. Morbidly obese THR patients were 65% more likely to undergo revision than those with a normal BMI
7. There was little difference between risks estimated using standard regression methods and those which explicitly accounted for the competing risk of death.

At the time paper 3 was written, the main source of large-scale, population-based information on the revision rate of THR/TKR operations within the UK was the National Joint Registry. Worldwide, a similar situation existed, with national registries (especially in Scandinavia) and insurance databases (mainly in the USA) being the only organisations with large population-based data and sufficient follow-up to report revision rates at sufficient levels of precision to estimate risks for certain subgroups.

Within the UK, smaller studies based on hospitals or groups of hospitals were much more common, but these typically comprised samples in the hundreds or single-figure thousands. Comparisons of revision risks between different levels of obesity were rare (McLaughlin and Lee, 2006), and rarely had large enough sample sizes to precisely report risk differences for the obese and morbidly obese.

The NJR had for several years included descriptive analyses of the number of THRs and TKRs by finely stratified BMI category levels, but it was not until after the analysis for paper 3 was complete that the NJR began to report inferences about outcomes with respect to BMI, and even then the outcome was for 90-day mortality and not revision (National Joint Registry, 2014).

The background regarding obesity and joint replacement in the UK leading up to the time when paper 3 was planned is arguably best summarised by the paper by Horan (Horan, 2006) who describes the lack of evidence for policy decisions made by certain NHS trusts (Davis and Porteous, 2007) to ration joint replacement operations for obese patients. Although the literature Horan cites is mainly based on complication rates arising from surgery (for which there was some
limited evidence for the morbidly obese), none of the referenced papers in Horan’s article are what might be called large-scale or population-based.

Given that the NJR was available as a comprehensive register of total joint replacements for almost the entire population of England and Wales, one may ask why it was necessary to find a different data source for the analysis reported in paper 3. Apart from the lack of geographical coverage for Scotland and Northern Ireland and also the lack of long term follow-up, both of which have been described earlier, there are other reasons which are more specific to paper 3.

Baseline BMI data is available in the NJR for a relatively low proportion of patients. This may partly explain why more inferential analyses based on BMI were not undertaken in the NJR annual reports prior to the publication of paper 3. In later reports, the NJR used methods to impute missing BMI data such as multiple imputation (Little and Rubin, 1987). In the latest available NJR report published in 2015, BMI is available for 75% of patients undergoing THR in 2014, but the report mentions that in 2006 only 17% of THR patients had baseline BMI. Although the NJR has clearly been successful in increasing the BMI data compliance, it was felt that the higher and more temporally consistent proportions of BMI available in population-based databases such as the CPRD were preferable for long-term survival analyses where the main predictor of interest was BMI. The other reason for choosing a data source other than the NJR for paper 3 was the need to allow for potential confounders. CPRD presented researchers with all the primary care records for selected patients, enabling adjustment for a full range of comorbidities, smoking and drinking status and other clinical and socio-demographic variables. This information was not available within the NJR.

The original motivation for answering the research question posed in paper 3 was to contribute population-based evidence to the policy argument over rationing of TJR among the obese, the counter argument to which was based on smaller studies. It was hoped that the top-down perspective of a national study might show whether, on a larger scale, the risk of revision differed between levels of obesity. A secondary motivation was to address methodological concerns about the use of statistical methods which did not account for the competing risk of death in survival studies of joint prostheses (Fennema and Lubsen, 2010).

The results from paper 3 provided the first population-based prosthesis survival analysis for THR and TKR for the whole of the UK, comparing the relative risk of revision within age, gender and BMI. The NJR, with its access to almost the entire record of joint replacements in England and Wales, had reported failure rates in its annual reports, but the estimation of relative risks in a survival model were less commonly undertaken. A notable exception is the paper estimating the risk of failure for hip prostheses with a metal-on-metal articulation (Smith et al., 2012). This type
of prosthesis was becoming more popular in the early 2000s but began to require revision at an alarmingly high rate. The study by Smith et al demonstrated the power of the NJR to answer specific research questions at a national level. Nevertheless, the question of BMI-specific risks for THR (and TKR) prostheses more generally remained unaddressed, with insufficient relevant data available within the NJR to answer this question.

The use of the CPRD’s large sample enabled paper 3 to estimate revision risks for the morbidly obese subgroup in possibly the largest numbers worldwide outside of national joint registers. Our CPRD data included over 1900 THR patients and over 1700 TKR patients who were morbidly obese at the time of their primary arthroplasty. Occasionally, small numbers of patients have proved enough to demonstrate a significantly higher revision risk for the morbidly obese (Amin et al., 2006), but this is not population-based evidence. Paper 3 reported a 65% increase in the subhazard of revision of morbidly obese THR patients as compared with those having a normal BMI. The precision was high, with a resulting p-value of 0.006, but the same effect was not apparent for TKR where only a weakly significant increase in risk was reported in spite of the large effect size (44%, p=0.04). Although the crude incidence of revision among the morbidly obese was higher for TKR than THR (2.5% against 1.7% - not reported in paper 3), the revision risk relative to those with normal BMI was lower for TKR.

