Epidemiology and economic evaluations relating to knee and hip replacement with evidence from routinely collected data



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ABSTRACT

Epidemiology and economic evaluations relating to knee and hip replacement with evidence from routinely collected data.

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Knee and hip replacement have been shown, in general, to be both effective and cost-effective when compared with non-surgical alternatives. There has been, however, uncertainty around individuals' risks of undergoing the procedures after diagnoses of osteoarthritis or rheumatoid arthritis, and patient outcomes after surgery. The first set of research questions answered in this thesis aimed to address the gaps in the evidence-base on patient prognosis under current practice. Routinely collected data from England and Catalonia, Spain, informed these analyses. In the research undertaken it was found that after a diagnosis of knee osteoarthritis, the lifetime risk of knee replacement was 30% for the average patient profile. Meanwhile, lifetime risk of hip replacement after a diagnosis of hip osteoarthritis was 14%, and lifetime risks of knee and hip replacement following a diagnosis of rheumatoid arthritis were 22% and 17%, respectively. It was also found that patients, on average, achieved more than 62% of their potential improvement in joint-specific outcomes after knee replacement, and more than 81% after hip replacement. Risks of post-operative complications were typically less than 1%, while lifetime risk of revision was 5% and 8% after knee and hip replacement for the average patient profile, respectively.

The second set of research questions which were addressed focused on the potential consequences of interventions which either reduce the risks of or improve outcomes after knee and hip replacement. Addressing these questions first required an understanding of outcomes under current practice, and this was provided by the preceding research. The effectiveness of tumour necrosis factor inhibitors on long-term risks of knee and hip replacement is not yet established, but if their use as a first-line therapy led to relative risk reductions of 20%, for example, 46 and 30 knee and hip replacements would be avoided per 1,000 individuals. This would also result in a combined procedure cost saving of over £300,000 for a cohort of that size. Meanwhile, one knee replacement is expected to be avoided for every 17 bariatric surgeries provided shortly after a diagnosis of knee osteoarthritis for individuals with a BMI of 40 (but otherwise average characteristics). Threshold prices, prices at which the net health benefits from funding the intervention would be zero, were estimated for computer or robot-assisted knee and hip replacement. Threshold prices for a 50% relative reduction in risk of revision were around £1,000, while they were approximately £10,000 for a 5% relative improvement in post-operative quality of life if unrevised.

These findings provide evidence to patients on their prognosis under current practice and will help to inform resource allocation decisions on interventions related to knee and hip replacement. Moreover, the research presented in this thesis also demonstrates the value of routinely collected data for considering the life course of a disease and its treatment.

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ABBREVIATIONS

APC: Admitted Patient Care
BMI: Body mass index
BSRBR-RA: British Society for Rheumatology Register for rheumatoid arthritis
CatSalut: *Servei Català de Salut*
cs: Conventional synthetic
CCG: Clinical commissioning group
CI: Confidence interval
CPRD: Clinical Practice Research Datalink
CMBD: *Conjunt Mínim Bàsic de Dades*
DMARD: Disease-modifying anti-rheumatic drug
EQ-5D-3L: EuroQol 5-dimension 3-level
GP: General practitioner
HES: Hospital Episode Statistics
IMD: Index of Multiple Deprivation
IQR: Interquartile range
PoPC: Percentage of potential change
PROMs: Patient-reported outcome measures
MEDEA: *Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales*
NHS: National Health System
NICE: National Institute for Health and Care Excellence
OHS: Oxford Hip Score
OKS: Oxford Knee Score
ONS: Office for National Statistics
QALY: Quality-adjusted life-year
SIDIAP: *Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària*
TNFi: Tumour necrosis factor inhibitors
UK: United Kingdom
USA: United States of America

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1. INTRODUCTION

Chapter summary

In this chapter I provide the context for the studies presented in this thesis and summarise the specific research questions addressed.

Evidence on the long-term risk of knee and hip replacement after a primary care diagnosis of osteoarthritis or rheumatoid arthritis has been lacking, and this motivated a research objective of estimating the lifetime risks of these procedures. While outcomes after knee and hip replacement have been assessed, patient heterogeneity in them is not fully understood. This prompted research objectives to better understand patient-reported outcomes, post-operative complications, and the lifetime risk of revision after knee and hip replacement.

Interventions are available which may reduce the risk of knee and hip replacement or improve outcomes after these procedures. Based on the findings from the initial research questions, further research objectives assessing the value of early initiation of tumour necrosis factor inhibitors (TNFi) after a diagnosis of rheumatoid arthritis, bariatric surgery after a diagnosis of knee osteoarthritis, and computer and robot-assisted knee and hip replacement were specified.

Knee and hip replacement: incidence and indications

In knee and hip replacement surgery, the articular surfaces from a joint are removed and replaced with artificial substitutes, known as prostheses or implants. They are two of the most common surgical procedures performed across high-income countries, with rates continuing to increase over recent years. Between 1991 and 2006 in the UK, age-standardised incidence rates of knee replacement increased from 43 (per 100,000 person years) to 140 for women and from 60 to 145 for men, while rates of hip replacement increased from 29 to 100 for women and from 36 to 89 for men.[1] If this trend continues, and given the ageing population and increasing rates of obesity, the annual number of knee and hip replacements performed in the UK could each increase from around 80,000 per year to over 1 million per year by 2035.[2] Similar trends have been reported in other high-income countries, such as the USA.[3,4]

Osteoarthritis is by far the most common indication for knee or hip replacement, and accounts for more than 95% of knee replacements and 90% of hip replacements in the UK.[5,6] In osteoarthritis, musculoskeletal tissue abnormalities first exist at a molecular but clinically silent level. This may then be followed by anatomic and physiological abnormalities, accompanied by joint pain.[7] Knee and hip replacement should, according to UK guidelines, be considered for those people with osteoarthritis for whom the condition is refractory to non-surgical treatment and whose joint-related symptoms have a substantial impact on their quality of life.[8] Persistent pain is the foremost reason for knee and hip replacement in osteoarthritis.[5,9]

Knee and hip replacement can also be undertaken for inflammatory arthropathies. The most common inflammatory arthritis in the UK is rheumatoid arthritis,[10] which accounts

for 1-2% of knee and hip replacements.[11] In rheumatoid arthritis, the preclinical phase of the disease is characterised by synovial inflammation in clinically uninflamed joints and presence of autoantibodies.[12,13] This is followed by further joint involvement, with potential joint pain, swelling, and tenderness.[14,15] As with osteoarthritis, pain is an important indication for knee and hip replacement for individuals with rheumatoid arthritis. However, maintaining or restoring function, correcting deformity or instability, and preventing or treating the failure of structures may also motivate surgery.[16,17] According to UK guidelines, knee and hip replacement should be considered for people with rheumatoid arthritis who have persistent pain, worsening joint function, progressive deformity, or persistent localised synovitis that has not responded to non-surgical management.[18]

Journeys to knee and hip replacement

In osteoarthritis

Osteoarthritis disease progression has often been assessed in terms of changes in features that can be observed radiographically, such as joint space narrowing, development of osteophytes, subchondral bone changes, and cyst formation.[19] In one community-based cohort from the UK, the baseline prevalence of radiographic knee osteoarthritis was 14%. This was defined as a Kellgren/Lawrence grade of 2 (indicating definite osteophytes and possible joint space narrowing) or more. Of those that could worsen (i.e. excluding those already in the most severe category at baseline), 33% had worsened by at least a grade after 15 years.[20] Another community-based study, from the USA, where all of the hips assessed had one or more baseline finding of radiographic osteoarthritis (including, but not limited to, definite joint space narrowing or

osteophytes, and a minimum joint space of 1.5mm or less) found that after 8 years, 65% of hips had worsened based on changes in one of a number of radiographic features (such as a decrease in minimum joint space of 0.5mm).[21] While comparisons between studies is difficult because of the variety in how progression has been measured,[22,23] findings do suggest that structural progression of osteoarthritis is not an inevitable process.

Studies of symptomatic progression in osteoarthritis have typically attempted to delineate patients into groups with similar trajectories in self-reported pain and function.[24–27] The groups identified vary across studies, both in the number of groups identified and their descriptions. However, as with structural progression, the findings from these studies of symptomatic progression suggest that osteoarthritis is not an inexorably deteriorating condition. Indeed, it has consistently been seen that some patients actually improve in their symptoms over time. In one study, for example, trajectories of knee pain were assessed using the pain subscale of the Western Ontario and McMaster Universities Arthritis Index. Individuals with, or at high risk of, knee osteoarthritis from two population cohorts from the UK and the USA were included. Based on six years of follow-up, 28% of the individuals were described as progressive, with 12% improving, and the remainder staying relatively stable (at differing levels of severity).[24] In another study, using similar data from the USA, 24% of those with knee and hip osteoarthritis were considered as having progressively worsened after 5 years, 18% had steadily improved, with the rest either stable over time or having had short-term fluctuations.[25]

While there is considerable evidence around the structural and symptomatic progression of osteoarthritis, studies have typically been detached from individuals' interactions with

the healthcare system. A small number of studies have assessed the risk of knee and hip replacement after diagnosis. In one study, individuals in the Netherlands who presented to their general practitioner (GP) with early knee or hip osteoarthritis were followed-up for up to 6 years. Of the 751 individuals who presented with knee pain, 19 (2.5%) had a knee replacement, and of the 538 with hip pain, 53 (9.8%) had a hip replacement.[28] In another study, individuals from Catalonia, Spain, with a diagnosis of knee osteoarthritis were identified in routinely collected data with follow-up of up to six years (with a median follow-up of 2.6 years). Of the 105,189 participants included, 7,512 (7.1%) had a knee replacement during their observed follow-up.[29] Aside from these studies, however, there is little evidence on the risk of knee and hip replacement after a diagnosis of knee or hip osteoarthritis.

With a lack of evidence on prognosis, a general negativity around a diagnosis of osteoarthritis has developed. The prevailing belief is that the development of osteoarthritis is an unavoidable consequence of aging and that further deterioration is inevitable.[30] One consequence of this pessimism surrounding the diagnosis of osteoarthritis is apathy or avoidance when managing people with the condition,[31] and this may help explain the limited adherence to treatment guidelines that has been observed.[32] As a result, a better understanding of prognosis after a diagnosis of osteoarthritis has been identified as a particular area of unmet need for patients.[33] Patients desire clear and understandable information.[34] An estimate of lifetime risk of knee and hip replacement would provide an answer to a patient's question "what is my risk of having a knee or hip replacement?".

In rheumatoid arthritis

In the absence of effective treatment, the progression of rheumatoid arthritis is one of steady joint erosion and damage, resulting in the destruction of both small and large joints.[15,16] As with osteoarthritis, progression in rheumatoid arthritis can be considered in both structural and symptomatic terms. Given the strong correlation between disease activity and symptoms in rheumatoid arthritis,[35] composite scores incorporating both have often been used.

In contrast with osteoarthritis, a range of effective pharmacological interventions are available for rheumatoid arthritis. As a result, rather than describing the natural history of the disease, recent research has instead assessed progression of rheumatoid arthritis in relation to alternative treatments. Moreover, the therapeutic approach to rheumatoid arthritis has evolved substantially in the last couple of decades, and is now primarily based around a 'treat to target' approach. As with other chronic conditions, such as diabetes mellitus, the aim of treatment is the restitution of a target health status.[36] This has led to studies focusing on the impact of alternative therapies on the regression of the disease to a given target. Disease remission has been defined in a way that captures both disease activity and symptoms,[37] as have other measures of improvement, such as the American College of Rheumatology 70% improvement criterion, where a 70% improvement is required to be achieved in at least five of the seven measures.[36]

As with osteoarthritis, no studies to date have estimated the lifetime risk of knee and hip replacement following a diagnosis of rheumatoid arthritis. A number of previous studies have assessed how risks of knee and hip replacement after a diagnosis of rheumatoid arthritis has changed over time, i.e. as treatment options and strategies have evolved.

Studies have found that the risk of knee and hip replacement fell between the 1980s and the 1990s and 2000s in the USA. In one study, the 10-year cumulative incidence of orthopaedic surgery fell from 27% for those diagnosed between 1980 to 1994, to 20% for those diagnosed between 1995 and 2007.[38] In another, those diagnosed between 1985 and 1995 were found to be less likely to undergo joint surgery than those diagnosed between 1955 and 1985.[39] However, a study from the UK found that while the risk of some procedures has fallen, rates of knee and hip replacement have remained similar between 1986 to 1999 and 2002 to 2012.[40] In this latter study, the 25-year cumulative incidence of major orthopaedic interventions, which included knee and hip replacement, was 22%.

These findings suggest that despite the advances in the management of rheumatoid arthritis, knee and hip replacement remain an important possibility after diagnosis. Indeed, knee and hip replacement can be expected to continue to be major outcomes in rheumatoid arthritis and a marker of treatment failure for the foreseeable future.[40]

Patient heterogeneity in paths to knee and hip replacement

There is a need to understand the lifetime risks of knee and hip replacement after diagnoses of osteoarthritis and rheumatoid arthritis. These risks can be expected to vary across individuals. Part of this variation is likely to be explained by the observable sociodemographic (e.g. age and sex) and clinical (e.g. disease status) characteristics of patients.[41]

Age at diagnosis is one characteristic that will undoubtedly influence lifetime risks through its relationship with mortality. The impact of age on the cause-specific risk of knee and hip replacement is less clear though. For example, while older age has

consistently been associated with an increased risk of structural progression in osteoarthritis,[22,23] evidence on its impact on symptomatic progression is mixed.[42] Moreover, those at an older age have been seen to have a lower risk of knee and hip replacement compared to younger patients with similar symptoms,[43] which is likely to be due to differences in willingness and fitness to undergo surgery. Sex is another characteristic that may have an important impact on the risks of knee and hip replacement. In osteoarthritis, being a woman has been associated with an increased risk of symptomatic progression,[23,42] but also with receiving surgery later in the disease course.[43] This may be due to differences in perceptions of the risks and benefits of knee and hip replacement and general preferences for surgery,[44] but also because of gender bias, with physicians more likely to recommend knee replacement to a male patient than an otherwise equivalent female patient.[45] A number of other modifiable and non-modifiable patient characteristics may also have effects on the risks of knee and hip replacement. This may be directly, with a higher body mass index (BMI), for example, associated with an increased risk of progression in knee osteoarthritis,[46] or through a relationship with mortality, as is likely to be the case for various potential comorbidities.

Consequently, there was a need to estimate the lifetime risks of knee and hip replacement after diagnoses of osteoarthritis and rheumatoid arthritis, and to assess the impact of patient heterogeneity in these risks. Such research is provided in Chapter 3 of this thesis.

Outcomes after knee and hip replacement

Patient-reported outcomes

Patient-reported pain and function are indications for knee and hip replacement, and so it follows that patient-reported pain and function after surgery should be considered a key measure of the effectiveness of surgery.[47] Numerous studies have shown that, on average, knee and hip replacement lead to sizeable improvements in patient-reported outcomes.[9,48] These gains are achieved relatively quickly, with most of the improvement from knee replacement realised after 3 months.[49] Oxford Knee Score (OKS) and Oxford Hip Score (OHS) are joint-specific patient-reported outcome measures for knee and hip replacement, respectively, with questions on both pain and function.[50–52] Scores range from 0 (worst) to 48 (best) for both measures. The minimally important change in OKS and OHS, i.e. the clinically relevant change in scores over time in a single group, has been estimated to be 9 and 11 points, respectively.[53] On average, patients far surpass these thresholds. Two studies of outcomes for knee and hip replacement in the UK found that patients improved on average by 16 points on the OKS after knee replacement and by 27 on the OHS after hip replacement.[54]

While there is little doubt that patient-reported outcomes improve markedly on average after knee and hip replacement, it is not necessarily the case that the entire change in scores is due to receipt of surgery. Part of the improvement may be due to regression to the mean, where individuals identified on the basis of poor scores improve upon later re-measurement, even without having received treatment. For example, in one analysis of observational data in which propensity scores were used to match individuals who received knee replacement with others who did not, around 33% of the post-operative

improvement for those receiving surgery was explained by regression to the mean.[55] Similarly, in one of the few randomised controlled trials comparing knee replacement with a non-surgical alternative, while the surgery group improved by 33 points in the mean score for four Knee Injury and Osteoarthritis Outcome Score subscales, the nonsurgical treatment group had a lower, but still sizeable, improvement of 16 points.[56]

Of even greater concern is that a sizeable minority of patients have a poor outcome after joint replacement surgery. In one study, where minimally important change in OKS and OHS were specified as 5 points (less than those established in the aforementioned study), 33% and 30% of patients who had knee and hip replacement failed to achieve this.[57] An alternative method for assessing change is to estimate how much of their potential change individuals attain. Using this approach, however, led to only a slightly more positive finding, with 30% and 26% of patients who had knee and hip replacement failing to achieve the minimal important change in this measure.[57] A seemingly straightforward measure of success is to assess patients' satisfaction with their outcomes. Studies have estimated 7% of patients to be dissatisfied after hip replacement and 20% to be dissatisfied after knee replacement.[58,59] While the interpretation of satisfaction is somewhat complicated given its relationship with various factors, such as pre-operative expectations which may be unrealistic,[60] it seems clear that an important minority of patients have poor outcomes following both knee and hip replacement.

While the average gains from surgery are, at least relative to baseline, well-known, the impact of patient characteristics on post-operative scores is less well established. Patients' pre-operative scores have been found to be key predictors of their post-operative scores after knee and hip replacement.[54,61–64] Individuals with lower pre-operative scores typically attain a greater change in scores after surgery, but still have a

worse overall post-operative score. In other words, individuals with a lower pre-operative score can expect to have a greater 'journey' but a worse 'destination' after surgery.[65] The full relationship between pre- and post-operative scores is not fully known, with most studies categorising pre-operative scores, assuming linearity, or using change in score as the dependent variable. Meanwhile, a range of other patient characteristics have been associated with, typically modest, differences in post-operative outcomes.[54,61,66–68] There is, however, relatively little evidence on the effects of characteristics not collected in hospital databases but rather seen in primary care records, such as BMI.

Further research was therefore warranted to better understand patient heterogeneity in patient-reported outcomes after knee and hip replacement, and findings related to this are summarised in Chapter 4 of this thesis.

Post-operative complications

Knee and hip replacement are major orthopaedic procedures and are accompanied by a risk of serious adverse events. While relatively rare, infection, venous thromboembolism, and myocardial infarction are among the most serious potential complications after surgery, with mortality also a possibility. Prosthetic joint infection is an infection involving the joint prosthesis and adjacent tissue, with most cases caused by the introduction of microorganisms at the time of surgery.[69] Venous thromboembolism includes both deep vein thrombosis, where a blood clot forms in the deep veins, and pulmonary embolism, where a clot breaks off and becomes lodged in the lungs.[70] Undergoing surgery increases the risk of venous thromboembolism, with the risk increasing further as the duration of surgery increases.[71] Cardiovascular risks also appear

to be increased after knee and hip replacement, with patients seen to have an increased risk of myocardial infarction in the immediate post-operative period.[72] Each of these conditions is potentially life-threatening.

The risks of post-operative complications after knee and hip replacement are relatively low, with most complications estimated to occur in less than one percent of patients.[73–78] While these complications are rare, there are already large numbers of patients at risk and, with the number of procedures increasing, the numbers of patients affected will likely also increase. It should be noted, however, that given the typical lack of a control group, the occurrence of various events, such as myocardial infarctions, are not necessarily all attributable to having undergone surgery.

As with patient-reported outcomes, there is a need to better understand patient heterogeneity in the risk of post-operative complications after knee and hip replacement. One area of particular interest is whether the risk of complications is similar for those with osteoarthritis and rheumatoid arthritis. Outside of surgery, rheumatoid arthritis has been linked with an increased risk of cardiovascular disease,[79–81] and, while the evidence is less conclusive, an increased general risk of venous thromboembolism[82] and a greater susceptibility for serious infections, due to both the disease itself and immunosuppressive treatments.[83] It is therefore plausible that individuals with rheumatoid arthritis may also be at a higher risk of adverse events following knee and hip replacement compared to those with osteoarthritis. A study of post-operative complications is presented in Chapter 5 of this thesis.

Revision procedures

As well as the short-term risk of post-operative complications, patients who have had a knee and hip replacement have a long-term risk of revision surgery, in which implant components are removed, added or exchanged. Prosthetic joint infection, as described above, is a major cause of early revision after knee and hip replacement.[5,6] In the longer-term, implant loosening becomes a key cause of revisions.[5,6] Revision procedures are associated with significant morbidity for individuals, with those undergoing revision surgery generally reporting worse patient-reported outcomes before and after revision procedures compared with those undergoing primary procedures.[84]

Estimates of the long-term risk of revision surgery have typically been based on Kaplan-Meier estimates for survival, where losses to follow-up are treated as noninformative. Based on this approach and using data from national registries, the risk of revision is around 28% and 42% for knee and hip replacement, respectively, at 25 years.[85,86] This approach provides estimates to a patient's question: "what is my risk of having a revision if I am still alive in 25 years?". Not all patients, however, will survive this long. Lifetime risks incorporate both risk of revision surgery and risk of mortality, therefore answering the question "what is my risk of having a revision?". One previous study estimated lifetime risk of revision after knee and hip replacement, with risks estimated to be between 4% and 8% for patients aged 70 years at their primary procedure.[87] This study assessed how the risk varied by age and gender, but did not consider other patient factors.

Consequently, as with the risk of the primary procedures, there was a need to estimate lifetime risks of revision after knee and hip replacement and, in particular, assess patient

heterogeneity in these risks. A study addressing these questions is summarised in Chapter 6.

Interventions to reduce the risk and improve the outcomes of knee and hip replacement

Economic evaluations of health interventions

Health interventions which reduce the risk of knee and hip replacement or improve outcomes after the procedures would lead to health gains. Health care resources, however, are finite and their use for one purpose necessarily means that alternative uses are foregone. Given an assumed objective of maximising population health given a fixed budget, resources should be channelled to courses of action which provide health gains greater than could be realised from the alternative uses which will be foregone.[41]

Cost-effectiveness analyses, a comparative analysis of costs measured in monetary terms and benefits measured in a unit of health, provide a means of assessing whether health interventions provide the requisite value for money to justify their adoption. The unit of health used could be condition-specific or generic, such as in terms of quality-adjusted life years (QALYs). The latter allows for comparisons across different areas of healthcare. The estimated incremental cost per QALY gained for a particular course of action can be compared against a cost-effectiveness threshold, with the cost-effectiveness threshold a proxy for opportunity cost.[88]

As well as assessing whether an established intervention is cost-effective at some given price, economic evaluations can also be used to estimate the threshold price for an intervention. A threshold price is a price at which the health benefits gained will be offset by equivalent health displaced due to opportunity cost (i.e. where the net health benefit

from funding the intervention would be zero).[89] The health technology would not be cost-effective at a higher price, while at a lower price it would be and population health would be improved. This approach has previously been proposed for use in the pricing of pharmaceuticals,[89] however its applications go beyond this. In particular, threshold prices can be used when considering the potential cost-effectiveness of innovation. Threshold prices can be estimated for some plausible range of potential improvements in the effectiveness of an intervention and these prices can then be used to consider whether innovation can likely be realised at a price which would be cost-effective.

Reducing the risk of knee and hip replacement in rheumatoid arthritis: TNFi as a first-line therapy

There are a range of pharmacological therapies currently available for rheumatoid arthritis. Guidelines recommend that therapies should be initiated as soon as diagnosis is made,[90] with a potential window of opportunity for achieving disease remission when treatment is initiated early in the disease course.[91] The general course of action is to initiate treatment with one of the available therapies and then, if successful in achieving a target of sustained remission or low disease activity and with acceptable toxicity, continue on therapy or otherwise switch to an alternative therapy and repeat the process.[90] The decision problem is thus broadly one of determining the optimal sequence of therapies to use.

The introduction of conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs) enabled better control of the symptoms of rheumatoid arthritis and a reduction in the destruction of cartilage and bone.[92] As a result, Methotrexate, a csDMARD, has become an anchor drug for rheumatoid arthritis, and is now commonly

used for first-line treatment as a monotherapy.[36] This approach achieves the American College of Rheumatology 70% improvement criterion or better response in up to 25% individuals treated.[36]

Biological DMARDs have emerged as an alternative to csDMARDs, with tumour necrosis factor inhibitors (TNFi) the first licensed agents.[14] Combination therapy of a csDMARD, such as Methotrexate, with a biological DMARD, such as a TNFi, can be expected to be even more effective than using the csDMARD alone.[93] The cost of biological DMARDs, with the price of original agents around £9,000 per year per patient,[94] has though meant that their use has been limited to later in the treatment pathway. The incremental cost per QALY gained when a TNFi is a first-line therapy in rheumatoid arthritis has been estimated to be over £60,000, far above the cost-effectiveness threshold of between £20,000 and £30,000 per QALY used by the English NHS.[95] The increased availability of biosimilar agents means that this conclusion may need to be revisited, with biosimilars a third or less of the cost of originators with comparable efficacy.[91,96] Given the results of economic evaluations to date, however, current guidelines for the English NHS restrict the use of TNFi until individuals diagnosed with rheumatoid arthritis have failed at least two csDMARDs and have a Disease Activity Score in 28 joints above 5.1.[97]

One aspect of the potential benefit from the earlier use of TNFi that has not been taken into account in economic evaluations is their potential long-term effect on the need for knee and hip replacement. Decision-analytic models used to estimate the cost-effectiveness of the use of biological DMARDs have typically not explicitly modelled the occurrence of joint replacements,[98,99] and so have not accounted for either the costs of such procedures or the morbidity associated with the need for them.

It can be expected that early initiation of TNFi could have an important effect on the long-term risks of knee and hip replacement. Clinical trials have assessed radiographic disease progression, and while in one meta-analysis the use of biological DMARDs was associated with a reduced risk of structural progression,[100] little effect was found in another.[101] Given the follow-up and sample sizes required, randomised trials have not assessed long-term effects of treatment on knee and hip replacement. Observational studies have started to emerge, but are yet to provide definitive evidence. Findings from research based on data from England, for example, is mixed. One study which assessed the impact of the introduction of the aforementioned guideline supporting the use of TNFi for those adults with the requisite disease severity and who had failed at least two csDMARDs, found it to be associated with a 34% relative reduction in the rates of knee replacement but, if anything, an increase in rates of hip replacement.[102] Meanwhile, a propensity score matched analysis of csDMARD users and TNFi users based on UK registry data found TNFi to be associated with a reduced risk of hip replacement, with this risk reduction only evident for those aged over 60, but with little effect on knee replacement risk.[103]

Estimating the potential long-term consequences of early initiation of TNFi would therefore help to inform a broader assessment of the potential benefits of this treatment strategy. Data on the number of knee and hip replacements avoided would provide an indication of health gain, given the morbidity associated with such procedures. The associated procedure costs saved, accounting for both primary and revision procedures avoided, would help to provide an estimate of future cost savings that may, in part, offset the costs of providing TNFi therapies. Informed by the findings from the initial

research presented in Chapter 3, 4, and 6 of this thesis, the impact of early initiation of TNFi is considered in Chapter 7.

Reducing the risk of knee replacement in knee osteoarthritis: bariatric surgery after diagnosis for obese individuals

Weight loss is one of the few interventions known to be effective for knee osteoarthritis,[46] due both to the increased biomechanical loading and systemic inflammation associated with being overweight or obese.[104] Randomised controlled trials have shown that weight loss strategies lead to improvements in pain and function among individuals with knee osteoarthritis.[105] While trials have had insufficient follow-up to assess the impact of weight loss interventions on the long-term risk of knee replacement, it can be hypothesised that sustained weight loss would lead to an enduring reduction in the risk of surgery, with previous studies finding that higher BMI is associated with a higher risk of knee replacement.[29,106]

To achieve a meaningful reduction in the long-term risk of knee replacement, weight loss needs to be maintained. Few interventions, however, have been found to achieve sustained long-term weight loss.[107] One of the few that has is bariatric surgery for individuals with morbid obesity. There are a number of alternative types of bariatric surgery, the most common being a gastric band (where a band is paced around the stomach), a gastric bypass (where the top part of the stomach is joined to the small intestine), and a sleeve gastrectomy (where part of the stomach is removed).[108] These procedures have each been shown to lead to rapid weight loss, which was maintained over a four year follow-up after surgery.[109] While the degree to which weight loss is

sustained longer-term is more uncertain, the reductions seen after surgery do appear to be mostly preserved.[110]

While costly to provide, bariatric surgery is considered to be a cost-effective use of limited health care resources for morbidly obese individuals, with an incremental cost per QALY gained of less than £4,000 for individuals with a BMI of 40 or more.[111] The value for money of the procedure is particularly favourable for those individuals who have Type 2 diabetes,[111] with bariatric surgery associated with resolution of the disease in 77% of patients.[112]

Bariatric surgery may, in a similar manner, have additional benefits when provided to those recently diagnosed with knee osteoarthritis, with additional health benefits from avoiding the need for a knee replacement and associated cost savings from the avoidance of orthopaedic procedures. An analysis assessing the potential effect of bariatric surgery on knee replacements is provided in Chapter 8 of this thesis, with this analysis drawing upon the findings from Chapters 3 and 6. This study complements the existing literature on the cost-effectiveness of the procedure, providing a broader picture of the benefits of bariatric surgery for this particular patient population.

Improving outcomes after knee and hip replacement: computer and robot-assisted surgery

Potential exists for innovation to lead to even better outcomes after knee and hip replacement than are currently realised. One area of technology designed to improve outcomes is that of computer and robot-assisted systems, which have been developed primarily to control component positioning and, in some cases, improve surgical precision.[113] While there is evidence that computer and robot-assisted surgery can lead

to better implant positioning, there is little evidence on their effect on long-term clinical outcomes.[114,115] The adoption of computer and robot-assisted knee and hip replacement would though require substantial investment by providers. The costs of purchasing a robotic system, for example, range from £290,000 to £2,000,000, while the cost of consumables for each procedure are around £1,400, and annual maintenance fees cost approximately £140,000.[116]

In the absence of robust data on the effectiveness of computer and robot-assisted knee and hip replacement and with costs varying substantially across systems, it is not yet possible to definitively assess whether adopting these technologies would be cost-effective. However, an early-stage economic evaluation can be performed in which threshold prices for the technologies are estimated. These threshold prices give the price at which the health benefits gained from adopting the technology will be offset by equivalent health displaced due to opportunity cost (i.e. where the net health benefit from funding the intervention would be zero).[89] Threshold prices can therefore be used to consider what health gains would need to be achieved, at a given cost, for the technologies to be considered cost-effective.

Threshold prices, estimated for a plausible range of potential improvements in the effectiveness of knee and hip replacement, are given in Chapter 9 of this thesis. This research is informed by the research on current outcomes after knee and hip replacement described in Chapters 4 and 6.

Research questions and objectives

The overarching aim in this thesis was to provide robust evidence which can be used to understand individuals' prognosis and inform decision-making concerning knee and hip replacement surgeries. This aim led to the following research objectives:

1) To assess the lifetime risk of knee replacement after a diagnosis of knee osteoarthritis; the lifetime risk of hip replacement after a diagnosis of hip osteoarthritis; and the lifetime risks of knee and hip replacement after a diagnosis of rheumatoid arthritis.
2) To assess the impact of patient characteristics on patient-reported outcomes after knee and hip replacement.
3) To assess the impact of patient characteristics on the risk of post-operative complications after knee and hip replacement.
4) To estimate the lifetime risks of revision after knee and hip replacement, assessing the impact of patient characteristics on these risks.

The findings from these studies helped to inform three further research objectives:

5) To estimate the number of procedures avoided and associated costs saved for potential risk reductions for knee and hip replacement from the use of TNFi as a first-line therapy in rheumatoid arthritis.
6) To estimate the number of knee replacements avoided, the associated procedure costs saved, and the incremental cost per knee replacement avoided from bariatric surgery performed shortly after diagnosis of knee osteoarthritis.
7) To estimate threshold prices for computer and robot-assisted knee and hip replacement.

Thesis structure

The table below shows the content covered in this and each of the following chapters.

Table 1.1: Thesis structure and outline

Chapter	Title	Content
1	Introduction	The context for the studies is provided and research questions are summarised.
2	Methods and data	The data sources and analytic methods used across the entire thesis are described.
3	Lifetime risk of knee and hip replacement following a diagnosis of osteoarthritis or rheumatoid arthritis	The lifetime risks of knee replacement after a diagnosis of knee osteoarthritis, hip replacement after a diagnosis of hip osteoarthritis, and knee and hip replacement after a diagnosis of rheumatoid arthritis are summarised.
4	Patient-reported outcome measures following knee and hip replacement	Patient-reported outcome measures before and after knee and hip replacement are assessed.

Chapter	Title	Content
5	Adverse events following joint replacement	Risks of post-operative complications after knee and hip replacement are described.
6	Lifetime risk of revision after knee and hip replacement	Lifetime risks of revision procedures after knee and hip replacement are summarised.
7	Potential effect from use of TNFi as a first-line therapy after a diagnosis of rheumatoid arthritis on knee and hip replacement	The procedures avoided and associated cost-savings are given for potential risk reductions due to the use of TNFi as a first-line therapy.
8	A cost-effectiveness analysis of bariatric surgery after a diagnosis of knee osteoarthritis	Procedures avoided, associated cost-savings, and the incremental cost per knee replacement avoided are summarised for bariatric surgery after diagnosis of knee replacement.

Chapter	Title	Content
9	Threshold prices for computer and robot-assisted knee and hip replacement	Threshold prices for potential improvements in outcomes after knee and hip replacement attained from the use of computer or robot-assisted surgery are detailed.
10	Discussion	The implications of the findings for current practice and future research are considered, along with a brief conclusion.

Associated publications

The research presented in this thesis has been reported in the publications detailed below.

Publications

- **E. Burn**, D.W. Murray, G.A. Hawker, et al (2019). Lifetime risk of knee and hip replacement following a GP diagnosis of osteoarthritis: a real-world cohort study. *Osteoarthritis and Cartilage* doi:10.1016/j.joca.2019.06.004.
- **E. Burn**, C. J. Edwards, D.W. Murray, et al (2019). Lifetime risk of knee and hip replacement following a diagnosis of RA: findings from a cohort of 13 961 patients from England. *Rheumatology* doi:10.1093/rheumatology/kez223.

- **E. Burn**, C.J. Edwards, D.W Murray, et al (2019). The effect of rheumatoid arthritis on patient-reported outcomes following knee and hip replacement: evidence from routinely collected data. *Rheumatology*, **58**, 1016-1024 doi:10.1093/rheumatology/key409.
- **E Burn**, C. Edwards, D Murray, et al (2018). The impact of rheumatoid arthritis on the risk of adverse events following joint replacement: a real-world cohort study. *Clinical Epidemiology*, Volume 10, 697-704 doi:10.2147/clep.s160347.
- **E. Burn**, C.J. Edwards, D.W. Murray, et al (2019). The impact of BMI and smoking on risk of revision following knee and hip replacement surgery: evidence from routinely collected data. *Osteoarthritis and Cartilage* doi:10.1016/j.joca.2019.05.012.
- **E. Burn**, D.W. Murray, R. Pinedo-Villanueva, et al (2019). Knee and hip replacements and the risk of revision. The Lancet, doi:10.1016/S0140-6736(19)31780-5
- **E. Burn**, C.J. Edwards, D.W. Murray, et al (2018). Trends and determinants of length of stay and hospital reimbursement following knee and hip replacement: evidence from linked primary care and NHS hospital records from 1997 to 2014. BMJ Open, 8, e019146 doi:10.1136/bmjopen-2017-019146.
- **E. Burn**, D. Prieto-Alhambra, T.W. Hamilton, et al. (2019) Threshold prices for computer and robot-assisted knee and hip replacements in the English NHS. Value in Health (in press)

Publications in preparation

- **E. Burn**, S. Hawley, D.W. Murray, et al (2019) Biologic therapies in rheumatoid arthritis: a modelling study of their potential long-term effect on knee and hip replacement.
- **E. Burn**, D.W. Murray, D. Prieto-Alhambra, et al (2019). Additional benefits from bariatric surgery for individuals recently diagnosed with knee osteoarthritis.

2. METHODS AND DATA

Chapter summary

In this chapter I describe the data sources and analytic methods used to address the research questions summarised in Chapter 1.

Linked primary care and hospital data from England and Spain informed the analyses of lifetime risks of knee and hip replacement after a diagnosis of osteoarthritis or rheumatoid arthritis, and risks of post-operative complications and lifetime risks of revision after knee and hip replacement. An additional dataset of routinely collected patient-reported outcome measures from England, linked to primary care and hospital data, informed analyses of patient-reported outcomes after the procedures.

Observed outcome scores and events were summarised. Ordinary least squares estimation (linear regression) and survival analysis were then used to assess the effects of explanatory factors on outcomes of interest. Decision-analytic modelling was used to extrapolate parametric survival models to estimate lifetime risks, and to provide the framework for assessing interventions which may reduce the need for or improve the outcomes of knee and hip replacement.

Data

Settings

Routinely collected healthcare data from the English National Health System (NHS) and *Servei Català de Salut* (CatSalut), the Catalan Public Health system, were used to inform the analyses presented in this thesis. The national health systems of Spain and the United Kingdom (UK) provide universal access to comprehensive health services which are free at the point of use and financed by general taxation. Both systems are somewhat devolved. In the UK, the English NHS organises health care services in England.[117] Meanwhile in Spain, CatSalut has primary authority over the organisation of health services within Catalonia and is one of 17 regional health administrations for autonomous communities of Spain.[118,119] In both healthcare systems, GPs act as gatekeepers to care. Diagnosis of osteoarthritis is typically made by GPs, with non-operative management of the condition then managed principally within primary care. Meanwhile, a diagnosis of rheumatoid arthritis is generally made by a specialist rheumatologist after a referral from a GP, with management then provided by a multidisciplinary team. For both osteoarthritis and rheumatoid arthritis, referral to an orthopaedic surgeon for an assessment for knee or hip replacement may be made. Knee and hip replacement will then, if warranted, be performed after an individual spends some time on a waiting list.

Data from the English NHS

The Clinical Practice Research Datalink (CPRD) is a large, representative database of anonymised records from general practices across the United Kingdom. CPRD contains a

broad range of data on patient demographics, prescriptions, clinical events (both symptoms and diagnoses), preventive care provided, tests, immunisations, specialist referrals, hospital admissions and their major outcomes, and details relating to death.[120] CPRD operates on a practice level with data from all patients registered with a participating practice available for research, except for those individuals who have requested to opt out of data sharing.[120] CPRD contains medical records and demographic details for around 7% of the UK population. Those individuals included are broadly representative of the general population in terms of age, gender, ethnicity, and BMI.[120–122] However, the practices included in CPRD may not be representative of practices in the UK in terms of geography and size.[120]

Hospital Episode Statistics (HES) Admitted Patient Care (APC) data are collected on all inpatient admissions to English NHS hospitals and admissions to independent sector hospitals paid for by the NHS, with hospital admissions covering any secondary care activity that requires a hospital bed.[123] HES APC contains information on diagnoses, procedures, dates of admission and discharge, and various geographical variables mapped from a patient's postcode. Admissions captured in HES APC are typically described in terms of finished consultant episodes, which are the continuous periods of care under one consultant, and spells, which are uninterrupted inpatient stays at one hospital.[124] Admissions can also be described in terms of continuous inpatient spells, which are continuous hospital stays and which may be made up of one or more finished consultant episodes (i.e. allowing for a patient to be transferred to a different hospital).

Deprivation figures from the Index of Multiple Deprivation (IMD) data produced by the Department for Communities and Local government are also reported in HES APC.[125] The IMD is an official measure of relative deprivation for small areas in England. Every small

area is ranked from 1 (most deprived) to 32,844 (least deprived), on the basis of income deprivation, employment deprivation, education, skills and training deprivation, health deprivation and disability, crime, barriers to housing and services, and living environment deprivation. These domains are combined using differing weights chosen on the importance in describing deprivation and their robustness.

The Office for National Statistic (ONS) mortality data contains information related to a person's death taken from the death certificate for all deaths registered in England and Wales. Deaths are recorded as registered which may differ to their occurrence, for example due to the need for a coroner's investigation (only when a coroner's investigation is completed can a death be registered).[126]

Linked data from CPRD and HES APC (CPRD-HES APC), which also included information from IMD and ONS, were used for analyses of risk of knee and hip replacement after a diagnosis of rheumatoid arthritis and post-operative complications and risk of revision after knee and hip replacement. This linked dataset covered 1997 to 2014. The use of CPRD-HES APC data meant that information from individuals' broad health care utilisation could be examined.

A further linkage to a dataset of routinely collected patient-reported outcome measures (PROMs) was also made. NHS PROMs is a dataset of patient-reported outcomes collected originally for four elective procedures, including knee and hip replacement.[127] With national data collection of PROMs starting in 2009, the linked dataset covered 2009 to 2014. PROMs data consist of two questionnaires completed by individuals undergoing surgery. The first questionnaire is completed during the period between when a patient has been passed fit for surgery and the surgery is performed. The second questionnaire is completed approximately six months following surgery. All providers of NHS-funded knee

and hip replacement in England are expected to invite patients to complete these questionnaires.[127] Patients are asked to fill out the Oxford Knee Score (OKS) and EuroQol 5-dimension 3-level (EQ-5D-3L) questionnaires before and after knee replacement, and Oxford Hip Score (OHS) and EQ-5D-3L before and after hip replacement.[52,128] These CPRD-HES APC-HES PROMs data informed the analyses of patient-reported outcomes after knee and hip replacement.

Data from CatSalut

The *Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària* (SIDIAP) is a database of anonymised records from general practices across Catalonia, Spain. SIDIAP contains patient records of 80% of the Catalan population and is highly representative of the population in terms of geographical, age, and sex distributions.[129] Similar to CPRD, SIDIAP contains data on patient demographics, diagnoses, treatments, lifestyle variables, and laboratory tests.[129] The *Conjunt Mínim Bàsic de Dades* (CMBD) is a database which contains details of admissions to every public and private hospital of Catalonia. As with HES APC, this database contains information on patient demographics, diagnoses, procedures, and the details of admission and discharge.[130] SIDIAP and CMBD data were linked, and SIDIAP-CMBD data informed an analysis of the risk of knee and hip replacement after a diagnosis of osteoarthritis. This linked dataset covered 2006 to 2015.

Study cohorts and index events

Study cohorts informing particular analyses are described below in Table 2.1. Index events were either diagnoses or procedures of interest.

For analyses of risk of knee and hip replacement after diagnosis of osteoarthritis, an index diagnosis of knee or hip osteoarthritis was identified in SIDIAP-CMBD. These diagnoses have previously been validated, with a sensitivity of 94% and specificity of 71% when compared to self-reported physician diagnosed osteoarthritis.[131] A further validation study, where using free text records were reviewed, confirmed the good quality of osteoarthritis diagnosis in SIDIAP.[132] For analyses of risk of knee and hip replacement after diagnosis of rheumatoid arthritis, the index diagnosis was identified in CPRD-HES APC. Diagnosis of rheumatoid arthritis has previously been validated for CPRD, with sensitivity and specificity found to be above 80%.[133] Those with an index diagnosis of osteoarthritis in SIDIAP were required to be aged 50 years or older at their index date (date of diagnosis), and have no prior diagnosis of inflammatory arthritis. Meanwhile, those with an index diagnosis of rheumatoid arthritis in CPRD were required to be aged 40 years or older at their index date. For both cohorts, individuals were excluded from the study if they had a history of knee or hip replacement prior to their index date.

For analyses of post-operative complications and revision surgery after knee and hip replacement, index procedures were identified in CPRD-HES APC. Procedures were based on the presence of relevant OPCS codes in hospital records.[134] For knee replacement, only individuals with a prior diagnosis of knee osteoarthritis or rheumatoid arthritis were included. A diagnosis of rheumatoid arthritis took precedence over one of knee osteoarthritis (i.e. taken as the index diagnosis). Laterality is not well recorded in the datasets. Individuals with a bilateral procedure, where both the left and right knee were replaced concurrently, were therefore excluded and only the first occurrence of a procedure for an individual was included in the analysis. Analogous inclusion criteria

were specified for hip replacement. The same individual could contribute to both the knee and hip replacement cohorts as these analyses were performed independently.

For analyses of patient-reported outcomes after knee and hip replacement, CPRD-HES APC-HES PROMs data were used. The same inclusion criteria as for post-operative complications and revision surgery was specified. In addition, study participants were required to have complete scores recorded for OKS/ OHS and EQ-5D-3L before and after surgery. Patterns of missing patient-reported outcomes are shown in Appendix Figure A.1 and Appendix Figure A.2, with the characteristics of those with and without missing data summarised in Appendix Table A.1. With the characteristics of those with and without missing data broadly similar, the complete case approach was used as imputation of outcome variables might only add noise to the estimates when data is missing completely at random.[135,136]

Table 2.1: Study cohorts

Study cohort	**Index event**	**Outcome of interest**	**Dataset**
Knee osteoarthritis	Knee osteoarthritis diagnosis	Knee replacement	SIDIAP-CMBD
Hip osteoarthritis	Hip osteoarthritis diagnosis	Hip replacement	SIDIAP-CMBD
Rheumatoid arthritis	Rheumatoid arthritis diagnosis	Knee replacement	CPRD-HES APC
Rheumatoid arthritis	Rheumatoid arthritis diagnosis	Hip replacement	CPRD-HES APC

Study cohort	Index event	Outcome of interest	Dataset
Knee replacement	Knee replacement procedure	Post-operative complications	CPRD-HES APC
Knee replacement	Knee replacement procedure	Revision surgery	CPRD-HES APC
Knee replacement	Knee replacement procedure	OKS/ EQ-5D-3L	CPRD-HES APC-HES PROMs
Hip replacement	Hip replacement procedure	Post-operative complications	CPRD-HES APC
Hip replacement	Hip replacement procedure	Revision surgery	CPRD-HES APC
Hip replacement	Hip replacement procedure	OHS/ EQ-5D-3L	CPRD-HES APC-HES PROMs

OKS: Oxford Knee Score, OHS: Oxford hip score, EQ-5D-3L: EuroQol 5-dimension 3-level, CPRD: Clinical Practice Research Datalink, HES APC: Hospital Episode Statistics Admitted Patient Care, PROMs: Patient Reported Outcome Measures, SIDIAP: *Sistema d'Informació pel Desenvolupament de la Investigació a l'Atenció Primària*, CMBD: *Conjunt Mínim Bàsic de Dades.*

Patient characteristics at time of index events

Patient characteristics were derived relative to the particular index events of interest. Age and sex were extracted from primary care data. Comorbidities were summarised using the Charlson score, a summary measure of comorbidity which classifies individuals according to their disease burden and includes conditions such as heart disease cancer,

liver disease, and cancer. Lifestyle factors, such as smoking and BMI, are not included in the calculation of the score. The original specification of the Charlson score was used for comorbidities at time of index diagnoses (identified using primary care records), while the Royal College of Surgeons Charlson score was used at time of index procedures (identified using hospital records). The latter scoring algorithm was developed for calculating the Charlson score in HES APC records, while avoiding the misclassification of complications that would occur if a simple count of diagnoses codes for a particular hospitalisation was performed.[137,138] The Charlson score was categorised as 0, 1, 2, or 3+ for the index diagnosis of osteoarthritis and index procedures, but was categorised as 0 or 1+ for the index diagnosis of rheumatoid arthritis as few study participants had multiple comorbidities. A higher Charlson score indicated a higher degree of comorbidity. Socioeconomic status for the index diagnosis of osteoarthritis and index procedures was measured in terms of IMD, with individuals grouped using quintiles (where a value of 1 indicated being in the least deprived group and 5 the most deprived group). Socioeconomic status for the index diagnosis of rheumatoid arthritis was summarised using *Mortalidad en áreas pequeñas Españolas y Desigualdades Socioeconómicas y Ambientales* (MEDEA), a census-based indicator that has a distinct category for those living in rural areas.[139] Participants were grouped using quintiles (where a value of 1 indicated being in the least deprived quintile and 5 in the most deprived group), or as living in a rural area.

The most recent record of BMI and smoking status (non-smoker, ex-smoker, or current smoker) before index events were identified and included only if they had been observed within a year of the index event. BMI was categorised following the World Health Organisation categories: normal or underweight (BMI <25), overweight (≥25 and <30),

obese class I (≥30 and <35), obese class II (≥35 and <40), and obese class III (≥40). Where categorisation was used for other continuous variables (primarily for summarising observed data), groups were defined using quartiles of the distributions.

Outcome events

Outcome events that were procedures were identified in a similar manner to index events. Knee and hip replacement (as outcomes relative to diagnoses of osteoarthritis or rheumatoid arthritis) were identified in SIDIAP-CMBD and CPRD-HES APC. Knee and hip revision (as outcomes relative to knee and hip replacement) were identified in CPRD-HES APC. As with primary procedures in CPRD-HES APC, revisions were identified based on the presence of relevant OPCS codes in hospital records.[134] Venous thromboembolism and myocardial infarction were identified on the basis of the primary diagnosis codes from hospital episodes. Prosthetic joint infection was identified by the primary diagnosis of a hospital episode and a subsequent operation code for either debridement, antibiotics, irrigation and retention of the prosthesis, or revision within a year of that episode.[140]

Outcome scores

Post-operative patient-reported outcome scores from questionnaires recorded in CPRD-HES APC-HES PROMs were also outcomes of interest after knee and hip replacement. The overall OKS and OHS scores, which range from 0 (worst) to 48 (best),[52] and the EQ-5D-3L derived health utility index, which ranges from -0.59 (worst) to 1 (best) after applying preference-based utility weights obtained from the general UK population, were extracted.[141]

Pre- and post-operative values for these scores and the change in scores were considered, along with the percentage of potential change (PoPC) achieved. PoPC summarises how much an individual improved (or worsened) relative to how much they potentially could have improved (or worsened), and ranges between -100% (i.e. an individual has worsened to the lowest possible score) and 100% (i.e. an individual has improved to the best possible score), with a value of 0% indicating no change. PoPC was developed for expressing improvement after knee and hip replacement.[57] It offers an alternative to absolute change in scores, with comparisons of absolute change potentially misleading as they do not differentiate for the baseline position of patients. For example, a patient who improved in OKS from 44 to 48 (the maximum possible score) would have the same absolute change as a patient who improved from 10 to 14. However, the former would have a PoPC of 100% (i.e. they improved to the best possible score), whereas the latter would have a PoPC of 11% (i.e. they reached 11% of their potential improvement).

In addition to considering the EQ-5D-3L index, changes between pre- and post-operative time points in individual dimensions and the overall profile were summarised, with each dimension either better, unchanged, or worse following surgery. The overall EQ-5D-3L profile was either better (i.e. at least one dimension had improved, with none worse), had a mixed change (i.e. some dimensions had improved but others had worsened), had no change, or was worse (i.e. at least one dimension had worsened, with none improving).

Statistical methods

Ordinary least squares estimation

Ordinary least squares estimation (linear regression) provides a framework for describing the effect of explanatory factors of interest on a continuous outcome of interest. In this thesis, ordinary least squares estimation was used to assess the impact of patient characteristics at time of surgery on post-operative patient-reported outcomes (OKS, OHS, and EQ-5D-3L index).

In a simple linear regression, the outcome variable is predicted on the basis of a single explanatory variable, with an assumption that there is an approximately linear relationship between the two. Coefficients for the intercept and slope are typically estimated by minimising the sum of the squares of the residuals (the difference between the actual value of the outcome variable in any observation and the fitted value given by the regression line).[142,143] This simple linear regression can be extended to incorporate multiple variables, with slope coefficients estimated for each.[142] Each slope coefficient gives the estimated effect on the outcome, holding all of the other explanatory variables fixed. A non-linear relationship between an explanatory factor and the outcome variable can also be incorporated in a variety of ways. One approach, which is used in this thesis, is to use restricted cubic splines, which allow for a flexible relationship.[144] Restricted cubic splines were used when their use led to a reduction in the Bayesian information criterion relative to that of a model with a linear relationship fitted, and to decide on how many knots to include if a non-linear relationship was incorporated.[144]

The outcomes of interest in the analyses were post-operative scores with pre-operative scores included as an explanatory variable, rather than using change in scores as the

outcome variable. This allows for potential non-linearity between pre- and post-operative scores to be incorporated. Age, gender, Charlson score, socioeconomic status (as measured by IMD quintile), BMI, and smoking status were also included as explanatory variables. Both univariable and multivariable models were estimated.

Only individuals who completed both pre- and post-operative questionnaires were included in the analysis. There were missing data for three of the explanatory variables included in these analyses: IMD, BMI and smoking status. While IMD was missing for only two participants, BMI and smoking status were missing in between 39% to 58% of study participants. Multiple imputation was used to account for these missing values, with the assumption that data were missing at random (where the probability of data being missing does not depend on the unobserved data, conditional on the observed data).[136] Explanatory variables and outcomes were used to impute 50 datasets, with pooled model coefficients and corresponding 95% confidence intervals calculated using Rubin's rules.

Survival analysis

Survival data measures the time to some event of interest, where the response variable (survival time) is the time until that event occurs.[144] In this thesis, survival data from SIDIAP-CMBD informed analyses of the risk of knee and hip replacement after a diagnosis of osteoarthritis. Survival data from CPRD-HES APC informed analyses of the risk of knee and hip replacement after a diagnosis of rheumatoid arthritis, post-operative complications after knee and hip replacement, and the risk of revision after knee and hip replacement.

The defining feature of survival data is that responses are times and larger observations take longer times to observe than smaller ones.[145] With time observed sequentially, data are typically censored with the event of interest not observed for all study participants. The study follow-up may end before the event occurs (administrative censoring) or an individual may leave the study before they experience the event (loss to follow-up). In both cases, if an individual does not have the event during their observed follow-up, their time to event is described as (right) censored.[146]

Survival distributions are usually described in terms of the survival function and the hazard function.[146] The survival function gives the probability that the event will occur after some given time or, in other words, the probability that the subject will survive at least until that time. The hazard function gives the probability that the event will occur in a small interval around a certain time, given that the event has not occurred before this time.[144]

The main focus in survival analysis is in comparing the survival patterns of different groups. There are two broad approaches typically used for this: the semi-parametric Cox model, and parametric models. The key difference between them is that the Cox model does not require an assumption about the underlying distribution for the event of interest, whereas parametric models do.[147] While this added requirement for parametric models introduces a further source of uncertainty, it allows for the extrapolation of survival time.[144] Various distributions can be used in parametric models. Under an exponential distribution the hazard is expected to be constant over time, while under Weibull and log-normal distributions the hazard is expected to either be declining or increasing as time passes. A spline-based distribution allows for a more complex relationship, such as a ‘bathtub’ shape where the hazard first decreases but later

increases, with the logarithm of the baseline hazard function modelled as a natural cubic spline function of log-time.[148] The choice of parametric model was based on intercept-only model fit to the observed data, assessed using the Akaike information criterion, and, if required, the plausibility of extrapolation.[149]

The effects of explanatory factors are, depending on the distribution used, described in terms of hazard ratios or acceleration factors. Proportional hazard models relate explanatory factors to the hazard function of the outcome of interest, with factors having a relative effect on the hazard. While spline-based parametric models can be estimated on different scales, for the purposes of the analyses presented in this thesis, they were also specified as proportional hazard models.[150] For both, hazard ratios are used to describe the relative change in the hazard associated with a one-unit increase in the explanatory factor.[151] The other parametric models described above were accelerated failure time models, where explanatory factors are related to survival time and shift the survival curve forward or backward.[145] Acceleration factors are used to describe the relative effect on survival time associated with a one-unit increase in the explanatory factor.[144] While a hazard ratio over one implies that an explanatory factor is harmful to survival, an acceleration factor over one implies it is beneficial for survival. As with ordinary least squares estimation, non-linear relationships between explanatory factors and the outcome of interest can be incorporated. As restricted cubic splines were not implemented in the software used for parametric survival modelling, polynomials were used to incorporate non-linearity if merited. Bayesian information criterion was also used to decide on whether to incorporate non-linearity and, if so, what degree of polynomial to include.