Paper 3 was also one of the first ever studies to present a large sample, national analysis of prosthesis survival allowing for the competing risk of death. Smith et al had already used a different method (flexible parametric survival) within a competing risks framework for the work on metal-on-metal hip failure (Smith et al., 2012), and other national register based examples from outside the UK were starting to be seen (Gillam et al., 2010). A debate about survival estimation without explicitly accounting for the competing risk of death had recently been highlighted in two papers (Fennema and Lubsen, 2010, Ranstam et al., 2011). The concerns were based on the fact that the two most commonly used statistical methods for time-to-event analysis (the product limit estimate of Kaplan-Meier plots and log rank tests, and Cox proportional hazards regression) treat censored event times as essentially the same. A censored event time is the length of time to a point at which the event of interest has not been observed, but at which follow-up is no longer possible. This may arise due to the end of the study period, or another reason. Where the outcome is, for example, all-cause mortality then this is not a problem, as there is no other possible event which precludes the risk of death. However, where all-cause mortality is not the event of interest, then other intervening events may either preclude the subsequent occurrence of the event of interest, or alter its probability of happening.
In the case of joint replacement being the event of interest, it is potentially problematic to treat death as the same type of censored event time as a patient leaving a study early or reaching the end of the defined study period. In elderly populations such as those who typically undergo TJR, the risk of death, which we call a competing risk, is considerably larger than the risk of undergoing joint replacement surgery, whether primary or revision. The methodological work of Fine and Gray (Gray, 1988, Fine and Gray, 1999) provided a framework which could present risks which cater for a defined competing risk or risks. Using competing risks regression, hazard ratios based on what Fine and Gray termed the *sub-distribution* can be estimated.

Paper 3 sought to compare risks using Cox regression with those obtained using Fine and Gray’s methods. Although the hazard ratio (from Cox) and the subhazard ratio (from Fine and Gray) have subtle differences in interpretation, the BMI risk results were very similar for both THR and TKR. Even when considering the adjustment covariates of age and gender, for which differentially the effects of death might be expected to have an effect, the hazards were still similar. These results from paper 3 do not clarify whether it is better to use Cox or Fine and Gray in studies with joint replacement as the event of interest, but it provides some evidence that at a population level the differences between them may be smaller than originally suspected.

Another important finding from paper 3 was the confirmation of a split temporal revision risk profile for THR. It was well known among orthopaedic surgeons that the indications for early revision in the weeks and months immediately following THR are mainly due to post-operative infection, whereas the longer term revision risks are due to a wider range of reasons including loosening, especially in cemented fixation, and lysis. Paper 3 used methods for the piecewise estimation of revision risk to partition the risk into early risk (to one year following THR) and late risk (over one year). This estimation was achieved within a competing risks framework, which is the first time such an estimation has been performed in studies of joint replacement. The results confirmed, at a population level that early revision risk due to morbid obesity exhibits a different profile to that for late revision (2.5 times greater for early revision with a non-significant reduction after one year post-THR). Figure 5.1 shows this graphically.

Since paper 3 was published in 2013, nothing has been added to the literature of revision risk in the UK at a population level. Meanwhile, the NJR has been gradually increasing its proportion of TJR data with baseline BMI. It is now debatable whether it would still be justifiable to use CPRD to effect a BMI-specific survival analysis for THR/TKR prostheses when the NJR has over 13 years of follow-up with an increasingly complete BMI base, yet a definitive analysis of the effect of BMI on revision using NJR data has yet to emerge.
Chapter 7 - Discussion

There are some methodological implications of paper 3, although it did not seek to extend the statistical methodology of competing risks survival analysis. Paper 3 suggests that the Cox proportional hazards model is actually quite robust in the presence of competing risks of modest magnitude in certain settings, and that in the study design phase, consideration should be given to the extent of differential competition by the substantive competing risk across the range of the explanatory variable of interest. This may then inform the choice of method (straight Cox or competing risks). On the other hand, one may view the evidence of paper 3 as suggesting that in the case of a potential substantial competing risk, a sensitivity analysis should be conducted, whether as competing risks versus a substantive Cox (or parametric survival) analysis, or vice versa. Furthermore, paper 3 may suggest that simple piecewise estimates of a hazard ratio can be useful, with an empirically chosen cut point, to explore multi-level risk profiles over time and also to perhaps circumvent the violation of the proportional hazards assumption necessary for the use of Cox regression.

Paper 3 may have some implications for policy and practice. The refusal of certain NHS trusts in the mid-2000s to operate on obese (not morbidly obese) patients is called into question by figures 5.1 and 5.2 which show that the cumulative incidence curves of revision risk for normal BMI patients is very close (within one percentage point) to that of obese patients at almost 20 years post-THR and post-TKR.