For some events of interest, their occurrence can be precluded by another event.[151] This is a situation of competing risks. In the absence of competing risks, the risk set is specified as the group of individuals that have not experienced the outcome at a given moment in time and therefore are at risk for the event. Where a competing risks exist, individuals who have a competing event can be removed from all later risk sets for the event of interest.[147] This then allows one to talk in terms of the cause-specific risks of each event, where no assumptions around the relationship between the competing outcomes is required and models can be specified for each risk separately.[147]

In the analyses presented in this thesis, the cumulative incidence of events of interest are described. Aside from mortality after knee and hip replacement, mortality was accounted for as a competing risk for the events of interest. Due to relatively few events for post-operative complications, no further statistical modelling was performed. Parametric models were estimated for risks of knee and hip replacement after a diagnosis of osteoarthritis and rheumatoid arthritis, and risks of revision after knee and hip replacement. These models were estimated for the cause-specific hazards of these events and the competing risk of mortality. Based on available data, follow-up was up to 9 years in the analysis of knee and hip replacement after a diagnosis of osteoarthritis, 15 years in the analysis of knee and hip replacement after a diagnosis of rheumatoid arthritis, and 10 years for the risk of revision after knee and hip replacement. Individuals were censored before this if they had an event of interest or the competing risk. In addition, for the risk of revision after knee and hip replacement, patients were also censored if they had a second index event, i.e. another knee or hip replacement, as laterality was not available and any subsequent revision procedures could not be attributed to a particular side. Age, gender, Charlson score, socioeconomic status (as

measured by IMD quintile or MEDEA depending on the dataset), BMI, and smoking status were also included as explanatory variables. Both univariable and multivariable models were estimated. As with ordinary least squares estimation models, missing data were addressed using multiple imputation and estimated hazard ratios/ acceleration factors with corresponding 95% confidence intervals calculated using Rubin's rules.

Decision-analytic modelling

Decision-analytic models were used to estimate lifetime risk of knee and hip replacement after a diagnosis of osteoarthritis, and lifetime risk of revision after knee and hip replacement. They were also used to assess the consequences from potential risk reductions for knee and hip replacement from the use of TNFi as a first-line therapy in rheumatoid arthritis and from bariatric surgery performed shortly after diagnosis of knee osteoarthritis. They were then used to estimate threshold prices for computer and robot-assisted knee and hip replacement.

Decision-analytic modelling provides a framework for synthesising data from multiple sources and extrapolating beyond the observed time horizon. State-based Markov models were used for the analyses presented in this thesis. In such models, a cohort of individuals are assumed to be in a particular health state at any given moment in time, with events represented as transitions from one state to another and with transitions occurring as time progresses in discrete increments (in these analyses, cycles were yearly). The models are memoryless, with the behaviour of the process subsequent to any cycle dependent only on its description in that cycle.[152,153]

Estimating lifetime risks of knee and hip replacement after a diagnosis of osteoarthritis or rheumatoid arthritis, and revision after a knee or hip replacement

The state-based Markov models used to estimate lifetime risk of knee and hip replacement after a diagnosis of knee or hip osteoarthritis or rheumatoid arthritis are shown in Figure 2.1, while the models used to estimate lifetime risk of revision after knee or hip replacement are shown in Figure 2.2. These models had three states. For assessing lifetime risk of knee replacement after a diagnosis of knee osteoarthritis, for example, the cohort began as being diagnosed with knee osteoarthritis and then they either remained in the *knee osteoarthritis* state, or progressed to either the *knee replacement* or *death* state as time progressed in yearly cycles. Analogous model structures were used for estimating the other lifetime risks of interest.

These models required estimates of two transition probabilities: to the event of interest (e.g. from *knee osteoarthritis* state to *knee replacement*), and to death. The transition probabilities to the event of interest were based exclusively on the parametric survival models estimated for these events. Models were extrapolated beyond the observed data to the full time-horizon of the model, with models running up until age reached 100. Transition probabilities for mortality were based on relevant parametric models over the time included in observed follow-up, after which risks were assumed to revert to estimates based on age- and sex-specific life tables. Life tables from Spain were used for the risk of knee and hip replacement after a diagnosis of osteoarthritis, with UK life tables used for the other risks.[154,155]

Models were first run for representative patient profiles, with explanatory factors used in the parametric models set at their average values (median if continuous and mode if categorical). The partial effect of characteristics on lifetime risks was then assessed by

varying the value of these characteristics while holding the rest fixed at their average. Transition probabilities from parametric models were based on the predicted survival functions for the given patient profile. As estimates were similar across multiply imputed datasets, lifetime risks were estimated using only the models developed on the first imputed dataset to reduce computational time. Parameter uncertainty was incorporated using 1,000 bootstrapped models. Cumulative incidence of the event of interest was given by the proportion of patients who transitioned to that event over time, while lifetime risk was given by the proportion of the cohort who transitioned to the event over the duration of the model.

Figure 2.1: State-based Markov models for estimating lifetime risks of a) knee replacement after a diagnosis of knee osteoarthritis, b) hip replacement after a diagnosis of hip osteoarthritis, c) knee replacement after a diagnosis of rheumatoid arthritis, and d) hip replacement after a diagnosis of rheumatoid arthritis.

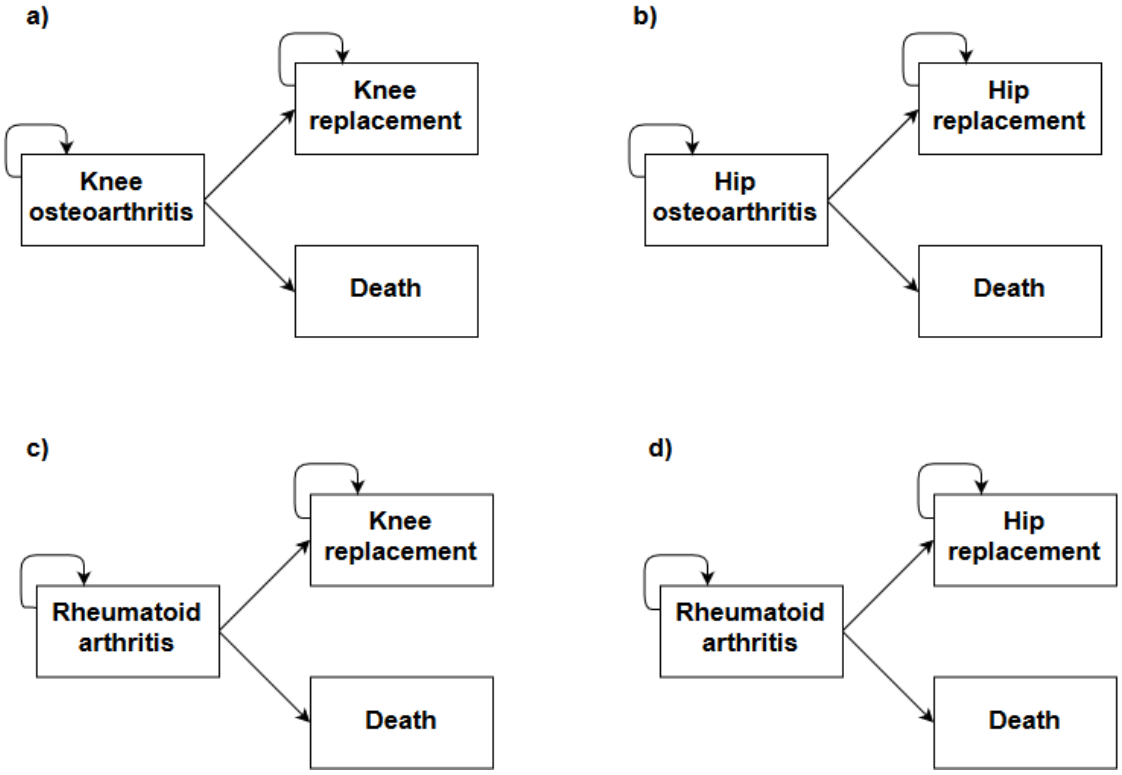
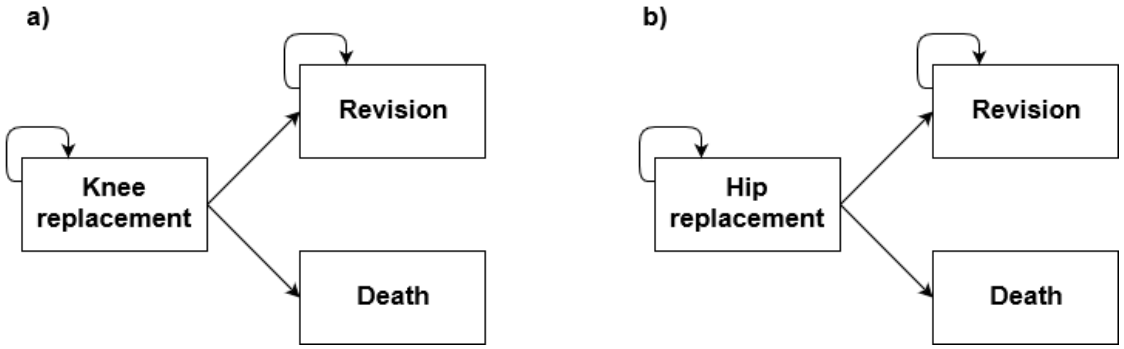


Figure 2.2: State-based Markov models for estimating lifetime risk of a) revision after a knee replacement, and b) revision after a hip replacement.



Estimating the potential impact of use of TNFi as a first-line therapy in rheumatoid arthritis on knee and hip replacements and associated procedure costs

The state-based Markov models used to estimate the potential impact of use of TNFi as a first-line therapy, relative to current practice (where csDMARDs are used as the first-line therapy), on knee and hip replacement and associated procedure costs are shown in Figure 2.3. Both the initial risk of undergoing a primary procedure and the subsequent risk of revision were incorporated. Individuals started by having a diagnosis of rheumatoid arthritis and were then at risk of transitioning from this diagnosis state to having a knee (or hip) replacement. After a knee (or hip) replacement, they were then at risk of revision. In all states, they also had a risk of death.

Estimates of transition probabilities to knee (or hip) replacement after a diagnosis of rheumatoid arthritis under current practice were based on the analysis of lifetime risk of knee and hip replacement. Transition probabilities for knee (or hip) replacement were re-estimated for a range of relative risks expressing the potential relative effects of using TNFi. For the base case analysis, it was assumed that any treatment effects would be maintained into the future. Given the inherent uncertainty around this assumption, treatment effects were assumed to last for only five years in a sensitivity analysis.

Transition probabilities for risk of revision after knee/ hip replacement were re-estimated using intercept-only exponential survival models (to facilitate the use of a state-based Markov model), which provided good approximations to the more complex models used in estimating the lifetime risk of revision. Risks of mortality were also drawn from the analysis of lifetime risks of knee and hip replacement.

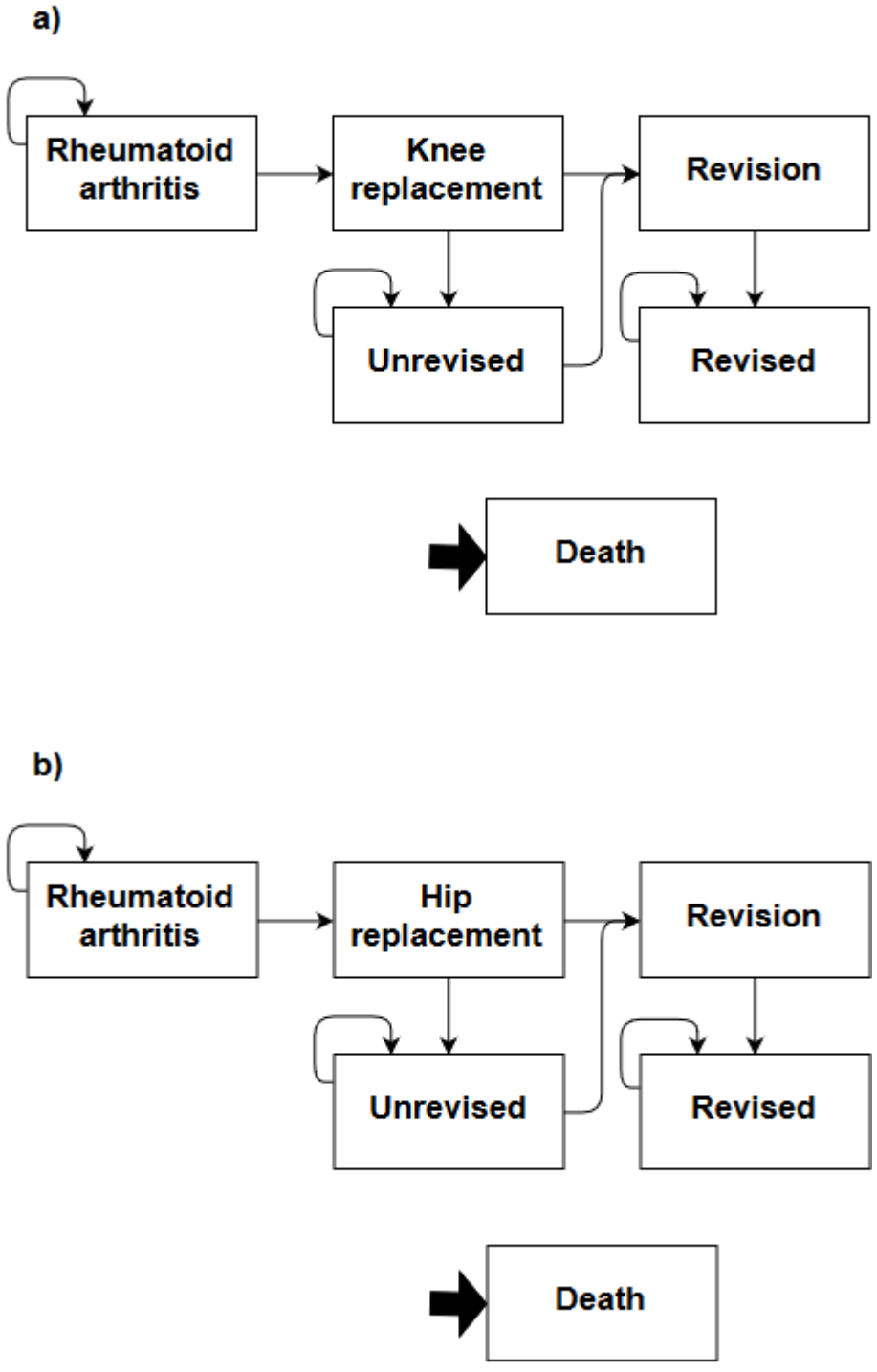
The costs of knee and hip replacements and subsequent revision procedures were based on the same study population that was used to assess lifetime risks of revision. Costs

could have been estimated for the finished consultant episode (the continuous periods of care under one consultant) in which the procedure was undertaken, or the hospital spell (the uninterrupted inpatient stay at one hospital) which included the finished consultant episode in which the procedure was undertaken.[124] Spell-level costs were estimated for the purposes of this thesis so as to capture the cost of the overall inpatient stay associated with the procedures. Healthcare resource groups were estimated for individual's hospital spells, with these grouping clinically similar treatments using common levels of healthcare resources. Spell-level reference costs were then applied at 2015/16 levels. These reference costs represent the cost (including the direct, indirect and overhead costs) of providing one unit of care in a given financial year.[124]

In line with guidelines, costs were discounted by 3.5% annually.[156] Generalised linear models with a gamma distribution and a log-link function were used to estimate the effect of patient characteristics on costs.[157] Costs were predicted based on the patient profile and assigned to the relevant model states.

Models were first run for 1,000 representative individuals with the average characteristics of those diagnosed with rheumatoid arthritis. The number of procedures and associated costs under the alternative strategies were estimated for these cohorts. The partial effect of age and sex was then estimated by re-running models for varying values of age and sex, while other explanatory factors were held fixed at their average. Uncertainty was captured using bootstrapping for the estimated models, as in the analyses of lifetime risks.

Figure 2.3: State-based Markov models for estimating cost savings associated with the use of TNFi as a first-line therapy in rheumatoid arthritis with respect to a) knee replacement, and b) hip replacement



A cost-effectiveness analysis of bariatric surgery shortly after a diagnosis of knee osteoarthritis

A similar model to that used to assess the potential impact of TNFi in rheumatoid arthritis was used for assessing the incremental cost per knee replacement avoided for bariatric surgery after diagnosis of knee osteoarthritis, as shown in Figure 2.4. Individuals started by having a diagnosis of knee osteoarthritis and were then at risk of transitioning from this diagnosis state to knee replacement. After a knee replacement, they were then at risk of revision. In all states, they also had a risk of death.

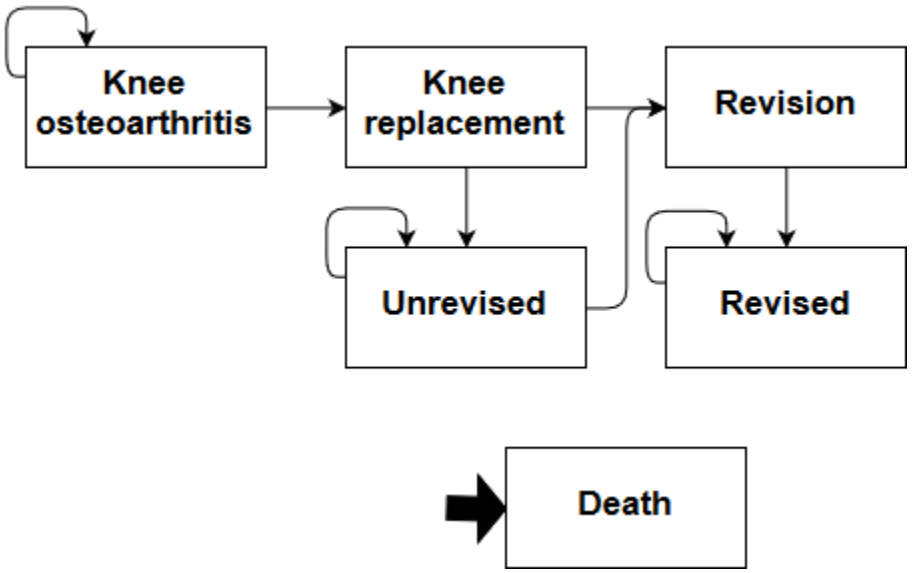
Estimates of transition probabilities to knee replacement after a diagnosis of knee osteoarthritis without bariatric surgery were based on current practice, as estimated in the analysis of lifetime risk of knee replacement. Bariatric surgery was assumed to be undertaken in the year after diagnosis of knee osteoarthritis. In the first year after surgery, individuals were given the same transition probability for knee replacement as without bariatric surgery and then, from the second year, probabilities were estimated for the lower BMI achieved through the intervention. Based on a recent systematic review and meta-analysis, bariatric surgery was expected to lead to a reduction in BMI of 14.32 (95% confidence interval (CI): 11.45 to 17.19).[158] For the base case analysis, it was assumed that this reduction would be maintained. For a sensitivity analysis, it was assumed that the reduction would be mitigated after 5 years.

Transition probabilities for risk of revision after knee replacement and costs of knee replacements and subsequent revisions were estimated in an analogous way as for estimating the potential impact of use of TNFi as a first-line therapy in rheumatoid arthritis. Meanwhile, the cost of bariatric surgery was estimated as the weighted average

of the costs of gastric band, gastric bypass, and sleeve gastrectomy, with costs based on those incurred in England and their use based on routine practice in the UK.[159,160]

The model was first run for 100 representative individuals diagnosed with knee osteoarthritis with a BMI of 40, but otherwise average characteristics of those undergoing the procedures. The cost per knee replacement avoided was estimated. The partial effect of age and sex was then estimated by re-running models for varying values of age and sex, while other explanatory factors were held fixed at their average. Uncertainty was accounted for in the same way as the previous models.

Figure 2.4*:* State-based Markov model for a cost effectiveness analysis of bariatric surgery for those diagnosed with knee osteoarthritis



Estimating threshold prices for potential improvements in outcomes due to the use of computer or robot-assisted knee and hip replacement

A state-based Markov model was also used to estimate threshold prices for improvements in the effectiveness of knee and hip replacement. A broadly similar model structure to that for estimating lifetime risk of revision after knee and hip replacement

was used, as shown in Figure 2.5. The study cohort begin by having a knee or hip replacement at time zero and were then at risk of revision or death. As yearly cycles passed, individuals remained in the unrevised state or moved to the revision state. After one year in the revision state they move to the revised state where they remained.

Under current practice, transition probabilities from knee/ hip replacement to revision and death were the same as those used to estimate lifetime risk of revision. The transition probabilities from both the revision and revised states to death were assumed to be equal to that of knee/ hip replacement to death. The costs of knee and hip replacement and subsequent revision were estimated in the same way as described for the previous models.

The quality of life associated with each state was based on the ordinary least squares estimation models described above. Post-operative EQ-5D-3L index was predicted given the patient profile specified. In the year following a primary, patients were expected to steadily progress from their pre-operative score (specified as part of the patient profile) to their post-operative score at six months, at which they would remain for the rest of the year. As scores have been seen to remain fairly stable over time,[161] those who remained unrevised were expected to remain at their post-operative score in subsequent years. The trajectory of quality of life following revision was assumed to be similar to primary procedures, with patients expected to progress from their pre-operative score to their post-operative score over six months, at which they were expected to remain. Based on previous research,[162] quality of life before and after revision was assumed to be 75% of that of the corresponding scores for the primary procedure.

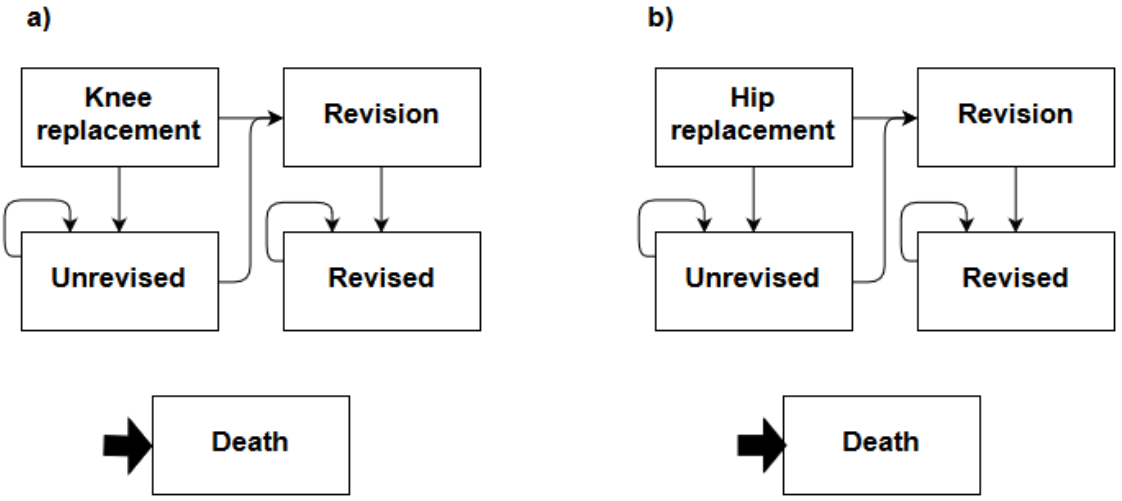
After estimating the costs and quality-adjusted life years (QALYs) associated with current practice, models were re-run for a relative reduction in the risk of revision, a relative

improvement in post-operative quality of life if unrevised, or a combination of both. Relative risk reductions for revision were incorporated by reducing the annual transition probability for revision by some given amount, with reductions ranging from 0% (i.e. no change in the probability of revision) to 50% (i.e. halving the annual probability of revision). Relative improvements in post-operative quality of life if unrevised were incorporated by increasing the estimated quality of life at six months following surgery for those in the unrevised health state in the model by 0% to 5%. The quality of life estimates for other health states remained unchanged.

In the base case analysis, threshold prices were then calculated for each given improvement in comparison to current practice at a cost-effectiveness threshold set at £20,000, the lower bound for the English NHS.[88] As sensitivity analyses, threshold prices were also estimated at £30,000, the upper bound for the English NHS, and at £13,000, which is thought to be closer to the true opportunity cost of healthcare spending in the English NHS.[163]

The model was first run for patient profiles with the average characteristics of those undergoing the procedures. The partial effect of age and sex on threshold prices was then estimated by re-running models for varying values of age and sex, while other explanatory factors were held fixed at their average. Uncertainty was accounted for in the same way as the previous models.

Figure 2.5: State-based Markov models for estimating a) threshold prices for computer or robot-assisted knee replacement, and b) threshold prices for computer or robot-assisted hip replacement



Software

The analyses presented in this thesis were performed using R.[164] Data preparation was performed predominantly using tidyvese packages,[165] in particular dplyr.[166] The mice package was used to implement multiple imputation.[167] Statistical modelling was performed using the rms and flexsurv packages.[168,169] Bespoke code was written for implementing the decision analytic models, broadly based on coding practices espoused by the Decision Analysis in R for Technologies in Health group.[170] The ggplot2 and ggridges packages were used for plotting.[171,172]

3. LIFETIME RISK OF KNEE AND HIP REPLACEMENT FOLLOWING A DIAGNOSIS OF OSTEOARTHRITIS OR RHEUMATOID ARTHRITIS

Chapter summary

In this chapter I describe the lifetime risk of knee replacement after a diagnosis of knee osteoarthritis, hip replacement after a diagnosis of hip osteoarthritis, and knee and hip replacement after a diagnosis of rheumatoid arthritis.

Lifetime risks after diagnosis of osteoarthritis were informed by routinely collected data from Catalonia, Spain, while those after diagnosis of rheumatoid arthritis were based on routinely collected data from England. State-based Markov models provided the framework for the analyses, with transition probabilities based on parametric survival models.

For the average patient profile, risk of knee replacement after a diagnosis of knee osteoarthritis was 30% (95% CI: 25% to 36%). Risk of hip replacement after a diagnosis of hip osteoarthritis was 14% (10% to 19%). Risks of knee and hip replacement following a diagnosis of rheumatoid arthritis were 22% (16% to 29%) and 17% (11% to 26%), respectively.

Younger age at diagnosis was typically associated with a higher lifetime risk of knee and hip replacement. Higher BMI was associated with a higher risk of knee replacement after a diagnosis of knee osteoarthritis. Being male was associated with a higher lifetime risk of hip replacement following a diagnosis of hip osteoarthritis, particularly at younger ages.

Background

As discussed in Chapter 1, the long-term prognosis for individuals diagnosed with osteoarthritis or rheumatoid arthritis is uncertain. Prognosis is the likelihood of future outcomes in patients with a given disease or health condition,[173] and knee and hip replacement are important potential outcomes for individuals with osteoarthritis or rheumatoid arthritis. To address this knowledge gap, in this chapter I provide estimates of the lifetime risk of knee and hip replacement. I also assess how patient characteristics affect these risks.

Study participants with osteoarthritis were from Catalonia, Spain, and had a follow up of up to 9 years. Those with a diagnosis with rheumatoid arthritis were from England, and had a follow of up to 15 years. These datasets were used because the respective diagnoses have been well validated in each.[132,133] Parametric survival models were estimated for risk of knee/ hip replacement and death. State-based Markov models were used to combine and extrapolate these survival models.

In this chapter, study participants and their cumulative incidence of knee and hip replacement and mortality are described. The timing of events and the impact of patient characteristics on cause-specific risks are summarised. Lifetime risks are then provided for the average patient profile and the partial effect of characteristics on these risks described.

Study participants

48,311, 15,105 and 13,961 individuals with knee osteoarthritis, hip osteoarthritis, and rheumatoid arthritis, respectively, were included. The characteristics of the individuals are summarised in Table 3.1. The median age was 69 for knee osteoarthritis, 70 for hip

osteoarthritis, and 64 for rheumatoid arthritis. All cohorts were majority female, with most individuals having few or no comorbidities.

Table 3.1: Characteristics of study participants

	Knee osteoarthritis	**Hip osteoarthritis**	**Rheumatoid arthritis**
N	48,311	15,105	13,961
Age (median [IQR])	69 [62, 77]	70 [62, 78]	64 [54, 73]
Age group* (n (%))			
1st (youngest)	11,436 (24)	3,503 (23)	3,216 (23)
2nd	11,212 (23)	3,666 (24)	3,720 (27)
3rd	13,034 (27)	3,944 (26)	3,212 (23)
4th (oldest)	12,629 (26)	3,992 (26)	3,813 (27)
Sex: male (n (%))	16,076 (33)	6,024 (40)	4,493 (32)
Charlson score (n (%))			
0	25,967 (54)	7,634 (51)	12,399 (89)

	Knee osteoarthritis	Hip osteoarthritis	Rheumatoid arthritis
1	12,258 (25)	3,779 (25)	
2	5,840 (12)	1,982 (13)	
3+	4,246 (9)	1,710 (11)	
1+			1,562 (11)
BMI (median [IQR])	30 [28, 34]	29 [27, 32]	27.1 [24, 31]
BMI group (n (%))			
Normal or underweight (<25)	2,401 (5)	1,170 (8)	1,701 (12)
Overweight (≥25 and <30)	9,550 (20)	3,444 (23)	988 (7)
Obese class I (≥30 and <35)	8,770 (18)	2,372 (16)	431 (3)
Obese class II (≥35 and <40)	3,538 (7)	788 (5)	225 (2)
Obese class III (≥40)	1,437 (3)	2,10 (1)	1,788 (13)

	Knee osteoarthritis	Hip osteoarthritis	Rheumatoid arthritis
Missing	22,615 (47)	7,121 (47)	8,828 (63)
IMD/ MEDEA quintile or rural (n (%))			
1 (least deprived)	4,708 (9)	1,726 (11)	3,132 (22)
2	6,971 (14)	2,326 (15)	3,118 (22)
3	8,676 (18)	2,666 (18)	2,988 (21)
4	9,472 (20)	2,736 (18)	2,700 (19)
5 (most deprived)	7,298 (15)	2,010 (13)	2,001 (14)
Rural	9,244 (19)	2,938 (20)	
Missing	1,942 (4)	703 (5)	22 (0)
Smoking status (n (%))			
Non-smoker	32,128 (67)	9,328 (62)	2,465 (18)

	Knee osteoarthritis	Hip osteoarthritis	Rheumatoid arthritis
Ex-smoker	6,307 (13)	2,334 (16)	2,452 (18)
Current smoker	4,140 (9)	1,656 (11)	1,642 (12)
Missing	5,736 (12)	1,787 (12)	7,402 (53)

*Age groups were based on quartiles. For knee osteoarthritis age groups were 50 to 62, 62 to 69, 69 to 77, 77 to 105, for hip osteoarthritis they were 50 to 62, 62 to 70, 70 to 78, 78 to 103, and for rheumatoid arthritis they were 40 to 54, 54 to 64, 64 to 73, 73 to 99. IMD: index of multiple deprivation. MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. BMI: body mass index; IQR: interquartile range

Cause-specific risks of knee and hip replacement

The 9-year cumulative incidence of knee replacement was 9.4% (CI: 8.9% to 9.9%) for individuals with knee osteoarthritis. Meanwhile, cumulative incidence of hip replacement was 11.6% (10.9% to 12.3%) for those with hip osteoarthritis. 15-year cumulative incidence of knee and hip replacement were 9.7% (8.8% to 10.7%) and 7.7% (6.8% to 8.7%) for individuals with rheumatoid arthritis.

Cumulative incidence stratified by explanatory factors of interest is detailed in Appendix Table B.1. For each of the cohorts, risks appear to differ by age at diagnosis, with

observed cumulative incidence generally lower for both the youngest and oldest patients. Men had a higher cumulative incidence of hip replacement after a diagnosis of hip osteoarthritis. Individuals with a higher BMI had a higher cumulative incidence of knee replacement after a diagnosis of knee osteoarthritis.

The timing to events appeared to also differ by age. The non-proportionality in age for cause-specific hazards for knee and hip replacement can be seen from the estimated hazards and cumulative hazards from intercept-only parametric models stratified by age groups, which are plotted alongside those from the observed data in Figure 3.1, Figure 3.2, Figure 3.3, and Figure 3.4 (alternative distributions considered for the parametric models are shown from Appendix Figure B.2 to Appendix Figure B.16). In general, older patients were more likely to have surgery shortly following diagnosis if they are ever to have surgery, as shown by the peak in the hazards shortly after diagnosis. Risks were closer to being evenly spread over time for younger patients. To account for this, age-stratified models were used for the analysis, with age included as a continuous explanatory factor within each of the models.

The estimated effect of patient characteristics on cause-specific risks of knee and hip replacement are described in Appendix Table B.2, Appendix Table B.3, Appendix Table B.4, and Appendix Table B.5. Estimates implied that age had a non-linear relationship with risk of knee and hip replacement. At younger ages, increasing age was generally associated with an increased risk of knee and hip replacement. An additional year of in age in the youngest age group had adjusted hazard ratios of 1.09 (1.05 to 1.12) for knee replacement after a diagnosis of knee osteoarthritis, 1.01 (0.98 to 1.05) for hip replacement after a diagnosis of hip osteoarthritis, 1.06 (1.00 to 1.14) for hip replacement after a diagnosis of rheumatoid arthritis, and an acceleration factor of 0.95

(0.91 to 0.99) for knee replacement after a diagnosis of rheumatoid arthritis (NB a hazard ratio over one implies an exposure is harmful to survival while an acceleration factor over one implies exposure is beneficial for survival). This risk then generally plateaued as age continued to increase. For hip replacement after a diagnosis of hip osteoarthritis risk then fell as age increased for older patients, with an additional year of age in the oldest age group having an adjusted hazard ratio of 0.89 (0.85 to 0.94). In addition, being a woman was typically associated with a reduced risk of hip replacement following a diagnosis of hip osteoarthritis particularly for younger patients. Indeed, in the youngest age group being a woman was associated with almost half the risk of hip replacement, with being a woman having an adjusted hazard ratio of 0.46 (0.36 to 0.59) for those aged between 50 and 62 at time of diagnosis. Higher BMI was associated with an increased risk of knee replacement following a diagnosis of knee osteoarthritis with, for example, an additional unit of BMI associated with an adjusted hazard ratio of 1.03 (1.01 to 1.05) for those aged between 62 and 69 at time of diagnosis.

Figure 3.1. Risks of knee replacement following a diagnosis of knee osteoarthritis. Hazards and cumulative hazards for each age strata from observed data and intercept-only parametric survival models (all of which were fitted with a spline-based distribution with 3 knots).

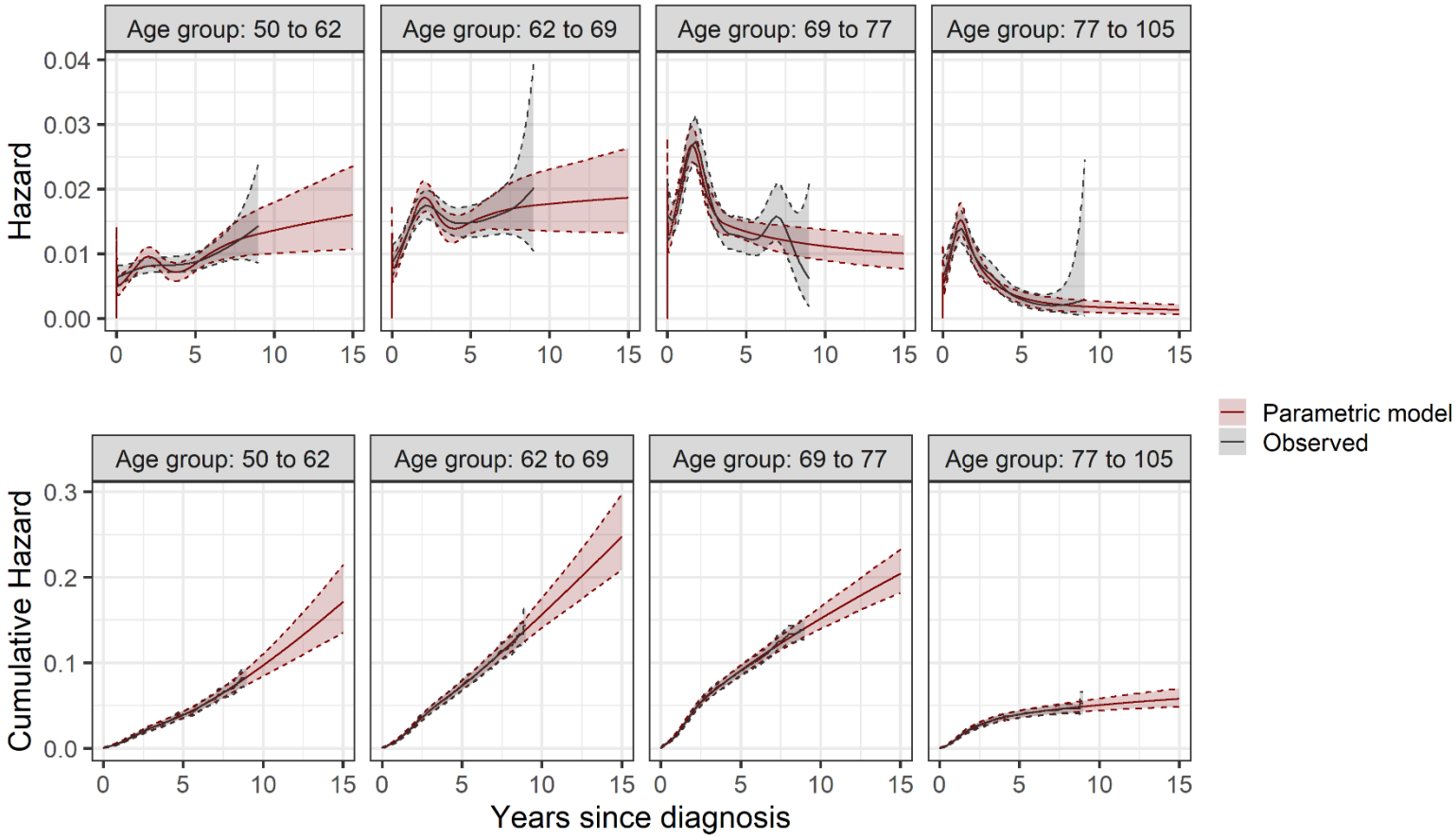


Figure 3.2. Risks of hip replacement following a diagnosis of hip osteoarthritis. Hazards and cumulative hazards for each age strata from observed data and intercept-only parametric survival models (all of which were fitted with a spline-based distribution with 3 knots).

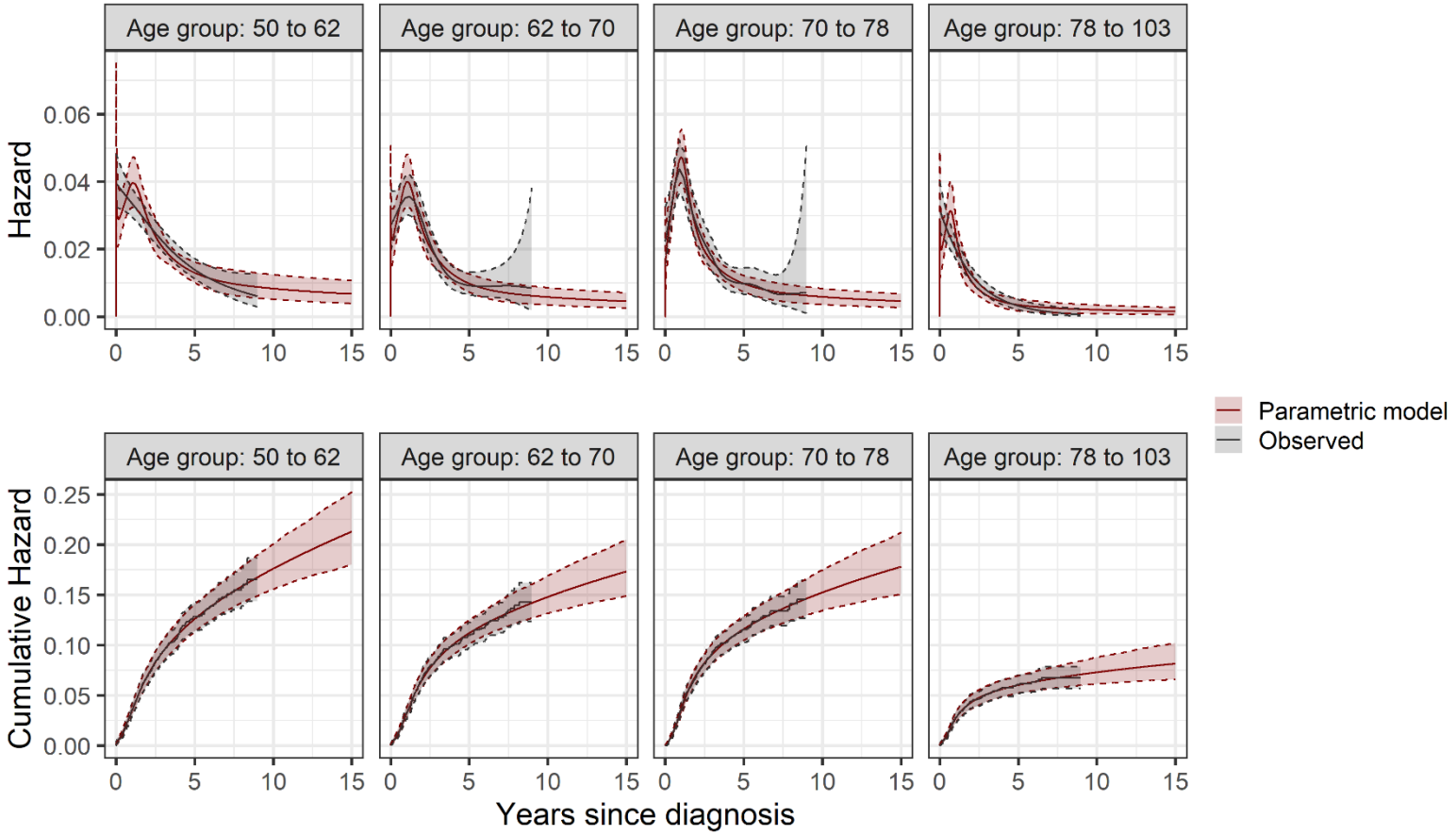


Figure 3.3. Risks of knee replacement following a diagnosis of rheumatoid arthritis. Hazards and cumulative hazards for each age strata from observed data and intercept-only parametric survival models (from youngest to oldest age strata, the chosen distributions were: Weibull, Weibull, log-logistic, and log-normal)

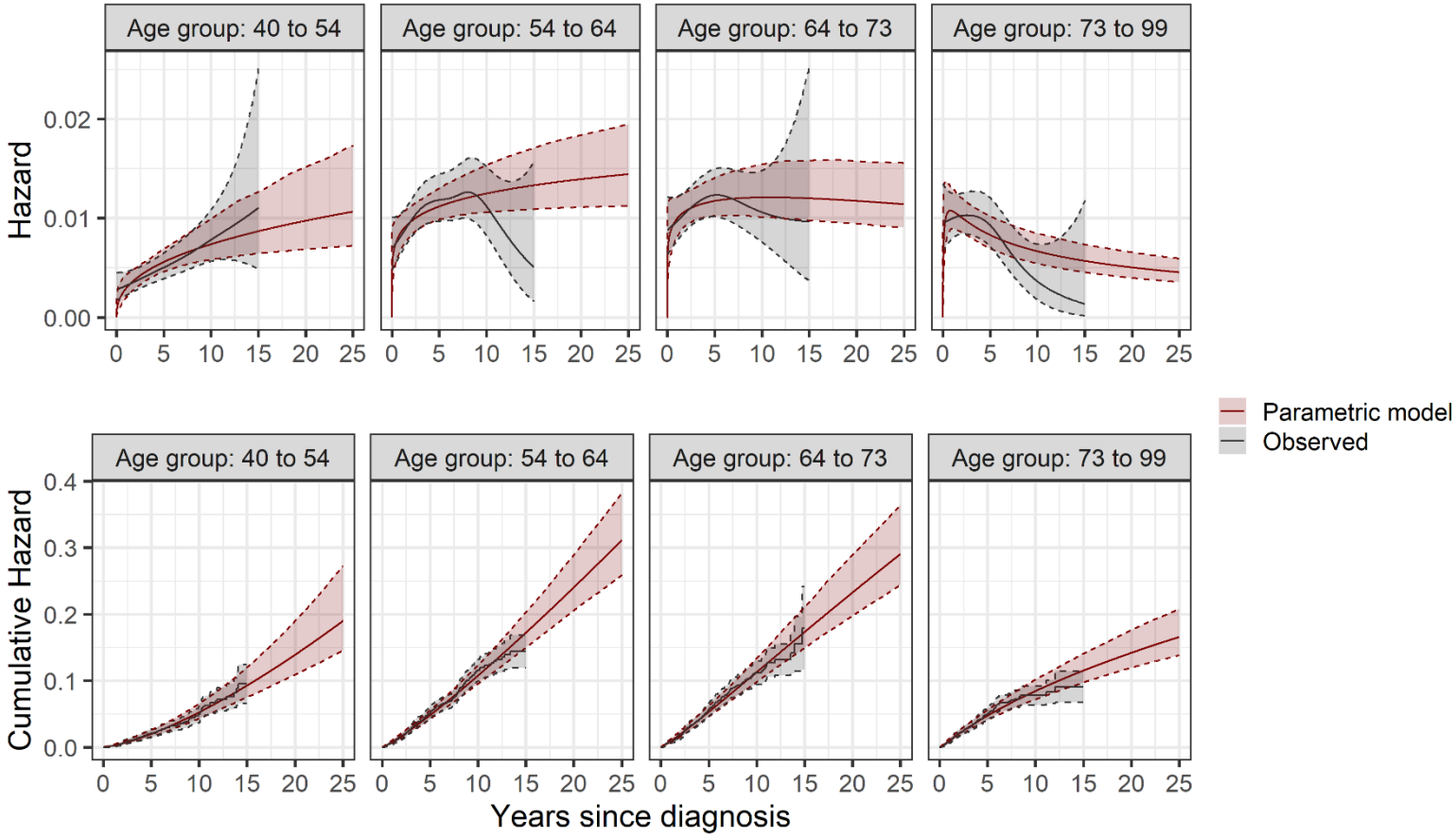
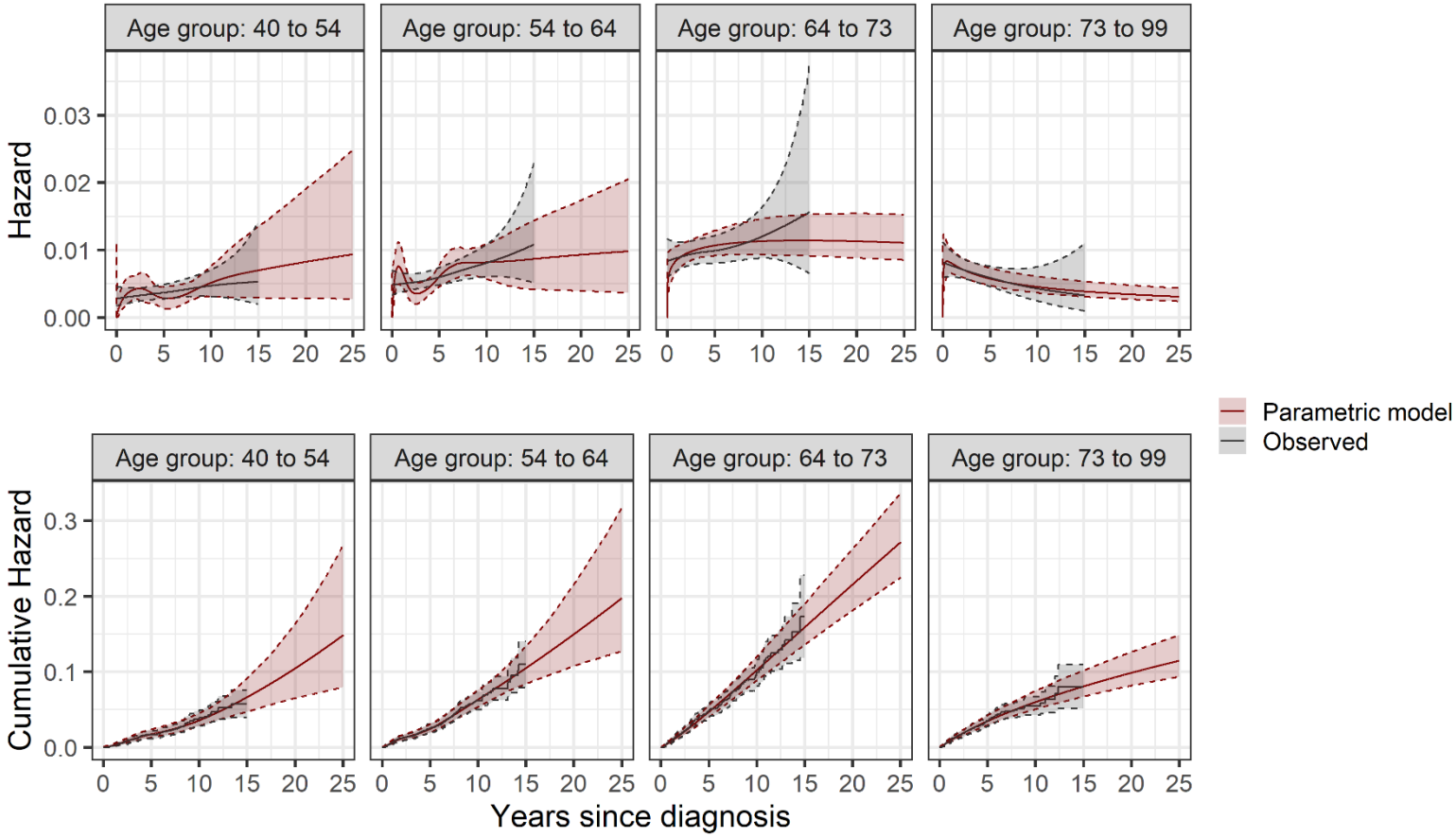


Figure 3.4. Risks of hip replacement following a diagnosis of rheumatoid arthritis. Hazards and cumulative hazards for each age strata from observed data and intercept-only parametric survival models (from youngest to oldest age strata, the chosen distributions were: spline with 3 knots, spline with 3 knots, log-logistic, log-normal).



Cause-specific risk of mortality

The cumulative incidence of mortality after 9 years following a diagnosis of osteoarthritis and after 15 years following a diagnosis of rheumatoid arthritis is summarised in Appendix Table B.6. Those in older age groups, men, those with more comorbidities, and ex-smokers had a noticeably higher cumulative incidence of death at the end of follow-up.

Hazards for mortality appeared to steadily increase over follow-up as individuals aged (see Appendix Table B.7). Estimates from parametric models implied that being at an older age, a man, having more comorbidities, or an ex-smoker was associated with an increased risk of mortality. While being a current smoker was generally not necessarily associated with an increased risk of mortality in unadjusted models, it was after controlling for differences in other patient characteristics (Appendix Table B.7).

Lifetime risks of knee and hip replacement

For the average profile of an individual diagnosed with knee osteoarthritis (a non-smoking 69-year-old woman in the fourth MEDEA quintile, with a Charlson score of 0 and a BMI of 30), the lifetime risk of knee replacement was estimated to be 30% (95% CI: 25% to 36%). For the average profile of an individual diagnosed with hip osteoarthritis (a non-smoking 70-year-old woman living rurally, with a Charlson score of 0 and a BMI of 29), the lifetime risk of hip replacement was estimated to be 14% (10% to 19%). Meanwhile, for the average profile of an individual diagnosed with rheumatoid arthritis (a non-smoking 64-year-old woman in the 1st IMD quintile, with a

Charlson score of 0 and a BMI of 27), the lifetime risks of knee and hip replacement were estimated to be 22% (16% to 29%) and 17% (11% to 26%), respectively.

The partial effect of patient characteristics on lifetime risks are shown in Figure 3.5, Figure 3.6, Figure 3.7, Figure 3.8, and Figure 3.9. As well as the generally higher lifetime risk for younger individuals, being a man was also generally associated with a higher lifetime risk of hip replacement than for women at younger ages following a diagnosis of hip osteoarthritis. An average 60-year-old man diagnosed with hip osteoarthritis, for example, had a 30% (25% to 36%) lifetime risk of hip replacement, while a similar 60-year-old woman had a 17% (12% to 24%) lifetime risk, as shown in Figure 3.5. A higher BMI was associated with a higher lifetime risk of knee replacement after a diagnosis of knee osteoarthritis (Figure 3.6). An increase in BMI from 25 to 35 while other explanatory variables remained at their average was expected to increase lifetime risk of knee replacement from 24% (20% to 28%) to 32% (26% to 37%).

Figure 3.5. Partial effect of age and sex on lifetime risks. Point estimates with 95% confidence intervals.

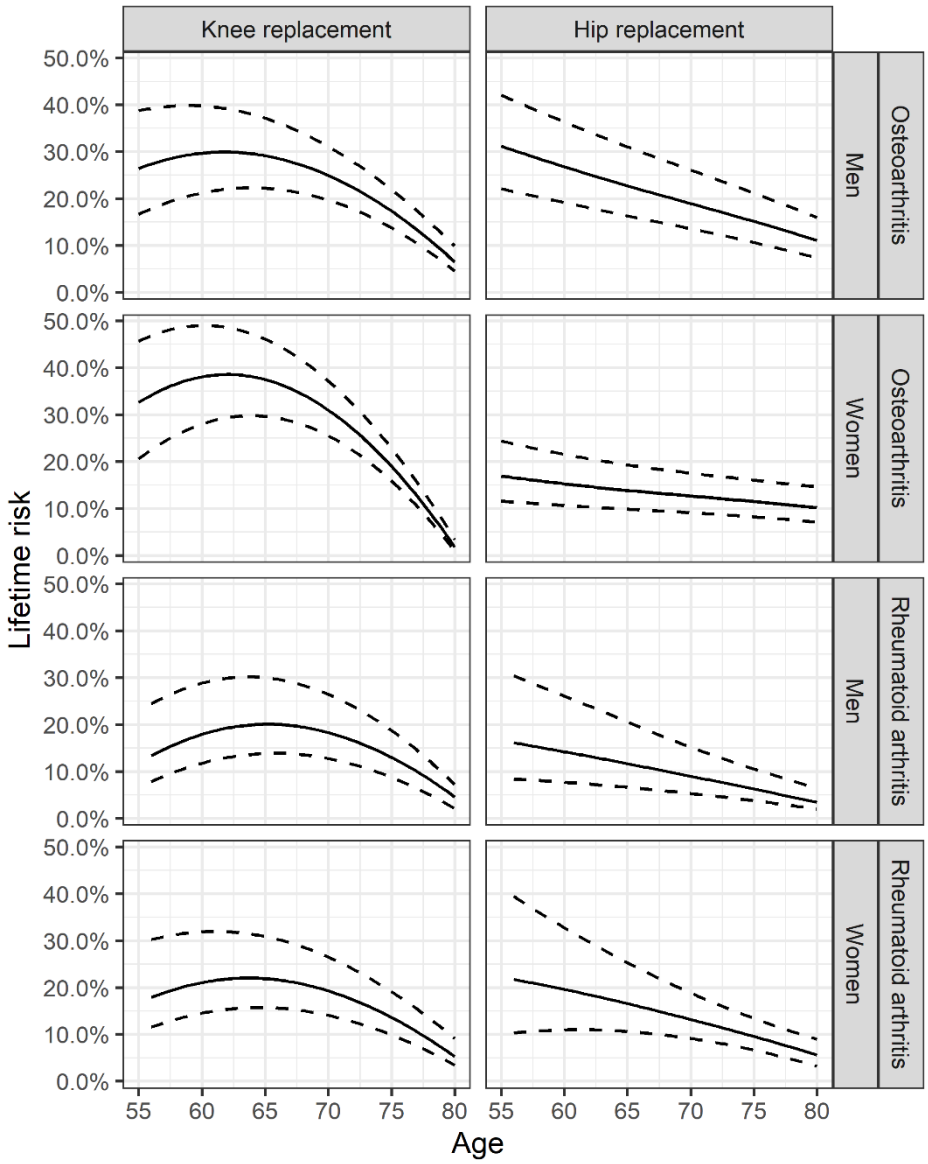


Figure 3.6. Partial effect of BMI on lifetime risks. Point estimates with 95% confidence intervals.

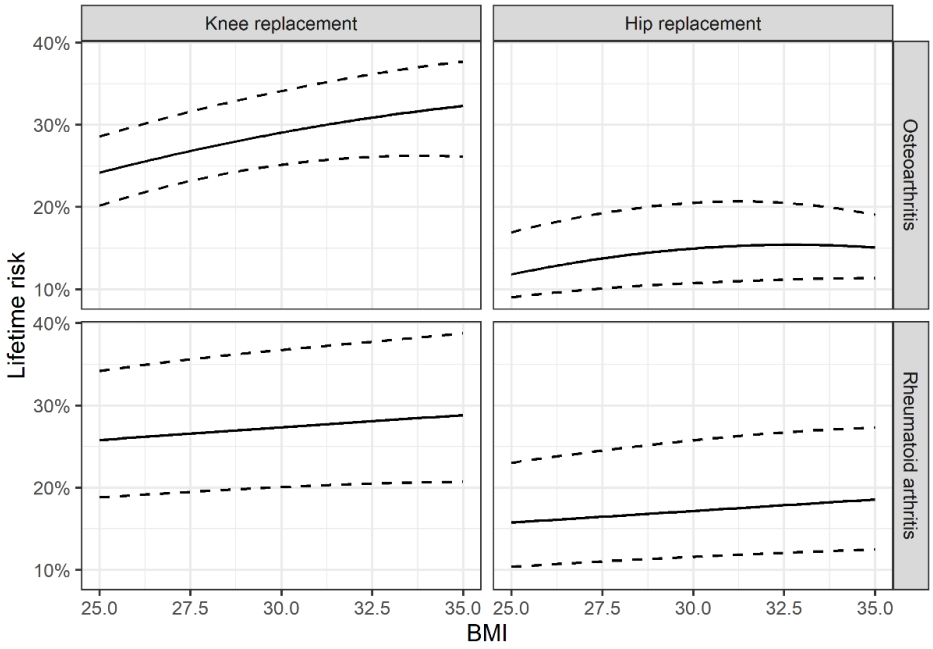


Figure 3.7. Partial effect of Charlson score on lifetime risks. Point estimates with 95% confidence intervals.

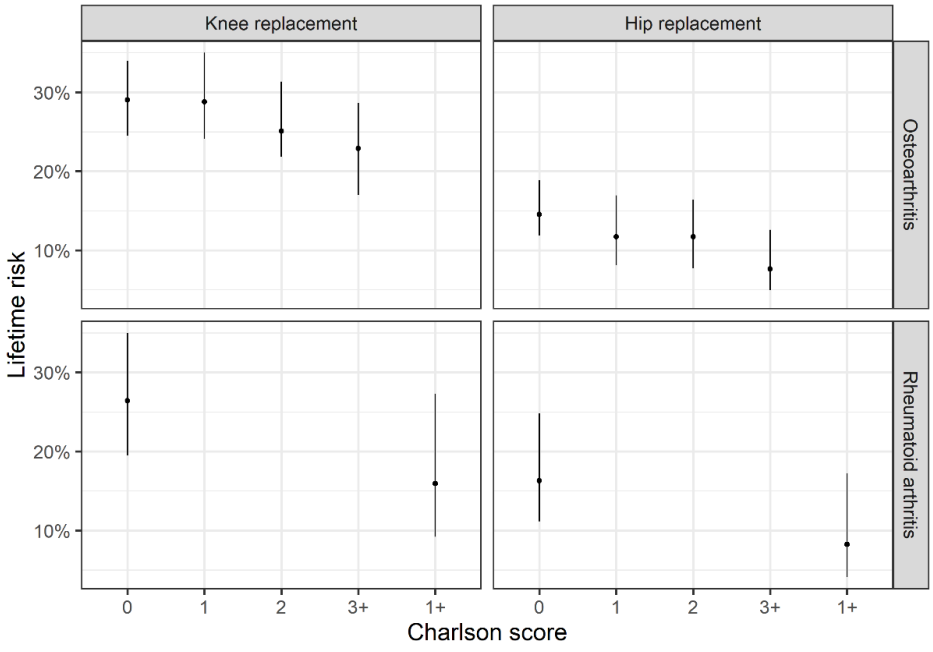


Figure 3.8. Partial effect of socioeconomic status on lifetime risks. Socioeconomic status was measure by MEDEA quintile for osteoarthritis and IMD quintile for rheumatoid arthritis, where quintile 5 represented the most deprived and for MEDEA there was a separate category for those living in a rural area (R). Point estimates with 95% confidence intervals.

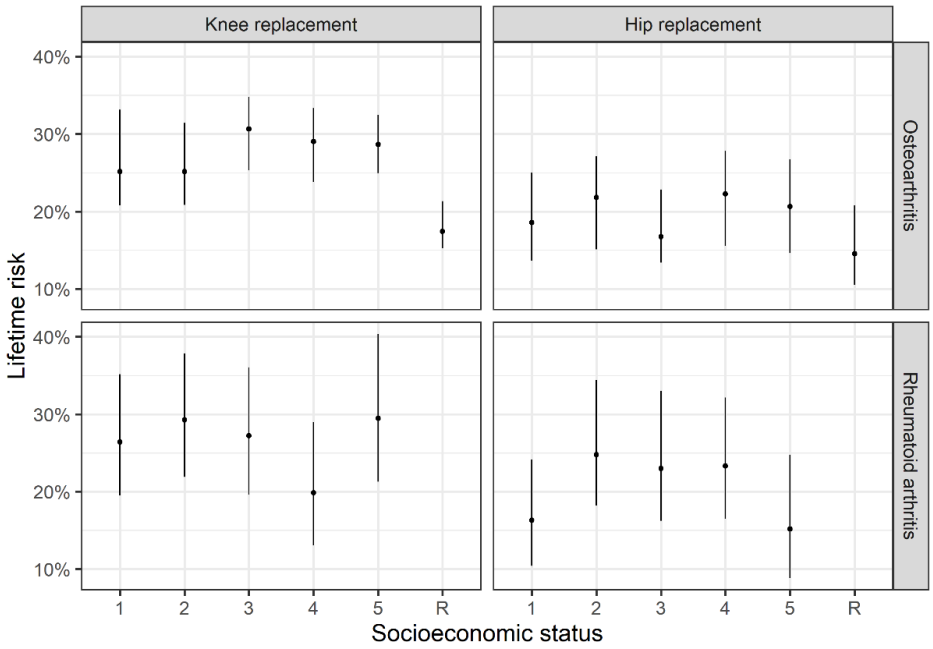
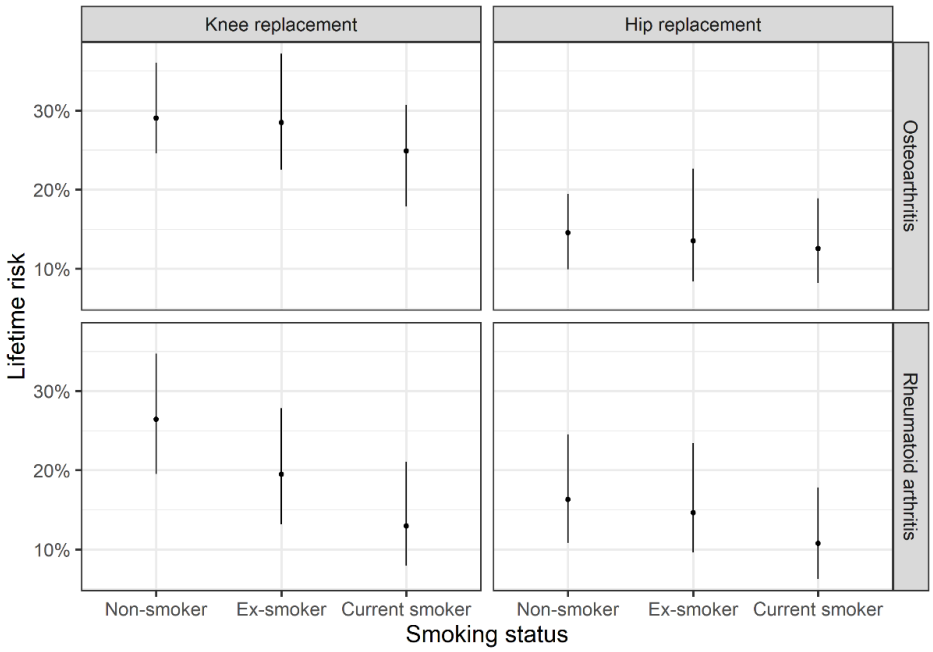


Figure 3.9. Partial effect of smoking status on lifetime risks. Point estimates with 95% confidence intervals.



Study findings in context

Lifetime risk of knee and hip replacement following a diagnosis of knee or hip osteoarthritis

As would be expected the lifetime risks of knee and hip replacement after a diagnosis of knee or hip osteoarthritis estimated here are higher than the lifetime risks for the general population,[174] which is illustrated in Figure 3.10. It is notable that, despite the prevailing belief that the development of osteoarthritis is an unavoidable consequence of aging and that further deterioration is inevitable,[30] knee and hip replacement are not bound to happen following a diagnosis of knee or hip osteoarthritis. This is true even for those diagnosed at a young age.

As discussed in chapter 1, no studies have previously used patient-level data to estimate lifetime risk of knee and hip replacement following a diagnosis of knee or hip osteoarthritis. One previous modelling study did combine prevalence and progression estimates from the literature to estimate that a 25-year old with no history of knee injury would have a 13.5% risk of developing osteoarthritis and a 6% risk of then going on to have a knee replacement over their lifetime.[175] This implied a 45% lifetime risk of knee replacement for those in the cohort who reached the state of being diagnosed with osteoarthritis. Although this is higher than the lifetime risks estimated here, it is not dramatically so.

For individuals diagnosed with knee or hip osteoarthritis who go on to have a knee or hip replacement, surgery was most likely to occur in the first few years after a primary care diagnosis. Cause-specific risks appear to generally peak in the second year after diagnosis. Given waiting times for surgery, it appears that there is a sizeable

proportion of patients for whom referral to surgery is made shortly following diagnosis. Although this may in part be explained by rapid progression of osteoarthritis for some patients,[19] it is likely driven primarily by a proportion of individuals being diagnosed at a late-stage in the disease process, at which point knee or hip replacement was already merited. The peak in risk is most pronounced for older patients. This may be because older patients are more likely to be receiving a diagnosis relatively late in the disease course. It may also be because for older patients the choice of having surgery is 'now or never', whereas for younger individuals a 'wait and see' option may be considered so as to minimize the need for future revision surgery.[87]

Age at diagnosis was a key determinant of the lifetime risk of knee and hip replacement following a diagnosis of knee or hip osteoarthritis, due to differences in the cause-specific risks of surgery and, in particular, of mortality. A reduced cause-specific risk for surgery for older patients is consistent with previous research which found those over 82 years of age to have less than half the risk of knee and hip replacement than younger patients.[43] This was the case even after controlling for severity of osteoarthritis symptoms, and so it is likely due to a reduced willingness to consider knee and hip replacement in the elderly because of a perceived worse risk-benefit trade-off for surgery.

As reflected by the study cohorts for knee and hip osteoarthritis being majority women, being a woman has previously been associated with an increased risk of developing osteoarthritis.[21] The results of this analysis suggest, however, that once diagnosed, young men have a higher lifetime risk of hip replacement than young women. Previous research has found that men are more likely to undergo knee and

hip replacement relative to their need.[176] This may be due to differences in the willingness to undergo surgery,[43] which may in turn be due to differences in perceptions of the risks and benefits of knee and hip replacement and general preferences for surgery.[44] However, this difference may also be in part due to gender bias, with physicians more likely to recommend knee replacement to a male patient than an otherwise equivalent female patient.[45]

Having a higher BMI has previously been associated with an increased risk of developing knee osteoarthritis,[177] greater structural and clinical progression of knee osteoarthritis,[23,42,178] an increased risk of undergoing knee replacement among the general population,[106] and an increased risk of knee replacement over six years after a diagnosis of osteoarthritis.[29] This latter study also used data from SIDIAP with participants followed up for a median of 2.6 years and it was found that obese patients had double the risk of knee replacement compared to those at a normal weight.[29] In our analysis, higher BMI was also associated with a meaningful increase in the lifetime risk of knee replacement following a diagnosis of knee osteoarthritis. BMI though appeared to have little effect on the risk of hip replacement. This discordance has previously been found in a large population-based cohort study,[46] and may be explained by differences in biomechanical effects (with the knee joint, a hinge joint, likely to be more susceptible to problems caused by changed mechanical loading compared to the hip joint, a ball-and-socket joint).[46]

Having more comorbidities and being a current or ex-smoker were, as would be expected, associated with a higher risk of mortality, and so less time at risk for knee and hip replacement. However, these factors had relatively little meaningful impact on cause-specific and overall lifetime risks for knee and hip replacement. There has

been relatively little research on the effect of these factors on the need or receipt of knee and hip replacement. Comorbidities are generally not considered as a barrier for referral to surgery. However, surgeons do consider how they might affect the risk-benefit trade-off from surgery and although comorbidities may not preclude surgery, they are considered in planning of peri-operative care.[179]

Socioeconomic status had relatively little meaningful impact on cause-specific risks for mortality or knee and hip replacement, and lifetime risk estimates were therefore relatively unaffected. Previous research from the UK has suggested that individuals in more deprived areas get less provision of knee and hip replacement relative to need.[176] Our findings suggest that this may not be the case in the Catalan healthcare system. Point estimates suggested that those living rurally appear to have a lower risk of knee replacement, although this was driven mostly by differences in mortality. The impact of socioeconomic status and rurality is likely to be highly context dependent. Findings for the whole of Spain may well be different to our findings for Catalonia, and international differences are likely to be even greater.

Lifetime risk of knee and hip replacement following a diagnosis of rheumatoid arthritis

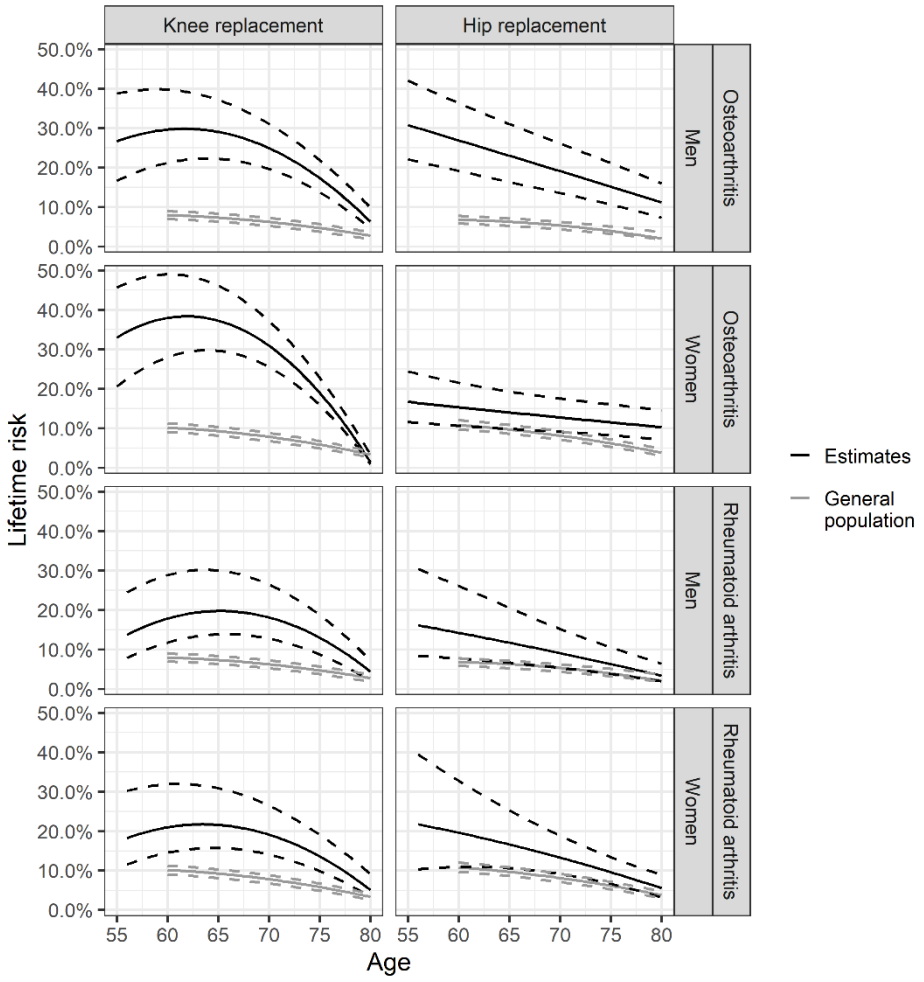
While lifetime risks of knee and hip replacement after a diagnosis of rheumatoid arthritis are generally lower than after a diagnosis of a knee or hip osteoarthritis, risks do appear to be higher than those of the general population,[174] as depicted in Figure 3.10. No previous study has estimated the lifetime risk of knee and hip replacement following a diagnosis of rheumatoid arthritis. A number of studies have described rates of knee and hip replacement for individuals with rheumatoid arthritis over a

constrained follow up,[38–40,180–184] and our findings of lifetime risks are broadly in line with what would be expected based on these studies.

Compared to osteoarthritis, the risk of knee and hip replacement had less of a peak following diagnosis and was generally more evenly distributed over time. This is likely due to rheumatoid arthritis being more consistently diagnosed relatively early in the disease course and the availability of effective non-surgical interventions. However, as with osteoarthritis, the distribution of risk over time varied by age at diagnosis. In line with these findings, previous research found that those aged over 80 with rheumatoid arthritis who underwent knee or hip replacement typically had their procedure more quickly following diagnosis as compared to younger patients.[180]

Similar to osteoarthritis, age at diagnosis of rheumatoid arthritis was a key determinant of lifetime risk of knee and hip replacement. This was primarily driven by the greater life expectancy and so time at risk for surgery. This finding is in accordance with previous research, with those aged over 80 seen to have lower risk of knee and hip replacement compared to younger patients,[180] and age seen to be an important predictor for orthopaedic joint surgery for those individuals recruited to the Norfolk Arthritis Register between 1990 to 1994.[181]

Figure 3.10. Partial effect of age and gender on lifetime risks compared with general population risks



Strength and limitations

This analysis was based on routinely collected data, with lifetime risks of knee and hip replacement estimated from time of diagnosis of knee or hip osteoarthritis or rheumatoid arthritis. Data was drawn from England for those diagnosed with rheumatoid arthritis and Catalonia for those diagnosed with osteoarthritis. These diagnoses have previously been validated for the respective data sources.[131,132,185] Instances of knee and hip replacement were identified in linked hospital records. Data from Catalonia captures admissions to every public and private hospital within the

region,[186] while data from England captured all admissions to publicly-funded hospitals and admissions to independent sector providers (private or charitable hospitals) paid for by the NHS. Especially in the latter case, therefore, there is a concern that privately-funded knee and hip replacements may have been missed leading to underestimates of lifetime risks.

Previous research has shown that there is variation in lifetime risk of knee and hip replacement for the general population across countries,[187,188] and this is likely to also be the case for lifetime risks after diagnoses of osteoarthritis and rheumatoid arthritis. Differences will likely be caused by both variation in need for surgery and in the provision of care. This then limits the generalisability of the results reported here.

The use of parametric survival models has allowed for a thorough assessment of the effects of patient characteristics on lifetime risk and a consideration of whether differences were due to impacts on cause-specific risks for surgery or mortality. However, this approach has disadvantages with, in particular, a need to extrapolate risks beyond follow-up. This leads to a relatively high degree of uncertainty, especially for younger patients, which is reflected in the wide confidence intervals around estimates for younger patients.

In addition, only those patient characteristics available in routinely collected data could be considered. A wide range of other factors are likely to influence lifetime risk, such as willingness to undergo knee or hip replacement and disease severity.[43,181,189]

The impact of treatments initiated after diagnosis can also be expected to have an important effect on lifetime risk. This is of particular relevance for rheumatoid arthritis with, for example, immediate initiation of treatment with disease-modifying antirheumatic drugs previously found to reduce risk of surgery when compared to a

delayed start.[184] Even where patient characteristics could be considered, estimates reflect effects on the receipt of surgery. The effect on need for surgery may well differ.

Conclusion

Knee and hip replacement remain an enduring risk following diagnosis of knee or hip osteoarthritis and rheumatoid arthritis, but in neither case are inevitable. Age at diagnosis is the key determinant of lifetime risks for these surgeries. Being a man is also associated with an increased risk of hip replacement following a diagnosis of hip osteoarthritis and BMI with an increased risk of knee replacement following a diagnosis of knee osteoarthritis.

4. PATIENT-REPORTED OUTCOME MEASURES FOLLOWING KNEE AND HIP REPLACEMENT

Chapter summary

In this chapter I describe patient-reported outcome measures before and after knee and hip replacement and assess the impact of patient heterogeneity.

Routinely collected patient-reported outcomes from England informed the analysis. Both the condition-specific Oxford Knee Score (OKS) and Oxford Hip Score (OHS), and the generic EuroQol 5-dimension 3-level (EQ-5D-3L) questionnaires were collected shortly before and six months after surgery. The observed responses were summarised and ordinary least squares estimation (linear regression) was used to assess the impact of patient characteristics at time of surgery on post-operative patient-reported outcomes.

Joint-specific outcomes and overall health-related quality of life were much improved at six months after surgery. On average, patients achieved 62% and 60% of their maximum potential improvement in OKS and EQ-5D-3L index after knee replacement, and 81% and 78% in OHS and EQ-5D-3L index after hip replacement. Pre-operative scores were a key determinant of post-operative scores, with post-operative scores expected to increase as pre-operative scores improved. Other patient characteristics had, at most, modest effects on outcomes which were unlikely to be clinically meaningful.

Background

As described in Chapter 1, while there has been considerable research on patient-reported outcomes after knee and hip replacement, there remains uncertainty around the effect of patient characteristics on outcomes. The analysis reported here was based on data from the NHS PROMs programme linked to individuals' inpatient hospital records, from HES APC, and primary care records, from CPRD. These datasets are described in more detail in Chapter 2. OKS and OHS were used to assess joint-specific health and EQ-5D-3L was used to assess overall, generic health-related quality of life prior to and six months after surgery.

In this chapter, I first summarise the change in observed scores before and after surgery, with both absolute change and percentage of potential change considered. Subsequently, I describe the estimated effects of patient characteristics at time of surgery on post-operative scores based on fitted ordinary least squares regressions (see Chapter 2 for further details on the methods used for these analyses).

Study participants

2,212 and 2,128 individuals who had a primary knee and hip replacement were included in the cohorts. The characteristics of the included individuals are summarised in Table 4.1. The median age was 70 for knee replacement and 69 for hip replacement. The majority of individuals in both cohorts were women, had an index diagnosis of osteoarthritis, and had no comorbidities.

Table 4.1. Characteristics of study participants

	Knee replacement	**Hip replacement**
N	2,212	2,128
Age at diagnosis (median [IQR])	70 [64, 76]	69 [63, 76]
Age at diagnosis group* (n (%))		
1st (youngest)	533 (24)	526 (25)
2nd	560 (25)	468 (22)
3rd	527 (24)	565 (27)
4th (oldest)	592 (27)	569 (27)
Sex: male (%)	1,012 (46)	908 (43)
Pre-operative OKS/ OHS (median [IQR])	19 [14, 24]	17 [12, 23]
Pre-operative OKS/ OHS group** (n (%))		
1st (worst)	544 (25)	490 (23)

	Knee replacement	Hip replacement
2nd	525 (24)	468 (22)
3rd	519 (24)	582 (27)
4th (best)	624 (28)	588 (28)
Pre-operative EQ-5D-3L index (median [IQR])	0.6 [0.1, 0.7]	0.5 [0.1, 0.6]
Pre-operative EQ-5D-3L index group*** (n (%))		
1st (worst)	541 (25)	489 (23)
2nd	497 (23)	537 (25)
3rd	384 (17)	570 (27)
4th (best)	790 (36)	532 (25)
Index diagnosis (n (%))		
OA	2,070 (94)	2,030 (95)

	Knee replacement	**Hip replacement**
RA	142 (6)	98 (5)
Charlson score (n (%))		
0	1558 (70)	1581 (74)
1+	654 (30)	547 (26)
BMI (median [IQR])	30 [27, 35]	29 [25, 32]
BMI group (n (%))		
Normal or underweight (<25)	143 (7)	229 (11)
Overweight (≥25 and <30)	400 (18)	408 (19)
Obese class I (≥30 and <35)	344 (16)	266 (13)
Obese class II (≥35 and <40)	198 (9)	98 (5)
Obese class III (≥40)	67 (3)	22 (1)

	Knee replacement	**Hip replacement**
Missing	1,060 (48)	1,105 (52)
IMD (n (%))		
1 (least deprived)	504 (23)	576 (27)
2	572 (26)	532 (25)
3	529 (24)	506 (24)
4	405 (18)	356 (17)
5 (most deprived)	201 (9)	157 (7)
missing	1 (0)	1 (0)
Smoking status (n (%))		
Non-smoker	636 (29)	580 (27)
Ex-smoker	615 (28)	520 (24)

	Knee replacement	Hip replacement
Current smoker	96 (4)	137 (6)
Missing	865 (39)	891 (42)

Groups for continuous variables were based on quartiles. *For knee replacement age groups were 43 to 64, 64 to 70, 70 to 76, and 76 to 94 years of age, and for the hip replacement cohort they were 31 to 63, 63 to 69, 69 to 76, and 76 to 94. ** OKS groups for knee replacement cohort were 2 to 14, 14 to 19, 19 to 24, and 24 to 43, OHS groups for hip replacement cohort were 0 to 12, 12 to 17, 17 to 23, 23 to 44. *** EQ-5D-3L groups for knee replacement cohort were -0.6 to 0.1, 0.1 to 0.6, 0.6 to 0.7, 0.7 to 1.0, EQ-5D-3L groups for hip replacement cohort were -0.6 to 0.1, 0.1 to 0.5, 0.5 to 0.6, 0.6 to 1.0. OA: osteoarthritis. RA: rheumatoid arthritis. IMD: index of multiple deprivation. BMI: body mass index; IQR: interquartile range.

Joint-specific scores after knee and hip replacement

Study participants who had a knee replacement improved from a median pre-operative OKS of 19 (interquartile range: 14 to 24) to a post-operative score of 37 (29 to 43) after surgery, with an average improvement of 17 (10 to 23) and a percentage of potential change (PoPC) of 62% (35% to 81%), see Appendix Table C.1 for details. 5.4% of study participants who had a knee replacement had a worse OKS after surgery, 0.7% had the same score, with the remaining 93.9% having improved. 78.1% of study participants achieved the minimally important change of at least 9 points. Study participants who had a hip replacement improved from a median pre-operative

OHS of 17 (12 to 23) to a post-operative score of 42 (36 to 46) after surgery, with an average improvement of 23 (16 to 29) and a PoPC of 81% (61% to 94%), see Appendix Table C.1. 1.7% of study participants who had a hip replacement had a worse OHS after surgery, 0.4% had the same score, with the remaining 97.9% having improved. 86.9% of study participants achieved the minimally important change of at least 11 points. The distributions for pre- and post-operative OKS/ OHS are shown in Figure 4.1, with change and PoPC in OKS/ OKS shown in Appendix Figure C.1 and Appendix Figure C.2, respectively.

OKS after knee replacement and OHS after hip replacement stratified by patient characteristics are detailed Appendix Table C.1. Individuals with lower pre-operative scores generally had lower post-operative scores but a greater absolute improvement than those with higher pre-operative scores. PoPC was broadly similar for different pre-operative scores. For knee replacement, those at a younger age and an older age had a lower PoPC than those closer to the median age. For hip replacement, those at an older age generally had a lower PoPC compared to younger individuals. Women generally had lower scores before and after knee and hip replacement, but the change in scores and PoPC were similar. The gain from undergoing surgery was similar regardless of index diagnosis, Charlson score, IMD quintile, and smoking status. PoPC appeared to generally fall for higher values of BMI.

The estimated effect of patient characteristics on OKS after knee replacement and on OHS after hip replacement are summarised in Appendix Table C.2, with the partial effect of characteristics shown from Figure 4.2 to Figure 4.9. It can be seen that after controlling for other explanatory factors, pre-operative scores are a key determinant of post-operative scores. While the relationship appears to be non-linear (see Figure

4.2), better pre-operative scores are expected to lead to better post-operative scores. Moving from a pre-operative OKS of 14 (the 25th percentile) to 24 (the 75th percentile) was expected to, all else being equal, result in post-operative OKS improving from 35.4 (34.3 to 36.4) to 39.3 (38.2 to 40.3) for knee replacement. Meanwhile, moving from a pre-operative OHS of 12 (the 25th percentile) to 23 (the 75th percentile) was expected to result in post-operative OHS improving from 40.7 (39.8 to 41.7) to 42.4 (41.5 to 43.4) for hip replacement.

Age at surgery was associated with a non-linear relationship with OKS and OHS after knee and hip replacement, respectively (see Figure 4.3). Moving from an age of 64 (the 25th percentile) to 76 (the 75th percentile) was expected to, all else being equal, result in post-operative OKS falling from 37.5 (36.5 to 38.6) to 36.8 (35.8 to 37.8) for knee replacement. Meanwhile, moving from an age of 63 (the 25th percentile) to 76 (the 75th percentiles) was expected to result in post-operative OHS falling from 42.6 (41.7 to 43.5) to 41.1 (40.2 to 42) for hip replacement.

After accounting for differences in other patient characteristics and pre-operative scores, higher BMI was associated with worse post-operative scores for knee and hip replacement. Moving from a pre-operative BMI of 27 (the 25th percentile) to 35 (the 75th percentile) was expected to, all else being equal, result in post-operative OKS falling from 38.1 (37 to 39.2) to 36.6 (35.5 to 37.7) for knee replacement. Meanwhile, moving from a pre-operative BMI of 25 (the 25th percentile) to 32 (the 75th percentile) was expected to result in post-operative OHS falling from 42.6 (41.6 to 43.5) to 41.7 (40.8 to 42.7) for hip replacement.

Being in the most deprived IMD group rather than the least deprived was associated with, all else being equal, OKS after knee replacement falling from 37.5 (36.4 to 38.6)

to 35.9 (34.4 to 37.4) and OHS after hip replacement falling from 42.1 (41.2 to 43.0) to 38.9 (37.5 to 40.3). The estimated effect of other patient characteristics on post-operative scores was relatively small.

Figure 4.1. Pre-operative and post-operative Oxford Knee Score (OKS) and Oxford Hip Score (OHS). Kernel density distributions with points showing observed data.

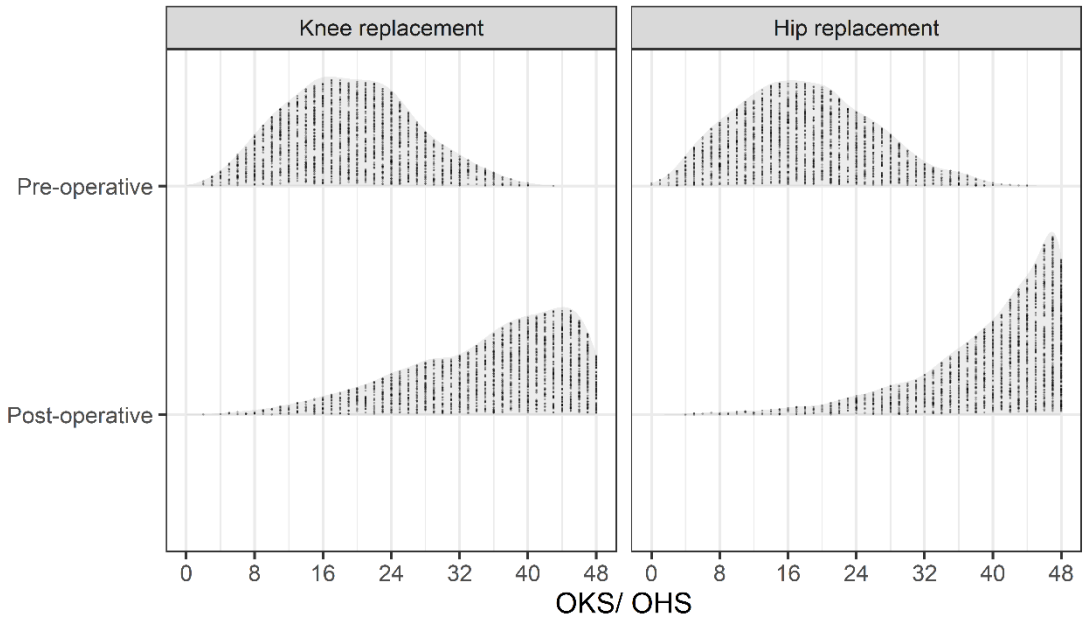


Figure 4.2. Partial effect of pre-operative OKS/ OHS on post-operative OKS/ OHS.

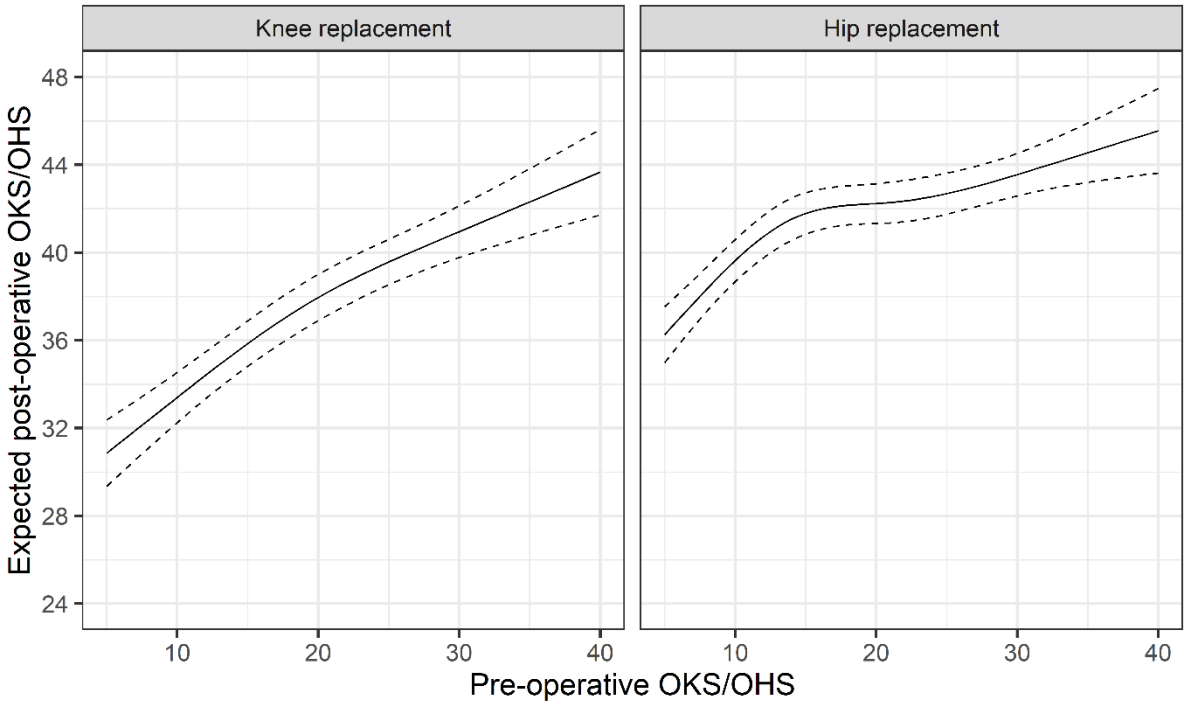


Figure 4.3. Partial effect of age at surgery on post-operative OKS/ OHS.

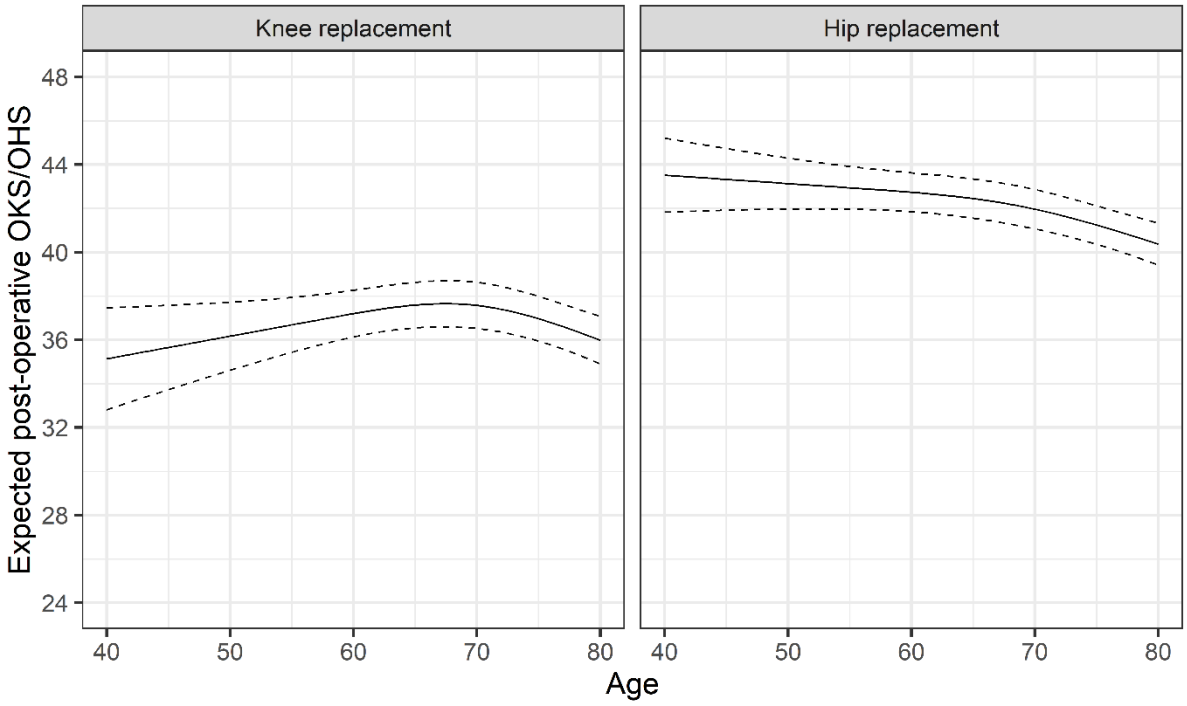


Figure 4.4. Partial effect of sex on post-operative OKS/ OHS.

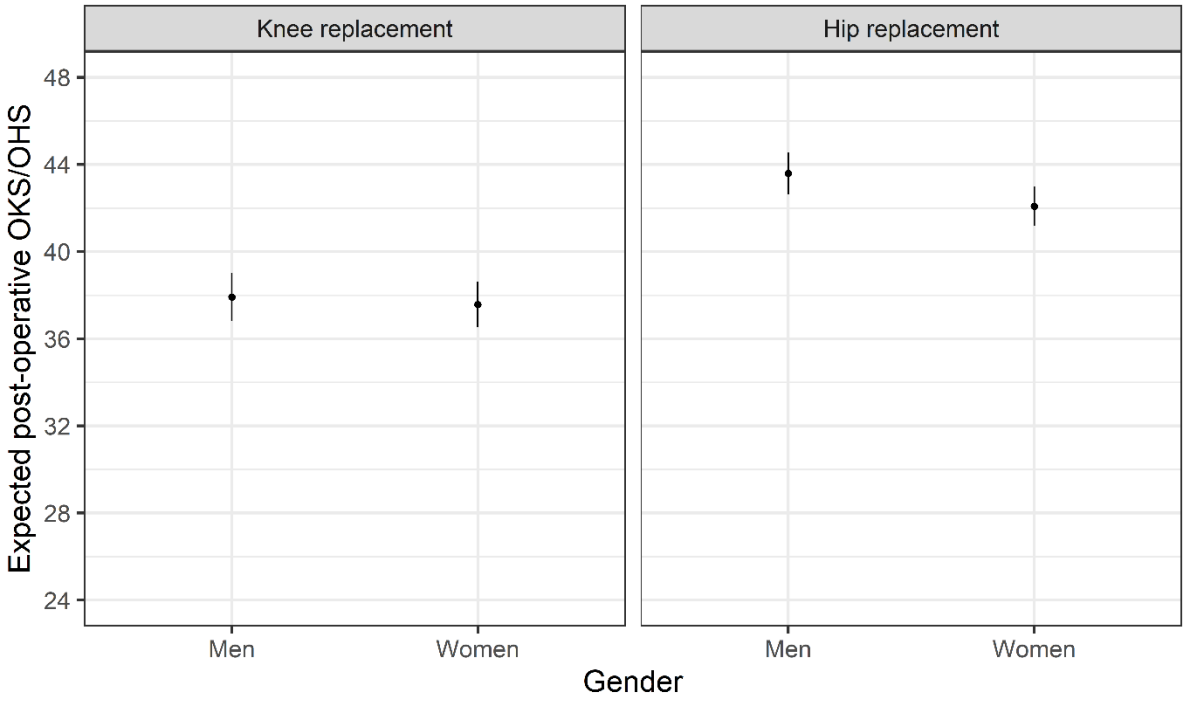


Figure 4.5. Partial effect of index diagnosis on post-operative OKS/OHS.

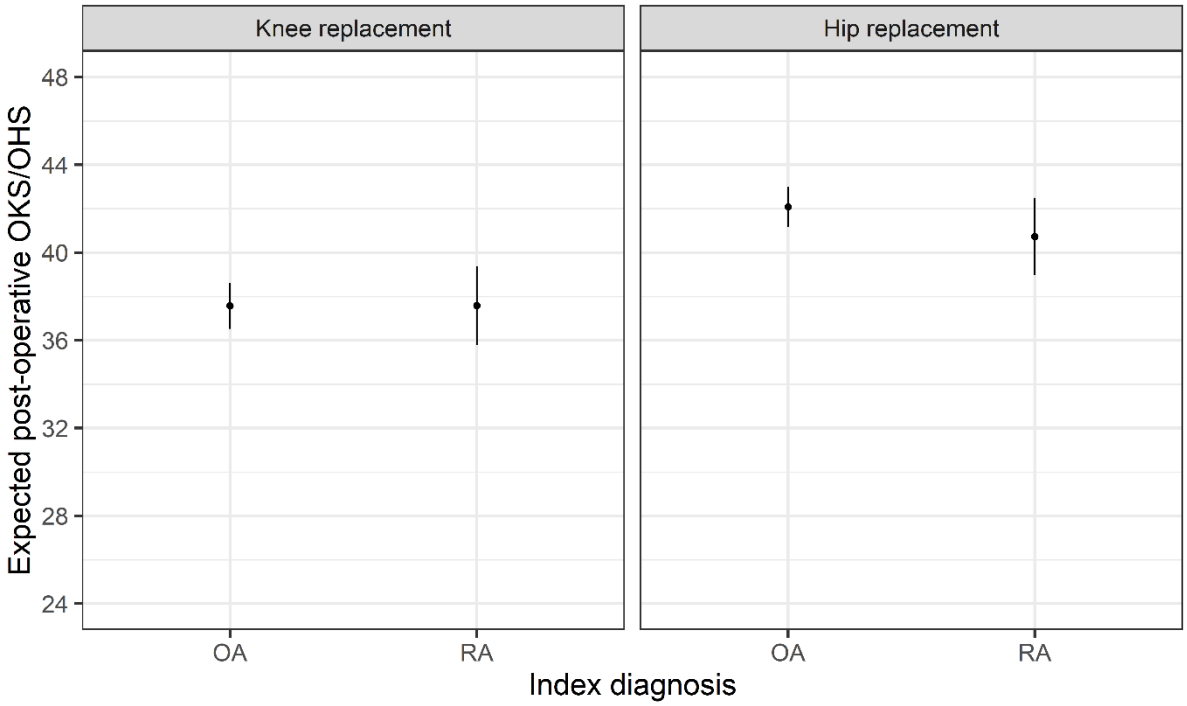


Figure 4.6. Partial effect of Charlson score on post-operative OKS/OHS.

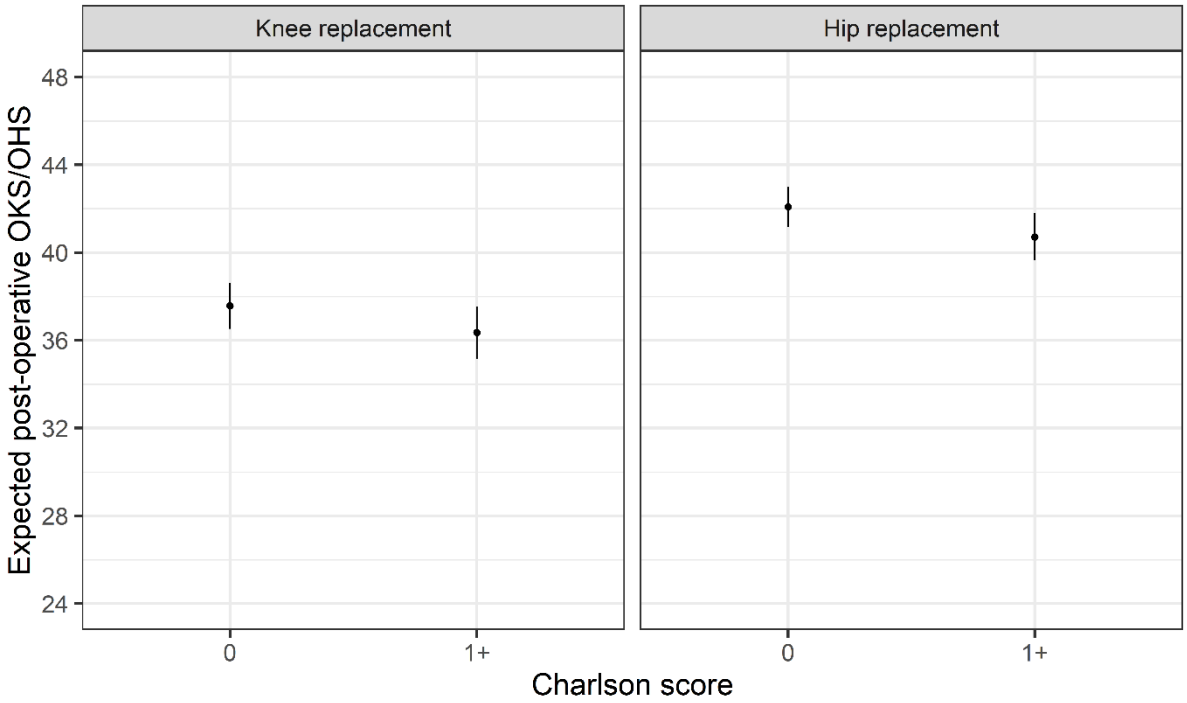


Figure 4.7. Partial effect of IMD on post-operative OKS/OHS

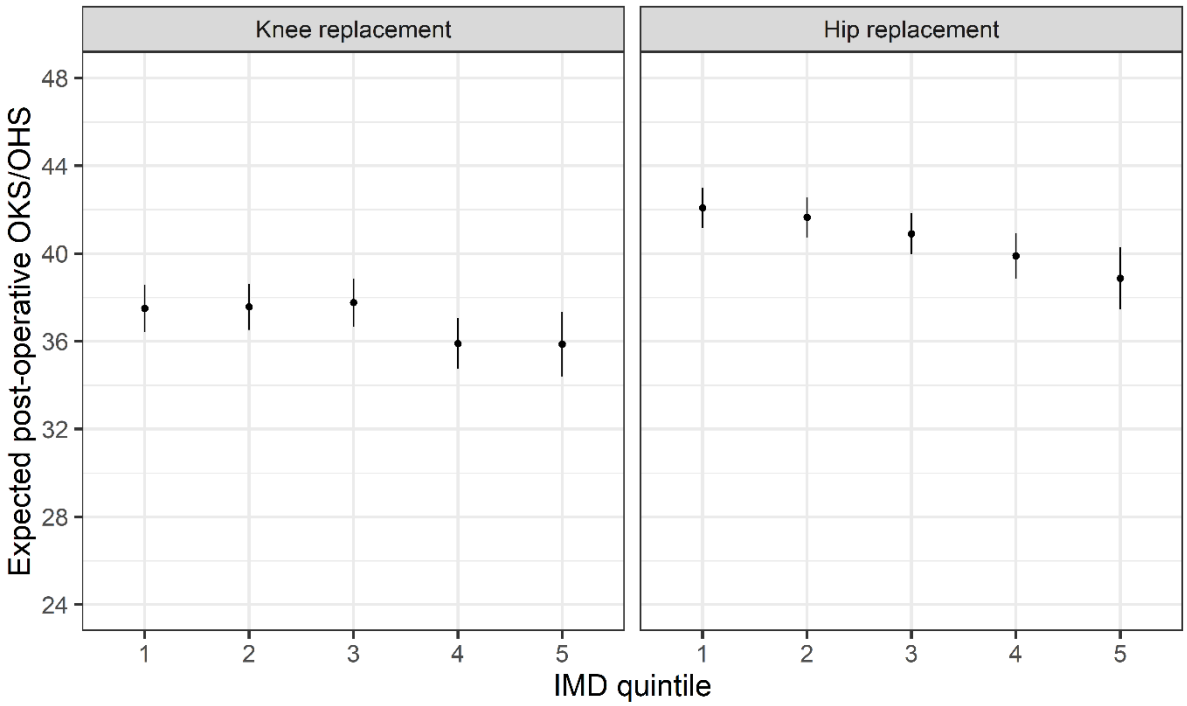


Figure 4.8. Partial effect of BMI on post-operative OKS/ OHS.

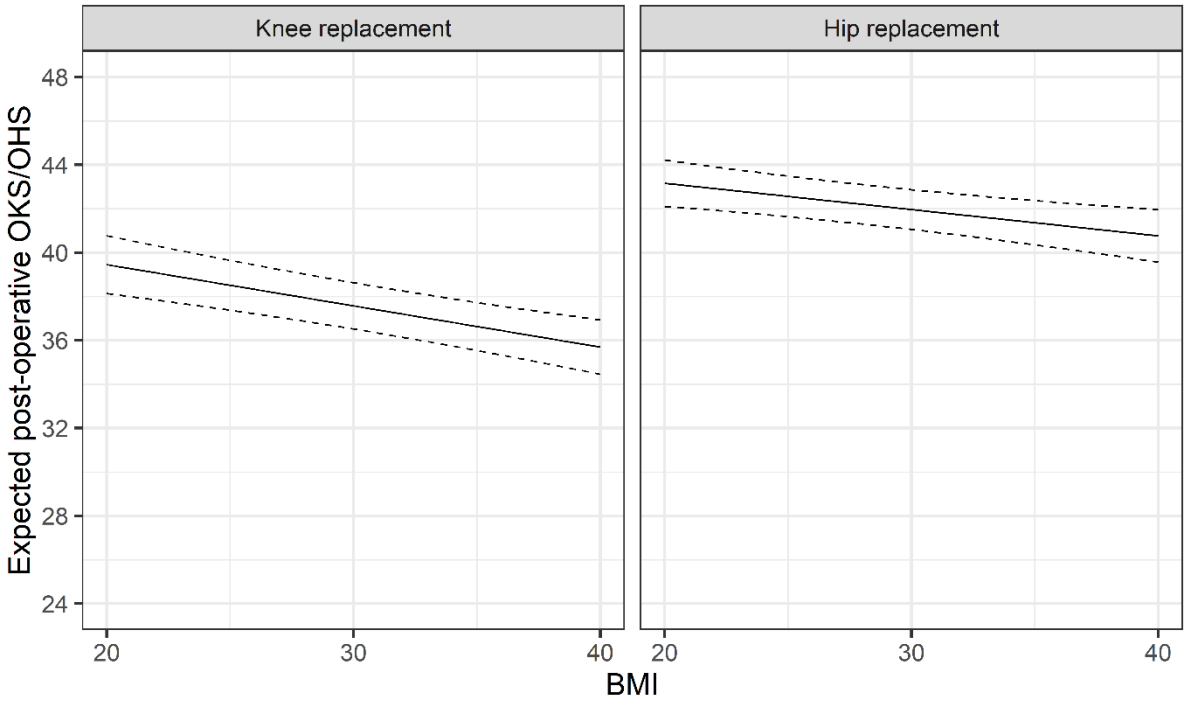
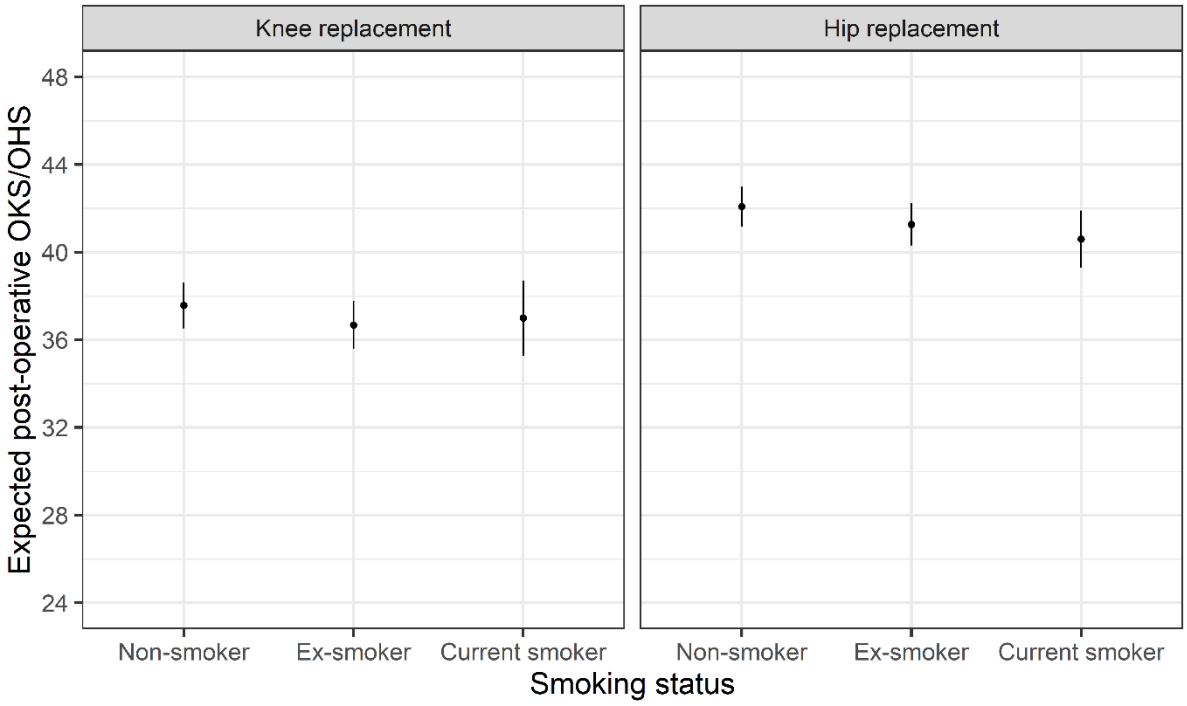


Figure 4.9. Partial effect of smoking status on post-operative OKS/OHS.