Paper 3 also finds that in the UK there is a low but significant risk of revision for each extra unit of BMI (2% for THR and 1.5% for TKR, both adjusted). While this is unlikely to be linear across the entire range of BMI, paper 3 does present evidence that this effect size is reasonably consistent from normal BMI through to morbidly obese.

Paper 3 cannot explain why there is an excess of revision risk with increasing BMI. However, work by Wallace and colleagues (Wallace et al., 2014) shows that obesity is associated with certain complications such as deep vein thrombosis (DVT) and pulmonary embolism (PE) which may occur after THR and TJR, and that higher levels of obesity (BMI of 35 and over) elevate the risk over those with a BMI of 30 to 35.

Strengths

One of the strengths of paper 3 is the length of follow-up and the population-based nature of the data on which it is based. Although only a few of the patients have post-TJR follow-up of over 20 years, this is due to the fact that the CPRD has been steadily growing since the late 1980s. Many patients have over 15 years of follow-up, as can be seen by observing the smoothness of the
cumulative incidence curves at that time point in figures 5.1 to 5.4, especially for some of the more populous BMI and age subgroups.

Another strength is the use of competing risks regression in addition to Cox regression, permitting a comparison between the two. The results suggested that in the case of the CPRD data on TJR used in paper 3, any bias introduced by not allowing for the competing risk of death while estimating revision risk is likely to be small.

Limitations

The analysis conducted for paper 3 has several methodological limitations, mostly related to data characteristics. CPRD and similar primary care databases rely on data recorded within general practice. The comprehensive nature of the data is a great strength in many ways, but there are also weaknesses in using routine data for research purposes for which it was not originally intended.

Firstly, the CPRD patients identified as having a THR or TKR event sometimes had more than one such event. Unlike the NJR, the CPRD has no information on whether a joint replacement was on the left or right hip or knee. This is not a problem for estimating incidence or lifetime risks, but in the case of prosthesis survival we do not know whether a TJR is left or right sided, nor can we match up a revision with a primary operation. This is a shortcoming of having to use Read codes for identifying joint replacements. It is strange that the Read code system contains many codes for different types of implant named after the surgeons who pioneered them, but does not contain basic data on laterality.

To establish a consistent method for identification, the first recorded primary operation (for hip and knee separately) was taken to be the defining THR or TKR. For revisions, it was assumed that the first revision subsequent to a defined primary indicated the event of interest – the failure of the prosthesis to function without the need for surgical intervention. Clearly there is a possibility that laterality is mismatched under this assumption. For example, a post-THR revision may actually be a revision to a contra-lateral THR performed before a patient’s practice began submitting data to the CPRD, or before the patient joined the practice. The NJR’s 2015 annual report states that 13.8% of primary hip replacement patients have had a contra-lateral primary replacement at some time (18.7% for TKR). This is a substantial proportion and implies that there may be an overestimation of the revision rate as estimated in paper 3 which may be of the order of 10%. However, with respect to the estimated relative risks of prosthesis failure between BMI categories, age groups and gender, it is difficult to envisage how the effect of mismatched primaries and revisions might differentially bias these comparisons. Nevertheless, in the longer
term the estimation of revision rates using the NJR will be clearly superior to CPRD due the detailed identification and linkage of procedures within patients. Nevertheless, the CPRD and similar databases will still have a role to play where researchers seek to estimate associations of joint replacement with variables not collected by the register.

Thus, paper 3 considerably enhanced our knowledge of the impact of BMI on the risk of failure. Finally, we wished to predict the likely future need for THR and TKR across the UK.

7.2.4 Paper 4 – Future projections

Paper 4 presented future projections for the level of total hip and knee replacement in the UK to 2035. The paper used CPRD data for the previous three papers, and built on the incidence rates produced in paper 1, using an external data source to extend those results to cover stratification by BMI in addition to age and gender. The future projections of THR and TKR made use of national population forecasts from the Office for National Statistics. Several modelling scenarios were presented and mathematical smoothing methods were borrowed and adapted from a government report on obesity in 2008.

In summary, the findings were that:

1. The number of THRs and TKRs performed in the UK in 2035 could be of the order of 96,000 and 119,000.
2. Different projection methods produced markedly different estimates of future activity.
3. Unmodified projections directly taken from a log-linear model are sensitive to the length of the estimation period and the curvature of the estimated exponential curve over time.
4. If the distribution of BMI within the UK population continues its trend of the past two decades then the increase in demand for TJR will be driven almost exclusively by the overweight and the obese.

The analysis for paper 4 was conducted between 2012 and 2014, with the paper published in early 2015. At the time of analysis, the literature contained two articles which estimated future TJR rates and counts. Birrell and colleagues (Birrell et al., 1999) used Swedish THR rates projected onto UK population forecasts from the ONS. The Swedish Hip Arthroplasty Register was well established and Sweden was thought to have a similar profile of hip disease. Projections were made using 1996 as a base, at ten-year intervals until 2026. The estimate for 2016 was approximately 76,000 THRs, and although the NJR reports over 83,000 hip replacements for 2014
(without THRs from Scotland), this is still an impressively accurate forecast for such a long timeframe. The same team did not publish similar projections for TKR.

The paper by Dixon et al (Dixon et al., 2004) built on its estimated incidence rates for THR and TKR to extend these trends linearly into the future. Their base period was 1991 to 2000 using data from Health Episode Statistics (for England only), and the projection was from 2000 up to 2010. Simple linear regression (ordinary least squares) was used to extend the trend line. The 2010 forecast for THR was 46,000 and for TKR 53,000. They additionally considered a static rate projection, using the rate from 2000 applied to the changing population forecast which produced lower estimates.

Both Birrell and Dixon considered two different projection scenarios, with each employing a static rate projection which assumes that rates stay at current levels and that only the population at risk change over time. Neither of these studies employ a log-linear regression approach to estimate incidence, which is the usual statistical estimation method for counts and rates. This may be because log-linear models produce exponential growth which may have been thought to be unrealistic in forecasting TJR over a long time frame.

Outside the UK, by far the most widely cited and influential work on forecasting future TJR rates was that by Kurtz and colleagues (Kurtz et al., 2007) in the USA, although other countries, for example Denmark (Pedersen et al., 2005), used similar methods. The methods employed by Kurtz were log-linear regression models, also known as Poisson regression, where incidence rates by age, gender and other demographic factors are modelled (as in paper 1), but these rates were then extended into the future as exponential projections, using the specific rates for each stratum. These future rates are then applied to some estimate of national population, usually easily obtainable from each country’s national statistical organisation.

All these papers correctly model the incidence rate and then apply the rate, either static or changing, onto reliable national forecasts of population. While it could be argued that linear projection, or application of a merely static rate onto population forecasts, might produce conservative estimates of growth, log-linear models have the potential to produce future estimates that are implausibly high.

Kurtz estimated that based on observed data from the US National Inpatient Sample gathered between 1990 and 2003, the projected number of THR operations in the USA by 2030 would rise to 572,000 with TKRs rising to 3.74 million. The same paper provides static rate projections using 2003 prevalence levels which, when applied to population estimates from the US Census Bureau, forecast the number of THRs to be 277,000 and TKRs 488,000 in 2030. Pedersen’s estimates of
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future rates of THR for Denmark in 2020 (Pedersen et al., 2005) also showed a large disparity between a static rate projection (c. 150 per 100,000) and a log-linear extrapolation (c. 400 per 100,000).

A criticism of purely extrapolated log-linear rates is that they only reflect the exponential curvature implicit within the estimation. While this may be appropriate for count data in certain scenarios (e.g. cell growth in laboratory experiments), where the count is effectively unconstrained locally, it is more questionable for situations where economic or other supply-side constraints provide limits to growth, even though these limits may be unknown or unspecified. However, the static rate projection which only takes into account future population growth makes the perhaps premature assumption that a supply/demand equilibrium has been reached. This is perhaps unrealistic if rates are seen to be rising right up to the baseline date for projection.

The motivation for paper 4 was that the currently available estimates of future TJR for the UK were either (a) short-term, (b) expired, (c) based on non-UK data (from Sweden for THR) or (d) not fully representative of the UK as a whole. We had seen almost a decade of rising incidence rates in the UK since the last projection baseline in 2000 and it was felt that new projections were needed. A novel element of paper 4 would be the use of BMI-specific strata in addition to age and gender. Finally, it was unknown whether a log-linear approach applied to UK data would produce plausible projected counts of TJR over the long projection timeframe of 25 years.

The results of paper 4 added to the knowledge base in several ways. They provided the first long-range projections of TKR in the UK, in addition to extending the forecast timeframe for THR used in Birrell et al. The results also found that log-linear methods did not provide sensible estimates of long-term activity, particularly for TKR. It is very hard to imagine a rate of TKR in the UK in 2035 which is some fifteen times the levels of 2010. Furthermore, the use of a projected BMI distribution to stratify rates showed how a conservative, static rate projection method could be combined with modelled future changes in BMI group proportions to explore how BMI might be a factor in future growth (which appeared to be the case for TKR).

Since the summer of 2014, when paper 4 was submitted for publication, three papers have been published on the subject of future projection of TJR. These papers, from New Zealand, Sweden and the UK, were published in the months after the submission of paper 4. The candidate was unaware of any of these projects during the analysis and review period for paper 4.

The paper from Sweden (Nemes et al., 2014) projected THR rates from 2013 to 2030 and used advanced methods to model rates using generalized asymptotic regression which constrains the otherwise exponential growth of the log-linear model such that an upper bound is applied to put
into effect a theoretical maximum THR rate. This is arguably superior to a static rate projection, but with three different methods used to estimate the upper bound, there is uncertainty about which should be chosen and why.