Health-related quality-of-life after knee and hip replacement

Study participants who had a primary knee replacement improved from a median pre-operative EQ-5D-3L index of 0.59 (IQR: 0.1 to 0.69) to a post-operative score of 0.76 (0.66 to 1) after surgery, with an average improvement of 0.31 (0.07 to 0.59) and a PoPC of 60% (21% to 100%), see Appendix Table C.3 for details. 8.4% of study participants who had a knee replacement had a worse EQ-5D-3L index after surgery, 10.2 % had the same score, with the remaining 81.4% having improved. 73.0% of study participants achieved the minimally important change of at least 0.074 points. Study participants who had a hip replacement improved from a median pre-operative EQ-5D-3L index of 0.52 (0.06 to 0.62) to a post-operative score of 0.85 (0.69 to 1) after surgery, with an average improvement of 0.41 (0.2 to 0.74) and a PoPC of 78.41 (48.78 to 100), see Appendix Table C.3. 4.7% of study participants who had a hip replacement had a worse EQ-5D-3L index after surgery, 5.4% had the same score, with the remaining 90.0% having improved. 85.7% of study participants achieved the minimally important change of at least 0.074 points. The distributions for pre- and post-operative EQ-5D-3L index are shown in Figure 4.10, with change and PoPC shown in Appendix Figure C.3 and Appendix Figure C.4, respectively.

EQ-5D-3L index after knee and hip replacement stratified by patient characteristics is detailed in Appendix Table C.3. As with OKS and OHS, individuals with lower pre-operative scores generally had lower post-operative scores but a greater absolute improvement than those with higher pre-operative scores. Change in EQ-5D-3L index after knee replacement was broadly similar for different age groups, although the youngest patients started and finished with lower scores. For hip replacement,

different age groups had similar pre-operative scores but older patients generally achieved a lower PoPC from surgery. As with OKS and OHS, women generally reported lower EQ-5D-3L index scores before and after surgery but the gain from surgery was broadly similar between sexes. Study participants with an index diagnosis of rheumatoid arthritis and those with other comorbidities, as measured by the Charlson score, had worse pre-operative EQ-5D-3L index compared to those with an index diagnosis of osteoarthritis and no other comorbidities, respectively. In both cases, although they had a similar absolute change in EQ-5D-3L index, they achieved a lower PoPC from surgery. Study participants who were obese had lower pre-operative EQ-5D-3L index for knee and hip replacement and generally achieved a lower PoPC than other study participants. Study participants in the lowest two IMD quintiles had lower pre-operative EQ-5D-3L index for knee and hip replacement, and although they had a similar absolute change in EQ-5D-3L index, they generally achieved a lower PoPC from surgery. Gains from surgery were broadly similar across smoking status.

The Pareto change in EQ-5D profiles for knee and hip replacement are summarised in Figure 4.11 and Figure 4.12, with an individual's profile having either become better (i.e. at least one dimension had improved, with none worse), had a mixed change (i.e. some dimensions had improved but others had worsened), had no change, or was worse (i.e. at least one dimension had worsened, with none improving). It can be seen that while 85.2% and 92.4% of those in the worst pre-operative EQ-5D-3L index group had a better profile after knee and hip replacement respectively, only 67.6% and 77.1% of those in the best pre-operative EQ-5D-3L index group had a better profile.

The estimated effect of patient characteristics on EQ-5D-3L index after knee and hip replacement are summarised in Appendix Table C.4, with the partial effect of

characteristics shown from Figure 4.13 to Figure 4.20. As with OKS and OHS, pre-operative EQ-5D-3L index was a key determinant of post-operative EQ-5D-3L index, as shown in Figure 4.13. Pre-operative EQ-5D-3L index had a non-linear relationship with post-operative EQ-5D-3L index for hip replacement, but for both knee and hip replacement better pre-operative EQ-5D-3L index was generally associated with better post-operative EQ-5D-3L index. Moving from a pre-operative EQ-5D-3L index of 0.10 (the 25th percentile) to 0.69 (the 75th percentile) was expected to, all else being equal, result in post-operative EQ-5D-3L index improving from 0.74 (0.71 to 0.77) to 0.85 (0.82 to 0.88) for knee replacement. Meanwhile, moving from a pre-operative EQ-5D-3L index of 0.06 (the 25th percentile) to 0.62 (the 75th percentile) was expected to result in post-operative EQ-5D-3L index improving from 0.84 (0.81 to 0.86) to 0.86 (0.84 to 0.89) for hip replacement.

Age at surgery had a non-linear relationship with EQ-5D-3L index after knee and hip replacement, respectively. EQ-5D-3L index was first expected to improve as age increased and then fall at highest age for knee replacement, while EQ-5D-3L index was expected fall as age increased for hip replacement (see Figure 4.14). Moving from an age of 64 (the 25th percentile) to 76 (the 75th percentile) was expected to, all else being equal, result in post-operative EQ-5D-3L index falling from 0.83 (0.8 to 0.86) to 0.82 (0.79 to 0.84) for knee replacement. Meanwhile, moving from an age of 63 (the 25th percentile) to 76 (the 75th percentiles) was expected to result in post-operative EQ-5D-3L index falling from 0.85 (0.82 to 0.88) to 0.82 (0.79 to 0.85) for hip replacement.

As with OKS and OHS, higher BMI was associated with worse post-operative scores for knee and hip replacement after accounting for differences in other patient

characteristics and pre-operative scores. Moving from a pre-operative BMI of 27 (the 25th percentile) to 35 (the 75th percentile) was expected to, all else being equal, result in post-operative EQ-5D-3L index falling from 0.85 (0.82 to 0.88) to 0.80 (0.77 to 0.83) for knee replacement. Meanwhile, moving from a pre-operative BMI of 25 (the 25th percentile) to 32 (the 75th percentile) was expected to result in post-operative EQ-5D-3L index falling from 0.86 (0.83 to 0.89) to 0.83 (0.80 to 0.86) for hip replacement.

Being in the most deprived IMD group rather than the least deprived was associated with, all else being equal, EQ-5D-3L index after knee replacement falling from 0.83 (0.8 to 0.86) to 0.79 (0.75 to 0.83) and EQ-5D-3L index after hip replacement falling from 0.84 (0.81 to 0.87) to 0.75 (0.71 to 0.79). The estimated effects of other patient characteristics on post-operative EQ-5D-3L index after knee and replacement were relatively small.

Figure 4.10. Pre-operative and post-operative Euroqol 5-dimension 3-level (EQ-5D-3L) index. Kernel density distributions with points showing observed data.

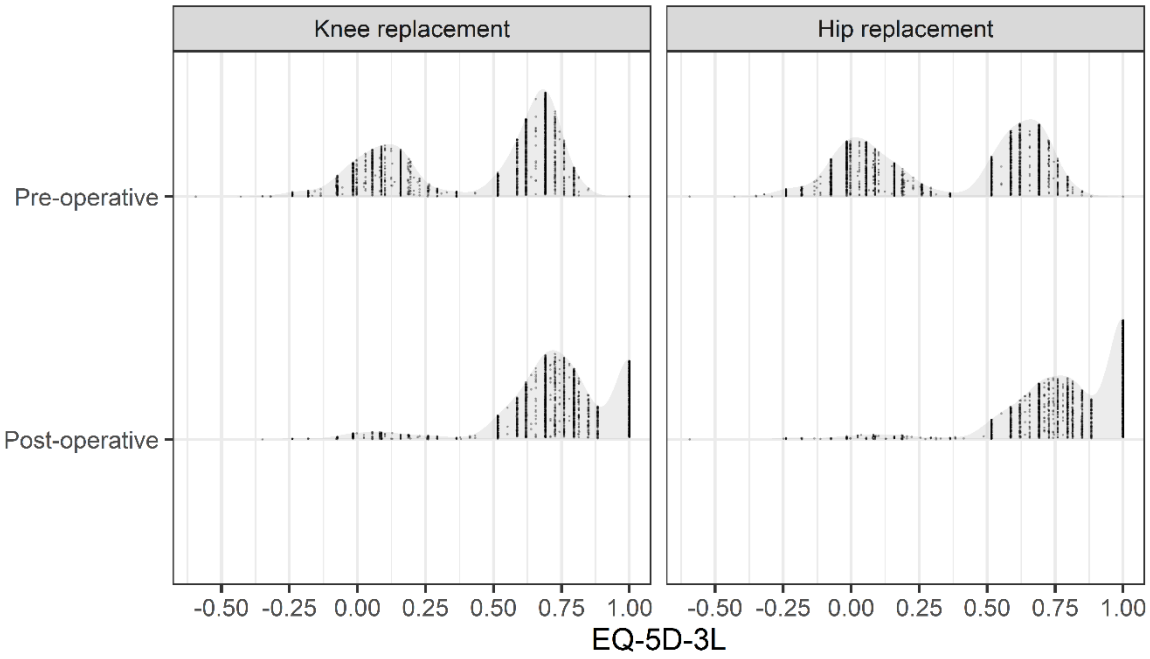


Figure 4.11. Pareto change in EQ-5D-3L for knee replacement. An individual's EQ-5D-3L profile was either better (i.e. at least one dimension had improved, with none worse), had a mixed change (i.e. some dimensions had improved but others had worsened), had no change, or was worse (i.e. at least one dimension had worsened, with none improving) after surgery.

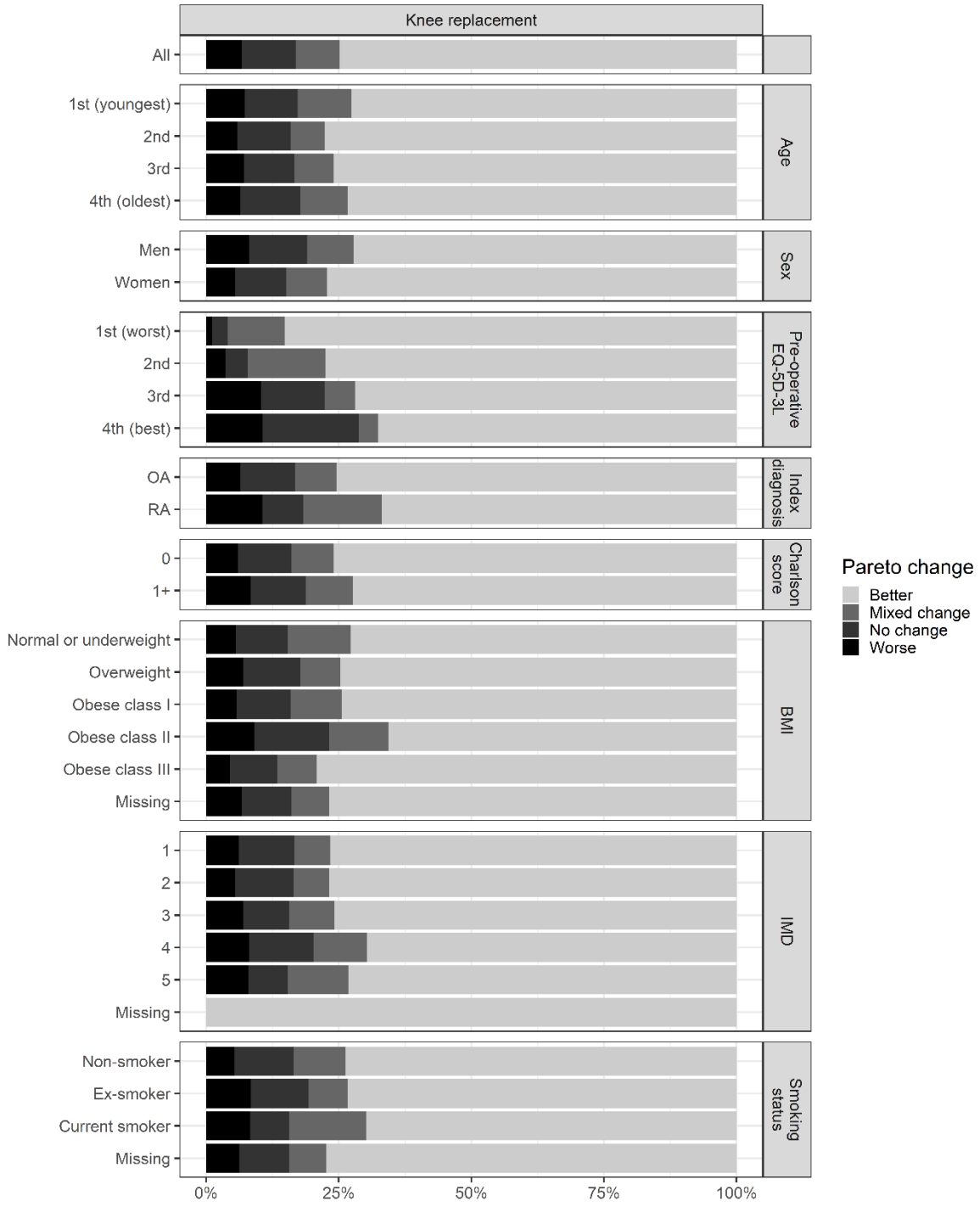


Figure 4.12. Pareto change in EQ-5D-3L for hip replacement. An individual's EQ-5D-3L profile was either better (i.e. at least one dimension had improved, with none worse), had a mixed change (i.e. some dimensions had improved but others had worsened), had no change, or was worse (i.e. at least one dimension had worsened, with none improving) after surgery.

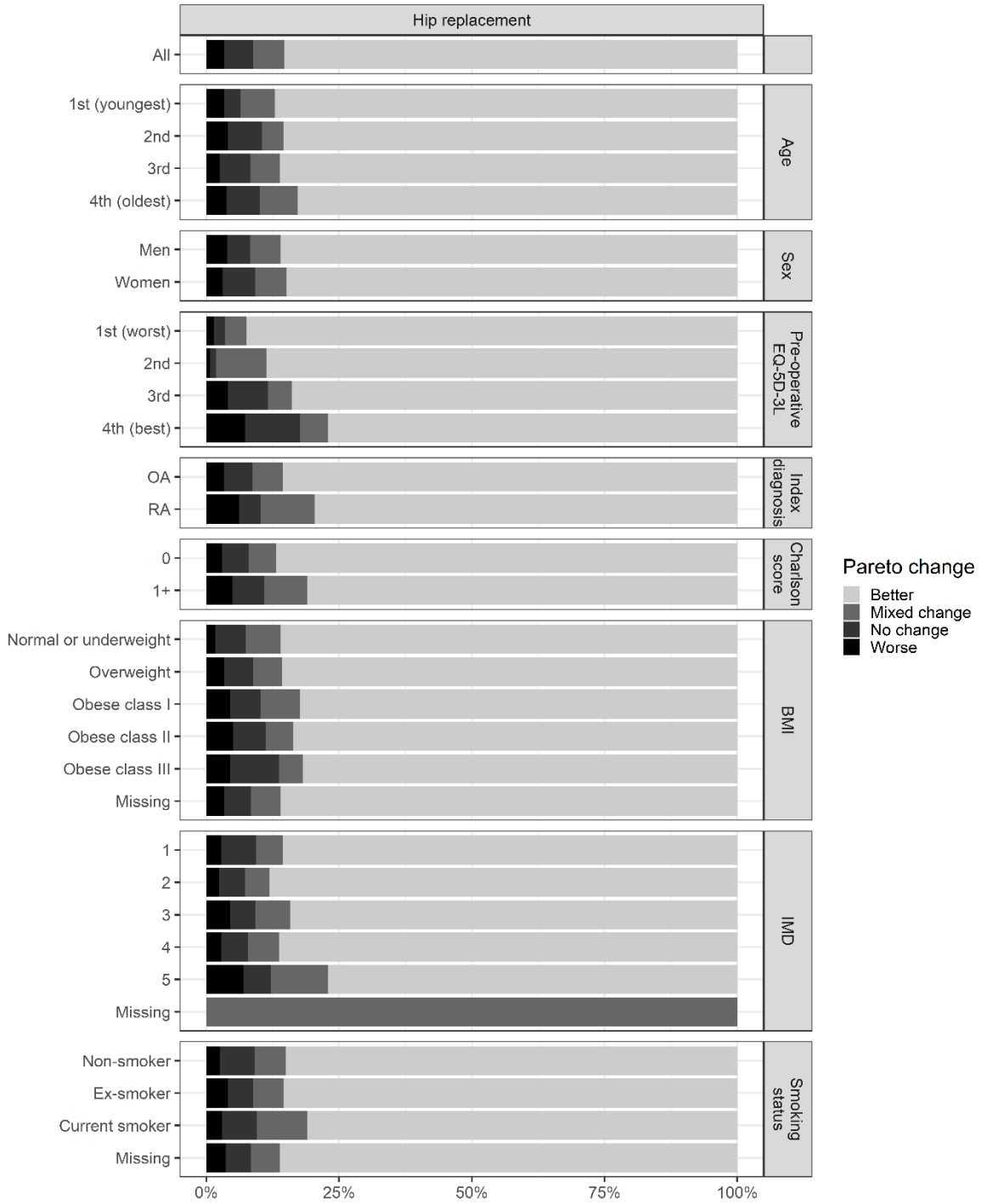


Figure 4.13. Partial effect of pre-operative EQ-5D-3L index on post-operative EQ-5D-3L index.

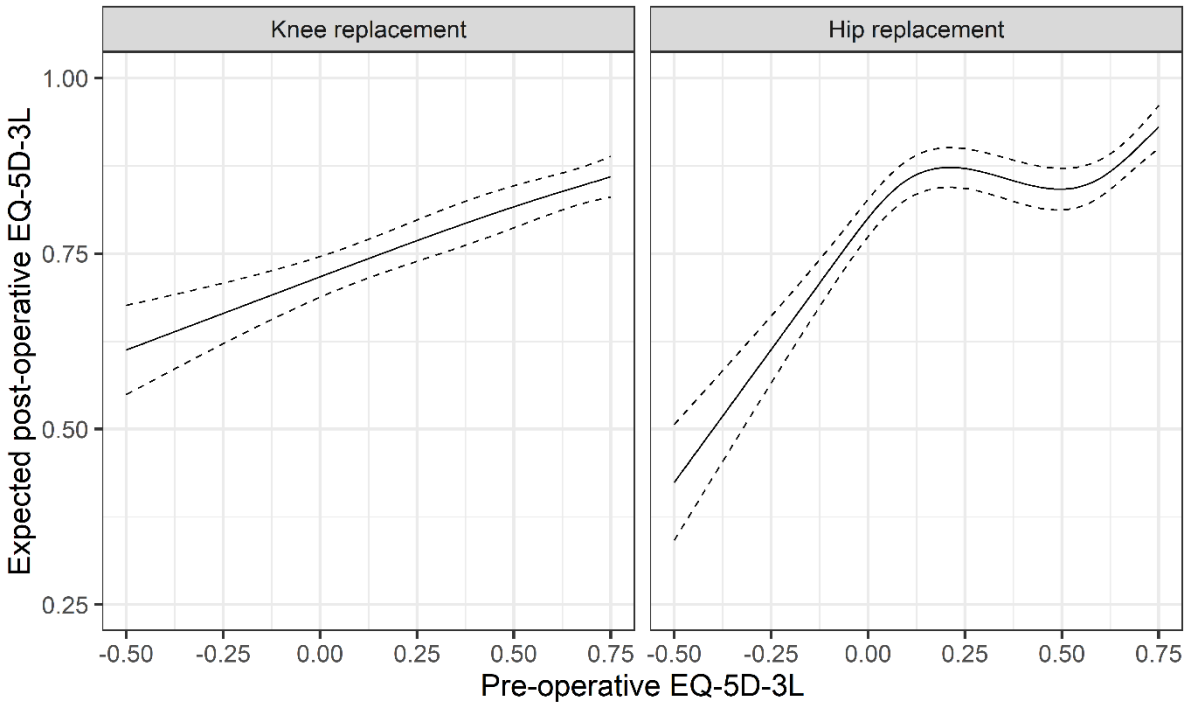


Figure 4.14. Partial effect of age on post-operative EQ-5D-3L index.

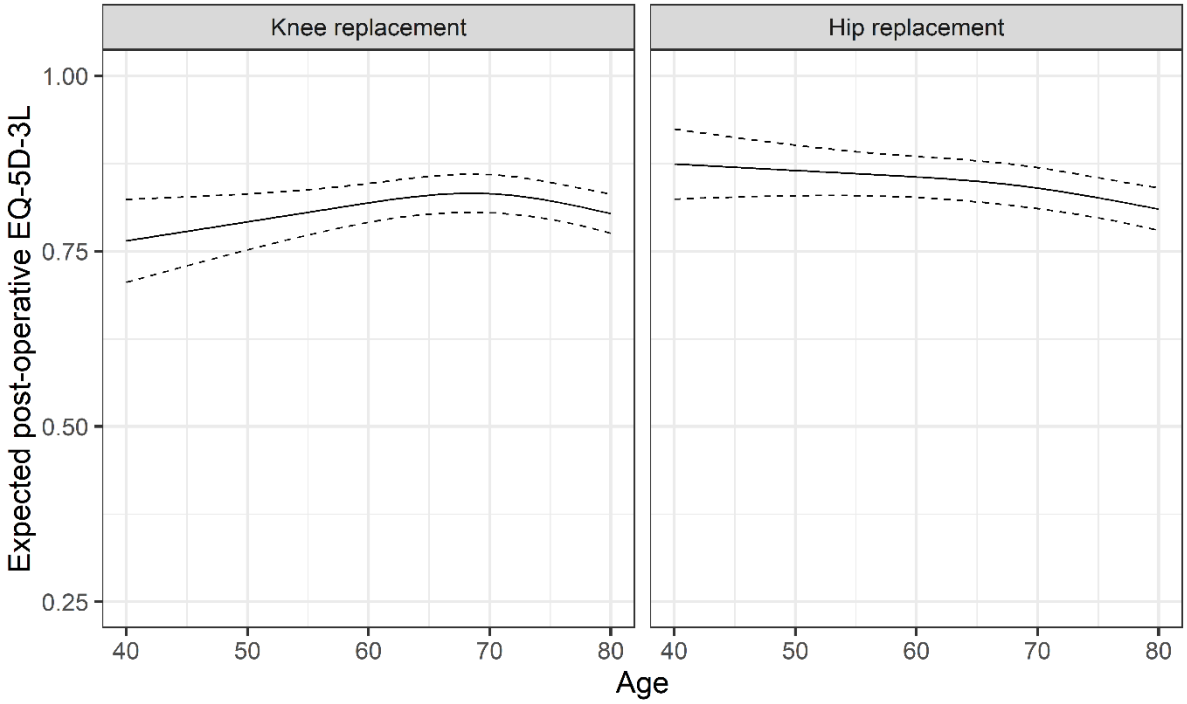


Figure 4.15. Partial effect of index diagnosis on post-operative EQ-5D-3L index.

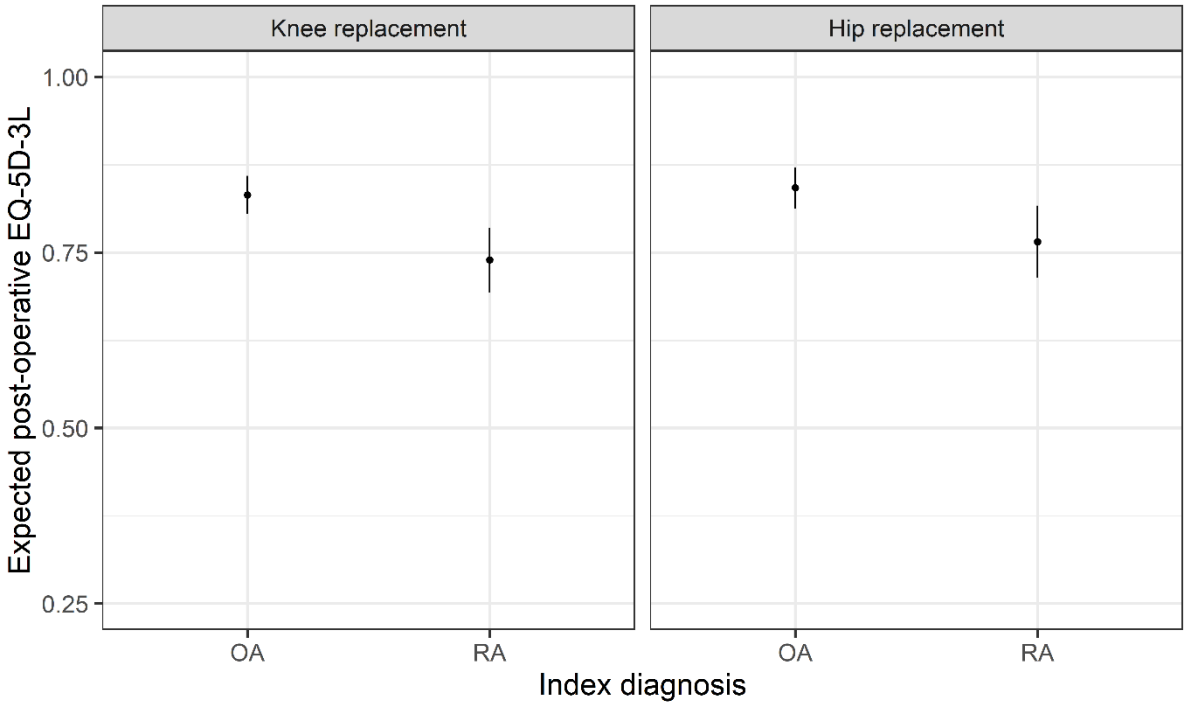


Figure 4.16. Partial effect of Charlson score on post-operative EQ-5D-3L index.

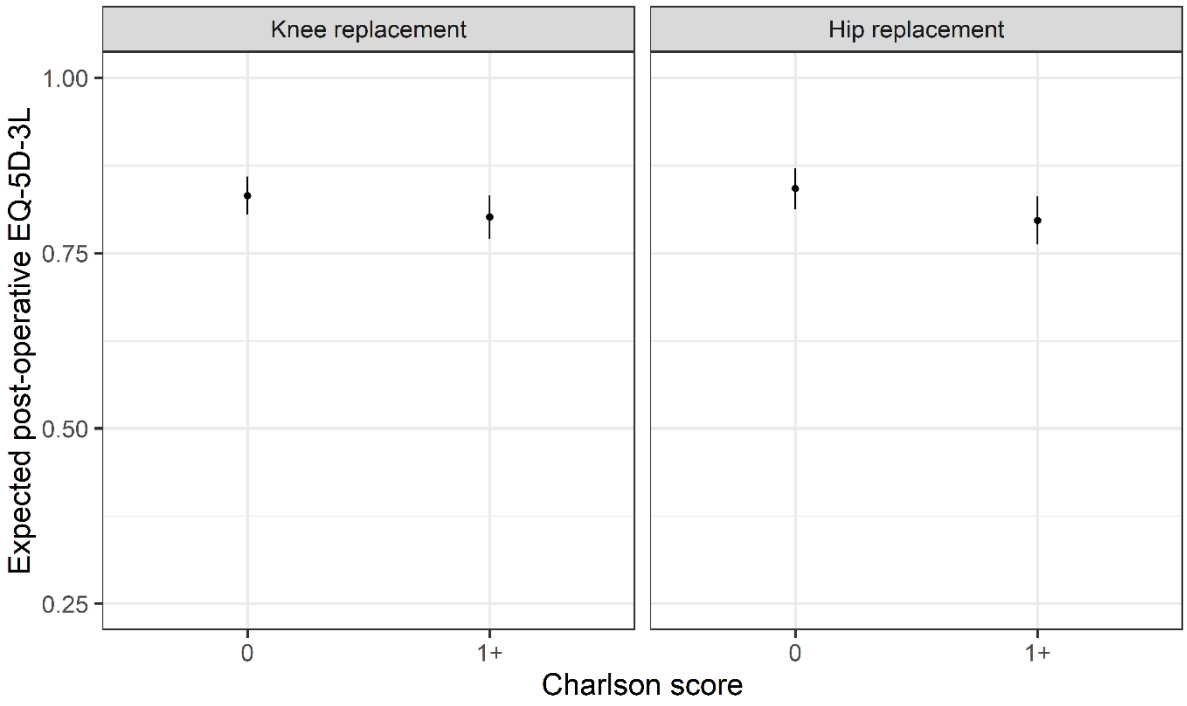


Figure 4.17. Partial effect of IMD on post-operative EQ-5D-3L index.

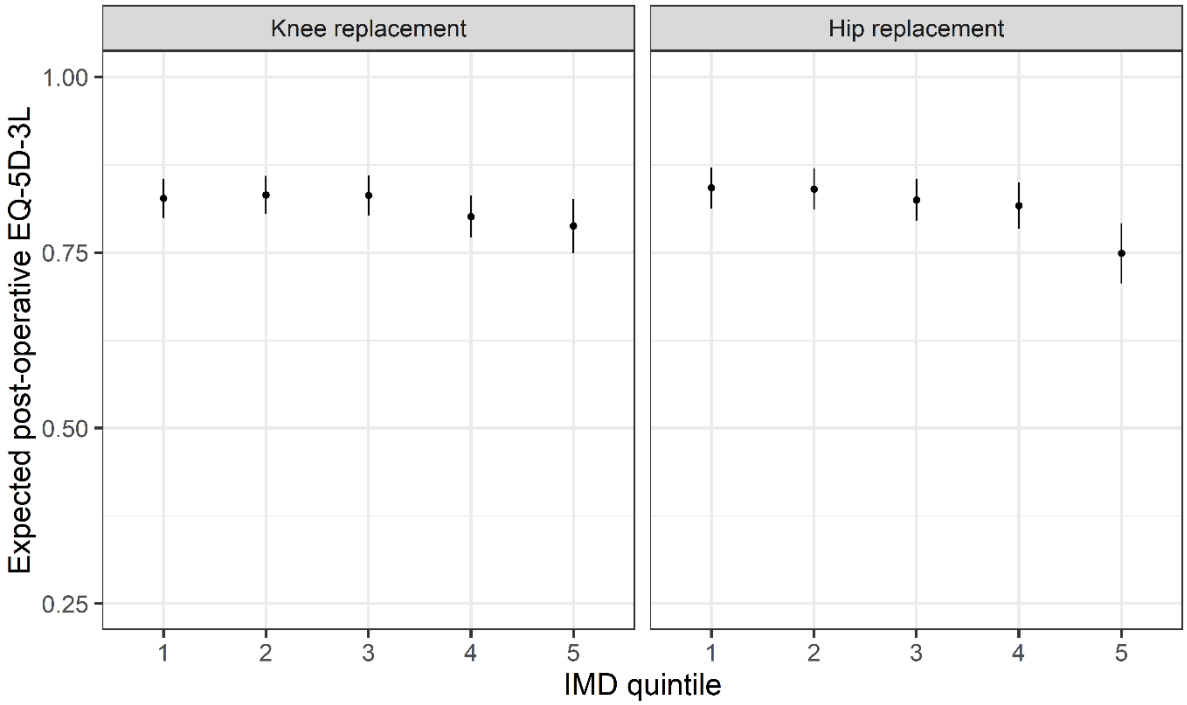


Figure 4.18. Partial effect of BMI on post-operative EQ-5D-3L index.

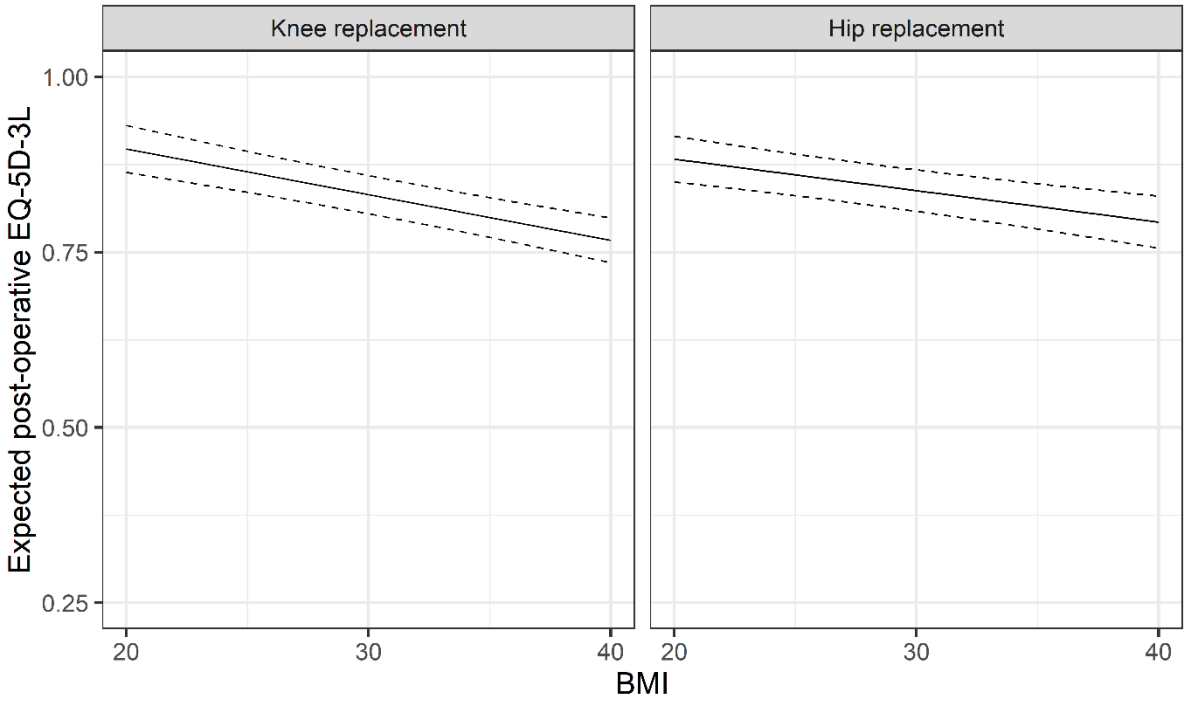


Figure 4.19. Partial effect of sex on post-operative EQ-5D-3L index.

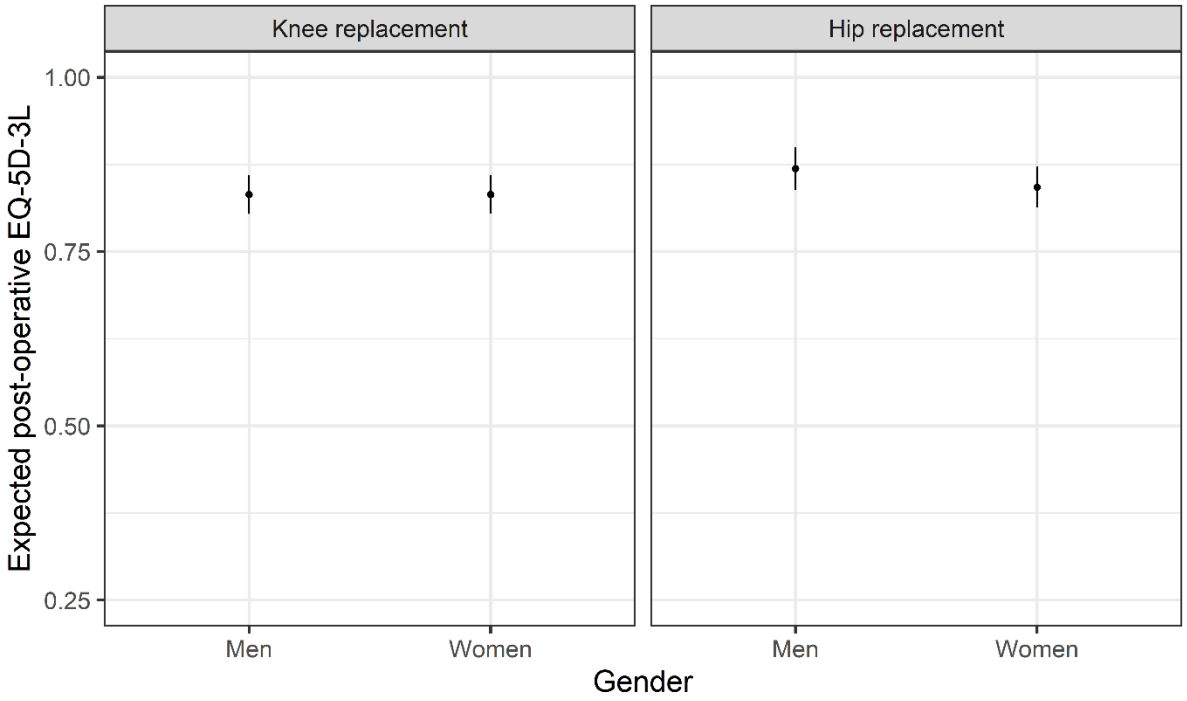
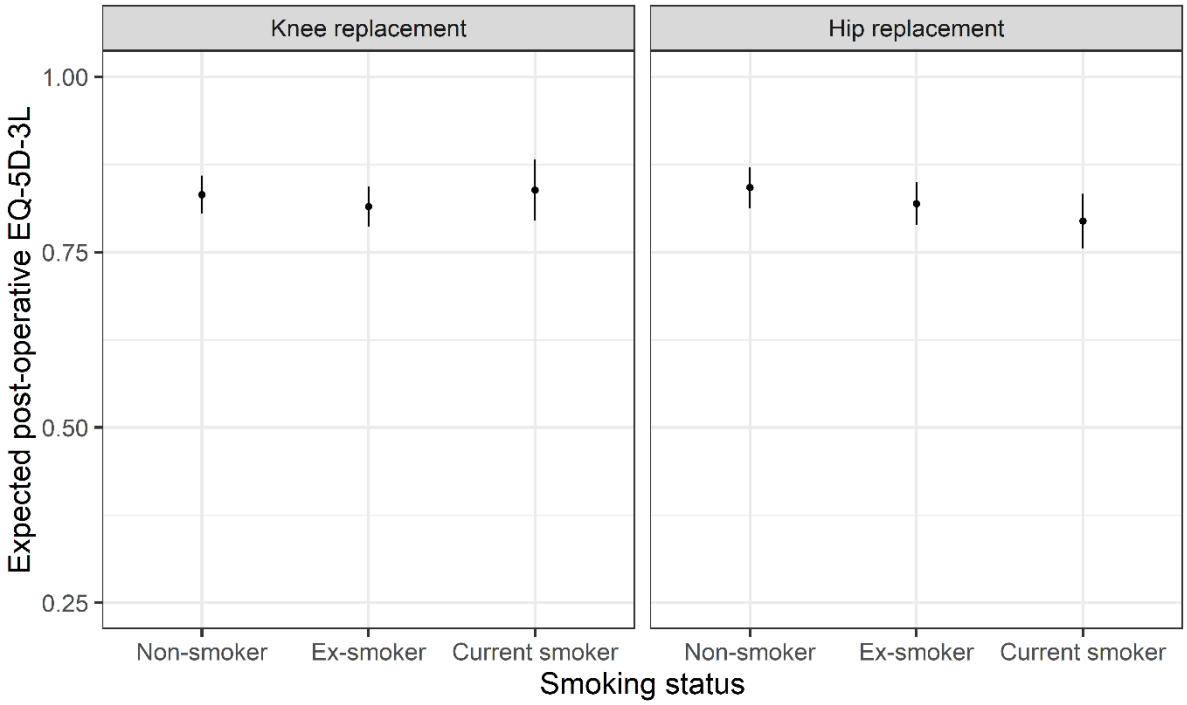


Figure 4.20. Partial effect of smoking status on post-operative EQ-5D-3L index.



Study findings in context

A range of different condition-specific and generic measures have been used to assess patient-reported outcomes in knee and hip replacement. Regardless of the measure used, previous research has consistently found that patients typically achieve significant improvements in patient-reported outcome measures after knee and hip replacement.[9,48] The minimally important change in OKS, OHS, and EQ-5D-3L index has been estimated to be 4 points, 5 points, and 0.074, respectively.[53,190] After knee replacement, 90% and 73% of study participants had achieved the minimal important change in OKS and EQ-5D-3L, respectively. Meanwhile, after hip replacement 96% and 86% of study participants met these targets.

Pre-operative scores have previously been found to be key predictors of post-operative patient-reported outcomes following knee and hip replacement.[54,61–64] As can be seen in the findings presented here, those individuals with a lower pre-operative score attain a greater absolute change in scores after surgery. However, even after controlling for other patient characteristics, lower pre-operative scores are associated with worse post-operative scores. In other words, individuals with a lower pre-operative score can expect to have a greater 'journey' but a worse 'destination' after surgery.[65] The relationship between pre-operative scores and post-operative scores for OKS after knee replacement and OHS and EQ-5D-3L index after hip replacement appears to be non-linear, with the size of the increase in post-operative scores generally being reduced as pre-operative scores reached higher levels and there was less potential for improvement. A similar non-linear relationship for EQ-5D-

3L index has previously been reported for patients undergoing hip replacement in Sweden.[191]

The other patient factors considered in the analyses reported here appeared to have a relatively modest impact on post-operative scores. Older age, higher BMI, and lower socioeconomic status were generally associated with slightly worse outcomes, all in line with the literature.[54,61,66] While they had little effect on joint-specific outcomes, an index diagnosis of rheumatoid arthritis and the presence of other comorbidities were associated with worse overall health-related quality of life. This is consistent with the literature,[67,68] and is unsurprising given that knee or hip replacement is targeted to a specific joint. Even where differences are seen across these patient characteristics, they are unlikely to be considered clinically meaningful. Indeed, while five percent of study participants reported worse OKS after knee replacement and two percent of study participants had a worse OHS after hip replacement, these individuals are not easily identified based on the characteristics considered in this study with all of the different patient profiles considered expected to achieve substantial gains after surgery on average. This is consistent with previous research, with restricting access to surgery using current prediction models expected to lead to worse overall health outcomes because of the difficulty in identifying those who would do worse after surgery.[192]

Strengths and limitations

This study has utilised data from a national programme collecting patient-reported outcomes before and after knee and hip replacements, allowing for large and representative cohorts of knee and hip replacement patients to be included.

Moreover, the linkage of these data to primary care records has allowed for the assessment of the impact of an unprecedented range of patient characteristics on outcomes. Considering both joint-specific outcomes and generic health-related quality of life meant that outcomes could be considered in detail. In addition, continuous variables (pre-operative score, age, and BMI) were not categorised and non-linearity was incorporated where merited which meant that the relationship between these variables and outcomes could be thoroughly assessed.

Only those individuals with no missing patient-reported outcomes were included in the analysis. While the observed characteristics of those with and without patient-reported outcomes recorded were similar, it is possible that data is missing not at random. Data may in fact be missing not at random if, for example, individuals with a poor outcome were more likely to not complete post-operative questionnaires.

Outcomes were only assessed at 6 months after surgery. While the full gains from undergoing surgery have typically been realised by this point,[49] it would have been of interest to consider whether relationships between patient characteristics and outcomes varied with time since surgery. In addition, although the impact of a range of patient factors were considered, there are others that were not available. In particular, patient expectations have been found to be a key determinant of patient-reported outcomes following surgery,[193] and surgeon and surgical centre factors are likely to affect patient outcomes.

Conclusions

Patient-reported outcome measures are much improved after knee and hip replacement. Room for further gains does exist though, particularly for knee

replacement where patients achieved around 60% of their maximum potential improvements on average. Pre-operative patient-reported outcome measures are a key determinant of post-operative measures; scores are expected to be better for those individuals who report better scores prior to surgery. Older age, higher BMI and lower socioeconomic status were generally associated with slightly worse outcomes, but the estimated effects, as with those of the other patient characteristics considered, are unlikely to be clinically meaningful.

5. POST-OPERATIVE COMPLICATIONS AFTER KNEE AND HIP REPLACEMENT

Chapter summary

In this chapter I describe the risks of post-operative complications after knee and hip replacement.

The analysis was informed by routinely collected data from England. Complications (myocardial infarction, venous thromboembolism, prosthetic joint infection, and mortality) were identified over the 90 days after surgery. The cumulative incidence of these events is described.

After 90 days following surgery, the risk of venous thromboembolism was 0.85% and 1.05%, the risk of myocardial infarction was 0.41% and 0.41%, the risk of prosthetic joint infections was 0.21% and 0.15%, the risk of mortality was 0.46% and 0.63% after knee and hip replacement, respectively. Risks of myocardial infarction and mortality appeared to be higher for older age groups, men, and those with comorbidities. In addition, risks of myocardial infarction after knee replacement and mortality after hip replacement also appeared to be higher for those individuals with an index diagnosis of rheumatoid arthritis.

Background

As described in Chapter 1, there remains uncertainty around the risks of post-operative complications after knee and hip replacement and, in particular, the role of patient heterogeneity. The analysis reported here is informed by data from CPRD-HES on individuals who had primary knee and hip replacement in England (see Chapter 2 for more details). The observed cumulative incidence of complications (myocardial infarction, venous thromboembolism, prosthetic joint infection, and mortality) at 90 days after surgery is reported. Both the overall cumulative incidence, and incidence stratified by patient characteristics is described.

Study participants

10,260 and 10,961 individuals were in the knee and hip replacement cohorts, respectively. The characteristics of the included individuals are summarised in Table 5.1. The median age was 71 for knee replacement and 70 for hip replacement. Both cohorts had more women, with most individuals having an index diagnosis of osteoarthritis and a Charlson score of 0.

Table 5.1. Characteristics of study participants

	Knee replacement	**Hip replacement**
N	10,260	10,929
Age at diagnosis (median [IQR])	71 [64, 77]	70 [62, 76]
Age at diagnosis quartile* (n (%))		

	Knee replacement	Hip replacement
1st (youngest)	2,480 (24)	2,539 (23)
2nd	2,604 (25)	2,806 (26)
3rd	2,487 (24)	2,478 (23)
4th (oldest)	2,689 (26)	3,106 (28)
Sex: male (n (%))	4,426 (43)	4,515 (41)
Index diagnosis (n (%))		
OA	9,409 (92)	10,295 (94)
RA	851 (8)	634 (6)
Charlson score (n (%))		
0	7,804 (76)	8,657 (79)
1+	2,456 (24)	2,272 (21)
BMI (median [IQR])	30 [27, 34]	28 [25, 32]
BMI group (n (%))		

	Knee replacement	Hip replacement
Normal or underweight (<25)	660 (6)	1,074 (10)
Overweight (≥25 and <30)	1,593 (16)	1,650 (15)
Obese class I (≥30 and <35)	1,467 (14)	1,087 (10)
Obese class II (≥35 and <40)	795 (8)	444 (4)
Obese class III (≥40)	264 (3)	114 (1)
Missing	5,481 (53)	6,560 (60)
IMD (n (%))		
1 (least deprived)	2,330 (23)	2,763 (25)
2	2,487 (24)	2,790 (26)
3	2,383 (23)	2,473 (23)
4	1,930 (19)	1,917 (18)

	Knee replacement	Hip replacement
5 (most deprived)	1,121 (11)	980 (9)
Missing	9 (0)	6 (0)
Smoking status (n (%))		
Non-smoker	2,737 (27)	2,535 (23)
Ex-smoker	2,442 (24)	2,228 (20)
Current smoker	486 (5)	713 (7)
Missing	4,595 (45)	5,453 (50)

*Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. IQR: interquartile range; OA: osteoarthritis; RA: rheumatoid arthritis; BMI: body mass index; IMD: index of multiple deprivation. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

Cumulative incidence of post-operative complications

The overall 90-day cumulative incidence of venous thromboembolism was 0.85% (0.67% to 1.03%) after knee replacement and 1.05% (0.86% to 1.25%) after hip replacement, as reported in Table 5.2. The 90-day cumulative incidence of myocardial

infarction was 0.41% (0.29% to 0.54%) after knee replacement and 0.41% (0.29% to 0.53%) after hip replacement, as detailed in Table 5.3. The 90-day cumulative incidence of prosthetic joint infections was 0.21% (0.12% to 0.30%) after knee replacement and 0.15% (0.08% to 0.22%) after hip replacement, as shown in Table 5.4, and the overall 90-day cumulative incidence of mortality was 0.46% (0.32% to 0.59%) after knee replacement and 0.63% (0.48% to 0.78%) after hip replacement, as reported in Table 5.5.

Risks of myocardial infarction and mortality appeared to be higher for older age groups, men, and those with a Charlson score of 1 or more. In addition, risks of myocardial infarction after knee replacement and mortality after hip replacement also appeared to be higher for those individuals with an index diagnosis of rheumatoid arthritis. The risks of venous thromboembolism and prosthetic joint infections after knee and hip replacement appeared to be broadly similar for different patient profiles.

The 90-day cumulative incidence of myocardial infarction for the youngest age groups was, for example, 0.08% (0.00% to 0.19%) after knee replacement and 0.12% (0.00% to 0.25%) after hip replacement, and 0.94% (0.57% to 1.30%) and 0.88% (0.55% to 1.21%) respectively for the oldest age groups. It was 0.66% (0.42% to 0.90%) and 0.42% (0.23% to 0.61%) for men, compared to 0.23% (0.10% to 0.35%) and 0.39% (0.24% to 0.55%) for women. It was 0.54% (0.25% to 0.83%) and 0.76% (0.40% to 1.12%) for those with a Charlson score of 1 or more, compared to 0.37% (0.24% to 0.51%) and 0.31% (0.20% to 0.43%) for those with a Charlson score of 0. And, after knee replacement, it was 0.95% (0.29% to 1.60%) for those with an index diagnosis of

rheumatoid arthritis compared to 0.36% (0.24% to 0.49%) for those with an index diagnosis of osteoarthritis.

The 90-day cumulative incidence of mortality was 0.12% (0.00% to 0.26%) after knee replacement and 0.08% (0.00% to 0.19%) after hip replacement for the youngest age groups and 0.98% (0.60% to 1.35%) and 1.46% (1.03% to 1.88%) for the oldest age groups. It was 0.53% (0.31% to 0.74%) and 0.76% (0.50% to 1.01%) for men, compared to 0.40% (0.24% to 0.56%) and 0.53% (0.36% to 0.71%) for women. It was 0.82% (0.46% to 1.18%) and 1.24% (0.78% to 1.70%) for those with a Charlson score of 1 or more, compared to 0.34% (0.21% to 0.47%) and 0.47% (0.32% to 0.61%) for those with a Charlson score of 0. And, after hip replacement, it was 1.11% (0.29% to 1.92%) for those with an index diagnosis of rheumatoid arthritis compared to 0.60% (0.45% to 0.75%) for those with an index diagnosis of osteoarthritis.