The paper from New Zealand (Hooper et al., 2014) projected incidence for both THR and TKR to 2026, stating that incidence rates were projected and applied to population forecasts. However, the projections in figure 4 of that paper are straight line projections suggesting that the log-linear growth is almost exactly linear over the incidence rate projection period of 15 years.

The paper from the UK (Patel et al., 2015) contained the most relevant findings for comparison with those from paper 4. It used NJR data from England and Wales from 2008 to 2012, omitting data from earlier years due to the lack of age and gender in substantial numbers of cases, as these were the chosen stratifying variables. The statistical methods used were standard log-linear methods for incidence rates, following the methods of Kurtz not only for exponential extrapolation of incidence rates, but also Kurtz’s alternative scenario of a constant incidence rate applied to population growth. Patel et al forecast 568,000 TKRs and 805,000 THRs by 2030 under the log-linear extrapolation, but these numbers fall to 186,000 TKRs and 187,000 THRs under the constant (static rate) assumption.

Compared with the work presented in this thesis, we see that Patel’s exponential extrapolations show THRs growing at a much faster rate than TKRs, the opposite to our findings of paper 4. Also we see from Patel et al (figure 2b) that by 2035 (the forecast horizon in paper 4), the THR forecast count would be well over 1 million, with TKR at somewhere between 700,000 and 800,000. Clearly, paper 4 is using a much longer base period (1991 to 2010) for estimation of the log-linear model than Patel et al (2008 to 2012), but both papers demonstrate the weakness of using an unmodified and unconstrained log-linear projection.

However, both paper 4 and Patel et al use forecasts based on static rate projection as their headline rate. Even considering the difference in length and timing of estimation period between the two papers, there is still a dramatic difference between 96,000 and 187,000 THRs or 119,000 and 186,000 TKRs. The actual difference is greater due to the five year gap in forecast horizon and the fact that the NJR data is for England and Wales only. Part of this difference may be explained by the fact that paper 4 used CPRD data rather than NJR, and that it also had an earlier base point (2010 versus 2012). The population forecast data for both papers was obtained from the ONS, and although sourced at different times, the differences are likely to be insignificantly small.

Where the difference most likely lies is in the difference between the estimated incidence rates within the stratifying variables of age, gender and (for paper 4 only) BMI. Even if paper 4 was to have used just age and gender specific incidence rates, the differential ranges in rates between
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the genders and between age groups could easily account for a substantial variation in the total forecast count of THRs and TKRs compared with Patel et al.

In late summer 2016, after the original submission of this thesis, the NJR published its 13th annual report (National Joint Registry, 2016), covering the period from the registry’s inception in April 2003 up to the end of December 2015. At around the same time, the Scottish Arthroplasty Project published its biennial report (Scottish Arthroplasty Project, 2016), providing new data for the calendar year 2015. These new data enabled an approximate comparison to be made between register data for 2015 and the projections for the same year provided in paper 4.

From tables 3.4 (page 35) and 3.21 (page 95) of the NJR’s 13th Annual Report, we find respectively that there were 83,886 primary hip and 94,023 primary knee replacements carried out in 2015 within England, Wales, Northern Ireland and the Isle of Man. The same tables enable deductions to be made for “non-total” primary hip (i.e. Resurfacings, 1%) and knee (i.e. Unicondylar, 9% and Patello-femoral joint, 1%) procedures. After making these deductions and adding the estimated number of THRs and TKRs from Figure 1a (page 4) of the Scottish Arthroplasty Report for 2016, we arrive at approximate UK estimates for 2015 of 90,800 THRs and 91,600 TKRs.

Although it is rather early to be assessing the accuracy of the projections of paper 4 based on a five-year time horizon, the estimates of THR and TKR counts in the UK for 2015 provided in tables 6.3 and 6.4 of paper 4 do underestimate the observed counts as recorded in the UK joint registries. The amount of underestimation is only 7% for TKR, but for THR the estimate from paper 4 is 20% which is a substantial shortfall. These comparisons use the paper 4 estimates based on 2010 THR/TKR incidence rates, as opposed to log-linear extrapolation, and they also use BMI category proportions which change over time as opposed to remaining at 2010 levels.

While these comparisons may seem to suggest that the projection methods of paper 4 may be lacking, one should reflect that the unconstrained log-linear (Poisson) model estimation used in the aforementioned papers by Kurtz et al and Patel et al would have considerably overestimated the UK counts of TJR, especially for the knee (see Tables 6.3 and 6.4, column 3). The true test of paper 4’s projected TJR counts will be in 10 or 15 years’ time, when the pragmatic combination of novel and standard projection methods may, in the light of changes in BMI distribution in the UK population, result in the extent of their underestimation comparing rather favourably with the extent of overestimation resulting from more conventional methodologies.