Table 5.2. Cumulative incidence of venous thromboembolism after knee or hip replacement

	Knee replacement		**Hip replacement**	
	VTE/ person years	**90-day cumulative incidence (% (95% CI))**	**VTE/ person years**	**90-day cumulative incidence (% (95% CI))**
Total	86/ 2463	0.85% (0.67% to 1.03%)	114/ 2631	1.05% (0.86% to 1.25%)
Age group*				
1st (youngest)	15/ 595	0.61% (0.30% to 0.92%)	32/ 612	1.27% (0.83% to 1.71%)

	Knee replacement		Hip replacement	
	VTE/ person years	**90-day cumulative incidence (% (95% CI))**	**VTE/ person years**	**90-day cumulative incidence (% (95% CI))**
2nd	25/ 625	0.97% (0.59% to 1.35%)	34/ 675	1.22% (0.81% to 1.63%)
3rd	27/ 597	1.10% (0.69% to 1.51%)	30/ 598	1.22% (0.79% to 1.65%)
4th (oldest)	19/ 646	0.72% (0.40% to 1.04%)	18/ 745	0.59% (0.32% to 0.86%)
Sex				
Male	39/ 1059	0.90% (0.62% to 1.18%)	46/ 1086	1.03% (0.74% to 1.33%)
Female	47/ 1404	0.81% (0.58% to 1.04%)	68/ 1545	1.07% (0.82% to 1.32%)
Index diagnosis				
OA	80/ 2256	0.86% (0.67% to 1.05%)	109/ 2477	1.07% (0.87% to 1.27%)
RA	6/ 206	0.71% (0.14% to 1.27%)	5/ 154	0.79% (0.10% to 1.48%)
Charlson				
0	61/ 1880	0.79% (0.59% to 0.99%)	91/ 2088	1.06% (0.84% to 1.28%)

	Knee replacement		Hip replacement	
	VTE/ person years	**90-day cumulative incidence (% (95% CI))**	**VTE/ person years**	**90-day cumulative incidence (% (95% CI))**
1+	25/ 583	1.04% (0.64% to 1.45%)	23/ 542	1.03% (0.61% to 1.45%)
BMI group (%)				
Normal or underweight (<25)	3/ 158	0.81% (0.57% to 1.05%)	11/ 257	1.14% (0.88% to 1.40%)
Overweight (≥25 and <30)	10/ 383	0.46% (0.00% to 0.98%)	14/ 397	1.04% (0.43% to 1.65%)
Obese class I (≥30 and <35)	15/ 348	1.05% (0.52% to 1.57%)	11/ 261	1.03% (0.42% to 1.63%)
Obese class II (≥35 and <40)	10/ 189	1.28% (0.49% to 2.07%)	2/ 107	0.46% (0.00% to 1.08%)
Obese class III (≥40)	4/ 63	1.55% (0.03% to 3.04%)	2/27	1.79% (0.00% to 4.23%)
Missing	44/ 1321	0.64% (0.24% to 1.03%)	74/ 1582	0.86% (0.41% to 1.30%)
IMD quintile (%)				
1st (least deprived)	18/ 559	0.78% (0.42% to 1.14%)	32/ 667	1.17% (0.76% to 1.57%)

	Knee replacement		Hip replacement	
	VTE/ person years	**90-day cumulative incidence (% (95% CI))**	**VTE/ person years**	**90-day cumulative incidence (% (95% CI))**
2nd	26/ 595	1.06% (0.65% to 1.46%)	27/ 671	0.98% (0.61% to 1.35%)
3rd	21/ 571	0.90% (0.51% to 1.28%)	22/ 595	0.90% (0.52% to 1.27%)
4th	12/ 466	0.63% (0.27% to 0.98%)	20/ 463	1.05% (0.59% to 1.51%)
5th (most deprived)	9/ 269	0.81% (0.28% to 1.34%)	13/ 234	1.36% (0.62% to 2.09%)
Missing	0/ 2	0.00% (0.00% to 0.00%)	0/ 1	0.00% (0.00% to 0.00%)
Smoking status				
Non-smoker	25/ 656	0.64% (0.00% to 1.36%)	23/ 609	0.99% (0.26% to 1.72%)
Ex-smoker	27/ 584	1.13% (0.70% to 1.55%)	21/ 535	0.95% (0.55% to 1.36%)
Current smoker	3/ 115	0.68% (0.44% to 0.92%)	7/ 172	1.17% (0.88% to 1.45%)
Missing	31/ 1108	0.93% (0.56% to 1.29%)	63/ 1314	0.92% (0.54% to 1.29%)

Cumulative incidence of venous thromboembolism (VTE) 90 days after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

Table 5.3. Cumulative incidence of myocardial infarction after knee or hip replacement

	Knee replacement		**Hip replacement**	
	MI/ person years	**90-day cumulative incidence (% (95% CI))**	**MI/ person years**	**90-day cumulative incidence (% (95% CI))**
Total	42/ 2470	0.41% (0.29% to 0.54%)	44/ 2641	0.41% (0.29% to 0.53%)
Age group*				
1st (youngest)	2/ 597	0.08% (0.00% to 0.19%)	3/ 616	0.12% (0.00% to 0.25%)
2nd	5/ 628	0.19% (0.02% to 0.36%)	5/ 680	0.18% (0.02% to 0.34%)
3rd	10/ 600	0.41% (0.16% to 0.66%)	9/ 602	0.37% (0.13% to 0.60%)
4th (oldest)	25/ 645	0.94% (0.57% to 1.30%)	27/ 743	0.88% (0.55% to 1.21%)
Sex				

	Knee replacement		Hip replacement	
	MI/ person years	**90-day cumulative incidence (% (95% CI))**	**MI/ person years**	**90-day cumulative incidence (% (95% CI))**
Male	29/ 1060	0.66% (0.42% to 0.90%)	19/ 1089	0.42% (0.23% to 0.61%)
Female	13/ 1410	0.23% (0.10% to 0.35%)	25/ 1552	0.39% (0.24% to 0.55%)
Index diagnosis				
OA	34/ 2263	0.36% (0.24% to 0.49%)	43/ 2487	0.42% (0.30% to 0.55%)
RA	8/ 206	0.95% (0.29% to 1.60%)	1/ 154	0.16% (0.00% to 0.48%)
Charlson				
0	29/ 1885	0.37% (0.24% to 0.51%)	27/ 2099	0.31% (0.20% to 0.43%)
1+	13/ 584	0.54% (0.25% to 0.83%)	17/ 543	0.76% (0.40% to 1.12%)
BMI group				
Normal or underweight (<25)	3/ 158	0.40% (0.24% to 0.57%)	8/ 257	0.26% (0.14% to 0.39%)

	Knee replacement		Hip replacement	
	MI/ person years	**90-day cumulative incidence (% (95% CI))**	**MI/ person years**	**90-day cumulative incidence (% (95% CI))**
Overweight (≥25 and <30)	9/ 383	0.46% (0.00% to 0.97%)	8/ 398	0.75% (0.23% to 1.27%)
Obese class I (≥30 and <35)	4/ 350	0.28% (0.01% to 0.55%)	10/ 261	0.93% (0.35% to 1.50%)
Obese class II (≥35 and <40)	3/ 190	0.38% (0.00% to 0.82%)	1/ 107	0.23% (0.00% to 0.67%)
Obese class III (≥40)	1/64	0.38% (0.00% to 1.13%)	0/ 27	0.00% (0.00% to 0.00%)
Missing	22/ 1325	0.57% (0.20% to 0.94%)	17/ 1592	0.49% (0.15% to 0.83%)
IMD quintile				
1st (least deprived)	9/ 561	0.39% (0.14% to 0.64%)	12/ 670	0.44% (0.19% to 0.68%)
2nd	8/ 598	0.33% (0.10% to 0.55%)	12/ 673	0.43% (0.19% to 0.68%)
3rd	12/ 573	0.51% (0.22% to 0.80%)	5/ 598	0.20% (0.03% to 0.38%)
4th	7/ 466	0.37% (0.09% to 0.63%)	11/ 464	0.58% (0.24% to 0.92%)

	Knee replacement		Hip replacement	
	MI/ person years	**90-day cumulative incidence (% (95% CI))**	**MI/ person years**	**90-day cumulative incidence (% (95% CI))**
5th (most deprived)	6/ 269	0.54% (0.11% to 0.97%)	4/ 235	0.41% (0.01% to 0.82%)
Missing	0/ 2	0.00% (0.00% to 0.00%)	0/ 1	0.00% (0.00% to 0.00%)
Smoking status				
Non-smoker	7/ 659	0.64% (0.00% to 1.36%)	12/ 611	0.42% (0.00% to 0.89%)
Ex-smoker	13/ 585	0.54% (0.25% to 0.83%)	15/ 536	0.68% (0.34% to 1.02%)
Current smoker	3/ 116	0.42% (0.23% to 0.60%)	3/ 173	0.26% (0.12% to 0.40%)
Missing	19/ 1110	0.26% (0.07% to 0.45%)	14/ 1322	0.48% (0.21% to 0.75%)

Cumulative incidence of myocardial infarction (MI) 90 days after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

Table 5.4. Cumulative incidence of prosthetic joint infections after knee or hip replacement

	Knee replacement		**Hip replacement**	
	PJI/ person years	**90-day cumulative incidence (% (95% CI))**	**PJI/ person years**	**90-day cumulative incidence (% (95% CI))**
Total	21/ 2473	0.21% (0.12% to 0.30%)	16/ 2646	0.15% (0.08% to 0.22%)
Age group*				
1st (youngest)	7/ 596	0.29% (0.07% to 0.50%)	4/ 616	0.16% (0.00% to 0.31%)
2nd	5/ 628	0.19% (0.02% to 0.36%)	3/ 681	0.11% (0.00% to 0.23%)
3rd	6/ 600	0.24% (0.05% to 0.44%)	4/ 602	0.16% (0.00% to 0.32%)
4th (oldest)	3/ 649	0.11% (0.00% to 0.24%)	5/ 747	0.16% (0.02% to 0.30%)
Sex				
Male	9/ 1063	0.21% (0.07% to 0.34%)	8/ 1091	0.18% (0.05% to 0.30%)
Female	12/ 1409	0.21% (0.09% to 0.32%)	8/ 1555	0.13% (0.04% to 0.21%)
Index diagnosis				
OA	19/ 2266	0.20% (0.11% to 0.30%)	14/ 2492	0.14% (0.07% to 0.21%)
RA	2/ 207	0.23% (0.00% to 0.56%)	2/ 154	0.32% (0.00% to 0.76%)
Charlson				
0	16/ 1887	0.21% (0.11% to 0.31%)	12/2101	0.14% (0.06% to 0.22%)

	Knee replacement		Hip replacement	
	PJI/ person years	**90-day cumulative incidence (% (95% CI))**	**PJI/ person years**	**90-day cumulative incidence (% (95% CI))**
1+	5/ 585	0.20% (0.03% to 0.38%)	4/ 545	0.18% (0.00% to 0.35%)
BMI group				
Normal or underweight (<25)	0/ 159	0.20% (0.08% to 0.32%)	2/ 258	0.14% (0.05% to 0.23%)
Overweight (≥25 and <30)	0/ 384	0.00% (0.00% to 0.00%)	2/ 399	0.19% (0.00% to 0.45%)
Obese class I (≥30 and <35)	3/ 350	0.21% (0.00% to 0.44%)	1/ 262	0.10% (0.00% to 0.28%)
Obese class II (≥35 and <40)	4/ 190	0.51% (0.01% to 1.01%)	2/ 107	0.45% (0.00% to 1.07%)
Obese class III (≥40)	3/63	1.15% (0.00% to 2.44%)	0/ 27	0.00% (0.00% to 0.00%)
Missing	11/ 1327	0.00% (0.00% to 0.00%)	9/ 1593	0.12% (0.00% to 0.29%)
IMD quintile				
1st (least deprived)	4/ 562	0.17% (0.00% to 0.34%)	5/ 671	0.18% (0.02% to 0.34%)
2nd	6/ 599	0.25% (0.05% to 0.44%)	2/ 675	0.07% (0.00% to 0.17%)
3rd	3/ 574	0.13% (0.00% to 0.27%)	2/ 598	0.08% (0.00% to 0.19%)
4th	8/ 466	0.42% (0.13% to 0.71%)	5/ 465	0.26% (0.03% to 0.49%)
5th (most deprived)	0/ 270	0.00% (0.00% to 0.00%)	2/ 235	0.20% (0.00% to 0.49%)

	Knee replacement		Hip replacement	
	PJI/ person years	**90-day cumulative incidence (% (95% CI))**	**PJI/ person years**	**90-day cumulative incidence (% (95% CI))**
Missing	0/ 2	0.00% (0.00% to 0.00%)	0/ 1	0.00% (0.00% to 0.00%)
Smoking status				
Non-smoker	6/ 659	0.42% (0.00% to 1.00%)	2/ 612	0.14% (0.00% to 0.43%)
Ex-smoker	5/ 587	0.21% (0.03% to 0.39%)	3/ 538	0.14% (0.00% to 0.29%)
Current smoker	2/ 116	0.18% (0.05% to 0.30%)	1/ 173	0.18% (0.07% to 0.30%)
Missing	8/ 1112	0.22% (0.04% to 0.40%)	10/ 1322	0.08% (0.00% to 0.19%)

Cumulative incidence of prosthetic joint infections (PJI) 90 days after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

Table 5.5. Cumulative incidence of mortality after knee or hip replacement

	Knee replacement		**Hip replacement**	
	Deaths/ person years	**90-day cumulative incidence (% (95% CI))**	**Deaths/ person years**	**90-day cumulative incidence (% (95% CI))**
Total	46/ 2476	0.46% (0.32% to 0.59%)	68/ 2649	0.63% (0.48% to 0.78%)
Age group*				
1st (youngest)	3/ 597	0.12% (0.00% to 0.26%)	2/ 617	0.08% (0.00% to 0.19%)
2nd	7/ 629	0.27% (0.07% to 0.47%)	8/ 681	0.29% (0.09% to 0.49%)
3rd	10/ 601	0.41% (0.16% to 0.66%)	13/ 603	0.53% (0.24% to 0.81%)
4th (oldest)	26/ 649	0.98% (0.60% to 1.35%)	45/ 748	1.46% (1.03% to 1.88%)
Sex				
Male	23/ 1065	0.53% (0.31% to 0.74%)	34/ 1093	0.76% (0.50% to 1.01%)
Female	23/ 1411	0.40% (0.24% to 0.56%)	34/ 1556	0.53% (0.36% to 0.71%)

	Knee replacement		Hip replacement	
	Deaths/ person years	**90-day cumulative incidence (% (95% CI))**	**Deaths/ person years**	**90-day cumulative incidence (% (95% CI))**
Index diagnosis				
OA	43/ 2269	0.46% (0.33% to 0.60%)	61/ 2494	0.60% (0.45% to 0.75%)
RA	3/ 207	0.36% (0.00% to 0.76%)	7/ 155	1.11% (0.29% to 1.92%)
Charlson				
0	26/ 1890	0.34% (0.21% to 0.47%)	40/ 2103	0.47% (0.32% to 0.61%)
1+	20/ 586	0.82% (0.46% to 1.18%)	28/ 546	1.24% (0.78% to 1.70%)
BMI group				
Normal or underweight (<25)	6/ 159	0.46% (0.28% to 0.64%)	9/ 258	0.72% (0.51% to 0.93%)
Overweight (≥25 and <30)	6/ 384	0.92% (0.18% to 1.65%)	7/ 399	0.85% (0.30% to 1.41%)
Obese class I (≥30 and <35)	6/ 351	0.41% (0.08% to 0.74%)	3/ 262	0.28% (0.00% to 0.59%)

	Knee replacement		Hip replacement	
	Deaths/ person years	**90-day cumulative incidence (% (95% CI))**	**Deaths/ person years**	**90-day cumulative incidence (% (95% CI))**
Obese class II (≥35 and <40)	3/ 190	0.39% (0.00% to 0.83%)	1/ 107	0.23% (0.00% to 0.67%)
Obese class III (≥40)	0/ 64	0.00% (0.00% to 0.00%)	1/27	0.87% (0.00% to 2.56%)
Missing	25/ 1329	0.38% (0.08% to 0.69%)	47/ 1594	0.43% (0.11% to 0.74%)
IMD quintile				
1st (least deprived)	10/ 562	0.43% (0.16% to 0.70%)	14/ 672	0.51% (0.24% to 0.78%)
2nd	13/ 599	0.53% (0.24% to 0.82%)	20/ 675	0.72% (0.41% to 1.04%)
3rd	8/ 575	0.34% (0.10% to 0.58%)	15/ 599	0.61% (0.30% to 0.92%)
4th	9/ 467	0.47% (0.16% to 0.78%)	11/ 466	0.58% (0.24% to 0.92%)
5th (most deprived)	6/ 270	0.54% (0.11% to 0.97%)	8/ 235	0.83% (0.26% to 1.40%)

	Knee replacement		Hip replacement	
	Deaths/ person years	**90-day cumulative incidence (% (95% CI))**	**Deaths/ person years**	**90-day cumulative incidence (% (95% CI))**
Missing	0/ 2	0.00% (0.00% to 0.00%)	0/ 1	0.00% (0.00% to 0.00%)
Smoking status				
Non-smoker	10/ 660	0.43% (0.00% to 1.01%)	14/ 613	0.56% (0.01% to 1.11%)
Ex-smoker	13/ 587	0.54% (0.25% to 0.83%)	8/ 538	0.36% (0.11% to 0.61%)
Current smoker	2/ 116	0.46% (0.27% to 0.66%)	4/ 173	0.78% (0.54% to 1.01%)
Missing	21/ 1113	0.37% (0.14% to 0.60%)	42/ 1324	0.56% (0.27% to 0.85%)

Cumulative incidence of mortality 90 days after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

Study findings in context

Findings from previous research have suggested that risks of post-operative complications are relatively low. In this study, the 90-day cumulative incidence was around 1% for venous thromboembolism, 0.4% for myocardial infarction, and 0.2% for prosthetic joint infection. All of these estimates are in line with previous research, such as two large studies which assessed complications using routinely collected hospital data from the USA.[77,78] Meanwhile, the 0.5% observed incidence of mortality in this study is in line with previous research from the English NHS.[75,76]

Increased rates of myocardial infarction and mortality were seen for older age groups, men, and those with comorbidities. This is also in concordance with previous research.[75,76,194] Increased rates of myocardial infarction were also seen for those with rheumatoid arthritis. Few previous studies have assessed whether those with rheumatoid arthritis are at higher risk of cardiovascular events after knee or hip replacement. One study which did, found that individuals with rheumatoid arthritis have an increased risk of cardiovascular death within six weeks of joint replacement.[195]

The observed incidence of venous thromboembolism and prosthetic joint infections after knee and hip replacement appeared to be broadly similar for different patient profiles in this analysis. Even in larger studies, few risk factors for venous thromboembolism have been identified.[196] Although some studies have found obesity, rheumatoid arthritis and some comorbidities (such as diabetes mellitus) to be associated with an increased risk of infection, findings for these factors are mixed.[69]

In general, one complication is expected to occur for every 19 knee or hip replacements undertaken.[197] The findings from this analysis, along with those from previous research, suggest that this picture may well be worse for older patients, men, and those with rheumatoid arthritis or other comorbidities. These groups, however, have higher baseline risks for such events. Consequently, it does not necessarily follow that these events will be avoided in the absence of knee and hip replacement surgery. Where indications are appropriate, undergoing surgery is still likely to be merited. However, a better understanding of risk profiles will allow for individuals to better understand their prognosis following surgery and help to inform the management of patients undergoing knee and hip replacement.

Strengths and limitations

The key strength of this study was that it was informed by routinely collected data, which allowed for a representative study population and a consideration of the potential impact of various patient characteristics on the risks of acute adverse events. However, with post-operative complications relatively rare, an even larger study population would have helped to provide the power required to assess patient heterogeneity in risks of complications in more detail.

The findings from this study provide useful prognostic information. However, as with previous studies in the literature, the causal effect of receipt of surgery on risks is not assessed. Such an analysis would require an assessment of the counterfactual of what would have happened if an individual had not received surgery. The lack of a control group means that this type of an analysis was not possible.

Conclusions

Post-operative complications are relatively rare after knee and hip replacement. Some patient characteristics are though associated with increased risks, and the results from this analysis will allow for patients to have a better understanding of their prognosis and help to inform the management of those undergoing surgery.

6. LIFETIME RISK OF REVISION AFTER A KNEE OR HIP REPLACEMENT

Chapter summary

In this chapter I describe the lifetime risk of revision procedures after knee and hip replacement.

Routinely collected data from England was used to inform these estimates. As with estimating lifetime risks of primary knee and hip replacement, state-based Markov models provided the framework for the analyses of lifetime risks of revision, with transition probabilities drawn from parametric survival models.

For the average patient profiles, risk of revision was 5% (95% CI: 4% to 7%) after knee replacement and 8% (6% to 12%) after hip replacement. Younger age was associated with an increased lifetime risk of revision. With other patient characteristics held at their average, lifetime risk of revision went from 18% (12% to 26%) and 19% (12% to 29%) for a 55-year-old man to 4% (2% to 5%) and 5% (4% to 8%) for an 80-year-old man for knee and hip replacement, respectively. Other differences in patient characteristics had relatively little impact on estimates of lifetime risk.

Background

The risk of revision procedures after knee and hip replacement is better understood than the risk of primary procedures after diagnoses of osteoarthritis and rheumatoid arthritis, which were examined in Chapter 3. However, lifetime risks of revision procedures are still not fully understood, especially the impact of patient heterogeneity in these risks. In this chapter I provide estimates of the lifetime risk of revision after knee and hip replacement and assess how patient characteristics affect such risks.

Study participants were individuals who underwent primary knee and hip replacement in England. Linked data from primary and secondary care informed the analyses with individuals followed-up for up to 10 years (see Chapter 2 for more details). As with the lifetime risk of primary procedures reported in Chapter 3, parametric survival models were estimated for revision procedures and death, and a state-based Markov model was used to combine and extrapolate these survival models.

In this chapter, study participants and their cumulative incidence of revision and mortality after knee and hip replacement are described. The timing of events and the impact of patient characteristics on cause-specific risks are summarised. Lifetime risks of revision are then provided for the average patient profile and for different values of patient characteristics as others are held at their average.

Study participants

The study cohorts for risk of revision after knee replacement were the same as those used in Chapter 5 to assess the risk of post-operative complications after surgery.

10,260 and 10,961 individuals were in the knee and hip replacement cohorts, respectively, with their characteristics summarised in Table 5.1.

Cause-specific risks of revision

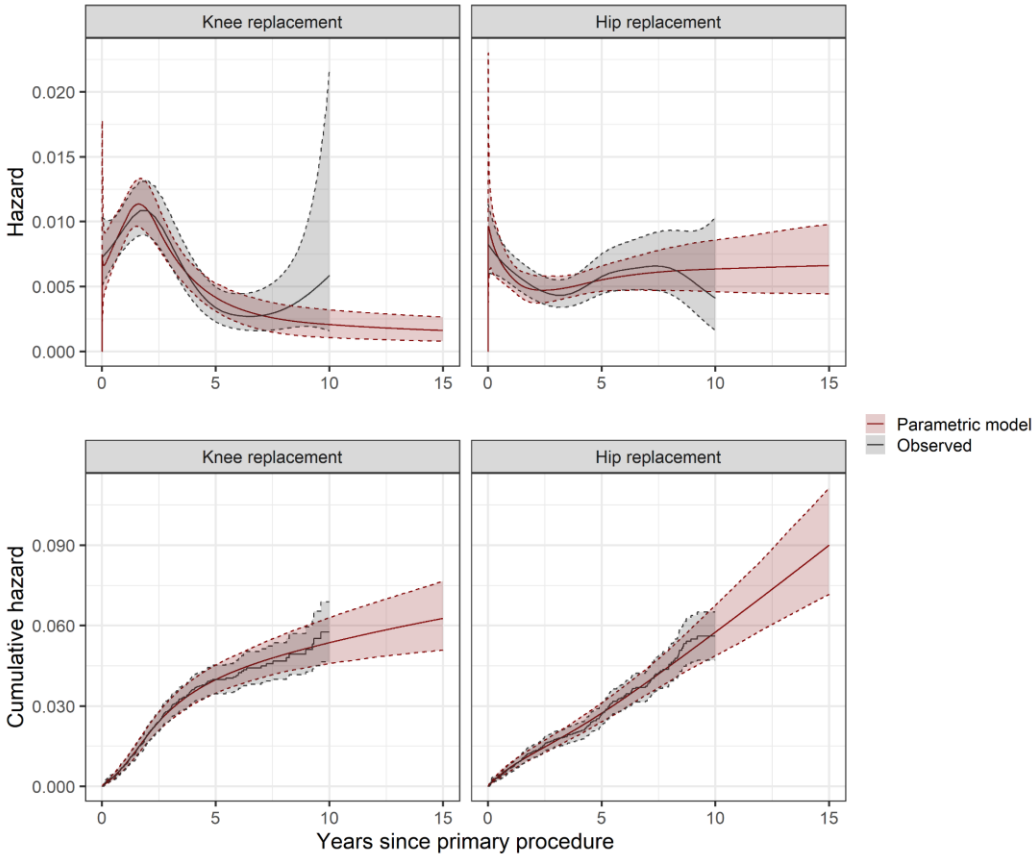
The 10-year cumulative incidence of revision after knee replacement was 5.1% (95% CI: 4.3% to 6.1%), while the 10-year cumulative incidence of revision after hip replacement was 4.9% (4.2% to 5.7%). Cumulative incidence stratified by explanatory factors of interest is detailed in Appendix Table D.1. For both knee and hip replacement, risk of revision appeared to most notably differ by age with observed cumulative incidence higher for younger patients.

Following knee replacement, the hazard for revision appeared to peak shortly after the primary procedure. Meanwhile, the hazard for revision appeared to be relatively steady after hip replacement, as shown in Figure 6.1 (alternative distributions considered for the parametric models are shown in Appendix Figure D.1 and Appendix Figure D.2). For both procedures, hazards appeared to deviate towards the end of follow up, with an increase for knee replacement and a decrease for hip replacement. This increases the uncertainty around the plausibility of the extrapolation of the risks.

In line with the observed cumulative incidence, being at an older age was associated with a reduced risk of revision in unadjusted models, particularly for knee replacement. This association remained after adjustment for patient characteristics, with an additional year of age associated with a hazard ratio of 0.95 (95% CI: 0.94 to 0.96) for revision after knee replacement and 0.99 (0.97 to 1.00) for revision after hip replacement (see Appendix Table D.2 for details). Being a man was associated with an increased risk of revision after knee replacement, with a hazard ratio of 1.31 (0.99 to

1.72) from the adjusted model. Point estimates suggested that an index diagnosis of rheumatoid arthritis and a Charlson score of 1 or more were associated with a reduced risk of revision after knee replacement but an increased risk after hip replacement, although these estimates had wide confidence intervals which crossed one. BMI appeared to have little effect on the risk of revision, with hazard ratios for a one-unit increase of 0.99 (0.96 to 1.03) and 1.02 (0.99 to 1.06) from adjusted models for knee and hip replacement, respectively. Lower socioeconomic status appeared to, if anything, be associated with a reduced risk of revision after both procedures. For example, being in the most deprived IMD quintile was associated with a hazard ratio of 0.59 (0.33 to 1.02) relative to being in the least deprived IMD quintile for revision after knee replacement. Estimates did not indicate a consistent reduction as socioeconomic status fell, however. Being a current smoker was associated with reduced risks of revision after knee and hip replacement, although confidence intervals crossed one.

Figure 6.1. Risks of revision after primary knee or hip replacement. Hazards and cumulative hazards from observed data and intercept-only parametric survival models (both of which were fitted with a spline-based distribution with 2 knots).



Cause-specific risks of death

The 10-year cumulative incidence of death after knee replacement was 27.0% (24.8% to 29.5%), while the 10-year cumulative incidence of death after hip replacement was 24.2% (22.6% to 25.9%). Cumulative incidence of mortality stratified by explanatory factors of interest is detailed in Appendix Table D.3. After both primary knee and hip replacement, risk of death was markedly different by age, index diagnosis, and Charlson score.

In general, hazards for mortality appeared to steadily increase over follow-up as individuals aged (details in Appendix Figure D.5). Older age, male gender, an index diagnosis of rheumatoid arthritis, a Charlson score of 1 or more, lower socioeconomic status, and being or having been a smoker were all associated with an increased risk of mortality (see Appendix Table D.4).

Lifetime risk of revision

For the average profile of an individual undergoing knee replacement (a non-smoking 71-year-old woman with an index diagnosis of knee osteoarthritis in the second least deprived IMD quintile, with a Charlson score of 0 and a BMI of 30), the lifetime risk of a revision procedure was estimated to be 5% (4% to 7%). For the average profile of an individual undergoing hip replacement (a non-smoking 70-year-old woman with an index diagnosis of hip osteoarthritis in the second least deprived IMD quintile, with a Charlson score of 0 and a BMI of 28), the lifetime risk of a revision procedure was estimated to be 8% (6% to 12%).

The partial effect of patient characteristics on lifetime risks are shown in Figure 6.2, Figure 6.3, Figure 6.4, Figure 6.5, Figure 6.6, and Figure 6.7. Age had a substantial effect on lifetime risk (see Figure 6.2), with younger patients having a higher annual risk of revision and greater life expectancy. Estimated lifetime risk of revision after knee replacement went from 18% (12% to 26%) for a 55-year-old man to 4% (2% to 5%) for an 80-year-old man, with other characteristics held at their average. Meanwhile, lifetime risk went from 19% (12% to 29%) for a 55-year-old man to 5% (4% to 8%) for an 80-year-old man after hip replacement, with other characteristics held at their average.

Figure 6.2. Partial effect of age and sex on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.

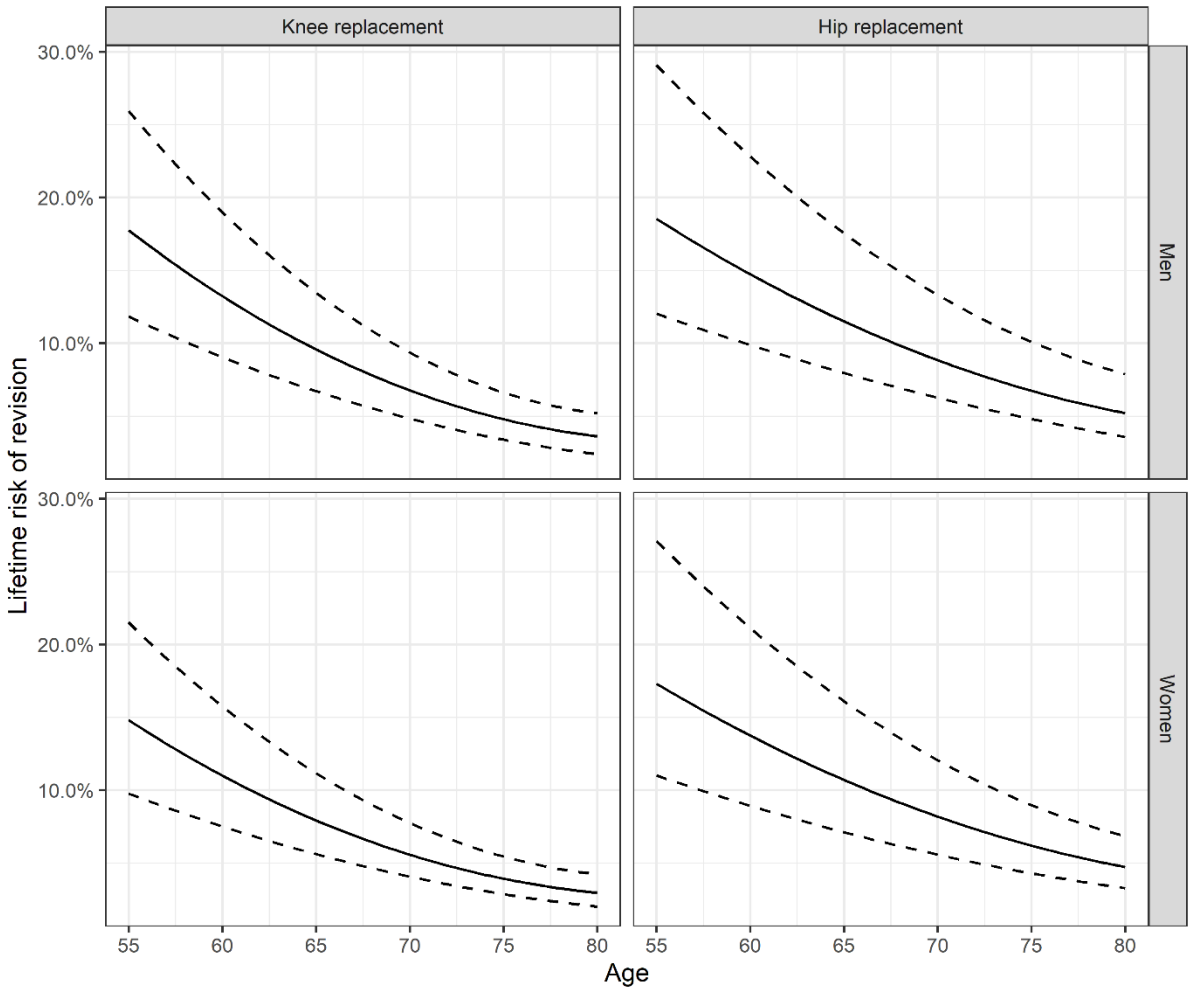


Figure 6.3. Partial effect of index diagnosis (OA: osteoarthritis, RA: rheumatoid arthritis) on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.

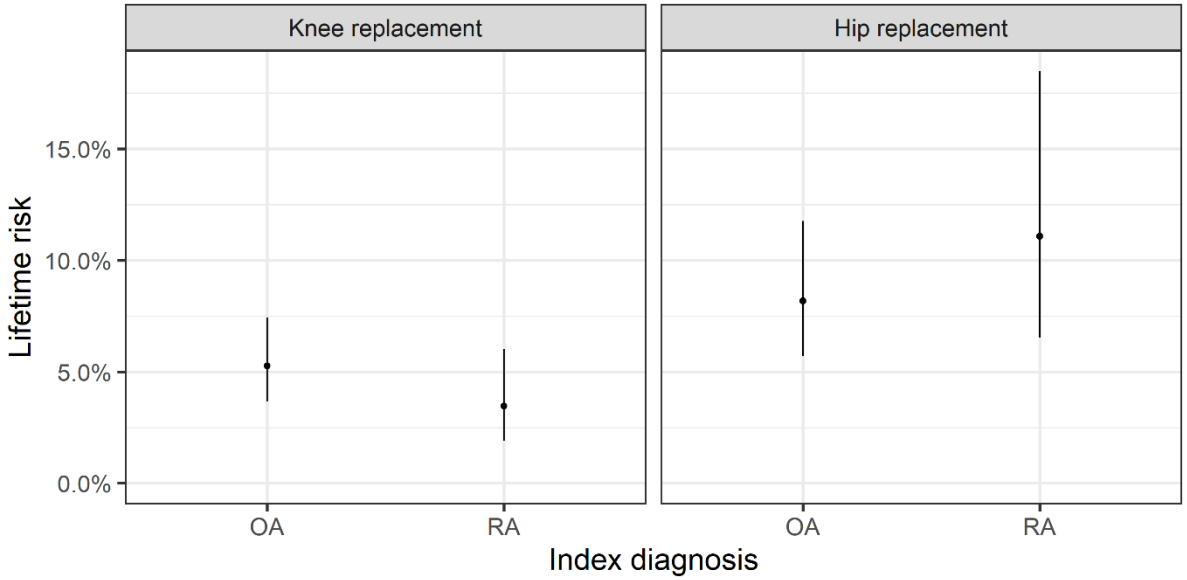


Figure 6.4. Partial effect of BMI on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.

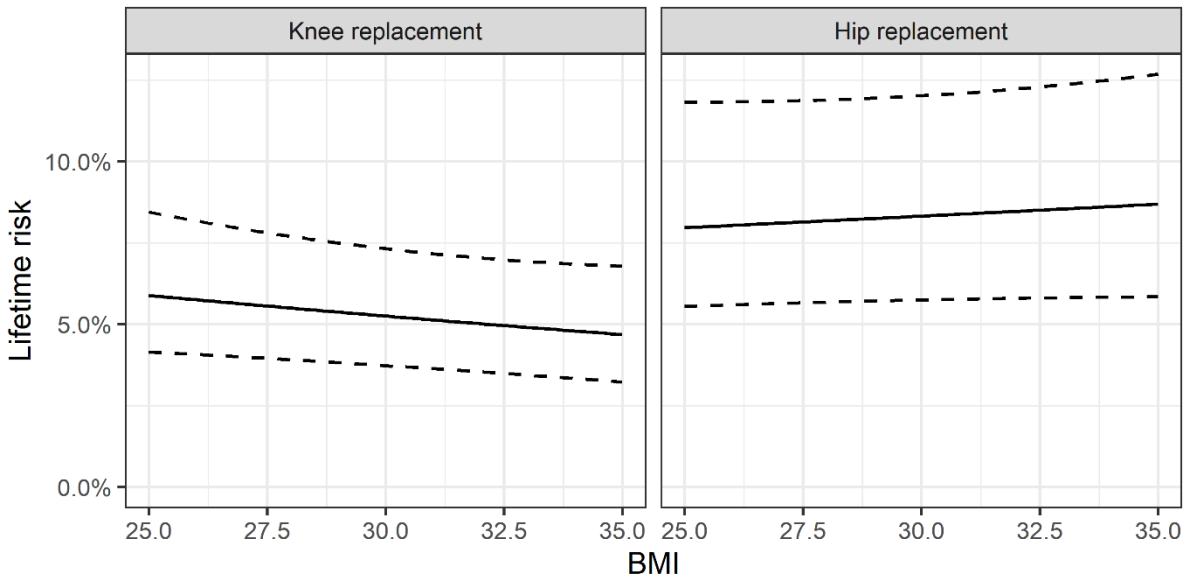


Figure 6.5. Partial effect of Charlson score on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.

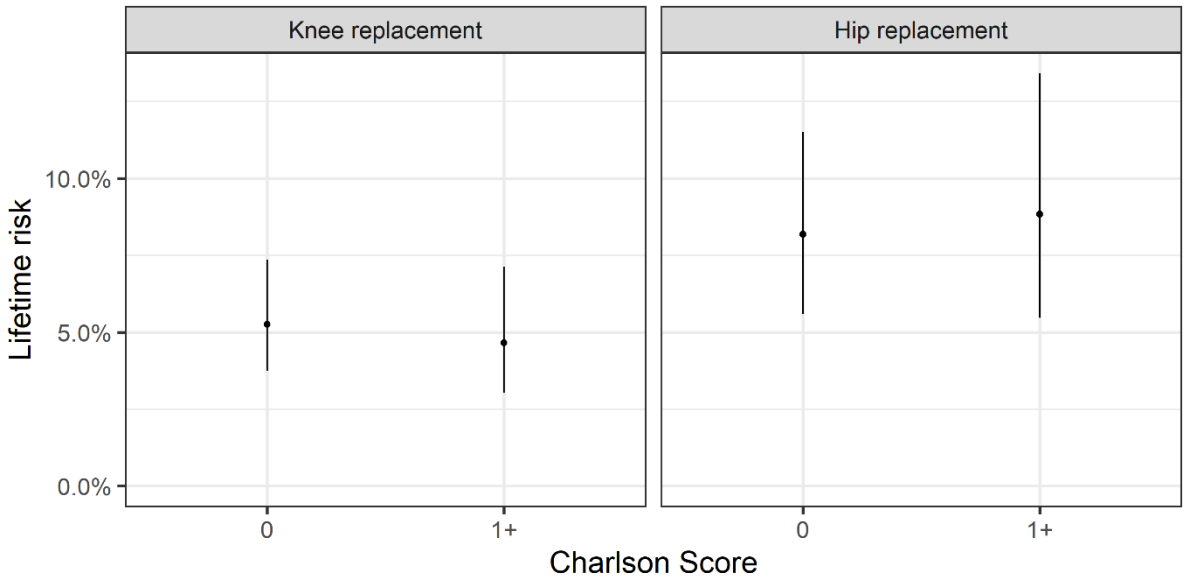


Figure 6.6. Partial effect of socioeconomic status (measured by IMD quintile) on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.

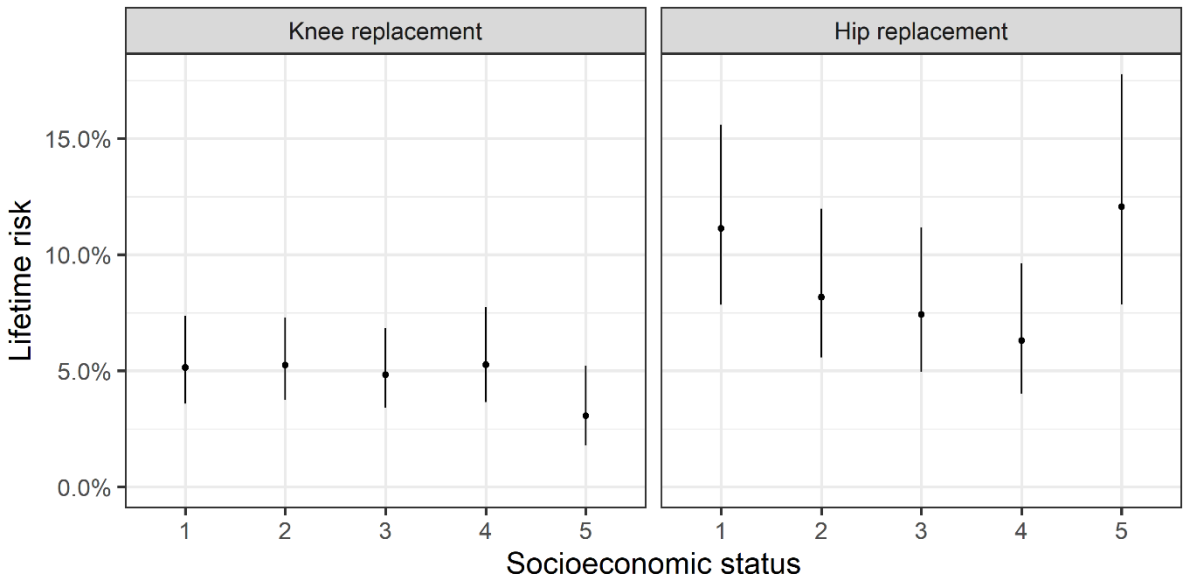
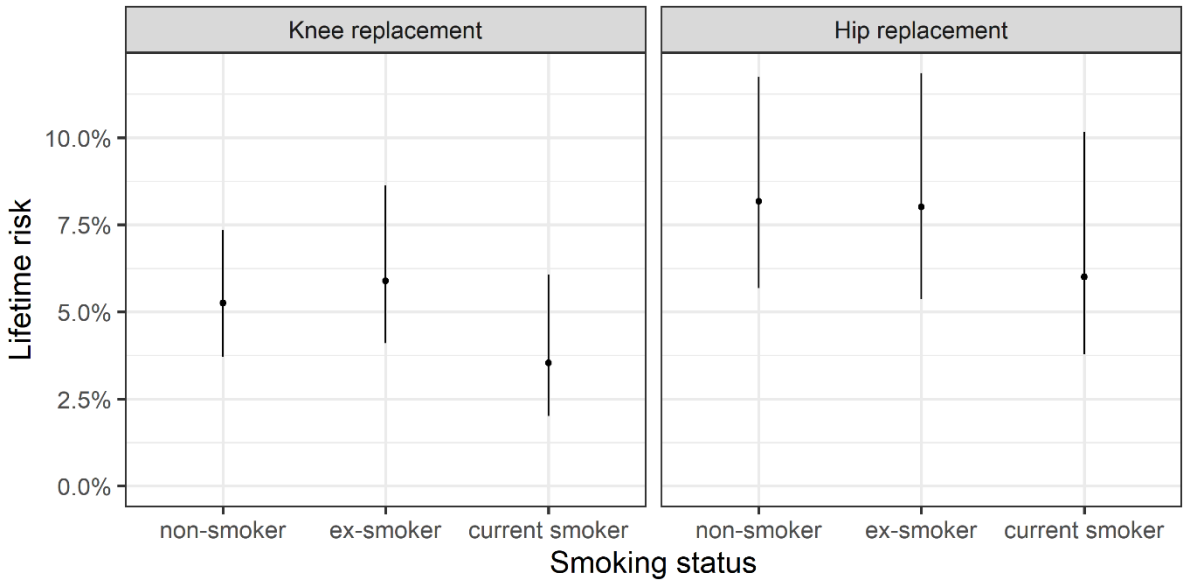


Figure 6.7. Partial effect of smoking status on lifetime risk of revision following a knee or hip replacement. Point estimates with 95% confidence intervals.



Study findings in context

Similar to the findings from this analysis, the one other study that has estimated the lifetime risk of revision after knee and hip replacement found it to be around 5% for those aged 70 years old at time of surgery.[87] Numerous other studies have also described annual incidence of revision procedures, with two recent systematic reviews summarising case series and cohort studies which have reported incidence of revision over 15 years or more following knee and hip replacement, respectively.[85,86] Direct comparisons are somewhat difficult because results from those studies are based on Kaplan-Meier estimates for survival, where the competing risk of mortality is not accounted for. These survival estimates therefore provide an answer to a patient's question: "what is my risk of having had a revision if I am still alive in 25 years?", rather than "what is my risk of having a revision?" which is answered by the

analyses reported in this chapter. To aid comparison, I have adjusted these risks from the literature to account for mortality, assuming that risk of revision was evenly distributed across time (i.e. has an exponential distribution) and incorporating estimates for the risk of mortality from UK life tables using a Markov model. The results are summarised below in Figure 6.8 and it can be seen that the probability of revision at 25 years is 5 to 10 percentage points lower than would be estimated based on Kaplan-Meier estimates alone. Even after accounting for the risk of mortality, however, risks of revision were still somewhat higher than estimated here.

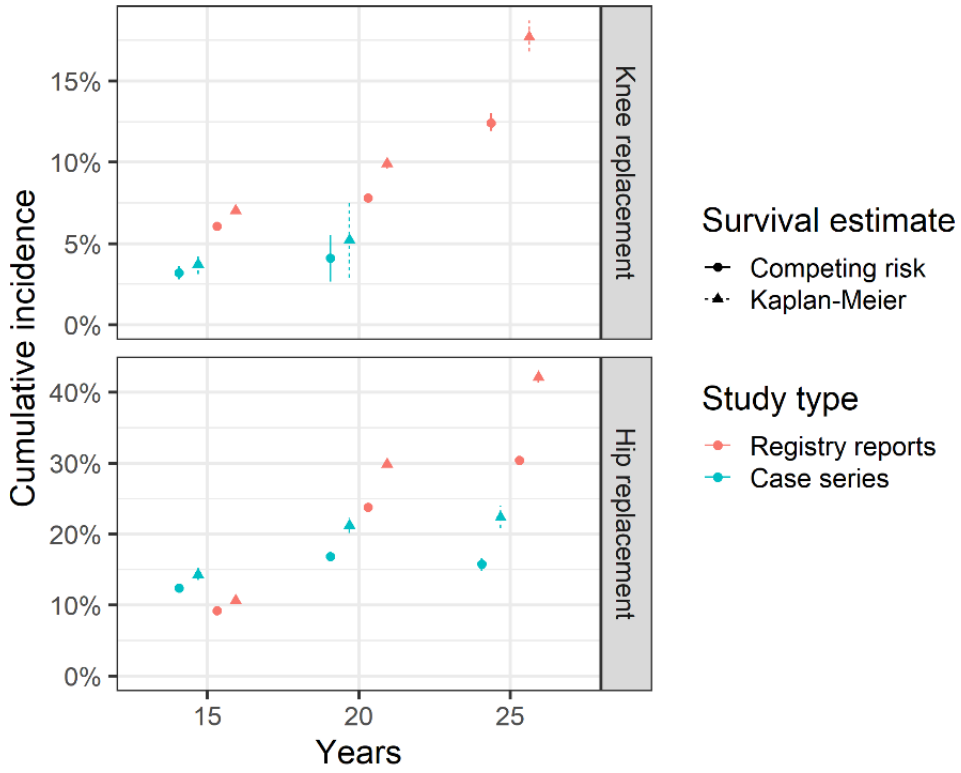
The study that previously estimated lifetime risk of revision after knee and hip replacement,[87] also considered how risks varied by age and sex. Risks for younger men were found to be particularly high, with a lifetime risk of 35% (31% to 39%) for knee replacement and 30% (95% CI: 27% to 33%) for hip replacement for those aged between 50 and 54 at time of surgery. These estimates are higher than those estimated here, which likely reflects the inherent uncertainty in estimating lifetime risks for younger patients for whom the majority of their risks are not based on observed follow-up, but rather an extrapolation of the risks observed in the early years following surgery. For those at older ages, where this limitation is much reduced, estimates of lifetime risks reported in this chapter are similar to those reported by Bayliss et al.[87]

In the analyses presented in this thesis, individuals' sex was generally not associated with statistically significant differences in risks of knee and hip replacement. However, confidence intervals were particularly wide for those at a younger age at diagnosis. Consequently, the difference seen in the study by Bayliss et al.[87] cannot be ruled out. Indeed, previous evidence suggests that men have an increased risk of revision

following both knee and hip replacement compared to women,[198,199] which may be explained by greater levels of physical activity.[199]

The relationship between other patient characteristics and lifetime risks of revision has not previously been studied, but research has assessed how such factors affect the risk of revision over constrained time horizons. As seen in the analyses reported in this chapter, most previous studies have not found BMI to have a meaningful effect on the overall risk of revision following knee and hip replacement.[198,200,201] There is though some evidence that revision risk may be raised for particularly high levels of BMI with, for example, individuals with morbid obesity (BMI greater than or equal to 40) previously found to have a significantly increased risk of revision after hip replacement.[202] The merit of incorporating a non-linear relationship between BMI and risk of revision was considered for the analyses in this chapter, however there was insufficient evidence to warrant its inclusion. The other factors considered were seen to have relatively little impact on lifetime risks of revision.

Figure 6.8. Implant survival estimates from the literature with and without accounting for competing risk of mortality



Strengths and limitations

As with the analyses of lifetime risk of knee and hip replacement after a diagnosis of osteoarthritis or rheumatoid arthritis presented in Chapter 3, lifetime risk of revision after knee and hip replacement estimated in this chapter were based on parametric survival models which were extrapolated using state-based Markov models. Consequently, this analysis has similar strengths and limitations to the analysis reported in Chapter 3. In particular, while the use of parametric survival models has allowed for an assessment of the effects of patient characteristics on lifetime risk of revision and a consideration of whether differences were due to impacts on cause-specific risks for revision or mortality, it has also required the extrapolation of risks beyond observed follow-up periods which necessarily introduces uncertainty,

especially for younger patients. Moreover, while the effect of observed patient characteristics on risks were considered, a range of other factors that were not observable in the data are likely to influence lifetime risk of revision, such as willingness to undergo and fitness for surgery.

Conclusions

Age at time of primary surgery is a key determinant of the lifetime risk of revision, with younger patients having both a higher annual risk of revision and a greater life expectancy, and so time at risk. The other patient characteristics considered, however, appeared to have little meaningful impact on the lifetime risk of revision.

7. POTENTIAL EFFECT FROM USE OF TNFI AS A FIRST-LINE THERAPY AFTER A DIAGNOSIS OF RHEUMATOID ARTHRITIS ON KNEE AND HIP REPLACEMENT

Chapter summary

In this chapter I describe the procedures avoided and cost savings associated with a potential reduction in the risk of knee and hip replacement for individuals with rheumatoid arthritis due to the use of tumour necrosis factor inhibitors (TNFi) as a first-line therapy, relative to usual practice in which their use is restricted to later in the treatment pathway.

Risks of knee and hip replacement after a diagnosis of rheumatoid arthritis under current practice were based on the analysis summarised in Chapter 3, with risks of revision after primary procedures based on the results from Chapter 6. With uncertainty around their long-term effect on need for knee and hip replacement, the impact from use of TNFi as a first-line therapy was considered by applying a range of relative risks to risks under current practice.

For a cohort of 1,000 individuals diagnosed with rheumatoid arthritis with the average profile of patients, relative risk reductions of 20% would, for example, lead to 46 and 30 fewer knee and hip replacements, respectively, with a combined cost-saving of over £300,000. These effects would, however, be dependent on the treatment effect being maintained. The number of procedures avoided and associated costs saved would be even greater for younger patients, given their higher lifetime risk of knee and hip replacement.

Background

As described in Chapter 1, the effect of TNFi use after a diagnosis of rheumatoid arthritis on risks of knee and hip replacement is not well-understood. Moreover, the impact of any relative risk reductions (or relative risk increases) on the cost-effectiveness profile of TNFi is not known. Drawing upon the findings from Chapters 3 and 6, the analysis reported in this chapter establishes the number of procedures that could be avoided and associated procedure cost savings from the use of TNFi if used as a first-line therapy, initiated shortly after diagnosis of rheumatoid arthritis.

A Markov model, summarised in Chapter 2, was used as the framework for analysis. A cohort of 1,000 individuals were included in the model, with all individuals starting with a diagnosis of rheumatoid arthritis. The model was first run for current practice, where TNFi are not used as a first-line therapy, with transition probabilities (representing risks of primary knee and hip replacement, subsequent revision, and death) based on the parametric models described in Chapters 3 and 6. The model was then run for an alternative treatment strategy of TNFi used as a first-line therapy, with relative risks (representing the effectiveness of using TNFi) applied to the risk of knee and hip replacement. Given uncertainty in their long-term effects on need for knee and hip replacement, various estimates of the relative effectiveness of TNFi are considered. The number of procedures and associated costs were then compared. It was assumed that any treatment effects would be maintained into the future for the base case analysis, with treatment effects assumed to last for only five years in a sensitivity analysis.

Procedures avoided and costs saved

Procedures and associated costs under the alternative strategies are summarised in Table 7.1, with incremental estimates detailed in Table 7.2. The number of procedures avoided for various relative risks for TNFi, relative to current practice, for a profile with the average profile of those diagnosed with rheumatoid arthritis are shown in Figure 7.1. The associated procedure costs avoided are shown in Figure 7.2. For example, for a relative risk of 0.8 for risk of knee replacement, TNFi would be expected to result in 46 (95% CI: 35 to 57) fewer primary knee replacements, 4 (3 to 6) fewer subsequent revision procedures, and a saving of £205,827 (£157,262 to £264,491) in associated procedure costs for a cohort of 1,000 individuals diagnosed with rheumatoid arthritis. Meanwhile, under the same relative risk for hip replacement, TNFi would be expected to result in 30 (21 to 43) fewer primary hip replacements, 2 (1 to 3) fewer subsequent revision procedures, and a saving of £137,569 (£97,182 to £204,180) in associated procedure costs for a cohort of 1,000 individuals diagnosed with rheumatoid arthritis.

The partial effects of age and gender on the number of procedures and associated procedure costs avoided for various relative risks for TNFi, relative to current practice, are shown in Figure 7.3 and Figure 7.4. In line with differences in expected lifetime risk of knee and hip replacement, it can be seen that a given relative risk has a bigger impact for younger patients. Relative risks of 0.8 would be expected to result in 37 (27 to 48) fewer knee and 40 (27 to 58) fewer hip replacements for a cohort of 1,000 women aged 60 years old diagnosed with rheumatoid arthritis. These expected reductions would fall to 15 (12 to 23) and 12 (8 to 18) if the cohort were aged 80.

If the effect of treatment lasted for only 5 years, the impact on number of procedures would be reduced (see details provided in Appendix Table E.1 and Appendix Table E.2). For relative risks of 0.8, TNFi would be expected to result in 13 (9 to 16) fewer knee replacements and 7 (5 to 11) fewer hip replacements for the cohort of 1,000 individuals with the average profile of those diagnosed with rheumatoid arthritis.

Table 7.1. Estimated procedures and procedure costs for current practice and TNFi for various relative risks (RRs). Results for base case analysis for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis.

	Current practice			**TNFi**		
	Primary procedures	**Revision procedures**	**Procedure costs (£)**	**Primary procedures**	**Revision procedures**	**Procedure costs (£)**
Knee replacement						
RR: 0.6	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	169 (122 to 230)	15 (11 to 21)	732,760 (531,662 to 1,011,025)
RR: 0.8	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	218 (159 to 292)	19 (14 to 27)	950,477 (695,244 to 1,297,229)

	Current practice			TNFi		
	Primary procedures	**Revision procedures**	**Procedure costs (£)**	**Primary procedures**	**Revision procedures**	**Procedure costs (£)**
RR: 1.2	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	306 (227 to 400)	28 (20 to 38)	1,350,984 (1,003,727 to 1,806,400)
RR: 1.4	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	346 (259 to 446)	31 (23 to 43)	1,535,211 (1,149,174 to 2,032,992)
Hip replacement						
RR: 0.6	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	102 (69 to 159)	7 (5 to 11)	456899 (311,753 to 725,094)

	Current practice			TNFi		
	Primary procedures	**Revision procedures**	**Procedure costs (£)**	**Primary procedures**	**Revision procedures**	**Procedure costs (£)**
RR: 0.8	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	133 (90 to 205)	9 (6 to 14)	599,166 (411,117 to 940,868)
RR: 1.2	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	192 (132 to 289)	13 (9 to 20)	869,784 (603,354 to 1,338,370)
RR: 1.4	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	219 (152 to 327)	15 (10 to 23)	998,485 (696,336 to 1,521,517)

Table 7.2. Estimated incremental effect of TNFi, relative to csDMARDs, on procedures and procedure costs for various relative risks (RRs). Results for base case analysis for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis.

	Incremental effect of TNFi		
	Primary procedures avoided	**Revision procedures avoided**	**Procedure costs avoided (£)**
Knee replacement			
RR: 0.6	95 (72 to 119)	9 (6 to 12)	423,543 (320,844 to 550,694)
RR: 0.8	46 (35 to 57)	4 (3 to 6)	205,827 (157,262 to 264,491)
RR: 1.2	-43 (-51 to -33)	-4 (-5 to -3)	-194,680 (-244,681 to -151,222)
RR: 1.4	-82 (-98 to -65)	-8 (-10 to -6)	-378,908 (-471,272 to -296,668)
Hip replacement			

	Incremental effect of TNFi		
	Primary procedures avoided	**Revision procedures avoided**	**Procedure costs avoided (£)**
RR: 0.6	61 (43 to 89)	4 (3 to 6)	279,836 (196,545 to 419,953)
RR: 0.8	30 (21 to 43)	2 (1 to 3)	137,569 (97,182 to 204,180)
RR: 1.2	-29 (-40 to -21)	-2 (-3 to -1)	-133,049 (-193,322 to -95,055)
RR: 1.4	-56 (-78 to -41)	-4 (-6 to -3)	-261,750 (-376,469 to -188,037)

Figure 7.1. Number of knee and hip replacements avoided for varying relative risks for TNFi relative to current practice under base case assumptions

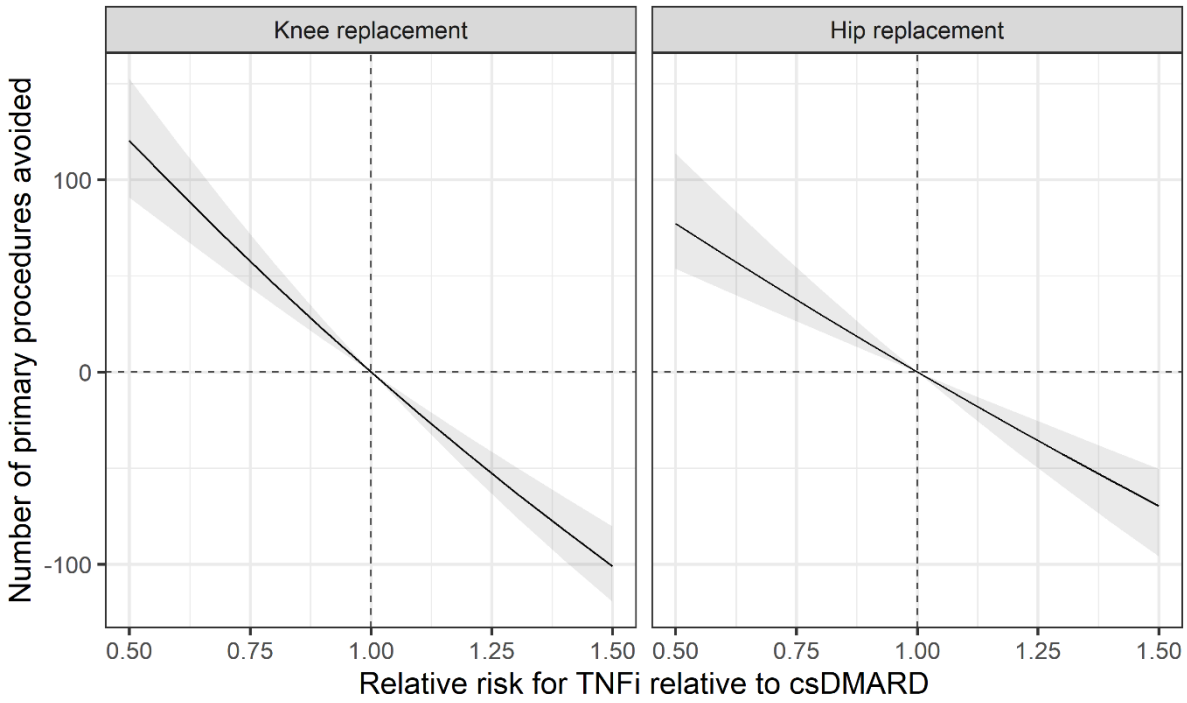


Figure 7.2. Procedure costs saved for varying relative risks for TNFi relative to current practice under base case assumptions

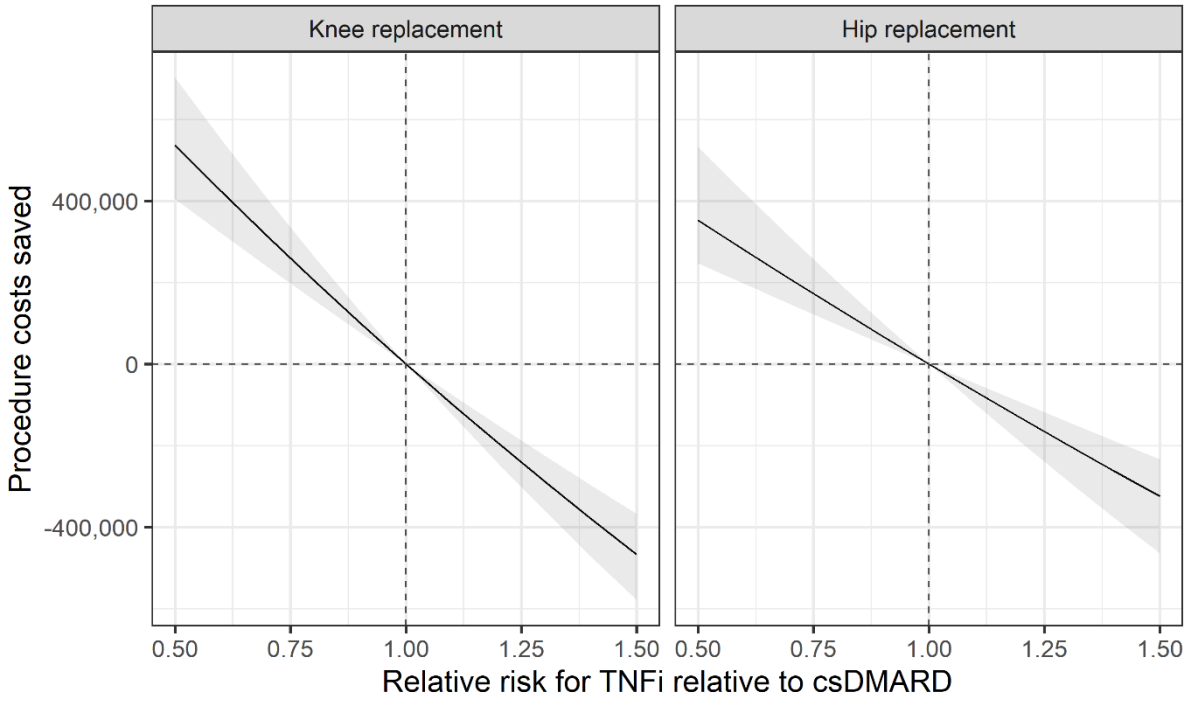


Figure 7.3. Partial effect of age and gender on number of knee and hip replacements avoided for varying relative risks for TNFi relative to current practice under base case assumptions.

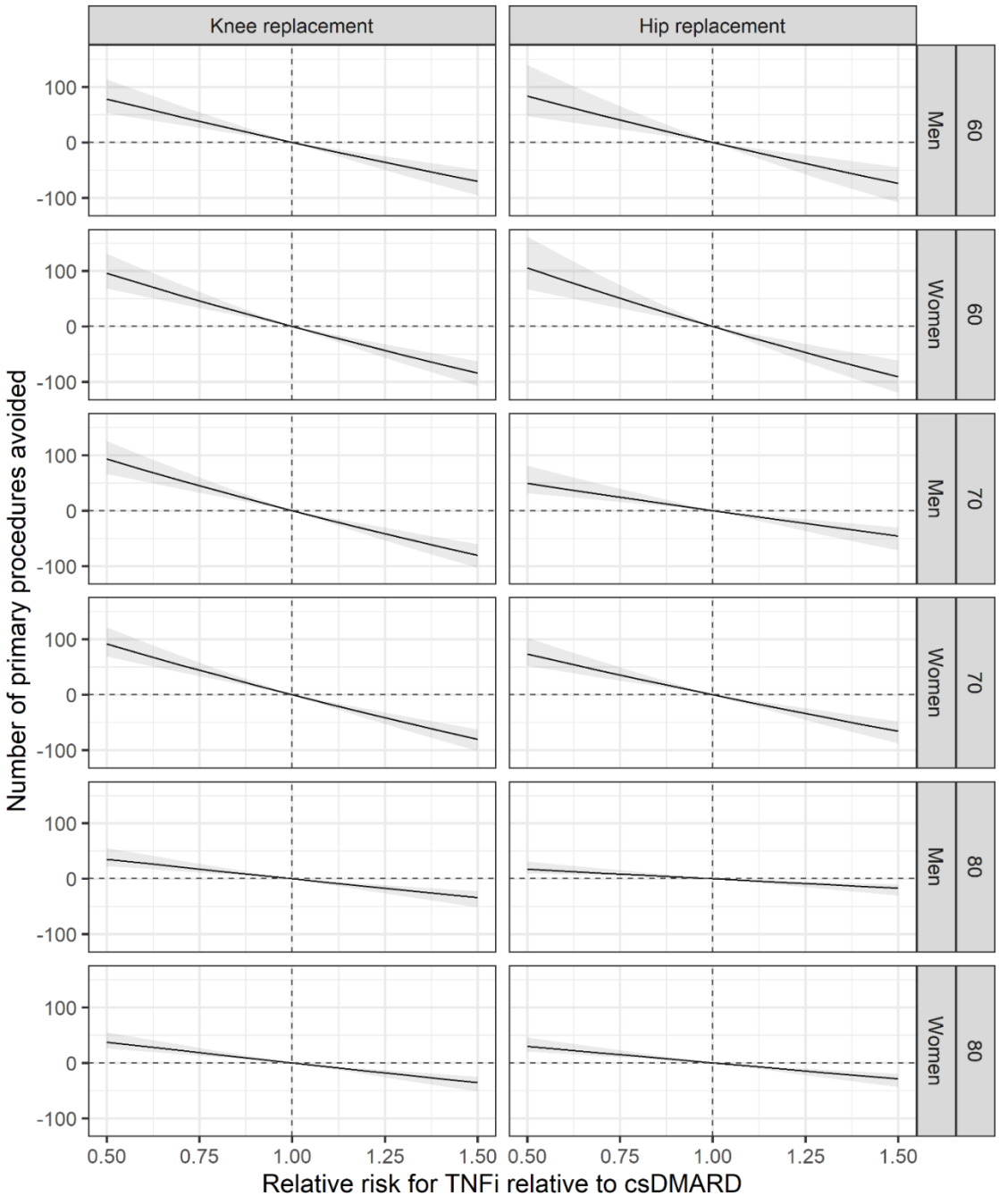
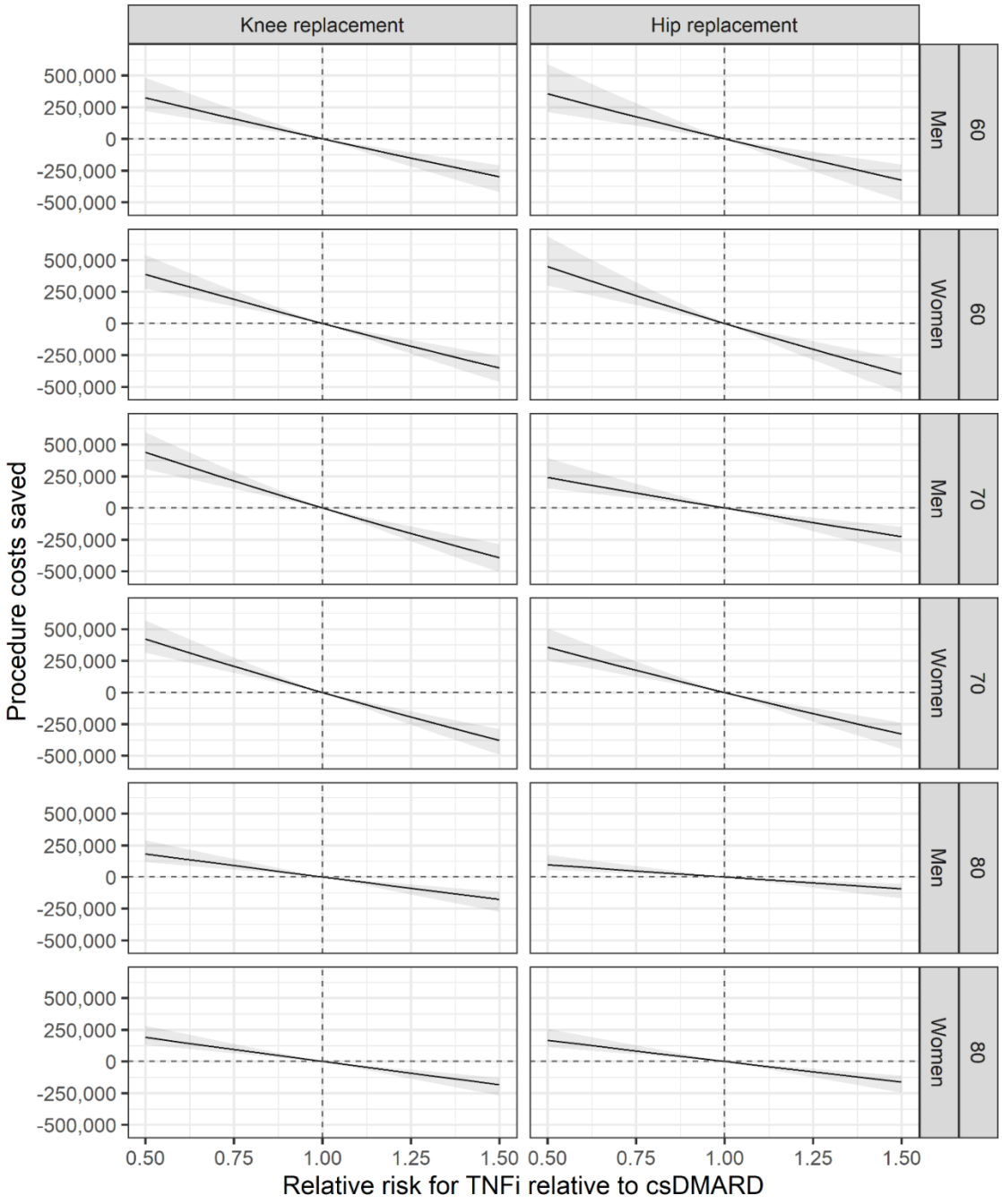


Figure 7.4. Partial effect of age and gender on procedure costs saved for varying relative risks for TNFi relative to current practice under base case assumptions



Study findings in context

Any relative risk reductions for knee and hip replacement that are realised due to the early initiation of TNFi would have an important impact on the overall number of procedures and associated costs, particularly if treatment effects were maintained. If TNFi were, for example, associated with a sustained relative risk reduction of 20% relative to usual practice, a cohort of 1,000 individuals diagnosed would be expected to go on to have 46 and 30 fewer knee and hip replacements, respectively.

On their own, the expected procedure cost savings of around £300 per person would only have a modest impact on the incremental costs of TNFi, with originator agents costing around £9,000 per year. A reduced risk of knee and/ or hip replacement would also though be associated with substantial health gains from avoiding the morbidity associated with the need for such procedures. The combination of these two factors would likely have a meaningful impact on the cost-effectiveness profile of TNFi. Moreover, the introduction of biosimilar agents means that the cost-effectiveness of TNFi needs to be revisited. These biosimilars come at a third or less of the cost of originators, with comparable efficacy,[91,96] and the effect of TNFi on long-term effects on knee and hip replacement will therefore likely gain greater importance.

The effect of TNFi on risk of knee and hip replacement is not yet well-understood. Randomised evidence is lacking and estimates from observational studies are mixed. The implications of estimates drawn from two studies based on data from England are shown in Figure 7.5 and Figure 7.6, with further details provided in Appendix Table E.3 and Appendix Table E.4. To use the decision-analytic model to estimate the effect of these estimates, hazard ratios were applied by converting baseline transition

probabilities to rates, re-estimating the rate given the hazard ratio, and converting the new rate back to a transition probability,[203] and uncertainty incorporated using triangular distributions with the lower and upper bounds equal to the lower and upper confidence intervals.

The first study was a propensity score matched analysis of csDMARD users and TNFI users. With the average age of those diagnosed with rheumatoid arthritis being 64, both the overall estimate and the estimates for those aged under and over 60 from the study were considered. While point estimates suggested that TNFi was associated with a reduced risk of hip replacement across the matched cohorts, with this risk reduction particularly pronounced and statistically significant for those age over 60, little effect was seen for knee replacement.[103] The second study was an interrupted time-series analysis of the Clinical Practice Research Datalink (CPRD), with the impact of National Institute for Health and Care Excellence (NICE) guidance recommending the use of TNFi (etanercept and infliximab) for those adults with a Disease Activity Score in 28 joints above 5.1 who had failed two csDMARDs assessed.[102] This approval was associated with 34% relative reduction in the rates of knee replacement but, if anything, an increase in rates of hip replacement.[102]

Outside of the UK, a propensity-score matched analysis of registry data from Denmark, initiating treatment with biologics, such as TNFi, was associated with a hazard ratio of 0.95 (95% CI: 0.65 to 1.40) for the composite outcome of knee and hip replacement.[204] Meanwhile, in another ecological study, the introduction of a guideline supporting the use of TNFi in Denmark was associated with a reduction in the rates of knee replacement, but little impact on rates of hip replacement.[205]

Figure 7.5. Number of knee and hip replacements avoided for varying relative risks for TNFi under base case assumptions, with specific effect estimates from the literature (BSRBR-RA: British Society for Rheumatology Biologics Register for rheumatoid arthritis; CPRD: Clinical Practice Research Datalink)

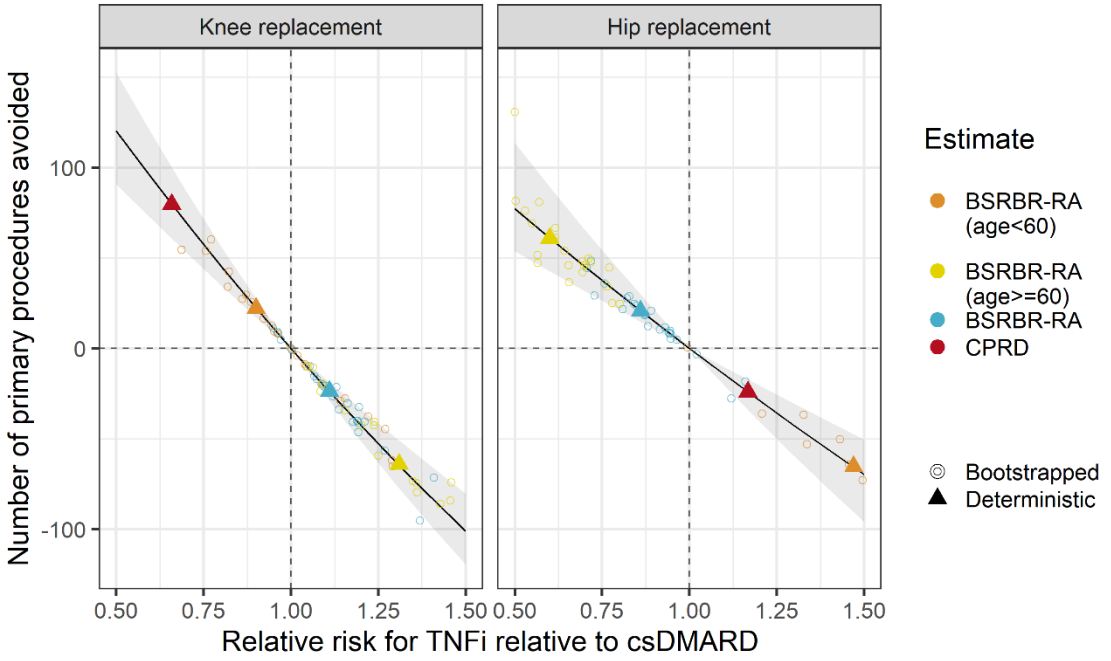
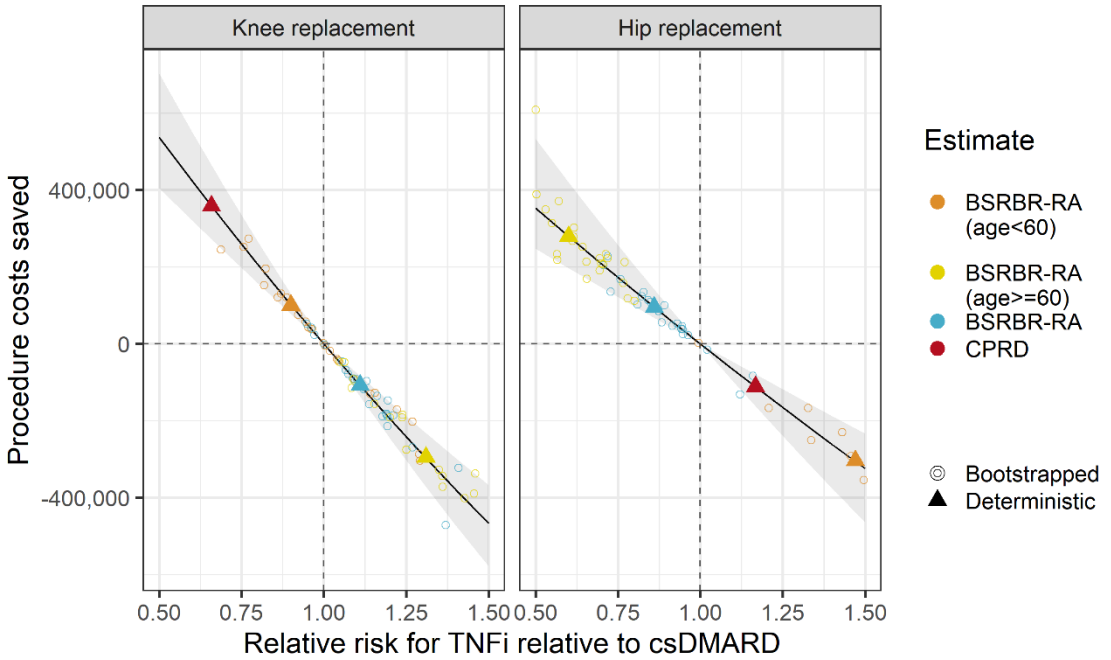


Figure 7.6. Procedure costs saved for varying relative risks for TNFi under base case assumptions, with specific effect estimates from the literature (BSRBR-RA: British Society for Rheumatology Biologics Register for rheumatoid arthritis; CPRD: Clinical Practice Research Datalink)



Strengths and limitations

The primary strength of this analysis is that the risks of knee and hip replacement under current practice have been informed by the previous analyses based on routinely collected data. Given the lack of definitive evidence on the effect of TNFi on long-term risks of knee and hip replacement, the impact of a range of relative risks were considered. No definitive answer as to their impact can therefore be provided. However, the findings from this analysis can be used to consider a range of current scenarios and as more evidence emerges as to the relative effects of TNFi, these estimates can inform a consideration of their implications.

The comparison made in this analysis is between that of current practice, taken to be initiation of a csDMARD after diagnosis of rheumatoid arthritis, with the use of TNFi as a first-line therapy after diagnosis. The earlier use of TNFi could, however, take a number of forms. For example, while biologic DMARDs could be as used as a first-line therapy along with a csDMARD as in the HIT HARD, OPTIMA and COMET trials,[206–208], initiation using a csDMARD, with step-up to a TNFi if the initial treatment fails may be equally effective.[93] It can be expected that this latter approach would therefore have comparable effects on knee and hip replacement as modelled in this analysis, but would differ in overall cost-effectiveness (given the lower proportion of patients that would be expected to receive the costly TNFi therapies). Other strategies outside the scope of this study, for example, include first-line therapy of combination csDMARDs.[93]

As with estimating lifetime risks of knee and hip replacement after a diagnosis of rheumatoid arthritis, an important limitation of this study is that the impact of disease

severity at diagnosis has not been modelled. The effect of initiating treatment with TNFi on knee and hip replacement may well vary depending on disease status at time of diagnosis. However, as this information was not available in the dataset used, it has not been possible to assess this.

Conclusions

The effect of TNFi on risk of knee and hip replacement is not yet well-understood, but relative risk reductions could translate into substantial differences in absolute risks of knee and hip replacement. Decision models, informed by evidence on current practice from Chapters 3 and 6, have allowed for a consideration of the impact of a range of relative risks.

On their own, given the cost of originator and biosimilar agents, the expected per person procedure cost savings would only have a modest impact on the incremental costs of TNFi. However, a reduced risk of knee and/ or hip replacement would also be associated with substantial health gains from avoiding the morbidity associated with the need for such procedures. The combination of these two factors would likely have a meaningful impact on the cost-effectiveness profile of TNFi. A wide range of potential estimates of effectiveness have been considered in this study, and as further evidence emerges the estimates produced here can be used to inform future decision making.

8. A COST EFFECTIVENESS ANALYSIS OF BARIATRIC SURGERY AFTER A DIAGNOSIS OF KNEE OSTEOARTHRITIS

Chapter summary

In this chapter I summarise the potential consequences of providing bariatric surgery to a cohort of 100 individuals newly diagnosed with knee osteoarthritis with a BMI of 40. This was compared to usual practice in which individuals would not be expected to undergo bariatric surgery.

Risk of knee replacement after a diagnosis of knee osteoarthritis without bariatric surgery was based on the analysis summarised in Chapter 3, with risk of revision after primary procedures based on the results from Chapter 6. Bariatric surgery was assumed to be undertaken in the year after diagnosis, with risks of knee replacement re-estimated for the lower weight expected to be realised after bariatric surgery.

For the cohort of 100 patients with a BMI of 40 but an otherwise average profile, bariatric surgery provided in the year after diagnosis was expected to lead to 7 (95% CI: 3 to 13) fewer primary knee replacements and 1 (0 to 1) fewer revision procedure, with £36,338 (£15,685 to £62,553) associated procedure costs saved. The estimated number needed to treat to avoid one knee replacement was 14 (8 to 31). The benefits from bariatric surgery would be even greater if concentrated among younger patients. For a cohort of 60-year-old women, for example, one knee replacement would be avoided for every 7 (4 to 13) bariatric surgeries provided.

Background

As described in Chapter 3, a higher BMI at diagnosis of knee osteoarthritis is associated with an increased lifetime risk of knee replacement. For those individuals overweight or obese at time of diagnosis, then, sustained weight loss can be expected to lead to a reduced risk of knee replacement (and subsequent revision procedures). This would improve health outcomes by avoiding the morbidity associated with the need for knee replacement and save costs associated with such procedures.

Bariatric surgery is one of the few weight loss interventions that has been shown to lead to substantial and sustained weight loss. While bariatric surgery is costly to provide, previous research has found the procedure to be cost-effective for obese individuals given the multitude of expected benefits from weight loss for this group. In addition, for specific populations the procedure is even more cost-effective. For example, bariatric surgery has been found to be particularly cost-effective for obese individuals with Type 2 diabetes.[111] The additional potential benefits of bariatric surgery for obese individuals with recently diagnosed knee osteoarthritis is not yet, however, known. This prompted the analysis presented in this chapter, informed by the findings from the preceding chapters of this thesis.

As with the previous chapter, a state-based Markov model (summarised in Chapter 2) was used as the framework for the analysis. Transition probabilities from diagnosis to knee replacement and death under usual practice were based on the survival models used to estimate lifetime risk of knee replacement in Chapter 3. Transition probabilities of revision after knee replacement were based on the survival models used to estimate lifetime risk of revision in Chapter 6.

For this analysis, bariatric surgery was assumed to be undertaken in the year after diagnosis of knee osteoarthritis. In the first year after surgery, individuals were assumed to have same probability of undergoing a knee replacement as under current practice and then, from the second year onwards, probabilities were estimated for the lower BMI expected to be realised after bariatric surgery. For the base case analysis, it was assumed that this reduction would be maintained. For a sensitivity analysis, it was assumed that the reduction would be mitigated after five years.

Potential effect of bariatric surgery on knee replacement procedures

Based on the findings from Chapter 3, a cohort of 100 individuals with a BMI of 40, but otherwise the average profile of those diagnosed with knee osteoarthritis, would be expected to have 33 primary knee replacements. Then, based on the findings from Chapter 6, it is expected that there would be 3 subsequent revision procedures. Bariatric surgery in the year after diagnosis was expected to result in 7 (3 to 13) fewer knee replacements and 1 (0 to 1) fewer revision procedure, as detailed in Table 8.1. One knee replacement is expected to be avoided per 14 (8 to 31) bariatric surgeries provided. The reduction in primary and revision surgeries was expected to save £36,338 (£15,685 to £62,553) associated procedure costs (see Figure 8.1 for details). Given the expected cost of bariatric surgery, it had an incremental cost per primary procedure avoided of £53,285, as illustrated in Figure 8.2.

The benefits of bariatric surgery (knee replacement and subsequent procedures avoided, and associated costs saved) would be more pronounced for younger patients, but broadly similar by gender, as can be seen in Figure 8.3 and Figure 8.4. This mirrors differences in individuals' baseline lifetime risk of knee replacement (as

described in Chapter 3). For a cohort of 100 60-year-old women, for example, 15 (8 to 24) knee replacements and 2 (1 to 2) subsequent revisions would be avoided, with £61,998 (£32,124 to £97,495) associated procedure costs saved. The incremental cost per primary procedure avoided for this cohort would be £24,569. If the reduction was maintained only for five years, the benefits in would be correspondingly reduced, with detailed figures provided in Appendix Table E.5.

Figure 8.1. Knee replacements avoided and associated procedure costs saved for a representative cohort of 100 individuals with a BMI of 40 and otherwise average characteristics receiving bariatric surgery following diagnosis of knee osteoarthritis. The solid triangle is the deterministic (expected) estimate, with hollow circles representing bootstrapped estimates.

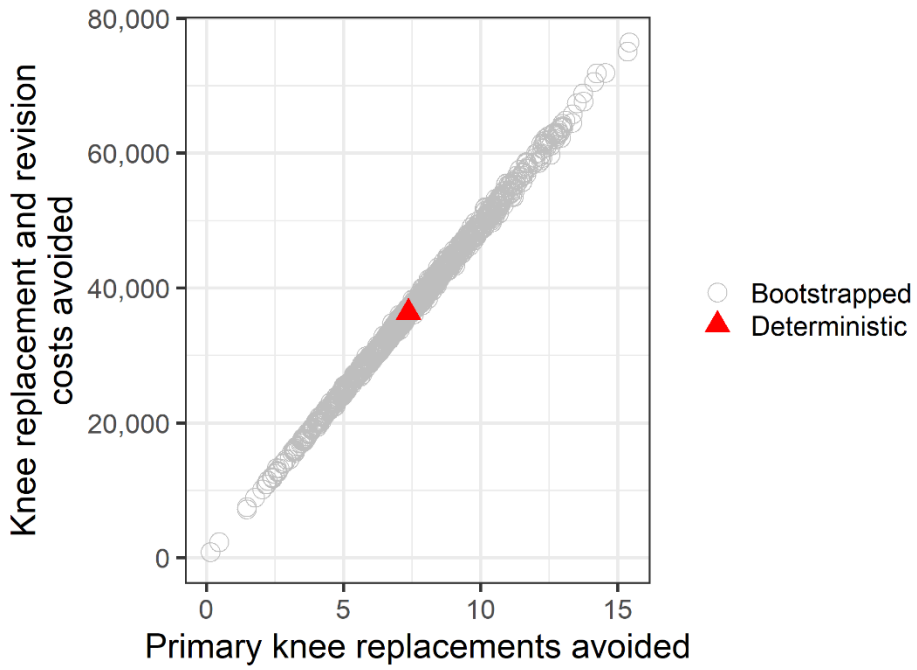


Figure 8.2. Incremental cost per primary knee replacement avoided for a representative cohort of 100 individuals with a BMI of 40 and otherwise average characteristics receiving bariatric surgery following diagnosis of knee osteoarthritis. The solid triangle is the deterministic (expected) estimate, with hollow circles representing bootstrapped estimates.

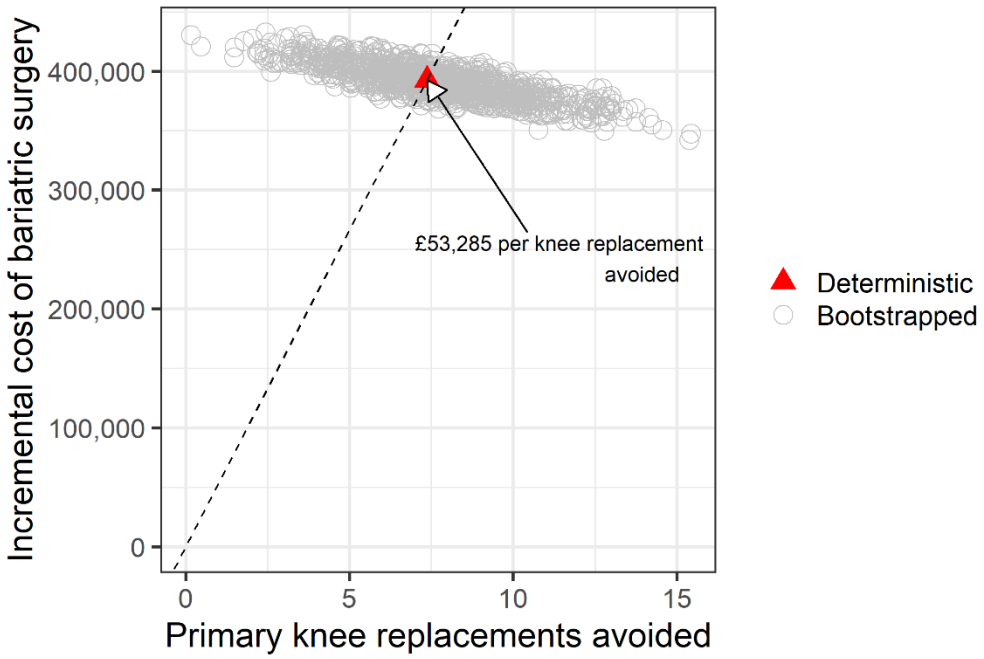


Figure 8.3. Knee replacements avoided and associated procedure costs saved for a representative cohort of 100 individuals with a BMI of 40 and varying in age and gender, but otherwise average characteristics, receiving bariatric surgery following diagnosis of knee osteoarthritis. The solid triangle is the deterministic (expected) estimate, with hollow circles representing bootstrapped estimates.

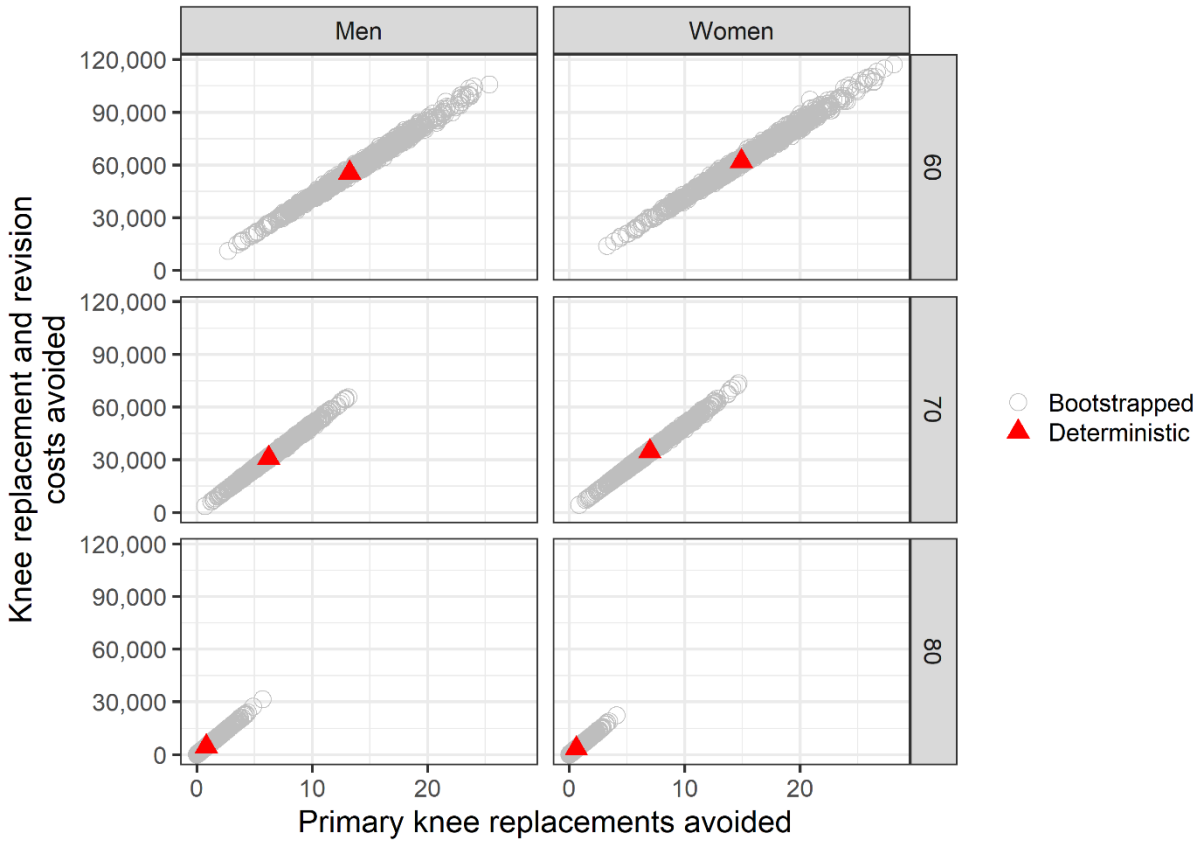


Figure 8.4. Incremental cost per primary knee replacement avoided for a representative cohort of 100 individuals with a BMI of 40 and varying in age and sex, but otherwise average characteristics, receiving bariatric surgery following diagnosis of knee osteoarthritis. The solid triangle is the deterministic (expected) estimate, with hollow circles representing bootstrapped estimates.

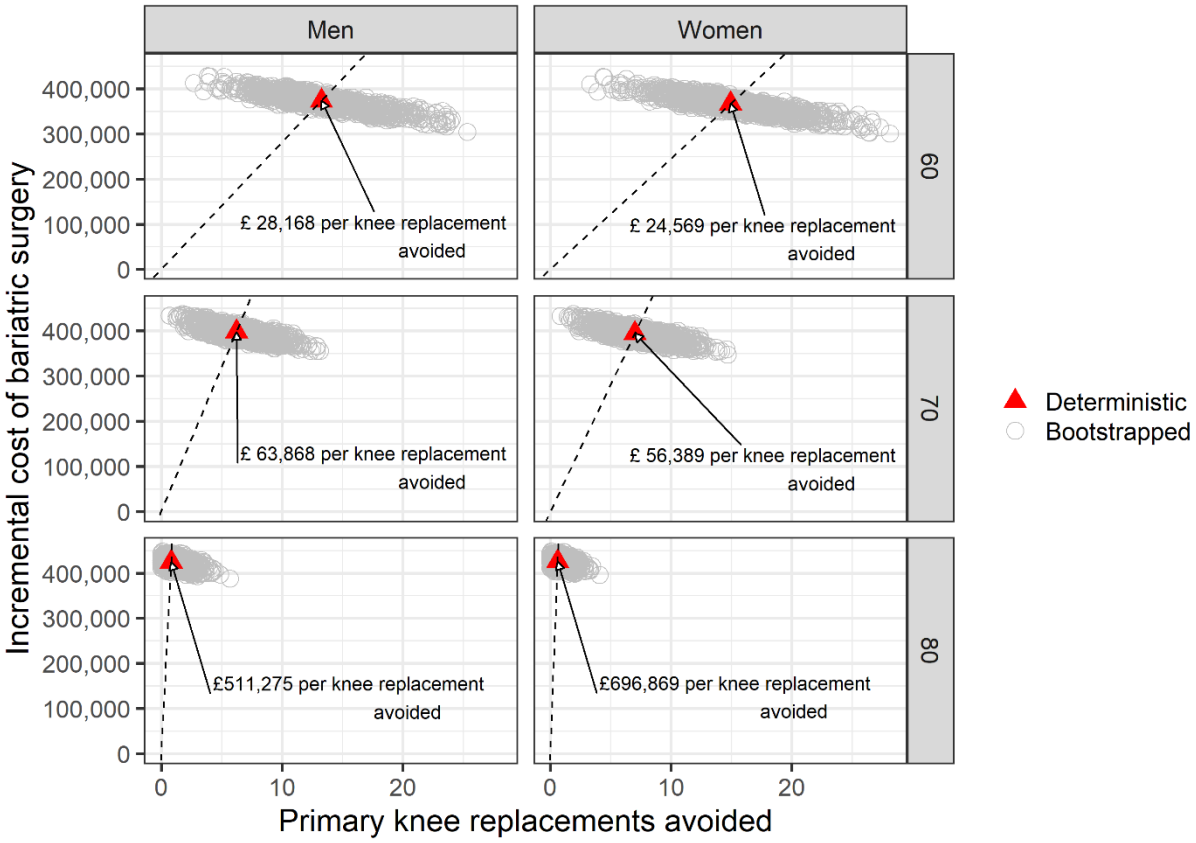


Table 8.1. Estimates for representative cohorts of 100 individuals with a BMI of 40, but otherwise average profile, under base case assumptions

Pathway	**Knee replacements**	**Revisions**	**Bariatric surgery costs (£)**	**Knee replacement and revision costs**	**Total cost (£)**	**Incremental cost per knee replacement avoided (£)**
Current practice	32.9 (27.0 to 39.6)	2.8 (2.3 to 3.4)		162,443 (135,317 to 195,234)	162,443 (135317 to 195,234)	
Bariatric surgery	25.5 (20.0 to 30.6)	2.2 (1.7 to 2.7)	428,968 (413,064 to 445,933)	126,105 (98,995 to 150,546)	555,073 (522,328 to 584,428)	
Difference	-7.4 (-3.2 to -12.7)	-0.6 (-0.3 to -1.1)	428,968 (413,064 to 445,933)	-36,338 (-15,685 to -62,553)	392,630 (363,711 to 419,125)	53,285

Study findings in context

Based on the research presented in Chapter 3, a higher BMI at time of diagnosis of osteoarthritis is associated with an increased subsequent risk of knee replacement. Weight loss for overweight and obese individuals has been seen to be one of the few effective interventions for knee osteoarthritis.[46] While studies have typically not had sufficient follow-up to assess the impact of weight loss on the risk of knee replacement, weight loss has consistently been seen to result in improvements in pain and function among individuals with knee osteoarthritis.[105]

Reducing the long-term risk of knee replacement will likely require weight loss to be maintained. Few non-surgical interventions, however, have been demonstrated to lead to sustained weight loss.[107] While an invasive surgical procedure which brings with it risks of a range of post-operative complications, bariatric surgery can be expected to result in sustained weight loss.[158]

Providing bariatric surgery is cost-effective for highly obese individuals.[111] Despite this, however, the provision of bariatric surgery in the UK has been limited, with the GPs rarely raising the possibility of bariatric surgery with eligible individuals.[209] Indeed, despite the greater prevalence of obesity in the UK and larger population, the number of bariatric surgeries performed is higher in countries such as the Netherlands and Belgium.[210] The under provision of bariatric surgery may be even greater for those with knee osteoarthritis, as has been seen in the USA.[211]

To date there has been little research into the effectiveness of bariatric surgery in a population with knee osteoarthritis. A randomised controlled trial comparing bariatric surgery to no bariatric surgery for individuals who are already on a waiting list for knee

replacement is ongoing.[212] However, as seen in the research presented in Chapters 4, 5, and 6 of this thesis and in the literature,[213] being overweight or obese seems to have little impact on the outcomes of knee replacement. The benefits from sustained weight loss for those with knee osteoarthritis are likely to be particularly pronounced when achieved earlier in the disease course, when the risk of knee replacement can be reduced.

The results from the study presented in this chapter suggest that bariatric surgery would be particularly beneficial when provided to younger individuals. Indeed, this is likely to be the case anyway, with those receiving bariatric in current practice typically in their mid-40s,[109] and obesity more likely to be seen for younger individuals being diagnosed with knee osteoarthritis.

Strengths and limitations

The primary strength of this analysis is that the outcomes under current practice are based on the previous analyses informed by routinely collected data. Current outcomes are taken to be reflective of no bariatric surgery, with few individuals in the study cohorts expected to have received the procedure after their diagnosis. Some may have had bariatric surgery, however. If this is the case, this may have led to the effect of BMI being underestimated (as only BMI at time of diagnosis was considered) and, in turn the potential benefits from bariatric surgery.

The effect of bariatric surgery on weight was based on a recent systematic review and meta-analysis, with numerous studies examining the effectiveness of bariatric surgery. These studies, however, typically had a follow-up of less than five years. This meant assumptions were required about how weight loss would be maintained into the future. For the base case analysis, it was assumed that weight loss would be maintained into the future. While

weight loss does seem to be maintained in the short-term,[158] longer-term treatment effects are not as well-known. The most pessimistic alternative assumption, that weight loss is only maintained for five years, was examined in a sensitivity analysis and did have a substantial effect on the results. Further research is therefore warranted to better understand the long-term weight loss trajectories after bariatric surgery.

In the modelling approach used, bariatric surgery was also assumed to only reduce the risk of knee replacement in the knee with an index diagnosis. However, bariatric surgery may well reduce risk of knee replacement in both knees, and so the full benefits of the procedure may have been somewhat underestimated.

Possibly the central limitation of this study is the assumption that those individuals who achieve a lower BMI through bariatric surgery would then be at the same risk of knee replacement as those individuals with a BMI of that level at time of diagnosis. This is necessarily uncertain and further research, ideally including randomised controlled trials, will be required to definitively establish the causal effect of bariatric surgery on the long-term risk of knee replacement.

Conclusions

Achieving sustained weight loss through bariatric surgery leads to many expected health benefits. For those individuals with a recent diagnosis of knee osteoarthritis, bariatric surgery may offer another dimension of benefit; reducing their risk of knee replacement. For 60-year-old women with a BMI of 40, for example, one knee replacement is expected to be avoided for every 7 bariatric surgeries provided.

9. THRESHOLD PRICES FOR COMPUTER AND ROBOT-ASSISTED KNEE AND HIP REPLACEMENT

Chapter summary

In this chapter I describe threshold prices for potential improvements in outcomes after knee and hip replacement, which might be attained from the use of computer or robot-assisted surgery.

Outcomes after knee and hip replacement under current practice were informed by the results from the studies summarised in Chapters 4 and 6. A decision-analytic model provided the framework for this analysis. Threshold prices were estimated for various given improvements in quality of life if unrevised and/ or revision risk after surgery.

For the average patient profile, a 50% relative reduction in risk of revision leads to a threshold price of £1,093 (£786 to £1,457) for knee replacement and £1,346 (£963 to £1829) for hip replacement at a cost-effectiveness threshold of £20,000 per quality-adjusted life year (QALY) gained. Meanwhile, a 5% relative improvement in post-operative quality of life if unrevised was found to be associated with a threshold price of £9,911 (£9,480 to £10,295) for knee replacement and £10,578 (£10,201 to £10,985) for hip replacement.

Background

As described in Chapter 1, computer and robot-assisted knee and hip replacement appears to result in better implant positioning than conventional procedures. This could lead to improvements in quality of life if unrevised and/ or a reduced risk of revision, but any such effects are yet to be established. The analysis reported in this chapter estimates threshold prices for given improvements in outcomes after knee and hip replacement. A Markov model, summarised in Chapter 2, was used as the framework for analysis. Transition probabilities (representing risks of revision and death) were estimated using the parametric models described in Chapter 6. Quality of life estimates are based on the ordinary least squares models for post-operative EQ-5D-3L index described in Chapter 4. The model was first run under current practice, with predictions from these models used. Given improvements in quality of life if unrevised and revision risk were incorporated by changing the predicted post-operative EQ-5D-3L index and transition probability for revision, respectively. Costs and outcomes under each improvement scenario were compared against those realised under current practice. For the base case analysis, the cost-effectiveness threshold was set at £20,000 per QALY gained. As a sensitivity analysis, cost-effectiveness thresholds of £13,000 and £30,000 were also considered.

Estimated threshold prices

A reduction in the relative risk of revision was incorporated in the model by reducing the estimated transition probabilities by a given amount. As described in Chapter 6, under current practice the lifetime risk of revision after knee replacement for the average patient profile is 5% (95% CI: 4% to 7%) after knee replacement and 8% (6% to 12%) after hip replacement. A 50% relative reduction in risk of revision resulted in lifetime risk of revision

falling to 3% (2% to 4%) and 4% (3% to 6%) after knee and hip replacement, respectively (see Figure 9.1). For knee replacement, this was expected to increase QALYs from 10.3 (9.9 to 10.7) to 10.4 (9.9 to 10.7) and reduce costs from £6,060 (£5,947 to £6,203) under current practice to £5,880 (£5,816 to £5,956). For hip replacement, QALYs remained similar at 11.0 (10.6 to 11.4) and 11.0 (10.7 to 11.4) but costs fell from £6,506 (£6,335 to £6,710) under current practice to £6,258 (£6,149 to £6,376) with the revision risk reduction. The corresponding threshold prices for a 50% relative reduction in risk of revision was £1,094 (£788 to £1,488) for knee replacement and £1,347 (£961 to £1,842) for hip replacement, shown in Figure 9.2.

An improvement in quality of life if unrevised was incorporated by increasing estimated post-operative EQ-5D-3L index by a given amount for those in the unrevised state, with quality of life for other model states remaining the same. The estimated improvement is assumed to be maintained into the future in the absence of a revision procedure. Figure 9.3 shows predicted quality of life if unrevised in the year after surgery for the average patient profile under current practice (i.e. with no improvement) and where predicted post-operative quality of life was improved by 5%. For the average patient profile, pre-operative EQ-5D-3L index was specified as 0.52 for knee replacement and 0.36 for hip replacement. These are approximately equivalent to an OKS of 24.8 and an OHS of 19.5. Under current practice, post-operative EQ-5D-3L index at six months was then expected to be 0.82 (95% CI: 0.79 to 0.85) and 0.86 (0.83 to 0.88) after knee and hip replacement, respectively. Meanwhile, under a 5% improvement, post-operative EQ-5D-3L index at six months was expected to be 0.86 (0.83 to 0.89) and 0.90 (0.87 to 0.93) after knee and hip replacement. This is approximately equivalent to an improvement in post-operative OKS from 38.3 to 40.1 after knee replacement, and an improvement in post-operative OHS from 41.7 to 43.6. A 5%

relative improvement in quality of life if unrevised was expected to increase QALYs after knee replacement from 10.3 (9.9 to 10.7) to 10.8 (10.4 to 11.2), and increase QALYs after hip replacement from 11.0 (10.6 to 11.4) to 11.5 (11.1 to 11.9). These results are shown in Figure 9.4. Costs remained unchanged. The corresponding threshold prices for a 5% improvement in post-operative quality of life if unrevised was £9911 (£9,476 to £10,296) for knee replacement and £10,578 (£10,171 to £10,982) for hip replacement, illustrated in Figure 9.5.

A combined 50% relative reduction in risk of revision and 5% improvement in post-operative quality of life if unrevised would result in QALYs increasing to 10.9 (10.4 to 11.3) after knee replacement and 11.6 (11.2 to 12.0) after hip replacement, with costs falling to £5,880 (£5,816 to £5,956) and £6,258 (£6,149 to £6,376). This had an associated threshold price of £11,182 (£10,691 to £11,721) for knee replacement and £12,134 (£11,616 to £12,701) for hip replacement (see Figure 9.6).

The partial effect of age and gender on threshold prices for a reduced risk of revision or improved post-operative quality of life if unrevised are shown in Figure 9.7, with threshold prices for improvements in both shown in Figure 9.8. Threshold prices were broadly similar regardless of sex, but were higher for younger patients. Younger patients have a higher lifetime risk of revision, as seen in Chapter 6, and so relative reductions in the risk translate into larger absolute gains, in terms of revisions avoided and costs saved. Similarly, with younger patients having a longer life expectancy they have more time to accrue benefits in post-operative quality of life, so relative reductions in the risk translate into larger absolute gains in quality-adjusted life-years. For example, a combined 50% relative reduction in risk of revision and 5% improvement in post-operative quality of life if unrevised for knee replacement would have a threshold price of £8,093 (£7,654 to £8,548) for an otherwise

average 80-year-old, which would increase to £15,507 (£14,740 to £16,121) if they were instead 60-years-old.

Threshold prices would necessarily change for different cost-effectiveness thresholds, as shown in Appendix Figure F.1. Threshold prices for a 5% improvement in post-operative quality of life if unrevised would, for example, be £14,866 (£14,214 to £15,444) for knee replacement and £15,867 (£15,257 to £16,473) for hip replacement at a cost-effectiveness threshold of £30,000 per additional QALY, but £6,442 (£6,159 to £6,692) and £6,876 (£6,611 to £7,138) at a cost-effectiveness threshold of £13,000.

Figure 9.1. Lifetime risk of revision under reduction in risk of revision for the average patient profile

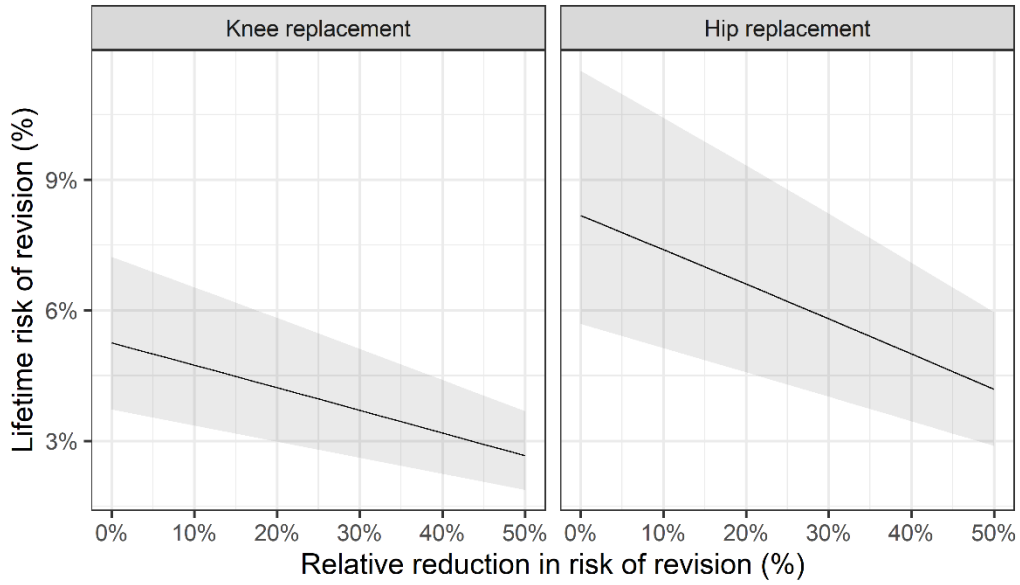


Figure 9.2. Threshold prices for reduced risk of revision for the average patient profile



Figure 9.3. Post-operative quality of life if unrevised under current practice and with a 50% reduction in risk for the average patient profile. OKS: Oxford Knee Score; OHS: Oxford Hip Score.