Although paper 4 contains no new statistical theory, it does contain novel combinations of methodologies. The use of a hyperbolic tangent function to constrain BMI group proportions, although pioneered in the ‘Tackling Obesity: Future Choices’ project report (McPherson, 2008), is
novel in its use to constrain a stratifying variable used to project estimates rates from a log-linear model. Its use was very much a pragmatic solution to prevent the extrapolation of a clearly linear 20-year historical trend for the increase/decrease of certain BMI group proportions turning into a situation where, for certain gender/age group/BMI group-specific strata, the projected proportions would exceed one or be less than zero well within the 25-year forecast timeframe. This impossible situation is circumvented if using purely log-linear projection, since the exponential nature of the model applies to individual strata and therefore although stratum-specific counts can be become very small or very large, the curvature implicit within the model prevents such violations. However, the exponential extrapolation of estimated log-linear model rates produced estimates from paper 4 which were thought to be implausibly high, and this phenomenon was also observed by Nemes et al who sought to asymptotically constrain regression estimated rates. The methods of paper 4 sacrifice the use of exponential projection for a static rate, but model future BMI distributional change among the UK population in a pragmatic fashion.

The main methodological implication of paper 4 is that unconstrained exponential projection from a log-linear model is flawed where there is unchecked growth of outcomes (counts or rates of THR/TKRs in the case of paper 4) which actually have plausible constraints, whether economic in terms of supply, or disease-driven within the population in terms of demand. Log-linear models are a natural choice for estimating incidence rates over time, but projection needs to be undertaken with care, taking into account the context, the base period and the possibility of constraints.

Paper 4 may have implications for policy in that it has produced forecasts of how demand for THR and TKR may grow in the future. The main observation is that the demand for TKR will continue to exceed that for THR and that this gap will widen, whichever of the different scenarios from paper 4 is assumed. However, this view is not supported by the results from Patel et al, which show similar numbers by 2030, unless one believes the log-linear projections showing THR rates being higher than TKR. As already mentioned, it is felt that the incorporation in paper 4 of BMI-specific strata for each age-group / gender combination may have contributed to these differences. Although there is some evidence from paper 1 and from recent annual NJR reports that incidence rates may be levelling off, it is suggested that it is the future growth and composition of the UK population which is likely to drive future levels of THR and TKR.

**Strengths**

The main strength of paper 4 is the inclusion of BMI as a stratifying variable in addition to age and gender. Furthermore, the length of the estimation period (20 years) for both the TJR rates and the
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BMI distributions ensured a stable base for the projections. Sensitivity analyses conducted with shorter periods of estimation gave similar results at 15 years and 10 years but below five years estimation became unstable.

The pragmatic method of incorporating BMI group proportion smoothing is also considered to be a strength, as it retains the population BMI trends over 20 years which show no sign of levelling off, yet applies a practical asymptotic limit at a gender/age group/BMI group level.

Limitations

There are several limitation of this work. The use of static incidence rates from 2010 assume that incidence rates abruptly level off and this is unlikely to be the case. However, given that TJR is largely driven by rates of osteoarthritis in the population, any future growth in rates ultimately depends on patient demand and willingness to undergo surgery.

Paper 4 did not provide any prediction intervals which would have enabled an assessment of confidence in the projection estimates for THR/TKR levels. Neither Birrell nor Dixon provided estimates of uncertainty. To provide estimates of uncertainty in paper 4 incorporating all the inputs (CPRD, HSE, ONS) would have been very difficult to do in a principled manner, and although confidence intervals for a purely log-linear extrapolation are obtainable (e.g. Patel et al), when applied to the methods in paper 4, they would not have fully accounted for the uncertainty of the estimates. It is acknowledged that any sensible interval for the projections in paper 4 would be wider than those produced in some of the later literature already described.

A further limitation is that although the age-gender-BMI profile of the THR/TKR population in the CPRD had been carried through into the projection, any past growth in the log-linear model had not. If we had followed the methods of Kurtz et al, then the estimate of 1.2 million TKRs by 2035 would be the headline result from paper 4, but this was considered highly implausible, hence the reason for choosing a static rate option. It would have been possible to retain log-linear projection and to adopt methods similar to those in Nemes et al, but even those require a choice between different types of regression method (Nemes used three different approaches).

Another more general limitation, also highlighted by Nemes et al, is that although historical data can assist in forecasting future trends, there are problems in simple extrapolation. So many factors could intervene to subtly or even dramatically change the supply and/or demand for THR/TKR. Other forms of surgical intervention could be pioneered which do not require total excision of the joint. Non-surgical therapies could be introduced (although none are on the horizon at present). Government or private enterprises could intervene to increase or reduce the supply of orthopaedic surgeons and hospitals. Patient perceptions and/or willingness to undergo
surgery could change. These are just a few of the uncertainties surrounding the projection of future TJR. As with any projections into the future, all it is possible to say is that if the same situation prevailing over the past period of estimation carries on prevailing in the future, then and conditional on the assumptions of the projection methodology, the projections provided may give some rough indication of future levels of activity. With no model inputs for supply-side constraints in any of the TJR models considered in the literature reviewed here, it is hard to have any absolute confidence in the accuracy of any of them over the long term, including those of paper 4.

Summary of the discussions

The previous discussions have critically examined the four papers in the context of the literature at the time of analysis, and since the time of each paper’s publication. The discussion of each element has been presented serially, in the order in which the analysis was undertaken, but the importance of each paper to the others has been explained, referring backwards or forwards as appropriate. In their totality, these four papers represent a thesis of work which has described the past and present in total joint arthroplasty in the UK, has widened the understanding of the risk of failure and has estimated the likely future needs for these types of operation.

7.3 Future research

Finally, having discussed the research contained in this thesis, it is instructive to consider how it might be extended. It is clear that for basic age-gender specific incidence of TJR in the UK, the registries are now the definitive source of information on temporal trends, mainly because they have now had sufficient time to gather data. However, unless the NJR and the Scottish Arthroplasty Project begin routinely reporting long-term temporal trends for their accumulated data, there remains a responsibility for researchers to apply for and analyse this registry data to report on trends.

However, for any analyses which seek to report on historic rates or counts at a more detailed level of stratification (e.g. social class, BMI), then routine primary care databases will continue to be valuable sources of population-based data, especially if the research questions involve clinical events or therapies.

Lifetime risks of TJR continue to be important to patients, but this work needs to be extended to extrapolate risk factors such as BMI and the onset of relevant clinical conditions, most notably osteoarthritis. There is arguably a need for an online risk calculator for TJR similar to FRAX™ (Kanis et al., 2008) for fracture risk or QRISK2 (Hippisley-Cox et al., 2008) for cardiovascular risk.
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The latter was actually constructed using routine primary care data and the development of THR and TKR risk calculators seems plausible using such data.

Time-to-event (survival) analysis has for many years been an important statistical tool for the assessment of risk factors for TJR failure, but usually the outcome is time from primary to revision surgery. It is underused at the population level for other outcomes, and the analysis of time from diagnosis of osteoarthritis to TJR is an open research area. A recent article by Leyland and colleagues (Leyland et al., 2016) analysed the BMI-specific risk of OA patients in a primary care database in Catalonia, and such a study for the UK seems well overdue, although exploratory work has already been carried out (Culliford et al., 2014).

An alternative method to the usual time-to-event analysis could be of use in explaining associations along the path from disease to TJR. Multi-state models could be used to estimate the risk of progressing through disease states (e.g. hip pain to hip OA to THR) using the longitudinal patient profiles held within primary care databases, and this has yet to be attempted anywhere so far.

Looking to the future, researchers continue to use data-driven projection methods to provide forecasts for levels of future TJR. Sophisticated methods (Nemes et al., 2014) have emerged which seek to adjust the usual log-linear estimates, but the fact remains that all these approaches are based on historical demand, with no supply-side limitations (e.g. number of hospitals and surgeons) constraining the future estimates. Until the elicitation of reliable supply-side forecasts are attempted, we will remain in the realm of mathematical extrapolation, tempered by subjective modification.
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7.4 Conclusion

In conclusion, this thesis has attempted to fill in some of the gaps in the body of population-level research on total hip and knee replacement in the United Kingdom. It has used ‘real world’ data to describe past levels of activity, to estimate current risks and to assess likely future trends.

The research studies within this thesis were designed with a focus on descriptive epidemiology by age and gender, applicable to the whole population rather than a disease-specific subgroup. The work has also addressed the population level of obesity, as an attempt to help explain the variation in longevity of hip and knee prostheses, and also as a stratifying factor for the projection of future levels of joint replacement.

It is hoped that the four papers presented in this thesis will provide a complement to past and future research outputs from joint registries and from orthopaedic surgeons, and that epidemiologists and statisticians will continue to estimate risks and describe trends in joint replacement using large-scale routinely collected data.
Appendix A  Code lists

A.1  Read codes for Total Hip Replacement

This list was used to select events in CPRD which could be described as a THR

<table>
<thead>
<tr>
<th>Read/OXMIS code</th>
<th>Read/OXMIS Term (Description)</th>
</tr>
</thead>
<tbody>
<tr>
<td>XE2n7</td>
<td>Primary total prosthetic replacement of hip joint NEC</td>
</tr>
<tr>
<td>XaF7k</td>
<td>Primary hybrid total replacement of hip joint NEC</td>
</tr>
<tr>
<td>XE08o</td>
<td>Other total prosthetic replacement of hip joint</td>
</tr>
<tr>
<td>XE08j</td>
<td>Total prosthetic replacement of hip joint using cement</td>
</tr>
<tr>
<td>XaF7j</td>
<td>Primary hybrid total replacement of hip joint</td>
</tr>
<tr>
<td>XE08k</td>
<td>Primary cemented total hip replacement</td>
</tr>
<tr>
<td>7K22y</td>
<td>Other specified total prosthetic replacement of hip joint</td>
</tr>
<tr>
<td>XaF7l</td>
<td>Prosthetic hybrid total replacement of hip joint</td>
</tr>
<tr>
<td>X606J</td>
<td>Total hip replacement</td>
</tr>
<tr>
<td>XE08m</td>
<td>Total prosthetic replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K20.16</td>
<td>Freeman total replacement of hip joint using cement</td>
</tr>
<tr>
<td>7K20000</td>
<td>Primary cemented total hip replacement</td>
</tr>
<tr>
<td>7K20.1G</td>
<td>THR - Total prosthetic replacement of hip joint using cement</td>
</tr>
<tr>
<td>7K21.13</td>
<td>Lord total replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K21.15</td>
<td>Monk total replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K20.1C</td>
<td>Muller total replacement of hip joint using cement</td>
</tr>
<tr>
<td>7K22.12</td>
<td>THR - Other total prosthetic replacement of hip joint</td>
</tr>
<tr>
<td>7K22000</td>
<td>Primary total prosthetic replacement of hip joint NEC</td>
</tr>
<tr>
<td>7K20.17</td>
<td>Furlong total replacement of hip joint using cement</td>
</tr>
<tr>
<td>7K21.16</td>
<td>Ring total replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K20.11</td>
<td>Arthroplasty of hip joint using cement</td>
</tr>
<tr>
<td>7K21.12</td>
<td>Furlong total replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K21.11</td>
<td>Freeman total replacement of hip joint not using cement</td>
</tr>
<tr>
<td>7K20.1F</td>
<td>Turner total replacement of hip joint using cement</td>
</tr>
<tr>
<td>7K20.1A</td>
<td>McKee total replacement of hip joint using cement</td>
</tr>
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</table>
Appendices

7K20.12 Aufranc total replacement of hip joint using cement
7K21.17 THR - Total prosthetic replacement hip joint without cement
7K21.00 Total prosthetic replacement of hip joint not using cement
7K20.14 Exeter total replacement of hip joint using cement
7K20.1D Pretoria total replacement of hip joint using cement
7K21.14 Madreporique total replacement of hip joint not using cement
7K20.18 Howse total replacement of hip joint using cement
7K20.1E Stanmore total replacement of hip joint using cement
7K22.00 Other total prosthetic replacement of hip joint
7K20300 Primary hybrid total replacement of hip joint NEC
7K20.1B Monk total replacement of hip joint using cement
7K20.13 Charnley total replacement of hip joint using cement
7K20.00 Total prosthetic replacement of hip joint using cement
7K20.15 Farrer total replacement of hip joint using cement
7K20011 Charnley cemented total hip replacement
7K21y00 Other specified total prosthetic replacement of hip joint not using cement
7K20y00 Other specified total prosthetic replacement of hip joint using cement
7K21000 Primary uncemented total hip replacement
7K21z00 Total prosthetic replacement of hip joint not using cement NOS
7K20z00 Total prosthetic replacement of hip joint using cement NOS
7K20400 Conversion to hybrid total hip replacement NEC
7K20100 Conversion to cemented total hip replacement
7K22100 Conversion to total prosthetic replacement of hip joint NEC
7K20600 Conversion from hybrid total prosth hip joint replace NEC
7K20x00 Conversion from cemented total hip replacement
7K21100 Conversion to uncemented total hip replacement
7K21x00 Conversion from uncemented total hip replacement
7K22y00 Other specified total prosthetic replacement of hip joint
## A.2 Read codes for Total Knee Replacement

This list was used to select events in CPRD which could be described as a TKR.

<table>
<thead>
<tr>
<th>Read/OXMIS code</th>
<th>Read/ OXMIS term</th>
</tr>
</thead>
<tbody>
<tr>
<td>X6060</td>
<td>Total knee replacement</td>
</tr>
<tr>
<td>XEO8w</td>
<td>Total prosthetic replacement of knee using cement</td>
</tr>
<tr>
<td>XEO8y</td>
<td>Total prosthetic replacement of knee joint not using cement</td>
</tr>
<tr>
<td>XEO90</td>
<td>Other total prosthetic replacement of knee joint</td>
</tr>
<tr>
<td>XEO91</td>
<td>Primary hybrid total knee replacement NEC</td>
</tr>
<tr>
<td>7K30.00</td>
<td>Total prosthetic replacement of knee joint using cement</td>
</tr>
<tr>
<td>7K30.11</td>
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## Glossary of Terms

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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CRR</td>
<td>Competing risks regression</td>
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<tr>
<td>GLM</td>
<td>Generalised Linear Model</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HOA</td>
<td>Hip osteoarthritis</td>
</tr>
<tr>
<td>KM</td>
<td>Kaplan-Meier</td>
</tr>
<tr>
<td>KOA</td>
<td>Knee osteoarthritis</td>
</tr>
<tr>
<td>MoM</td>
<td>Metal-on-metal</td>
</tr>
<tr>
<td>MoP</td>
<td>Metal-on-polyethylene</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<td>OLS</td>
<td>Ordinary Least Squares</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PH</td>
<td>Proportional hazards</td>
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<tr>
<td>SHR</td>
<td>Subhazard ratio</td>
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