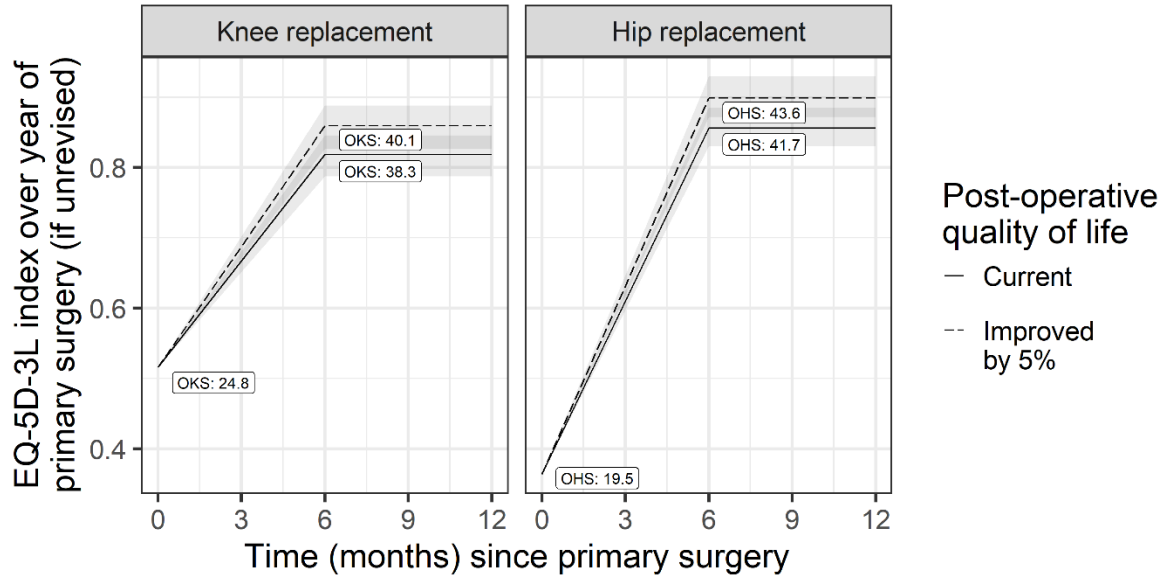


Figure 9.4. Quality-adjusted life-years (QALYs) for improvements in post-operative quality of life if unrevised for the average patient profile



Figure 9.5. Threshold prices for improved post-operative quality of life if unrevised for the average patient profile

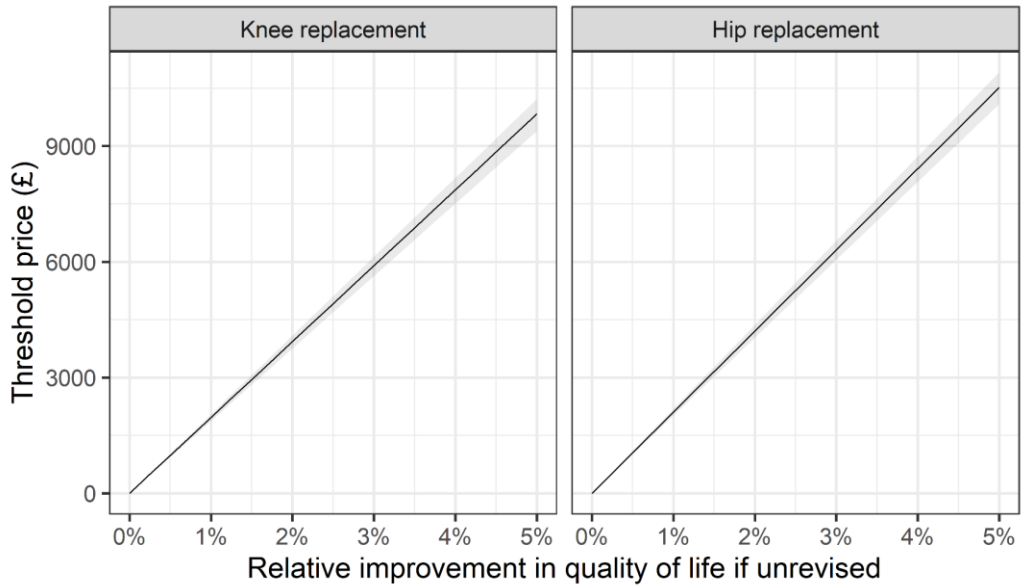


Figure 9.6. Threshold prices for reduced risk of revision and improved post-operative quality of life if unrevised for the average patient profile

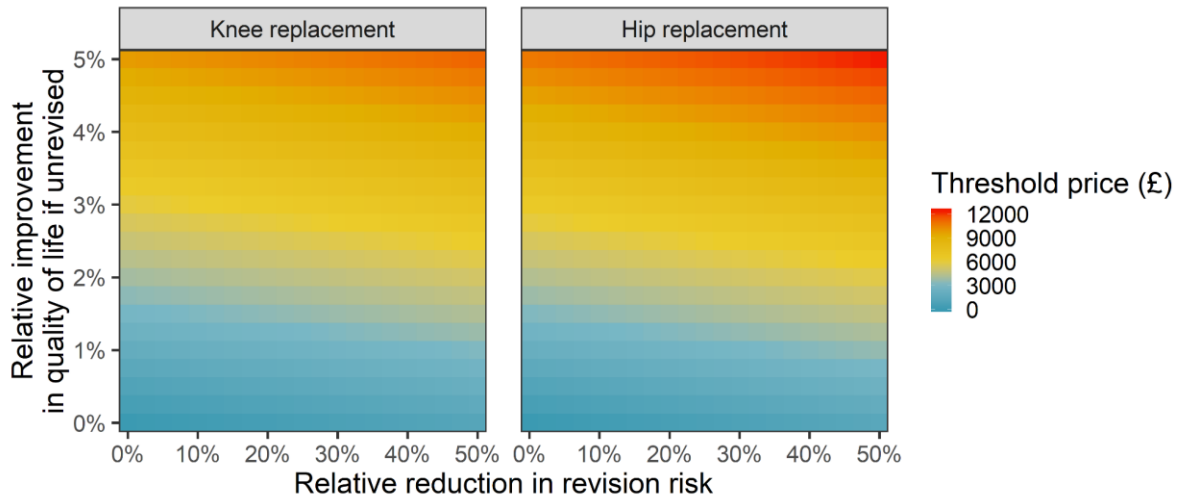


Figure 9.7. Partial effect of age and sex on threshold prices for reduced risk of revision or improved post-operative quality of life if unrevised

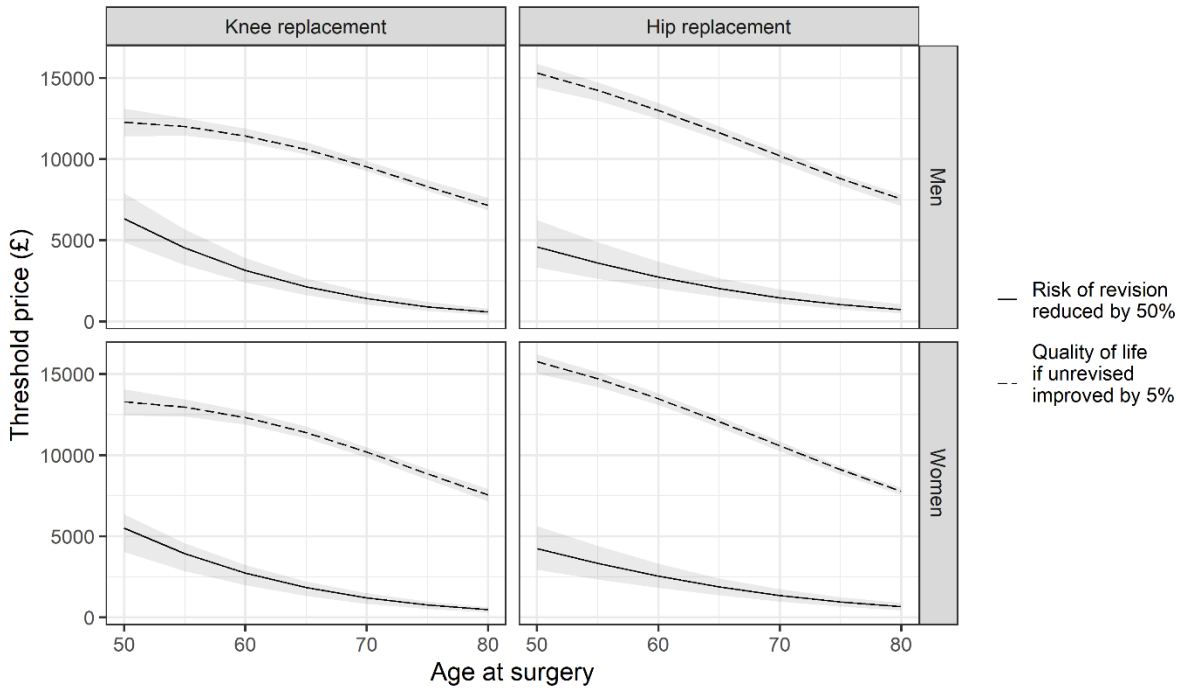
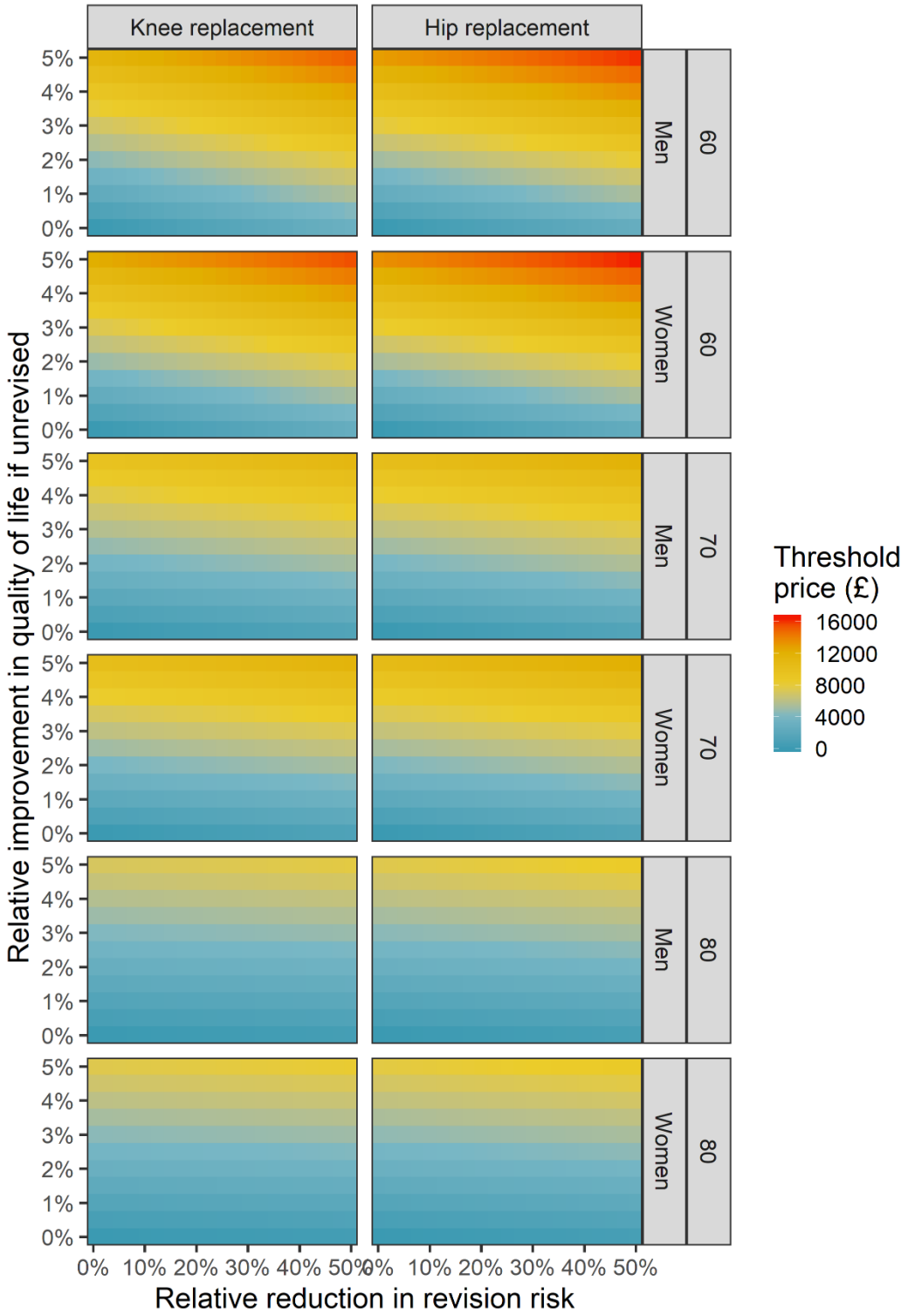


Figure 9.8. Partial effect of age and sex on threshold prices for combined reduced risk of revision and improved post-operative quality of life if unrevised



Study findings in context

A range of computer navigation and robotic-assisted systems have been developed to control component positioning and, in some cases, improve surgical precision in knee and hip replacement.[113] These systems have been found to lead to better implant positioning in both knee and hip replacement.[214] As yet, however, there is relatively little evidence that these improvements have translated into better clinical outcomes, either in short-term patient-reported outcomes or long-term risk of revision.[113] However, one large study of computer navigation in knee replacement in Australia, where over 20% of procedures are computer-assisted, was able to assess revision risk using data from the national joint replacement registry. In this study it was found that while revision risk was similar for older patients regardless of whether their knee replacement was computer-assisted or conventional, computer-assistance led to a 20% relative reduction in the risk of revision for patients aged less than 65 years of age.[215]

Given the uncertainty in the effectiveness of computer and robot-assisted knee and hip replacement, it is not possible to definitively answer whether they are a cost-effective use of health care resources. The results from this study provides a means of considering what effects would be needed for a given additional cost incurred for computer or robot-assisted surgery. The current costs of purchasing a robot system range from £290,000 to £2,000,000.[116] In addition to the fixed cost of purchasing a robot-assisted system, the consumables for each procedure cost around £1,400 and annual maintenance fees could cost £140,000,[116] and they also typically extend operating time.

Even after setting aside the upfront cost of buying the system, the variable costs would result in an approximate £1,700 additional cost per patient for a hospital with a caseload of

500 knee and hip replacements per year, the average in the English NHS,[216] and assuming it was used for all patients. On its own, even halving the risk of revision would unlikely be sufficient for the technology to be considered to provide sufficient value for money in England. Some additional gain in quality of life if unrevised would likely also be required to be considered cost-effective. While per patient costs would be somewhat reduced in higher volume centres, computer or robot-assisted knee and hip replacement would still need to have a large impact on clinical outcomes to be considered cost-effective at current prices. As prices fall over time, the scale of improvement in effectiveness required will necessarily fall. However, robust evidence that some improvement is gained will still be required.

Strengths and limitations

As with the previous chapter, the primary strength of this study is that it has been informed by routinely collected health data on risks of revision and mortality, quality of life after surgery, and costs incurred for surgical procedure. This has allowed for robust estimates of the current costs and health outcomes after knee and hip replacement under current practice.

With the effectiveness of computer and robot-assisted surgery not yet established for clinical outcomes, any assessment of their potential value will necessarily be speculative. Given the lack of evidence of effectiveness, threshold prices have been estimated for a range of potential effects. These threshold prices can help inform a consideration of the potential cost-effectiveness of these technologies, however definitive answers will need to be made when robust evidence becomes available on both relative effectiveness and costs. The effects may also differ from assumptions made here. For example, improvements in quality of life if unrevised may only be temporary while changes in the risks of revision may

be driven by differences in particular modes of implant failure, leading to risk reductions for revision varying over time. Moreover, effects may be seen in outcomes not well captured in the model used for this analysis, such as post-operative complications.

The threshold prices estimated in this study are also specific to the English NHS, with model inputs derived from routinely collected data from the health system and improvements measured against the cost-effectiveness threshold used by the National Institute for Health and Care Excellence (NICE) to make adoption recommendations. However, while we have used the lower bound for the cost-effectiveness threshold put forward by NICE, the true threshold may be less.[163] If this is the case then threshold prices would be correspondingly lower. Moreover, both the current consequences of knee and hip replacement and the willingness to pay for improvements in outcomes can be expected to vary across countries. While differences may be relatively small in other publicly funded health systems in high-income countries, threshold prices can be expected to be considerably higher in the USA, given fewer restraints on the costs of interventions that are adopted, while threshold prices may be lower in low- and middle-income countries where the ability to pay for improvements is less.

Conclusions

To be considered cost-effective, computer and robot-assisted knee and hip replacement will need to demonstrate meaningful improvements in outcomes relative to their cost. At current prices these gains will have to be substantial, and any reductions in the risk of revision will likely need to also be accompanied by improvements in post-operative quality of life. The threshold prices estimated in this study provide valuable information as to the

health gains required for computer and robot-assisted knee and hip replacement to be cost-effective at a given price.

10. DISCUSSION

Chapter summary

In this chapter I summarise the key results from the studies performed, consider the implications for future research, and offer a brief conclusion.

While an important possibility, knee and hip replacement are not inevitable after diagnoses of osteoarthritis and rheumatoid arthritis. Those individuals who do undergo a knee or hip replacement typically achieve substantial improvements in joint-specific and generic patient-reported outcomes, and risks of post-operative complications are relatively low. While revisions are enduring risk after knee and hip replacement, absolute risks are modest, particularly for older patients. Informed by the findings from this initial research, the potential consequences of interventions which reduce the need for or improve outcomes from knee and hip replacement have been assessed.

The findings from this thesis will help to inform patients on their prognosis under current practice and will help to inform resource allocation decisions on interventions related to knee and hip replacement. The research presented in this thesis also highlights the value of routinely collected data. Considering the entirety of a disease and its treatment will necessarily require information about outcomes under current practice, and analyses of routinely collected data can provide this.

Summary of key results

The overall aim in this thesis was to provide robust evidence which can be used to understand individuals' prognosis and inform decision-making concerning knee and hip replacement. The studies summarised in the preceding chapters have helped to achieve this aim.

Knee and hip replacement are not inevitable after diagnoses of osteoarthritis or rheumatoid arthritis. As seen in Chapter 3, for the average patient profiles, lifetime risk of knee replacement after a diagnosis of knee osteoarthritis was 30%, lifetime risk of hip replacement after a diagnosis of hip osteoarthritis was 14%, and lifetime risks of knee and hip replacement following a diagnosis of rheumatoid arthritis were 22% and 17%, respectively. In most cases, risks of these procedures were highest in the first two years after diagnosis. Lifetime risks of knee and hip replacement were higher for younger patients. Lifetime risk of knee replacement was increased after a diagnosis of knee osteoarthritis for those with a higher BMI, and risk of hip replacement after a diagnosis of hip osteoarthritis was higher for young men compared to young women.

Those individuals who do undergo a knee or hip replacement typically attain a substantial improvement in both joint-specific outcomes and overall health-related quality of life. As detailed in Chapter 4, for example, patients achieved 62% of their potential improvement in OKS after knee replacement, and 81% of their potential improvement in OHS after hip replacement. The key determinant of post-operative patient-reported outcomes was pre-operative scores, with post-operative scores expected to increase as pre-operative scores improved. Other patient characteristics assessed, some of which are currently used to

restrict access to surgery, appeared to have little meaningful impact on post-operative scores.

Post-operative complications after surgery are relatively rare, but findings from Chapter 5 showed that risks of myocardial infarction and mortality appear to be higher for older age groups, men, and those with comorbidities. Risks of myocardial infarction after knee replacement and mortality after hip replacement also appear to be higher for those individuals with an index diagnosis of rheumatoid arthritis. Revisions are an enduring risk after surgery. However, as with primary procedures, they are not inevitable. As detailed in Chapter 6, risks were relatively low for the average patient profile, with the lifetime risk of revision around 5% after knee replacement and 8% after hip replacement. Similar to the lifetime risk of having a primary knee/ hip replacement after a diagnosis of osteoarthritis or rheumatoid arthritis, age was the key determinant of lifetime risk of revision.

Interventions which reduce the risk of knee and/ or hip replacement could offer substantial benefits, both in terms of the procedure costs avoided for the healthcare system and the health gains for individuals. Reducing the risk of knee and hip replacement after a diagnosis of rheumatoid arthritis may be achieved through the early initiation of TNFi, although current estimates of treatment effect are mixed. The analysis described in Chapter 7 showed that relative risk reductions of 20% would, for example, lead to 46 and 30 fewer knee and hip replacements, respectively, with a combined cost-saving of over £300,000 for a cohort of 1,000 individuals with the average profile of those diagnosed with rheumatoid arthritis. Meanwhile, reducing BMI among those diagnosed with knee osteoarthritis and who are overweight or obese could lead to a reduction in the risk of knee replacement. The analysis described in Chapter 8 demonstrated that for a cohort of 100 patients with a BMI of 40, but otherwise with the average characteristics of those diagnosed with knee

osteoarthritis, bariatric surgery would be expected to result in 7 fewer knee replacements, saving around £36,000 in associated procedure costs. In both cases, benefits from the interventions would be even greater for younger patients who have higher lifetime risks of knee and hip replacement.

There also remains room for improvement in outcomes after knee and hip replacement, either from increases in post-operative quality of life or a reduction in the risk of revision. The use of computer or robot-assisted surgery could lead to such improvements. However, the effectiveness of these technologies is not yet well-established. In Chapter 9, results showed that, for the average patient profiles, a 50% relative reduction in risk of revision had a threshold price of around £1,000 and £1,300 for knee and hip replacement, respectively. Meanwhile, a 5% relative improvement in post-operative quality of life if unrevised, equivalent to a two-point improvement in Oxford Knee Score/ Oxford Hip Score, had threshold prices of around £10,000 for both knee and hip replacement. As with interventions which reduced the risk of knee and hip replacements, the benefits from improvements in the effectiveness of knee and hip replacement are particularly pronounced for younger patients. Those at a younger age at time of surgery have both a higher lifetime risk of revision and more time to accrue benefits from improvements in quality of life.

Limitations of the research

A series of epidemiological studies were presented in chapters 3 to 6, all of which were underpinned by routinely collected data. With the data collection not undertaken primarily for research purposes, the accuracy of coding is a concern. Although, where possible, validated coding algorithms were used to identify exposures and outcomes of interest, even these are known not to have perfect sensitivity and specificity. There is, therefore, the

potential for both false positives (individuals wrongly identified as having the exposure or outcome of interest) and false negatives (individuals wrongly identified as not having the exposure or outcome of interest).

There was missing data in PROMs and in smoking status and BMI. Multiple imputation was used for smoking status and BMI, while a complete case approach was used for patient-reported outcomes. The latter approach, in particular, may have led to potential bias if those who complete patient-reported outcome measures are systematically different to those who do not. Meanwhile, some variables that would have been of interest were simply not collected. One consequence, for example, was that analyses focused on receipt of knee and hip replacement (which was observed), rather than need for knee and hip replacement (which was not observed).

A range of statistical methods were applied, all of which make various assumptions. One area of particular ambiguity is around the use of parametric survival models to estimate lifetime risks. The application of such models requires assumptions about survival beyond observed follow-up. In the absence of data to externally validate these assumptions, choice of distributions was made based on their perceived plausibility, which is necessarily a subjective judgement.

A number of early-stage economic evaluations were presented in chapters 7 to 9. The decision modelling frameworks used imposed a number of simplifying assumptions, for example around how weight loss after bariatric surgery would be maintained in the long-term. Moreover, given the nature of these studies, the specific decision problems considered were somewhat speculative. More definitive assessments will not only require more evidence on costs and effectiveness, but also a more precise description of the alternative courses of action being considered. For example, with regards to bariatric

surgery after a diagnosis of knee OA, how the bariatric surgery would be offered to eligible individuals and when it would be performed. Moreover, the consistent use of QALYs would allow for the value for money of interventions to be compared against cost-effectiveness thresholds, although this would also require further evidence, such as on individuals' health-related quality of life at time of OA diagnosis.

Implications for current practice

The act of medical diagnosis is the classification of an individual as either having or not having a certain disease,[217] and a key moment where patients require information on their prognosis.[173] The information from this thesis on lifetime risks of knee and hip replacement should allow clinicians to better inform patients about their prognosis at the time of diagnosis. These estimates should be particularly valuable for those with osteoarthritis, where there has been limited adherence to treatment guidelines partly due to the pessimism surrounding the condition, with it considered an unavoidable consequence of aging with further deterioration inevitable.[30–32] The findings from this thesis have revealed that the knee and hip replacement are by no means inevitable. This is consistent with previous research on the radiographic and symptomatic progression of osteoarthritis,[20,21,25] and will provide valuable evidence with which to inform patients on their prognosis following diagnosis.

Diagnosis is also an opportune moment for interventions to be initiated. In rheumatoid arthritis there is a choice between a range of pharmacological therapies, with TNFi a more effective but more costly first-line therapy. In this thesis another potential benefit from TNFi has been considered, that of reducing the risk of knee and hip replacement. While such effects are currently uncertain, the results from this thesis can be used to consider the

implications of relative risk reductions as further evidence emerges and can be used in evaluations of the value for money of these therapies as they come off patent. For osteoarthritis, there are few effective interventions available. One effective change though is weight loss for overweight and obese individuals with knee osteoarthritis. While few interventions have been shown to lead to sustained weight loss, bariatric surgery has and is considered to be cost-effective for morbidly obese individuals.[111] Use of bariatric surgery, however, is limited and particularly so in the UK.[210] Indeed, only 17% of clinical commissioning groups (CCGs) in England are adhering to national guidelines, with a number requiring individuals to have a BMI of over 50 to be eligible for bariatric surgery.[218] The findings from this thesis demonstrate another dimension of benefit from bariatric surgery when provided to those with a recent diagnosis of knee osteoarthritis, with one knee replacement avoided for every seven bariatric surgeries provided to 60-year-olds with a BMI of 40.

Even if risks are reduced, knee and hip replacement will remain an important treatment option for the foreseeable future. Evidence from this thesis further demonstrates that, in general, patient-reported outcomes improve dramatically after surgery, post-operative complications are relatively rare, and that the majority of patients will not undergo a revision procedure. While pre-operative scores are a key determinant of post-operative patient-reported outcomes, and age is a key determinant of lifetime risk and is associated with higher risks of complications, few other patient characteristics considered were found to have a meaningful impact on the overall risk-benefit trade-off from undergoing surgery. This included both BMI and smoking, yet a number of CCGs in the English NHS currently restrict access to surgery on the basis of these two factors.[219] In 2015, 31% and 12% of CCGs had mandatory policies limiting referral for joint replacement on the basis of patients' BMI

and smoking status, respectively.[220] The principal justification for this rationing has focused on clinical benefits, with those with a high BMI or smoking considered more likely to have a poor outcome.[221] However, given the findings from this thesis, this belief seems to be misguided.

While computer and robot-assisted knee and hip replacement have been adopted in other countries, such as in the USA and Australia, they are not routinely used in the English NHS. This seems appropriate given the current context, with these systems coming at a high cost and little existing evidence that they lead to meaningful improvements in patient outcomes. If future evidence emerges demonstrating these techniques to be effective, consideration will also be needed as to whether they are cost-effective. The findings from this thesis provide a framework for considering what improvements in outcomes would be required to justify incurring the costs of such technologies.

Implications for future research

Understanding outcomes from current practice using routinely collected data

Assessing patient outcomes under current practice can be used to develop evidence on prognosis: the likelihood of future outcomes in patients with a given disease or health condition, which should be used to help shape clinical practice.[173] Routinely collected data offers a valuable resource for understanding outcomes under current practice, with typically large and representative study populations, and providing information that is often infeasible or impossible to obtain elsewhere.[222] In this thesis, routinely collected data have been used to develop insights into prognosis at time of diagnosis of osteoarthritis or rheumatoid arthritis, and at time of knee or hip replacement. As demonstrated by these studies, drawing out useful information from real-world data requires the use of

appropriate analytic methods. Estimating lifetime risks of knee and hip replacement and subsequent revision, for example, required the use of flexible parametric survival modelling, which allowed for extrapolation and a thorough assessment of patient heterogeneity.

Even with continued development of analytic methods to account for some of the known limitations of routinely collected data, these data will still have limitations for fully understanding patient prognosis under current practice.

The fundamental limitation is that data are generally not collected for the primary purpose of research. One consequence is a concern about data quality, as seen, for example, with the substantial under-recording of osteoarthritis in primary care databases in England.[223] Another result, is that important variables of interest may not be collected. For the studies in this thesis, the recording of disease severity at diagnosis would have allowed for another important dimension of patient heterogeneity to be considered. Moreover, while patient-reported outcomes were available prior to and six months after knee and hip replacement, such outcome variables are rarely available in routinely collected data. Proxy variables could be used to make inferences about individuals' health trajectories, such as diagnoses and prescriptions used to indicate health problems, and this may well become an important area of research.

Assessing alternative courses of action at a point in time

Economic evaluations provide an organised consideration of alternative courses of action,[224] such as adopting (or choosing not to adopt) a new health care technology. In the absence of high-quality evidence on effectiveness, early-stage economic evaluations, which are investigative in nature, can be performed.[225] Such analyses were undertaken in this thesis, and while they cannot provide definitive information on the value for money of a particular

course of action, they do offer a framework for a broad assessment of potential value. Setting threshold prices for computer and robot-assisted knee and hip replacement does not, for example, provide an immediate answer to whether they should be funded, but rather establishes a basis for informing this decision as further evidence on their effectiveness emerges.

Later-stage economic evaluations provide a more conclusive assessment of the value for money of interventions.[225] These evaluations require robust evidence of effectiveness, with counterfactual prediction (causal inference) using data to predict certain features of the world as if the world had been different.[226] Any approach used to provide such estimates will have potential sources of bias. Randomised trials provide the 'gold-standard' for determining efficacy of interventions,[227] with randomisation increasing the likelihood that treatment allocation is undertaken independently of both known and unknown patient characteristics.[228] Biases in randomised controlled trials, however, can arise from a failure to maintain the original randomised status of participants when comparing outcomes and differential loss to follow-up.[229] In contrast, studies based on routinely collected data offer the potential to assess the real-world effectiveness of an intervention, and study designs which emulate target trials can help to avoid common methodologic pitfalls.[230] However, bias can still occur from residual confounding due to unobserved and/or poorly measured confounders.[228] Ultimately, aiming to undertake a single, 'perfect' study is likely to be misguided. A more pragmatic approach would be to employ a range of analytic approaches to answer the same underlying causal question, with considerations of the key sources of bias in each.[231] Consistent findings across the different approaches would increase the confidence that estimated effects reflect the 'true' causal effect.[229]

Moving towards whole disease modelling

Evaluations of health care interventions are generally piecewise, estimating their consequences at an isolated point within a broader pathway of care.[232] This approach treats the funding of health interventions as independent. However, in reality, the adoption of interventions will typically have impacts on the merit of both downstream and upstream courses of action.[232] In osteoarthritis, for example, the cost-effectiveness of knee and hip replacement depends on both the non-surgical interventions provided before surgery, and the management of patients after surgery. For example, the introduction of disease-modifying osteoarthritis drugs,[233] comparable to DMARDs for rheumatoid arthritis, may change the profile of individuals undergoing, and likely outcomes from, knee and hip replacement. In addition, the adoption of technologies which improve outcomes of revision surgery may also change the expected value of the preceding primary procedures.

A more general, whole disease approach to decision modelling would allow for a broader assessment which accounts for these interdependencies.[232] In disease policy models, a model is developed which captures all relevant aspects of a disease and its treatment, with the ability to simultaneously assess a range of potential interventions along the disease course. Underpinning a disease policy model is a disease logic model, which describes the natural history of a disease. Health care (diagnostic and treatment) pathways are then overlaid.[232] The outcomes can then be estimated for a particular health care pathway, accounting for the impact of the particular interventions provided on individual's trajectories.

The feasibility of such an approach was assessed for prostate cancer and atrial fibrillation. While the development of the models required a substantial investment of time, taking

around two years, the models developed were able to assess a range of NICE guidelines for the management of these conditions.[234]

The development of disease policy models for osteoarthritis and rheumatoid arthritis could be used to identify the combination of courses of action along the disease course that lead to the best health outcomes, 'gold standard' care. Moreover, the value for money of various pathways, and interventions within them, could be established. This would help to underpin evidence-based guidelines for the management of these conditions.

Conclusion

The research presented in this thesis, informed by routinely collected data, has added to the evidence base regarding prognosis in osteoarthritis and rheumatoid arthritis, in particular with respect to knee and hip replacement. These findings have also helped to inform assessments of interventions which reduce the risk of these procedures or improve outcomes after they have been performed. The findings of this thesis have demonstrated the value of routinely collected data for helping to better understand the entirety of a disease and inform assessments of its treatment.

11. REFERENCES

1. Culliford DJ, Maskell J, Beard DJ, Murray DW, Price AJ, Arden NK. Temporal trends in hip and knee replacement in the United Kingdom: 1991 TO 2006. *J Bone Jt Surg - Br Vol*. 2010;92-B(1):130-135. doi:10.1302/0301-620X.92B1.22654
2. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK. Future projections of total hip and knee arthroplasty in the UK: Results from the UK Clinical Practice Research Datalink. *Osteoarthr Cartil*. 2015;23(4):594-600. doi:10.1016/j.joca.2014.12.022
3. Kurtz SM, Ong KL, Lau E, Bozic KJ. Impact of the Economic Downturn on Total Joint Replacement Demand in the United States. *J Bone Jt Surg*. 2014;96(8):624-630. doi:10.2106/JBJS.M.00285
4. Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. *J Bone Joint Surg Am*. 2007;89:780-785. doi:10.2106/JBJS.F.00222
5. Carr AJ, Robertsson O, Graves S, et al. Knee replacement. *Lancet*. 2012;379(9823):1331-1340. doi:10.1016/S0140-6736(11)60752-6
6. Ferguson RJ, Palmer AJR, Taylor A, Porter ML, Malchau H, Glyn-Jones S. Hip replacement. *Lancet*. 2018;392(10158):1662-1671. doi:https://doi.org/10.1016/S0140-6736(18)31777-X
7. Kraus VB, Blanco FJ, Englund M, Karsdal MA, Lohmander LS. Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. *Osteoarthr Cartil*. 2015;23(8):1233-1241. doi:10.1016/j.joca.2015.03.036
8. NICE. Osteoarthritis: Care and management in adults (Clinical guideline CG177). 2014;(February).

9. Pivec R, Johnson AJ, Mears SC, Mont MA. Hip arthroplasty. *Lancet*. 2012;380(9855):1768-1777. doi:10.1016/S0140-6736(12)60607-2

10. National Joint Registry for England Northern Ireland and the Isle of Man W. *12th Annual Report*.; 2015. http://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Reports/12th annual report/NJR Online Annual Report 2015.pdf.

11. Green M, Wishart N, Young E, Mccormack V, Swanson M. NJR 14th Annual Report. *Natl Jt Regist 14th Annu Rep*. 2017;1821(December 2016).

12. Nielen MMJ, Van Schaardenburg D, Reesink HW, et al. Specific Autoantibodies Precede the Symptoms of Rheumatoid Arthritis: A Study of Serial Measurements in Blood Donors. *Arthritis Rheum*. 2004;50(2):380-386. doi:10.1002/art.20018

13. Kraan MC, Versendaal H, Jonker M, et al. Asymptomatic synovitis precedes clinically manifest arthritis. *Arthritis Rheum*. 1998;41(8):1481-1488. doi:10.1002/1529-0131(199808)41:8<1481::AID-ART19>3.0.CO;2-O

14. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. *Lancet*. 2010;376(9746):1094-1108. doi:10.1016/S0140-6736(10)60826-4

15. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum*. 2010;62(9):2569-2581. doi:10.1002/art.27584

16. Wilkinson JM, Stanley D, Getty CJM. Surgical management of the rheumatoid patient. *Curr Orthop*. 2004:357-370. doi:10.1016/j.cuor.2004.06.007

17. National Institue for Health and Clinical Excellence (NICE). Rheumatoid arthritis in adults: management. 2009.

18. National Institue for Health and Clinical Excellence Guideline. Rheumatoid arthritis in adults: management. *NICE Clin Guidel*. 2009;(February 2009):1-35.

19. Cooper C, Adachi JD, Bardin T, et al. How to define responders in osteoarthritis. 2013;29(6):719-729. doi:10.1185/03007995.2013.792793

20. Leyland KM, Hart DJ, Javaid MK, et al. The Natural History of Radiographic Knee Osteoarthritis A Fourteen-Year Population-Based Cohort Study. 2015;64(7):2243-2251. doi:10.1002/art.34415

21. Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly. The framingham study. *Arthritis Rheum*. 1997;40(4):728-733. doi:10.1002/art.1780400420

22. Chapple CM, Nicholson H, Baxter GD, Abbott JH. Patient characteristics that predict progression of knee osteoarthritis: A systematic review of prognostic studies. *Arthritis Care Res*. 2011;63(8):1115-1125. doi:10.1002/acr.20492

23. Wright AA, Cook C, Abbott JH. Variables Associated With the Progression of Hip Osteoarthritis : A Systematic Review. 2009;61(7):925-936. doi:10.1002/art.24641

24. Nicholls E, Thomas E, van der Windt DA, Croft PR, Peat G. Pain trajectory groups in persons with, or at high risk of, knee osteoarthritis: Findings from the Knee clinical assessment study and the osteoarthritis initiative. *Osteoarthr Cartil*. 2014;22(12):2041-2050. doi:10.1016/j.joca.2014.09.026

25. Leffondré K, Abrahamowicz M, Regeasse A, et al. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. *J Clin Epidemiol*. 2004;57(10):1049-1062. doi:10.1016/j.jclinepi.2004.02.012

26. Verkleij SPJ, Hoekstra T, Rozendaal RM, et al. Defining discriminative pain trajectories in hip osteoarthritis over a 2-year time period. *Ann Rheum Dis*. 2012;71(9):1517-1523.

doi:10.1136/annrheumdis-2011-200687

27. Bastick AN, Verkleij SPJ, Damen J, et al. Defining hip pain trajectories in early symptomatic hip osteoarthritis - 5 year results from a nationwide prospective cohort study (CHECK). *Osteoarthr Cartil*. 2016;24(5):768-775. doi:10.1016/j.joca.2015.11.023

28. Bastick AN, Damen J, Agricola R, Brouwer RW, Bindels PJ, Bierma-Zeinstra SM. Characteristics associated with joint replacement in early symptomatic knee or hip osteoarthritis: 6-year results from a nationwide prospective cohort study (CHECK). *Br J Gen Pract*. 2017;67(663):e724-e731. doi:10.3399/bjgp17x692165

29. Leyland KM, Judge A, Javaid MK, et al. Obesity and the Relative Risk of Knee Replacement Surgery in Patients With Knee Osteoarthritis A Prospective Cohort Study. 2016;68(4):817-825. doi:10.1002/art.39486

30. Paskins Z, Sanders T, Hassell AB. Comparison of patient experiences of the osteoarthritis consultation with GP attitudes and beliefs to OA: A narrative review. *BMC Fam Pract*. 2014;15(1):1-10. doi:10.1186/1471-2296-15-46

31. Egerton T, Diamond LE, Buchbinder R, Bennell KL, Slade SC. A systematic review and evidence synthesis of qualitative studies to identify primary care clinicians' barriers and enablers to the management of osteoarthritis. *Osteoarthr Cartil*. 2017;25(5):625-638. doi:10.1016/j.joca.2016.12.002

32. Healey EL, Afolabi EK, Lewis M, et al. Uptake of the NICE osteoarthritis guidelines in primary care: A survey of older adults with joint pain. *BMC Musculoskelet Disord*. 2018;19(1):1-9. doi:10.1186/s12891-018-2196-2

33. Victor C, Ross F, Axford J. Capturing lay perspectives in a randomized control trial of a health promotion intervention for people with osteoarthritis of the knee. *J Eval Clin Pr*. 2004;10(1):63-70.

34. Chou L, Ellis L, Papandony M, et al. Patients' perceived needs of osteoarthritis health information: A systematic scoping review. *PLoS One*. 2018;13(4):1-24. doi:10.1371/journal.pone.0195489

35. Hobbs KF, Cohen MD. Rheumatoid arthritis disease measurement: A new old idea. *Rheumatol (United Kingdom)*. 2012;51(SUPPL. 6):21-27. doi:10.1093/rheumatology/kes282

36. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: Strategies, opportunities and challenges. *Nat Rev Rheumatol*. 2015;11(5):276-289. doi:10.1038/nrrheum.2015.8

37. Felson DT, Smolen JS, Wells G, et al. American college of rheumatology/European league against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis Rheum*. 2011;63(3):573-586. doi:10.1002/art.30129

38. SHOURT CA, CROWSON CS, GABRIEL SE, MATTESON EL. Utilization of Orthopedic Surgery Among Patients with Rheumatoid Arthritis 1980–2007: A Population-based Study Focused on Surgery Rates, Sex, and Mortality. *J Rheumatol*. 2012;39(3):481-485. doi:10.3899/jrheum.111056

39. Da Silva E, Doran MF, Crowson CS, O'Fallon WM, Matteson EL. Declining use of orthopedic surgery in patients with rheumatoid arthritis? Results of a long-term, population-based assessment. *Arthritis Rheum*. 2003;49(2):216-220. doi:10.1002/art.10998

40. Nikiphorou E, Carpenter L, Morris S, et al. Hand and foot surgery rates in rheumatoid arthritis have declined from 1986 to 2011, but large-joint replacement rates remain unchanged: Results from two UK inception cohorts. *Arthritis Rheumatol*. 2014;66(5):1081-1089. doi:10.1002/art.38344

41. Sculpher M. Subgroups and heterogeneity in cost-effectiveness analysis. *Pharmacoeconomics*. 2008;26(9):799-806. doi:10.2165/00019053-200826090-00009

42. Bastick AN, Runhaar J, Belo JN, Bierma-Zeinstra SMA. Prognostic factors for progression of clinical osteoarthritis of the knee: a systematic review of observational studies. *Arthritis Res Ther*. 2015;17(1):152. doi:10.1186/s13075-015-0670-x

43. Hawker GA, Guan J, Croxford R, et al. A prospective population-based study of the predictors of undergoing total joint arthroplasty. *Arthritis Rheum*. 2006;54(10):3212-3220. doi:10.1002/art.22146

44. Borkhoff CM, Hawker GA, Wright JG. Patient gender affects the referral and recommendation for total joint arthroplasty. *Clin Orthop Relat Res*. 2011;469(7):1829-1837. doi:10.1007/s11999-011-1879-x

45. Borkhoff CM, Hawker GA, Kreder HJ, Glazier RH, Mahomed NN, Wright JG. The effect of patients' sex on physicians' recommendations for total knee arthroplasty. *Can Med Assoc J*. 2008;178(6):681-687. doi:10.1503/cmaj.071168

46. Reijman M, Pols HAP, Bergink AP, et al. Body mass index associated with onset and progression of osteoarthritis of the knee but not of the hip: The Rotterdam Study. *Ann Rheum Dis*. 2007:158-162. doi:ard.2006.053538

47. Price AJ, Longino D, Rees J, et al. Are pain and function better measures of outcome than revision rates after TKR in the younger patient? *Knee*. 2010;17(3):196-199. doi:10.1016/j.knee.2009.09.003

48. Carr AJ, Robertsson O, Graves S, et al. Knee replacement. *Lancet*. 2012;379(9823):1331-1340. doi:10.1016/s0140-6736(11)60752-6

49. Schilling C, Dowsey MM, Clarke PM, Choong PF. Using Patient-Reported Outcomes for Economic Evaluation : Getting the Timing Right. *Value Heal*. 2016;19(8):945-950.

doi:10.1016/j.jval.2016.05.014

50. Harris KK, Price AJ, Beard DJ, Fitzpatrick R, Jenkinson C, Dawson J. Can pain and function be distinguished in the Oxford Hip Score in a meaningful way? : an exploratory and confirmatory factor analysis. *Bone Joint Res*. 2014;3(11):305-309. doi:10.1302/2046-3758.311.2000313

51. Harris K, Dawson J, Doll H, et al. Can pain and function be distinguished in the Oxford Knee Score in a meaningful way? An exploratory and confirmatory factor analysis. *Qual Life Res*. 2013;22(9):2561-2568. doi:10.1007/s11136-013-0393-x

52. Murray DW, Fitzpatrick R, Rogers K, et al. The use of the Oxford hip and knee scores. *J Bone Jt Surg Br*. 2007;89(8):1010-1014. doi:10.1302/0301-620X.89B8.19424

53. Beard DJ, Harris K, Dawson J, et al. Meaningful changes for the Oxford hip and knee scores after joint replacement surgery. *J Clin Epidemiol*. 2015;68(1):73-79. doi:10.1016/j.jclinepi.2014.08.009

54. Judge A, Arden NK, Batra RN, et al. The association of patient characteristics and surgical variables on symptoms of pain and function over 5 years following primary hip-replacement surgery: a prospective cohort study. *BMJ Open*. 2013;3(3):e002453. doi:10.1136/bmjopen-2012-002453

55. Schilling C, Petrie D, Dowsey MM, Choong PF, Clarke P. THE IMPACT OF REGRESSION TO THE MEAN ON ECONOMIC EVALUATION IN QUASI-EXPERIMENTAL PRE – POST STUDIES : THE EXAMPLE OF TOTAL KNEE REPLACEMENT USING DATA FROM THE. 2016. doi:10.1002/hec.3475

56. Skou ST, Roos EM, Laursen MB, et al. A Randomized, Controlled Trial of Total Knee Replacement. *N Engl J Med*. 2015;373(17):1597-1606. doi:10.1056/NEJMoa1505467

57. Kiran A, Hunter DJ, Judge A, et al. A novel methodological approach for measuring

symptomatic change following total joint arthroplasty. *J Arthroplasty*. 2014;29(11):2140-2145. doi:10.1016/j.arth.2014.06.008

58. Anakwe RE, Jenkins PJ, Moran M. Predicting Dissatisfaction After Total Hip Arthroplasty: A Study of 850 Patients. *J Arthroplasty*. 2011;26(2):209-213. doi:10.1016/j.arth.2010.03.013

59. Price AJ, Alvand A, Troelsen A, et al. Knee replacement. *Lancet*. 2018;392(10158):1672-1682. doi:10.1016/S0140-6736(18)32344-4

60. Dunbar MJ, Richardson G, Robertsson O. I can't get no satisfaction after my total knee replacement: rhymes and reasons. *Bone Joint J*. 2013;95-B(11):148-152. doi:10.1302/0301-620X.95B11.32767

61. Judge A, Arden NK, Cooper C, et al. Predictors of outcomes of total knee replacement surgery. *Rheumatology*. 2012;51(10):1804-1813. doi:10.1093/rheumatology/kes075

62. Arden N, Altman D, Beard D, et al. Lower limb arthroplasty: can we produce a tool to predict outcome and failure, and is it cost-effective? An epidemiological study. *Program Grants Appl Res*. 2017;5(12):1-246. doi:10.3310/pgfar05120

63. Sanchez-Santos MT, Garriga C, Judge A, et al. Development and validation of a clinical prediction model for patient-reported pain and function after primary total knee replacement surgery. *Sci Rep*. 2018;(March 2017):1-9. doi:10.1038/s41598-018-21714-1

64. Jiang Y, Sanchez-Santos MT, Judge AD, Murray DW, Arden NK. Predictors of Patient-Reported Pain and Functional Outcomes Over 10 Years After Primary Total Knee Arthroplasty: A Prospective Cohort Study. *J Arthroplasty*. 2017;32(1):92-100.e2. doi:10.1016/j.arth.2016.06.009

65. Katz JN. Editorial: Appropriateness of total knee arthroplasty. *Arthritis Rheumatol*.

2014;66(8):1979-1981. doi:10.1002/art.38688

66. Santaguida PL, Hawker GA, Hudak PL, et al. Patient characteristics affecting the prognosis of total hip and knee joint arthroplasty: a systematic review. *Can J Surg*. 2008;51(6):428-436. doi:10.1016/S0008-428X(08)50119-6

67. Borstlap M, Zant JL, Van Soesbergen M, Van der Korst JK. Effects of total hip replacement on quality of life in patients with osteoarthritis and in patients with rheumatoid arthritis. *Clin Rheumatol*. 1994;13(1):45-50. http://www.ncbi.nlm.nih.gov/pubmed/8187443.

68. Kirwan JR, Currey HLF, Freeman MAR, Snow S, Young PJ. Overall Long-Term Impact of Total Hip and Knee Joint Replacement Surgery on Patients with Osteoarthritis and Rheumatoid Arthritis. *Rheumatology*. 1994;33(4):357-360. doi:10.1093/rheumatology/33.4.357

69. Kapadia BH, Berg RA, Daley JA, Fritz J, Bhave A, Mont MA. Periprosthetic joint infection. *Lancet*. 2016;387(10016):386-394. doi:10.1016/S0140-6736(14)61798-0

70. Kreutzer L, Minami C, Yang A. Preventing venous thromboembolism after surgery. *JAMA - J Am Med Assoc*. 2016;315(19):2136. doi:10.1001/jama.2016.1457

71. Kim JYS, Khavanin N, Rambachan A, et al. Surgical Duration and Risk of Venous Thromboembolism. *JAMA Surg*. 2018;150(2). doi:10.1001/jamasurg.2014.1841

72. Lu N, Misra D, Neogi T, Choi HK, Zhang Y. Total joint arthroplasty and the risk of myocardial infarction: a general population, propensity score-matched cohort study. *Arthritis Rheumatol (Hoboken, NJ)*. 2015;67(10):2771-2779. doi:10.1002/art.39246

73. Liddle AD, Judge A, Pandit H, Murray DW. Adverse outcomes after total and unicompartmental knee replacement in 101 330 matched patients: a study of data from the National Joint Registry for England and Wales. *Lancet*. 2014;384(9952):1437-

1445. doi:10.1016/s0140-6736(14)60419-0

74. Graves N, Wloch C, Wilson J, et al. A cost-effectiveness modelling study of strategies to reduce risk of infection following primary hip replacement based on a systematic review. *Health Technol Assess (Rockv)*. 2016;20(54):1-144. doi:10.3310/hta20540

75. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 45-day mortality after 467779 knee replacements for osteoarthritis from the National Joint Registry for England and Wales: An observational study. *Lancet*. 2014;384(9952):1429-1436. doi:10.1016/S0140-6736(14)60540-7

76. Hunt LP, Ben-Shlomo Y, Clark EM, et al. 90-day mortality after 409 096 total hip replacements for osteoarthritis, from the National Joint Registry for England and Wales: A retrospective analysis. *Lancet*. 2013;382(9898):1097-1104. doi:10.1016/S0140-6736(13)61749-3

77. Schnaser EA, Browne JA, Padgett DE, Figgie MP, D'Apuzzo MR. Perioperative Complications in Patients With Inflammatory Arthropathy Undergoing Total Hip Arthroplasty. *J Arthroplasty*. 2016;31(10):2286-2290. doi:10.1016/j.arth.2016.03.023

78. Stundner O, Danninger T, Chiu Y-L, et al. Rheumatoid arthritis vs osteoarthritis in patients receiving total knee arthroplasty: perioperative outcomes. *J Arthroplasty*. 2014;29(2):308-313. doi:10.1016/j.arth.2013.05.008

79. Crowson CS, Liao KP, Davis JM, et al. Rheumatoid arthritis and cardiovascular disease. *Am Heart J*. 2013;166(4). doi:10.1016/j.ahj.2013.07.010

80. Peters MJL, Symmons DPM, McCarey D, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis*. 2010;69(2):325-331. doi:10.1136/ard.2009.113696

81. Avina-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of Cardiovascular Mortality in Patients With Rheumatoid Arthritis: A Meta-Analysis of Observational Studies. *Arthritis Rheum Care Res*. 2008;59(12):1690-1697. doi:10.1002/art.24092

82. Bacani AK, Gabriel SE, Crowson CS, Heit JA, Matteson EL. Noncardiac vascular disease in rheumatoid arthritis: Increase in venous thromboembolic events? *Arthritis Rheum*. 2012;64(1):53-61. doi:10.1002/art.33322

83. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatol (United Kingdom)*. 2013;52(1):53-61. doi:10.1093/rheumatology/kes305

84. Greidanus N V., Peterson RC, Masri BA, Garbuz DS. Quality of Life Outcomes in Revision Versus Primary Total Knee Arthroplasty. *J Arthroplasty*. 2011;26(4):615-620. doi:10.1016/j.arth.2010.04.026

85. Evans JT, Walker RW, Evans JP, Blom AW, Sayers A, Whitehouse MR. How long does a knee replacement last ? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet*. 2019;393(10172):655-663. doi:10.1016/S0140-6736(18)32531-5

86. Evans JT, Evans JP, Walker RW, Blom AW, Whitehouse MR, Sayers A. How long does a hip replacement last ? A systematic review and meta-analysis of case series and national registry reports with more than 15 years of follow-up. *Lancet*. 2019;393(10172):647-654. doi:10.1016/S0140-6736(18)31665-9

87. Bayliss LE, Culliford D, Monk AP, et al. The effect of patient age at intervention on risk of implant revision after total replacement of the hip or knee: a population-based cohort study. *Lancet*. 2017;389(10077):1424-1430. doi:10.1016/S0140-

6736(17)30059-4

88. McCabe C, Claxton K, Culyer AJ. The NICE cost effectiveness threshold: What it is and what it means. *Pharmacoeconomics*. 2008;2(9):733-744.

89. Claxton K, Briggs A, Buxton MJ, et al. Value based pricing for NHS drugs: an opportunity not to be missed? *BMJ*. 2008;336(7638):251-254. doi:10.1136/bmj.39434.500185.25

90. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis*. 2017;76(6):960-977. doi:10.1136/annrheumdis-2016-210715

91. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. *Lancet*. 2017;389(10086):2338-2348. doi:10.1016/S0140-6736(17)31491-5

92. Cost A, Art T, Strategies CT, Arthritis R. E DITORIAL Improvement at Any Cost ? The Art and Science of Choosing Treatment Strategies for Rheumatoid Arthritis. 2017;(May):2017-2019. doi:10.1038/nrrheum

93. Nam JL, Ramiro S, Gaujoux-Viala C, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis*. 2014;73(3):516-528. doi:10.1136/annrheumdis-2013-204577

94. Stevenson MD, Wailoo AJ, Tosh JC, et al. The cost-effectiveness of sequences of biological disease-modifying antirheumatic drug treatment in England for patients with rheumatoid arthritis who can tolerate methotrexate. *J Rheumatol*. 2017;44(7):973-980. doi:10.3899/jrheum.160941

95. Stevenson M, Archer R, Tosh J, et al. Adalimumab, etanercept, infliximab,

certolizumab pegol, golimumab, tocilizumab and abatacept for the treatment of rheumatoid arthritis not previously treated with disease-modifying antirheumatic drugs and after the failure of conventional disease-modifyin. *Health Technol Assess (Rockv)*. 2016;20(35). doi:10.3310/hta20350

96. NHS England. Reference prices for Adalimumab: letter from Matthew Swindells. https://www.england.nhs.uk/publication/reference-prices-for-adalimumab-letter-from-matthew-swindells/. Published 2019.

97. NICE. *Rheumatoid Arthritis in Adults: Management*.; 2018.

98. Madan J, Ades AE, Welton NJ. An overview of models used in economic analyses of biologic therapies for arthritis-From current diversity to future consensus. *Rheumatology*. 2011;50(SUPPL. 4):10-18. doi:10.1093/rheumatology/ker240

99. Barton P. Development of the Birmingham rheumatoid arthritis model: Past, present and future plans. *Rheumatology*. 2011;50(SUPPL. 4):32-38. doi:10.1093/rheumatology/ker244

100. Kuriya B, Arkema E V., Bykerk VP, Keystone EC. Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission. *Ann Rheum Dis*. 2010;69(7):1298-1304. doi:10.1136/ard.2009.118307

101. Graudal N, Jürgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: Meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. *Arthritis Rheum*. 2010;62(10):2852-2863. doi:10.1002/art.27592

102. Hawley S, Cordtz R, Dreyer L, et al. Association between NICE guidance on biologic

therapies with rates of hip and knee replacement among rheumatoid arthritis patients in England and Wales: An interrupted time-series analysis. *Semin Arthritis Rheum*. 2017:1-6. doi:10.1016/j.semarthrit.2017.09.006

103. Hawley S, Ali MS, Cordtz R, et al. Impact of TNF inhibitor therapy on joint replacement rates in rheumatoid arthritis : a matched cohort analysis of BSRBR-RA UK registry data. *Rheumatology*. 2019. doi:10.1093/rheumatology/key424

104. Thijssen E, Van Caam A, Van Der Kraan PM. Obesity and osteoarthritis, more than just wear and tear: Pivotal roles for inflamed adipose tissue and dyslipidaemia in obesity-induced osteoarthritis. *Rheumatol (United Kingdom)*. 2014;54(4):588-600. doi:10.1093/rheumatology/keu464

105. D WZP, Moskowitz RWMD, Nuki GMB, et al. OARSI recommendations for the management of hip and knee osteoarthritis , Part II : OARSI evidence-based , expert consensus guidelines. 2008;(December 2007). doi:10.1016/j.joca.2007.12.013

106. Franklin J, Ingvarsson T, Englund M, Lohmander LS. Sex differences in the association between body mass index and total hip or knee joint replacement resulting from osteoarthritis. *Ann Rheum Dis*. 2009;68(4):536-540. doi:10.1136/ard.2007.086868

107. McTigue KM, Harris R, Hemphill B, et al. Screening and Interventions for Obesity in Adults: Summary of the Evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2003;139(11):933. doi:10.7326/0003-4819-139-11-200312020-00013

108. NHS. Weight loss surgery. https://www.nhs.uk/conditions/weight-loss-surgery/types/. Accessed July 1, 2019.

109. Douglas IJ, Bhaskaran K, Batterham RL, Smeeth L. Bariatric Surgery in the United Kingdom: A Cohort Study of Weight Loss and Clinical Outcomes in Routine Clinical Care. *PLoS Med*. 2015;12(12):1-18. doi:10.1371/journal.pmed.1001925

110. Sjöström L, Lindroos A-K, Peltonen M, et al. Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 Years after Bariatric Surgery. *N Engl J Med*. 2004;351(26):2683-2693. doi:10.1056/NEJMoa035622

111. Picot J, Jones J, Colquitt JL, et al. The clinical effectiveness and cost-effectiveness of bariatric (weight loss) surgery for obesity: A systematic review and economic evaluation. *Health Technol Assess (Rockv)*. 2009;13(41). doi:10.3310/hta13410

112. Buchwald H, Avidor Y, Braunwald E, et al. Bariatric Surgery. *JAMA*. 2004;292(14):1724. doi:10.1001/jama.292.14.1724

113. List JP Van Der, Chawla H, Joskowicz L, Pearle AD, Pearle AD. Current state of computer navigation and robotics in unicompartmental and total knee arthroplasty: a systematic review with meta - analysis. *Knee Surgery, Sport Traumatol Arthrosc*. 2016;24(11):3482-3495. doi:10.1007/s00167-016-4305-9

114. Shenoy R, Nathwani D. Evidence for robots. *Sicot-J*. 2017;3:38. doi:10.1051/sicotj/2017020

115. Jacofsky DJ, Allen M. Robotics in Arthroplasty: A Comprehensive Review. *J Arthroplasty*. 2016;31(10):2353-2363. doi:10.1016/j.arth.2016.05.026

116. Karuppiah K, Sinha J. Robotics in trauma and orthopaedics. *Ann R Coll Surg Engl*. 2018;100:8-18. doi:10.1308/rcsann.supp1.8

117. OCED. United Kingdom: Country Health Profile 2017. 2017:20. doi:10.1787/888933593874

118. OECD. Spain: Country Health Profile, State of Health in the EU 2017. *OECD Publ Paris/European Obs Heal Syst Policies, Brussels*. 2017:1-20. http://dx.doi.org/10.1787/9789264283565-en.

119. García-Armesto S, Begoña Abadía-Taira M, Durán A, Hernández-Quevedo C, Bernal-

Delgado E. Spain: Health system review. *Health Syst Transit*. 2010;12(4):1-295, xix-xx.

120. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098

121. Mathur R, Bhaskaran K, Chaturvedi N, Leon DA, Grundy E, Smeeth L. Completeness and usability of ethnicity data in UK-based primary care and hospital databases. 2013;36(4):684-692. doi:10.1093/pubmed/fdt116

122. Bhaskaran K, Forbes HJ, Douglas I, Leon DA, Smeeth L. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). 2013:1-8. doi:10.1136/bmjopen-2013-003389

123. Herbert A, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol*. 2017:1-10. doi:10.1093/ije/dyx015

124. Stefania L, James M. The Impact of Hospital Costing Methods on Cost-Effectiveness Analysis : A Case Study. 2018. doi:10.1007/s40273-018-0673-y

125. Department for Communities and Local Government. *The English Indices of Deprivation 2015 – Frequently Asked Questions (FAQs)*.; 2016.

126. HSCIC, Health and Social Care information centre. A Guide to Linked Mortality Data from Hospital Episode Statistics and the Office for National Statistics. 2015;(May):1-20. http://www.hscic.gov.uk/media/11668/HES-ONS-Mortality-Data-Guide/pdf/guide_to_linked_ONS_HES_mortality_data_V4_040613.pdf.

127. NHS Digital. *Patient Reported Outcome Measures (PROMs) in England: A Guide to PROMs Methodology*.; 2017.

128. Devlin NJ, Parkin D, Browne J. Patient-reported outcome measures in the NHS: new

methods for analysing and reporting EQ-5D data. *Heal Econ*. 2010;19(8):886-905. doi:10.1002/hec.1608

129. Garcı M, Hermosilla E, Prieto-alhambra D, Fina F, Rosell M, Williams T. Construction and validation of a scoring system for the selection of high-quality data in a Spanish populationRefereed paper primary care database (SIDIAP). 2011:135-146.

130. CatSalut. Conjunt mínim bàsic de dades (CMBD). https://catsalut.gencat.cat/ca/proveidors-professionals/registres-catalegs/registres/cmbd/. Accessed April 23, 2019.

131. Prieto-alhambra D, Nogues X, Javaid MK, et al. HHS Public Access prospective multinational cohort study (GLOW). 2016;72(6):911-917. doi:10.1136/annrheumdis-2012-201451.An

132. Prieto-alhambra D, Judge A, Javaid MK, Cooper C, Diez-perez A, Arden NK. Incidence and risk factors for clinically diagnosed knee, hip and hand osteoarthritis: influences of age, gender and osteoarthritis affecting other joints. *Ann Rheum Dis*. 2014;(73):1659-1664. doi:10.1136/annrheumdis-2013-20335

133. Thomas SL, Edwards CJ, Smeeth L, Cooper C, Hall AJ. How accurate are diagnoses for rheumatoid arthritis and juvenile idiopathic arthritis in the general practice research database? *Arthritis Care Res*. 2008;59(9):1314-1321. doi:10.1002/art.24015

134. NJR. OPCS Codes relevant to procedures recorded on the NJR. http://www.njrcentre.org.uk/njrcentre/Portals/0/Documents/England/Data collection forms/OPCS Procedure codes relevant to NJRv5.pdf?ver=2017-07-18-144930-523. Published 2017. Accessed December 21, 2016.

135. von Hippel PT. Regression with Missing Ys: An Improved Strategy for Analyzing Multiply Imputed Data. *Sociol Methodol*. 2007;37(1):83-117. doi:10.1111/j.1467-

9531.2007.00180.x

136. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067

137. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987. doi:10.1016/0021-9681(87)90171-8

138. Armitage JN, Van Der Meulen JH. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. *Br J Surg*. 2010;97(5):772-781. doi:10.1002/bjs.6930

139. Domínguez-Berjón MF, Borrell C, Cano-Serral G, et al. [Constructing a deprivation index based on census data in large Spanish cities(the MEDEA project)]. *Gac Sanit*. 2008. doi:10.1157/13123961

140. Graves N, Wloch C, Wilson J, et al. A cost-effectiveness modelling study of strategies to reduce risk of infection following primary hip replacement based on a systematic review. *Heal Technol Assess*. 2016;20(54). doi:10.3310/hta20540

141. Dolan P. Modeling valuation for EuroQol health states. *Med Care*. 1997;35(11):1095-1108. doi:10.1097/00005650-199711000-00002

142. James G, Witten D, Hastie T, Tibshirani R. *An Introduction to Statistical Learning*. Vol 103. New York, NY: Springer New York; 2013. doi:10.1007/978-1-4614-7138-7

143. Dougherty C. *Introduction to Econometrics*.; 2016.

144. Harrell , FE. *Regression Modeling Strategies*. Cham: Springer International Publishing; 2015. doi:10.1007/978-3-319-19425-7

145. Hougaard P. Fundamentals of Survival Data. *Biometrics*. 1999;55(1):13-22. doi:10.1111/j.0006-341X.1999.00013.x

146. Rao SR, Schoenfeld DA. Survival methods. *Circulation*. 2007;115(1):109-113. doi:10.1161/CIRCULATIONAHA.106.614859

147. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170(2):244-256. doi:10.1093/aje/kwp107

148. Royston P, Parmar MKB. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med*. 2002;21(15):2175-2197. doi:10.1002/sim.1203

149. Latimer NR. Survival Analysis for Economic Evaluations Alongside Clinical Trials—Extrapolation with Patient-Level Data Inconsistencies, Limitations, and a Practical Guide. *Med Decis Mak*. 2013;33(6):743-754. doi:10.1177/0272989X12472398

150. Jackson C. flexsurv: A Platform for Parametric Survival Modeling in R. *J Stat Softw*. 2016;70(1):1-33. doi:10.18637/jss.v070.i08

151. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation*. 2016;133(6):601-609. doi:10.1161/CIRCULATIONAHA.115.017719

152. Sonnenberg F a., Beck JR. Markov Models in Medical Decision Making: A practical Guide. *Mdecial Decis Mak*. 1993;13(4):322-338. doi:10.1177/0272989X9301300409

153. Briggs A, Sculpher M. An Introduction to Markov Modelling for Economic Evaluation. 1998;13(4):397-409.

154. INE. Life tables for the population of Spain 1991-2009.

155. Office for National Statistics. National life tables: UK (2013-2015). https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed

August 9, 2018.

156. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. *Natl Inst Heal Care Excell*. 2013;(April):1-93. doi:10.2165/00019053-200826090-00002

157. Mihaylova B, Briggs A, O'Hagan A, Thompson SG. Review of statistical methods for analysing healthcare resources and costs. *Health Econ*. 2011;20(8):897-916. doi:10.1002/hec.1653

158. Chang SH, Stoll CRT, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery an updated systematic review and meta-analysis, 2003-2012. *JAMA Surg*. 2014;149(3):275-287. doi:10.1001/jamasurg.2013.3654

159. Doble B, Welbourn R, Carter N, et al. Multi-Centre Micro-Costing of Roux-En-Y Gastric Bypass, Sleeve Gastrectomy and Adjustable Gastric Banding Procedures for the Treatment of Severe, Complex Obesity. *Obes Surg*. 2019;29(2):474-484. doi:10.1007/s11695-018-3553-9

160. NBSR. The UK National Bariatric Surgery Registry: Second Registry Report 2014. http://www.bomss.org.uk/wp-content/uploads/2018/11/Extract_from_the_NBSR_2014_Report-2.pdf. Published 2014. Accessed June 24, 2019.

161. Burn E, Sanchez-Santos MT, Pandit HG, et al. Ten-year patient-reported outcomes following total and minimally invasive unicompartmental knee arthroplasty: a propensity score-matched cohort analysis. *Knee Surgery, Sport Traumatol Arthrosc*. 2016. doi:10.1007/s00167-016-4404-7

162. Burn E, Liddle AD, Hamilton TW, et al. Cost-effectiveness of unicompartmental compared with total knee replacement: a population-based study using data from the

National Joint Registry for England and Wales. *BMJ Open*. April 2018. doi:10.1136/bmjopen-2017-020977

163. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health Technol Assess (Rockv)*. 2015;19(14):1-504. doi:10.3310/hta19140

164. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2016.

165. Wickham H, Averick M, Bryan J, et al. Welcome to the Tidyverse. *J Open Source Softw*. 2019;4:1-6. doi:10.21105/joss.01686

166. Wickham H, Francois R. dplyr: A Grammar of Data Manipulation. R package version 0.5.0. 2016.

167. Groothuis-oudshoorn K. mice : Multivariate Imputation by Chained. 2011;45(3).

168. Harrell , FE. rms: Regression Modeling Strategies. R package version 5.1-0. 2017.

169. Jackson C. flexsurv : A Platform for Parametric Survival Modeling in R. *J Stat Softw*. 2016;70(8). doi:10.18637/jss.v070.i08

170. Krijkamp E, Alarid-Escudero F, Enns EA, Jalal H, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: A tutorial. *Med Decis Mak*. 2018;In Press(3):31. doi:10.1093/biostatistics/manuscript-acf-v5

171. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis*. New York: Springer-Verlag; 2009. doi:10.1007/978-0-387-98141-3

172. Wilke CO. ggridges: Ridgeline Plots in “ggplot2.” 2018.

173. Croft P, Altman DG, Deeks JJ, et al. The science of clinical practice: disease diagnosis or patient prognosis? Evidence about “what is likely to happen” should shape clinical practice. *BMC Med*. 2015;13(1):20. doi:10.1186/s12916-014-0265-4

174. Culliford DJ, Maskell J, Kiran A, et al. The lifetime risk of total hip and knee arthroplasty: Results from the UK general practice research database. *Osteoarthr Cartil*. 2012;20(6):519-524. doi:10.1016/j.joca.2012.02.636

175. Suter LG, Smith SR, Katz JN, et al. Projecting Lifetime Risk of Symptomatic Knee Osteoarthritis and Total Knee Replacement in Individuals Sustaining a Complete Anterior Cruciate Ligament Tear in Early Adulthood. *Arthritis Care Res (Hoboken)*. 2016;69(2):201-208. doi:10.1002/acr.22940

176. Judge A, Welton NJ, Sandhu J. Equity in access to total joint replacement of the hip and knee in England : cross sectional study. :1-10. doi:10.1136/bmj.c4092

177. Cooper C, Snow S, Mcalindon TE, et al. Risk Factors for the Incidence and Progression of Radiographic Knee Osteoarthritis. *Arthritis Rheum*. 2000;43(5):995-1000. doi:10.1002/1529-0131(200005)43:5<995::AID-ANR6>3.0.CO;2-1

178. Bastick AN, Belo JN, Runhaar J, Bierma-Zeinstra SMA. What Are the Prognostic Factors for Radiographic Progression of Knee Osteoarthritis? A Meta-analysis. *Clin Orthop Relat Res*. 2015;473(9):2969-2989. doi:10.1007/s11999-015-4349-z

179. Podmore B, Hutchings A, Durand M, et al. Comorbidities and the referral pathway to access joint replacement surgery : an exploratory qualitative study. 2018:1-8.

180. Waljee J, Zhong L, Baser O, Yuce H, Fox DA, Chung KC. The Incidence of Upper and Lower Extremity Surgery for Rheumatoid Arthritis Among Medicare Beneficiaries. *J Bone Jt Surgery-American Vol*. 2015;97(5):403-410. doi:10.2106/JBJS.N.00802

181. Gwinnutt JM, Symmons DPM, MacGregor AJ, et al. Predictors of and outcomes following orthopaedic joint surgery in patients with early rheumatoid arthritis followed for 20 years. *Rheumatol (United Kingdom)*. 2017;56(9):1510-1517. doi:10.1093/rheumatology/kex172

182. Wolfe F, Zwillich SH. The long-term outcomes of rheumatoid arthritis: A 23-year prospective, longitudinal study of total joint replacement and its predictors in 1,600 patients with rheumatoid arthritis. *Arthritis Rheum*. 1998;41(6):1072-1082. doi:10.1002/1529-0131(199806)41:6<1072::AID-ART14>3.0.CO;2-G

183. Massardo L, Gabriel SE, Crowson CS, O'Fallon WM, Matteson EL. A population based assessment of the use of orthopedic surgery in patients with rheumatoid arthritis. *J Rheumatol*. 2002;29(1):52-56.

184. Verstappen SMM, Hoes JN, Ter Borg EJ, et al. Joint surgery in the Utrecht Rheumatoid Arthritis Cohort: The effect of treatment strategy. *Ann Rheum Dis*. 2006;65(11):1506-1511. doi:10.1136/ard.2005.049957

185. Hawley S, Delmestri A, Judge A, Edwards, Christopher J. Cooper C, Arden NK, Prieto-Alhambra D. Total Hip and Knee Replacement Among Incident Osteoarthritis and Rheumatoid Arthritis Patients Within the UK Clinical Practice Research Datalink (CPRD) Compared to Hospital Episode Statistics (HES): A Validation Study. *Pharmacoepidemiol Drug Saf*. 2016.

186. CatSalut. Minimum Basic Data Set (MDS). https://catsalut.gencat.cat/ca/proveidors-professionals/registres-catalegs/registres/cmbd/index.html#googtrans(ca%7Cen). Accessed May 26, 2019.

187. Ackerman IN, Bohensky MA, de Steiger R, et al. Substantial rise in the lifetime risk of primary total knee replacement surgery for osteoarthritis from 2003 to 2013: an international, population-level analysis. *Osteoarthr Cartil*. 2017;25(4):455-461. doi:10.1016/j.joca.2016.11.005

188. Ackerman IN, Bohensky MA, de Steiger R, et al. Lifetime Risk of Primary Total Hip Replacement Surgery for Osteoarthritis From 2003 to 2013: A Multinational Analysis

Using National Registry Data. *Arthritis Care Res (Hoboken)*. 2017;69(11):1659-1667. doi:10.1002/acr.23197

189. Huynh C, Puyraimond-zemmour D, Maillefert JF, et al. Factors associated with the orthopaedic surgeon ' s decision to recommend total joint replacement in hip and knee osteoarthritis : an international cross-sectional study of 1905 patients. *Osteoarthr Cartil*. 2018;26(10):1311-1318. doi:10.1016/j.joca.2018.06.013

190. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res*. 2005;14(6):1523-1532. doi:10.1007/s11136-004-7713-0

191. Gordon M, Greene M, Frumento P, Rolfson O, Garellick G, Stark A. Age- and health-related quality of life after total hip replacement. *Acta Orthop*. 2014;85(3):244-249. doi:10.3109/17453674.2014.916492

192. Arden N, Altman D, Beard D, et al. Lower limb arthroplasty: can we produce a tool to predict outcome and failure, and is it cost-effective? An epidemiological study. *Program Grants Appl Res*. 2017;5(12):1-246. doi:10.3310/pgfar05120

193. Judge A, Cooper C, Arden NK, et al. Pre-operative expectation predicts 12-month post-operative outcome among patients undergoing primary total hip replacement in European orthopaedic centres. *Osteoarthr Cartil*. 2011;19(6):659-667. doi:10.1016/j.joca.2011.03.009

194. Singh JA. Epidemiology of Knee and Hip Arthroplasty: A Systematic Review [§]. *Open Orthop J*. 2011;5(1):80-85. doi:10.2174/1874325001105010080

195. Tropea J, Brand CA, Bohensky M, Van Doornum S. Myocardial infarction and mortality following joint surgery in patients with rheumatoid arthritis: a retrospective cohort study. *Arthritis Res Ther*. 2016;18(1):69. doi:10.1186/s13075-016-0958-5

196. Singh JA, Jensen MR, Harmsen WS, Gabriel SE, Lewallen DG. Cardiac and thromboembolic complications and mortality in patients undergoing total hip and total knee arthroplasty. *Ann Rheum Dis*. 2011;70(12):2082-2088. doi:10.1136/ard.2010.148726

197. Giori NJ, Amanatullah DF, Gupta S, Bowe T, Harris AHS. Risk Reduction Compared with Access to Care. *J Bone Jt Surg*. 2018;100(7):539-545. doi:10.2106/JBJS.17.00120

198. Prokopetz JJ, Losina E, Bliss RL, Wright J, Baron JA, Katz JN. Risk factors for revision of primary total hip arthroplasty: a systematic review. *BMC Musculoskelet Disord*. 2012;13(1):251. doi:10.1186/1471-2474-13-251

199. Singh JA, Kwoh CK, Richardson D, Chen W, Ibrahim SA. Sex and Surgical Outcomes and Mortality After Primary Total Knee Arthroplasty: A Risk-Adjusted Analysis. *Arthritis Care Res (Hoboken)*. 2013;65(7):1095-1102. doi:10.1002/acr.21953

200. Kerkhoffs GMMJ, Servien E, Dunn W, Dahm D, Bramer JA, Haverkamp D. The Influence of Obesity on the Complication Rate and Outcome of Total Knee Arthroplasty. *J Bone Jt Surgery-American Vol*. 2012;94(20):1839-1844. doi:10.2106/JBJS.K.00820

201. Culliford D, Maskell J, Judge A, Arden NK. 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 UK general practice research database. *BMJ Open*. 2013;3(11):e003614. doi:10.1136/bmjopen-2013-003614

202. Hanna SA, McCalden RW, Somerville L, Howard JL, Naudie DD, MacDonald SJ. Morbid Obesity Is a Significant Risk of Failure Following Revision Total Hip Arthroplasty. *J Arthroplasty*. 2017;32(10):3098-3101. doi:https://dx.doi.org/10.1016/j.arth.2017.05.014

203. Gray A, Clarke PM, Wolstenholme JL, Wordsworth S. *Applied Methods of Cost-Effectiveness Analysis in Healthcare*. Oxford University Press; 2010. https://econpapers.repec.org/RePEc:oxp:obooks:9780199227280.

204. Cordtz R, Hawley S, Prieto-Alhambra D, et al. INCIDENCE OF JOINT REPLACEMENT SURGERY AMONG BIOLOGICS AND NON-BIOLOGICS TREATED PATIENTS WITH RHEUMATOID ARTHRITIS: A PROPENSITY SCORE MATCHED COHORT STUDY FROM DENMARK. In: *Poster Presentations*. Vol 95. BMJ Publishing Group Ltd and European League Against Rheumatism; 2019:297.1-297. doi:10.1136/annrheumdis-2019-eular.991

205. Cordtz RL, Hawley S, Prieto-Alhambra D, et al. Incidence of hip and knee replacement in patients with rheumatoid arthritis following the introduction of biological DMARDs: An interrupted time-series analysis using nationwide Danish healthcare registers. *Ann Rheum Dis*. 2018;77(5):684-689. doi:10.1136/annrheumdis-2017-212424

206. Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naïve patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis*. 2013;72(6):844-850. doi:10.1136/annrheumdis-2012-201612

207. Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis*. 2013;72(1):64-71. doi:10.1136/annrheumdis-2011-201247

208. Emery P, Breedveld F, van der Heijde D, et al. Two-year clinical and radiographic

results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: A two-year, double-blind, randomized study. *Arthritis Rheum*. 2010;62(3):674-682. doi:10.1002/art.27268

209. Owen-Smith A, Donovan J, Coast J. Experiences of accessing obesity surgery on the NHS: A qualitative study. *J Public Heal (United Kingdom)*. 2017;39(1):163-169. doi:10.1093/pubmed/fdv209

210. Angrisani L, Santonicola A, Iovino P, Formisano G, Buchwald H, Scopinaro N. Bariatric Surgery Worldwide 2013. *Obes Surg*. 2015;25(10):1822-1832. doi:10.1007/s11695-015-1657-z

211. Gong Y, Selzer F, Deshpande B, Losina E. Trends in procedure type, patient characteristics, and outcomes among persons with knee osteoarthritis undergoing bariatric surgery, 2005–2014. *Osteoarthr Cartil*. 2018;26(11):1487-1494. doi:10.1016/j.joca.2018.07.007

212. ANZCTR. The Arthroplasty and Bariatric Surgery (ABS) study: a randomised controlled trial to determine the efficacy of laparoscopic adjustable gastric banding prior to total knee arthroplasty in obese patients with osteoarthritis. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=347700.

213. Smith TO, Aboelmagd T, Hing CB, MacGregor A. Does bariatric surgery prior to total hip or knee arthroplasty reduce post-operative complications and improve clinical outcomes for obese patients? *Bone Joint J*. 2016;98-B(9):1160-1166. doi:10.1302/0301-620X.98B9.38024

214. Deep K, Shankar S, Mahendra A. Computer assisted navigation in total knee and hip arthroplasty. *Sicot-J*. 2017;3:50. doi:10.1051/sicotj/2017034

215. De Steiger RN, Liu YL, Graves SE. Computer navigation for total knee arthroplasty

reduces revision rate for patients less than sixty-five years of age. *J Bone Jt Surg - Am Vol*. 2015;97(8):635-642. doi:10.2106/JBJS.M.01496

216. NJR. 12-MONTH PRACTICE PROFILE (1 YEAR). http://www.njrsurgeonhospitalprofile.org.uk/HospitalProfile?hospitalName=Nuffield Orthopaedic Centre. Accessed July 8, 2019.

217. Vickers AJ, Basch E, Kattan MW. Against Diagnosis. *Ann Intern Med*. 2008;149(3):200. doi:10.7326/0003-4819-149-3-200808050-00010

218. BOMSS and RCS. Patient access to bariatric surgery. http://www.bomss.org.uk/wp-content/uploads/2017/03/RCS-and-BOMSS-Bariatric-report-2017.pdf. Published 2017. Accessed July 7, 2019.

219. Shaw D. Delaying surgery for obese patients or smokers is a bad idea. *Bmj*. 2016;5594(October):i5594. doi:10.1136/bmj.i5594

220. The Royal College of Surgeons of England. Smokers and overweight patients soft targets for NHS savings. 2016.

221. Pillutla V, Maslen H, Savulescu J. Rationing elective surgery for smokers and obese patients: responsibility or prognosis? *BMC Med Ethics*. 2018;19(1):28. doi:10.1186/s12910-018-0272-7

222. Dreyer NA. Making Observational Studies Count. *Epidemiology*. 2011;22(3):295-297. doi:10.1097/ede.0b013e3182126569

223. Yu D, Jordan K, Peat G. Underrecording of osteoarthritis in United Kingdom primary care electronic health record data. *Clin Epidemiol*. 2018;Volume 10:1195-1201. doi:10.2147/CLEP.S160059

224. Drummond MF, Sculpher MJ, Claxton K, et al. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford: Oxford: Oxford University Press; 2015.

https://books.google.co.uk/books?id=lvWACgAAQBAJ.

225. Sculpher M, Drummond M, Buxton M. The iterative use of economic evaluation as part of the process of health technology assessment. *J Heal Serv Res Policy*. 1997;2(1):26-30. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10180650.

226. Hernán MA, Hsu J, Healy B. Data science is science's second chance to get causal inference right: A classification of data science tasks. 2018;2480. doi:10.1080/09332480.2019.1579578

227. Sherman RE, Andersen SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375:2293-2297. doi:10.1056/NEJMsb1609216

228. Sharma M, Nazareth I, Petersen I. Observational studies of treatment effectiveness: worthwhile or worthless? *Clin Epidemiol*. 2019;11:35-42.

229. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *Int J Epidemiol*. 2017;45(6):dyw314. doi:10.1093/ije/dyw314

230. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol*. 2016;183(8):758-764. doi:10.1093/aje/kwv254

231. Munafò MR, Davey Smith G. Repeating experiments is not enough. *Nature*. 2018;553(7689):399-401. doi:10.1038/d41586-018-01023-3

232. Tappenden P, Chilcott J, Brennan A, Squires H, Stevenson M. Whole Disease Modeling to Inform Resource Allocation Decisions in Cancer: A Methodological Framework. *Value Heal*. 2012;15(8):1127-1136. doi:10.1016/j.jval.2012.07.008

233. Karsdal MA, Michaelis M, Ladel C, et al. Disease-modifying treatments for osteoarthritis (DMOADs) of the knee and hip : lessons learned from failures and

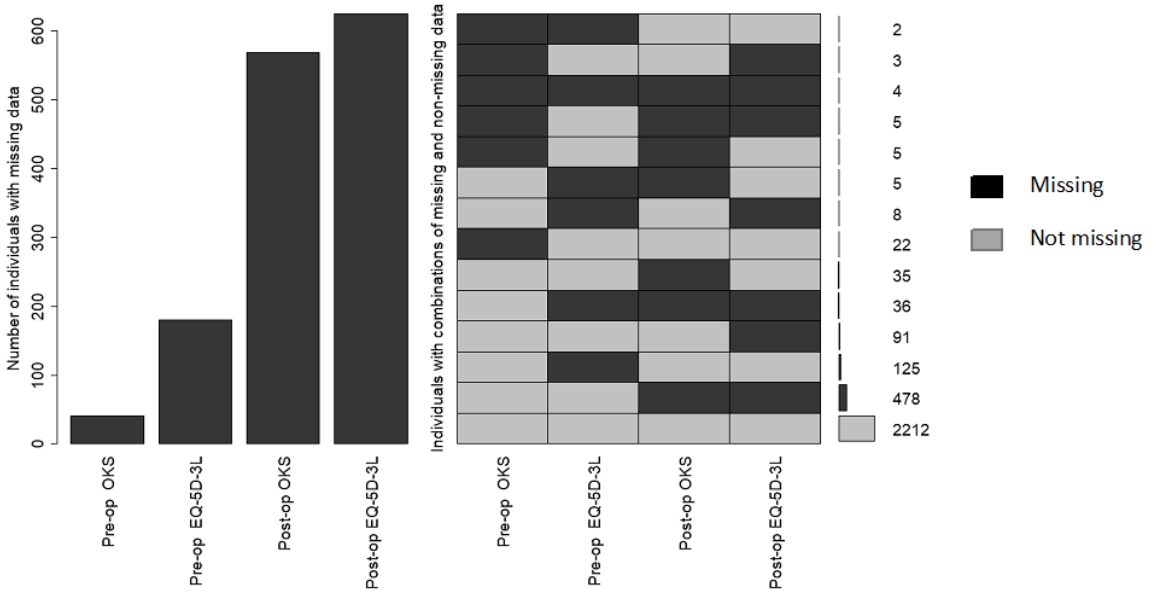
opportunities for the future. *Osteoarthr Cartil*. 2016;24(12):2013-2021. doi:10.1016/j.joca.2016.07.017

234. Lord J, Willis S, Eatock J, et al. Economic modelling of diagnostic and treatment pathways in National Institute for Health and Care Excellence clinical guidelines: the Modelling Algorithm Pathways in Guidelines (MAPGuide) project. *Health Technol Assess (Rockv)*. 2013;17(58):1-150. doi:10.3310/hta17580

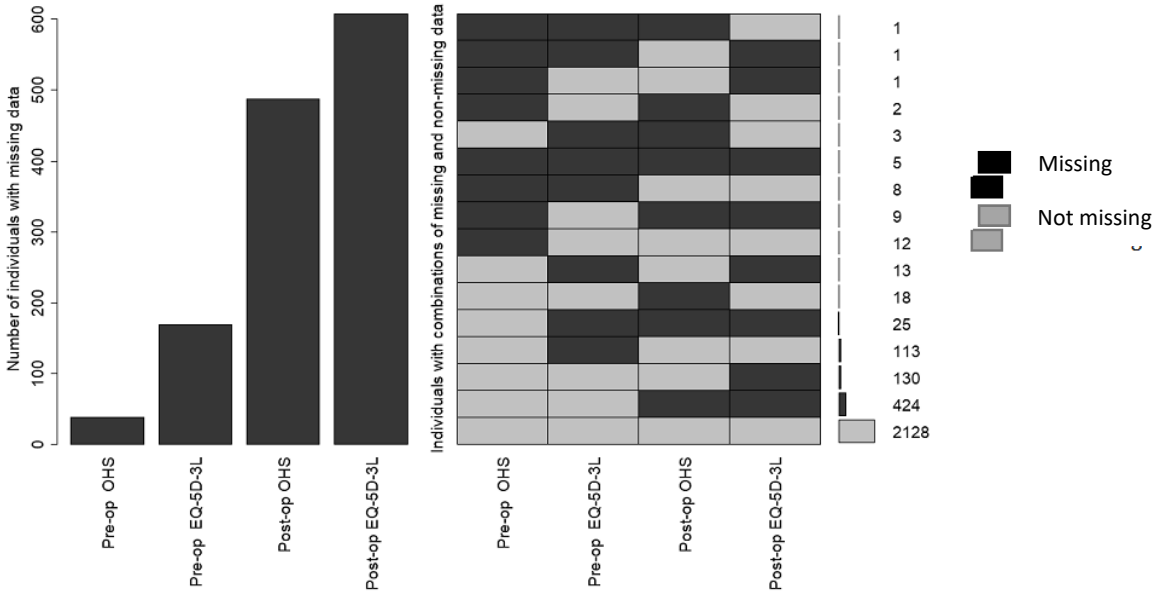
12. APPENDICES

A.

Appendix Figure A.1. Patterns of missing data for total knee replacement cohort. OKS: Oxford Knee Score. EQ-5D-3L: EuroQol 5-dimension 3-level.



Appendix Figure A.2. Patterns of missing data for total hip replacement cohort. OHS: Oxford Hip Score. EQ-5D-3L: EuroQol 5-dimension 3-level.



Appendix Table A.1. Characteristics of individuals with all PROMs completed compared to those with missing PROMs.

	TKR			THR		
	Complete PROMs	Missing PROMs	SMD	Complete PROMs	Missing PROMs	SMD
N	2,212	819		2,128	765	
Age (median [IQR])	70 [64, 76]	69 [62, 76]	0.08	69 [63, 76]	69 [61, 76]	0.08
Gender: Female (n (%))	1200 (54)	477 (58)	0.08	1220 (57)	467 (61)	0.08
Diagnosis: RA (n (%))	142 (6)	67 (8)		98 (5)	48 (6)	0.07
Charlson score (n (%))			0.03			0.08
0	1558 (70)	567 (69)		1581 (74)	541 (71)	
1+	654 (30)	252 (31)		547 (26)	224 (29)	
BMI (median [IQR])	30 [27, 35]	31.3 [27, 36]	0.1	28.6 [25, 32]	29 [25, 32]	0.09
BMI missing (n (%))	1060 (48)	400 (49)	0.02	1105 (52)	402 (53)	
Smoking status (n (%))			0.11			0.22
Non-smoker	636 (29)	206 (25)		580 (27)	175 (23)	
Ex-smoker	615 (28)	219 (27)		520 (24)	171 (22)	
Current smoker	96 (4)	47 (6)		137 (6)	95 (12)	
Missing	865 (39)	347 (42)		891 (42)	324 (42)	
IMD quintile (n (%))			0.14			0.18
1	504 (23)	170 (21)		576 (27)	172 (23)	
2	572 (26)	184 (23)		532 (25)	186 (24)	
3	529 (24)	200 (24)		506 (24)	175 (23)	
4	405 (18)	161 (20)		356 (17)	142 (19)	

5	201 (9)	103 (13)	157 (7)	90 (12)
Missing	1 (0)	1 (0)	1 (0)	0 (0)

Comparison of the characteristics of individuals with and without patient recorded outcome measures (PROMs) recorded before and six months following total knee replacement (TKR) and total hip replacement (THR). SMD: standardised mean difference, RA: rheumatoid arthritis, BMI: body mass index, IMD: index of multiple deprivation.

B.

Appendix Table B.1: Cumulative incidence of knee or hip replacement following a diagnosis of knee or hip osteoarthritis or rheumatoid arthritis

	Knee osteoarthritis		**Hip osteoarthritis**		**Rheumatoid arthritis**		**Rheumatoid arthritis**	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
Total	2561/ 209,508	9.37% (8.85% to 9.92%)	1247/ 60,723	11.58% (10.87% to 12.34%)	672/ 76,104	9.69% (8.75% to 10.73%)	493/ 77,000	7.69% (6.80% to 8.71%)
Age group* (%)								
1st (youngest)	452/ 54,625	7.76% (6.86% to 8.78%)	359/ 14,779	14.99% (13.31% to 16.88%)	95/ 19,371	8.51% (6.42% to 11.27%)	70/ 19,419	5.31% (3.93% to 7.16%)
2nd	730/ 49,643	12.97% (11.47% to 14.67%)	329/ 15,124	12.95% (11.45% to 14.65%)	233/ 22,390	12.21% (10.53% to 14.17%)	138/ 22,917	9.05% (7.12% to 11.50%)

	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
3rd	1,002/ 56,855	12.28% (11.41% to 13.21%)	371/ 16,491	12.83% (11.45% to 14.38%)	194/ 17,705	12.12% (9.73% to 15.11%)	175/ 17,839	11.65% (9.39% to 14.47%)
4th (oldest)	377/ 48,386	4.36% (3.67% to 5.17%)	188/ 14,328	5.86% (5.06% to 6.78%)	150/ 16,638	5.98% (5.03% to 7.12%)	110/ 16,825	4.72% (3.78% to 5.91%)
Gender								
Male	790/ 69,000	8.37% (7.60% to 9.23%)	609/ 37,361	14.49% (13.34% to 15.74%)	213/ 23,541	10.38% (8.43% to 12.78%)	128/ 23,927	6.64% (5.23% to 8.42%)
Female	1,771/ 140,508	9.86% (9.19% to 10.58%)	638/ 23,362	9.68% (8.79% to 10.65%)	459/ 52,563	9.39% (8.39% to 10.51%)	365/ 53,073	8.17% (7.07% to 9.44%)
Charlson								

	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
0	1,416/ 120,475	9.66% (8.93% to 10.45%)	718/ 32,869	13.18% (12.13% to 14.31%)	623/ 68,762	10.19% (9.17% to 11.32%)	454/ 69,617	8.05% (7.07% to 9.15%)
1	702/ 52,364	9.44% (8.63% to 10.33%)	300/ 14,917	10.84% (9.57% to 12.27%)				
2	284/ 22,691	9.53% (7.81% to 11.62%)	149/ 7,450	10.60% (8.81% to 12.76%)				
3+	159/ 13,978	6.26% (5.22% to 7.51%)	80/ 5,487	6.00% (4.78% to 7.54%)				
1+					49/ 7,342	5.13% (3.85% to 6.84%)	39/ 7,383	4.33% (3.09% to 6.07%)

	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
BMI group (%)								
Normal or underweight (<25)	62/ 9,556	6.31% (2.96% to 13.46%)	67/ 4,361	7.80% (6.07% to 10.02%)	55/ 7,819	9.59% (8.51% to 10.81%)	47/ 7,855	7.47% (6.54% to 8.55%)
Overweight (≥25 and <30)	424/ 39,791	8.47% (7.33% to 9.79%)	254/ 13,534	11.07% (9.59% to 12.77%)	46/ 4,496	6.39% (4.79% to 8.54%)	28/ 4,539	6.71% (4.26% to 10.55%)
Obese class I (≥30 and <35)	543/ 37,410	10.51% (9.47% to 11.66%)	205/ 9,630	12.58% (10.68% to 14.81%)	34/ 1,875	11.36% (7.25% to 17.80%)	8/1,972	7.76% (4.73% to 12.74%)
Obese class II (≥35 and <40)	278/ 15,260	13.90% (11.86% to 16.29%)	82/ 3,074	13.72% (11.01% to 17.09%)	12/ 950	17.07% (10.57% to 27.56%)	5/ 968	3.83% (1.82% to 8.04%)

	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
Obese class III (≥40)	97/ 6,015	14.30% (10.90% to 18.76%)	15/ 886	10.09% (6.02% to 16.90%)	70/ 8,143	16.42% (8.93% to 30.19%)	61/ 8,197	3.76% (1.57% to 8.97%)
Missing	1157/ 101,476	8.61% (7.93% to 9.35%)	624/ 29,238	11.90% (10.90% to 13.00%)	455/ 52,821	10.20% (6.72% to 15.48%)	344/ 53,469	12.92% (7.61% to 21.95%)
IMD/ MEDEA quintile or rural (%)								
1st (least deprived)	218/ 20,180	7.36% (6.37% to 8.51%)	146/ 6,946	11.74% (9.93% to 13.87%)	131/ 17,115	9.53% (7.14% to 12.74%)	101/ 17,249	6.82% (5.27% to 8.83%)
2nd	367/ 30,180	9.96% (8.49% to 11.67%)	210/ 9,095	12.69% (10.97% to 14.68%)	173/ 17,223	11.08% (9.10% to 13.48%)	141/ 17,396	10.90% (8.41% to 14.12%)

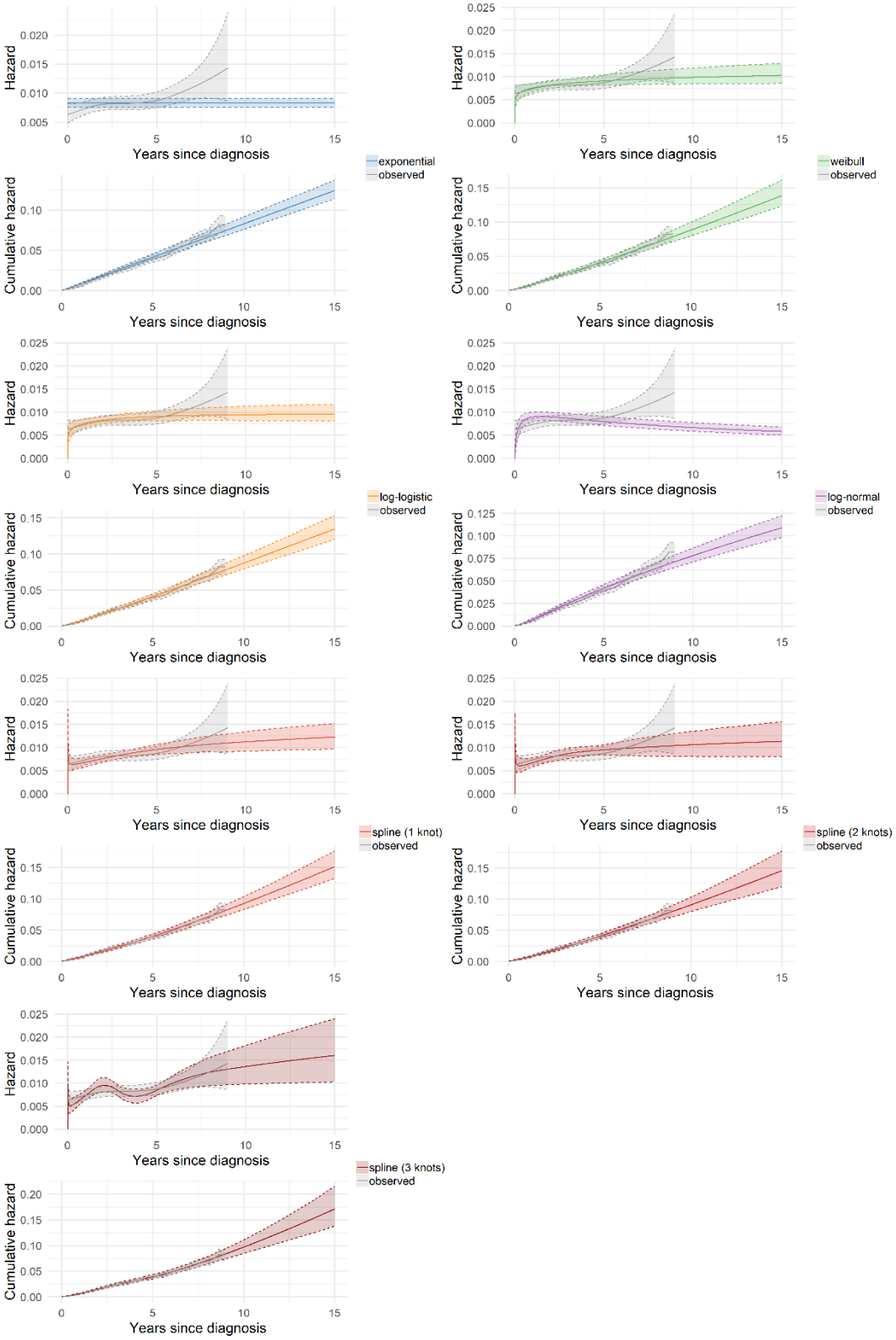
	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
3rd	478/ 37,924	10.28% (8.78% to 12.02%)	204/ 10,565	10.44% (8.95% to 12.18%)	150/ 16,104	9.86% (8.00% to 12.15%)	104/ 16,355	7.78% (6.03% to 10.03%)
4th	606/ 41,932	11.73% (10.34% to 13.31%)	246/ 11,088	13.21% (11.45% to 15.25%)	126/ 14,789	8.82% (7.24% to 10.74%)	93/ 14,924	7.04% (5.42% to 9.14%)
5th (most deprived)	448/ 31,745	10.94% (9.74% to 12.29%)	189/ 8,634	14.09% (11.78% to 16.86%)	90/ 10,748	8.91% (6.88% to 11.54%)	54/ 10,938	4.94% (3.69% to 6.61%)
Rural	377/ 39,555	6.65% (5.84% to 7.56%)	213/ 11,587	9.75% (8.36% to 11.37%)				
Missing	67/ 7,992	4.56% (3.55% to 5.86%)	39/ 2,807	6.49% (4.72% to 8.92%)	2/ 125	10.21% (2.72% to 38.41%)	0/ 137	0.00%

	Knee osteoarthritis		Hip osteoarthritis		Rheumatoid arthritis		Rheumatoid arthritis	
	Knee replacements /person years	**9-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**9-year cumulative incidence (% (95% CI))**	**Knee replacements /person years**	**15-year cumulative incidence (% (95% CI))**	**Hip replacements /person years**	**15-year cumulative incidence (% (95% CI))**
Smoking status								
Non-smoker	1729/ 133,845	9.69% (8.94% to 10.50%)	697/ 36,458	10.38% (9.54% to 11.29%)	105/ 11,153	10.27% (7.56% to 13.96%)	86/ 11,220	11.04% (6.42% to 19.00%)
Ex-smoker	285/ 23,815	9.38% (7.42% to 11.85%)	208/ 8,150	13.12% (11.41% to 15.10%)	89/ 10,538	7.31% (5.64% to 9.47%)	72/ 10,548	6.60% (4.52% to 9.62%)
Current smoker	179/ 17,950	7.43% (6.28% to 8.79%)	167/ 6,393	16.16% (13.39% to 19.50%)	46/ 7,480	5.59% (3.96% to 7.88%)	45/ 7,508	6.08% (4.15% to 8.91%)
Missing	368/ 3,3897	8.89% (7.95% to 9.95%)	175/ 9,721	11.45% (9.85% to 13.31%)	432/ 46,933	10.16% (9.05% to 11.40%)	290/ 47,724	7.41% (6.42% to 8.54%)

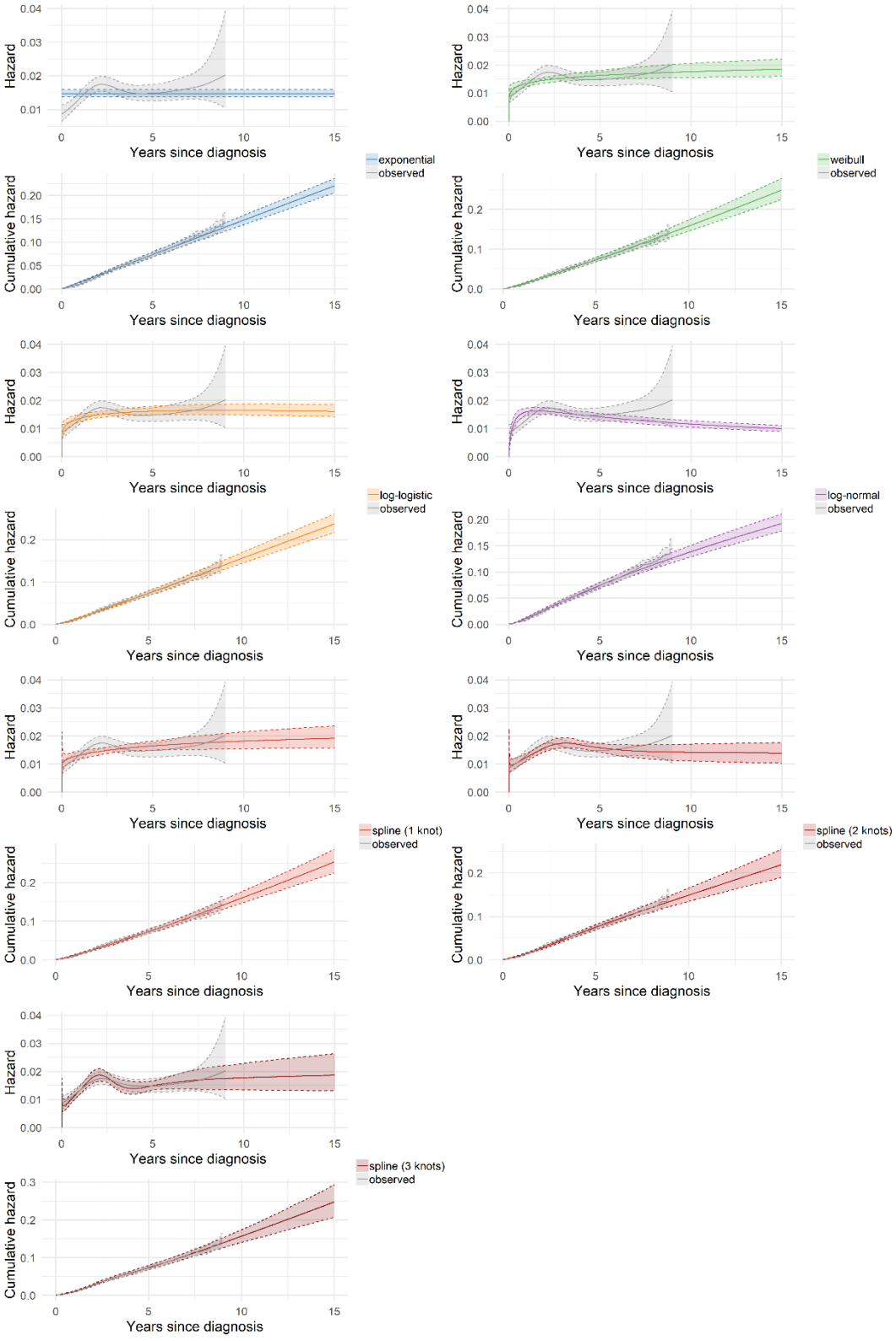
Cumulative incidence of knee or hip replacement 9 years after a diagnosis of knee or hip osteoarthritis. *Age groups for knee osteoarthritis cohort: 50 to 62, 62 to 69, 69 to 77, 77 to 105; age groups for hip osteoarthritis cohort: 50 to 62, 62 to 70, 70 to 78, 78 to 103; age groups for

rheumatoid arthritis cohorts: 40 to 54, 54 to 64, 64 to 73, 73 to 99. MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. BMI: body mass index; CI: confidence interval; HR: hip replacement; KR: knee replacement; OA: osteoarthritis

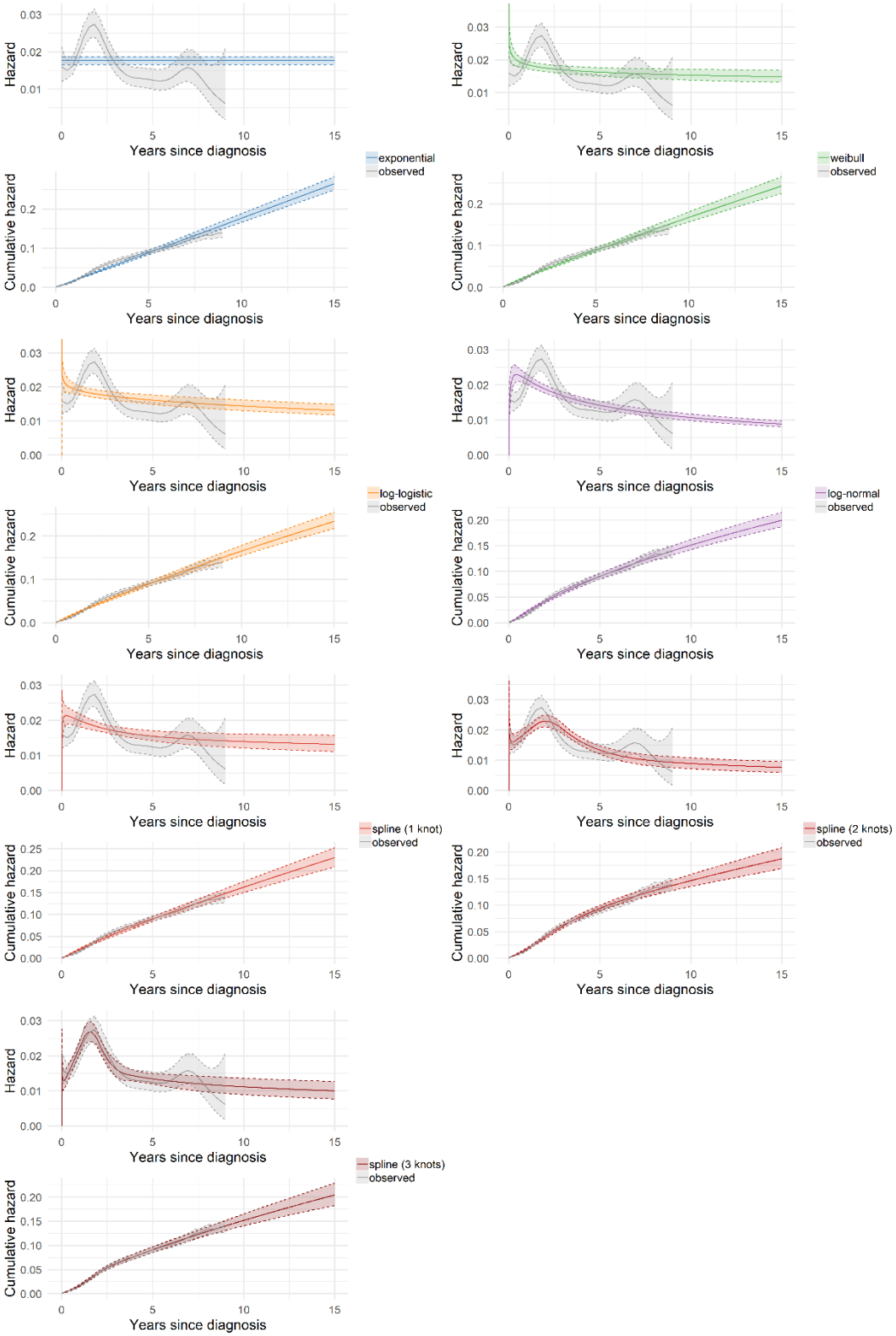
Appendix Figure B.1. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of knee osteoarthritis for 1st age quartile: 50 to 62. The spline-based distribution with 3 knots was chosen.



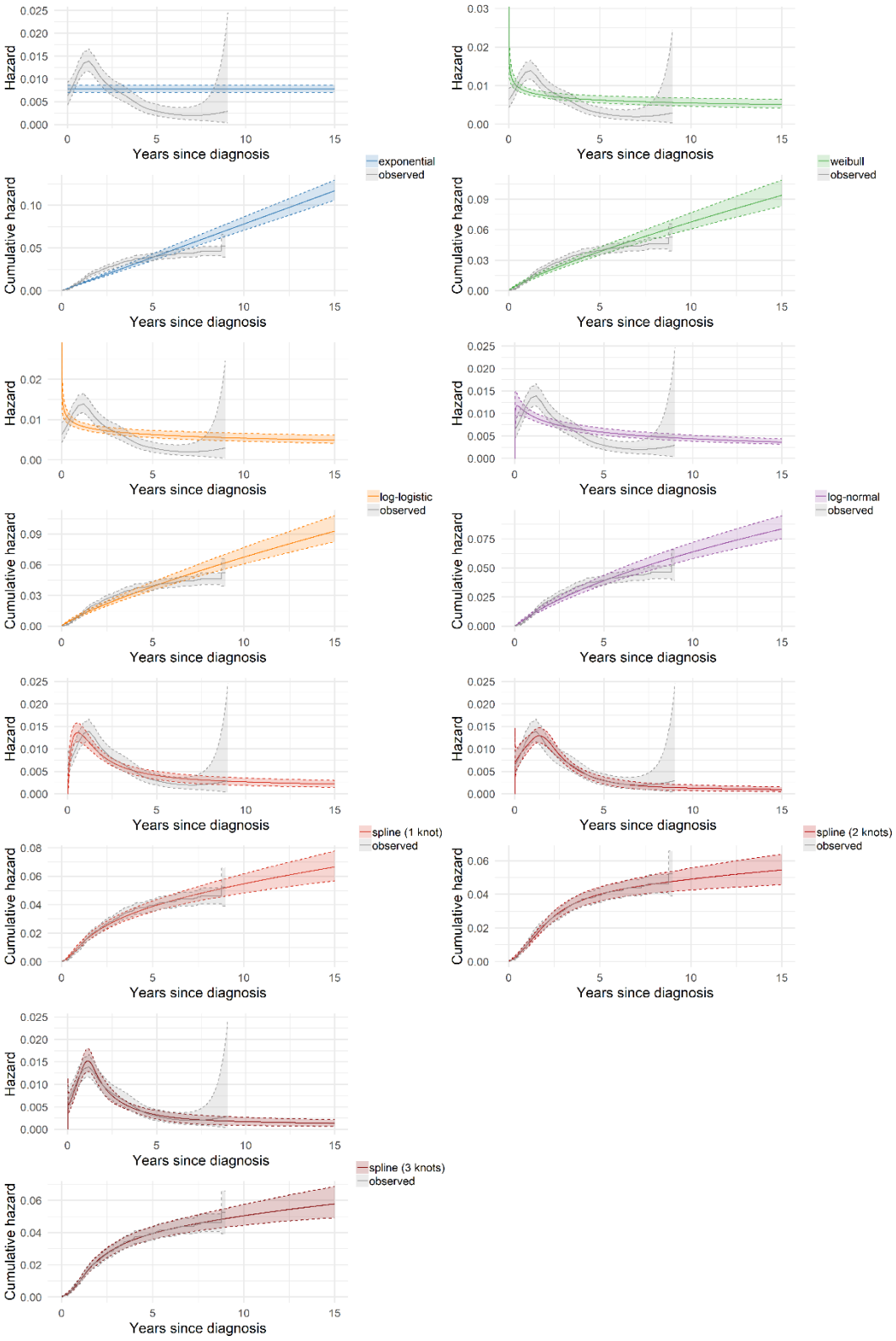
Appendix Figure B.2. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of knee osteoarthritis for 2nd age quartile: 62 to 69. The spline-based distribution with 3 knots was chosen.



Appendix Figure B.3. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of knee osteoarthritis for 3rd age quartile: 69 to 77. The spline-based distribution with 3 knots was chosen.



Appendix Figure B.4. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of knee osteoarthritis for 4th age quartile: 77 to 105. The spline-based distribution with 3 knots was chosen.



Appendix Table B.2: Estimated effect of explanatory factors on cause-specific risk of knee replacement following a diagnosis of knee osteoarthritis

	1st age quartile: 50 to 62		**2nd age quartile: 62 to 69**		**3rd age quartile: 69 to 77**		**4th age quartile: 77 to 105**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Age	1.09 (1.06 to 1.13)	1.09 (1.05 to 1.12)	1.01 (0.97 to 1.04)	1.00 (0.97 to 1.04)	0.95 (0.92 to 0.97)	0.95 (0.93 to 0.98)	1.22 (0.88 to 1.69)	1.20 (0.85 to 1.69)
Age^2	-	-	-	-	-	-	0.98 (0.97 to 1.00)	0.98 (0.97 to 1.00)
Gender								
male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
female	1.00 (0.82 to 1.21)	1.07 (0.85 to 1.35)	1.29 (1.10 to 1.51)	1.24 (1.02 to 1.51)	1.18 (1.03 to 1.35)	1.11 (0.94 to 1.32)	0.76 (0.62 to 0.94)	0.68 (0.53 to 0.87)
Charlson								
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
1	1.58 (1.28 to 1.95)	1.48 (1.18 to 1.85)	1.00 (0.84 to 1.19)	0.98 (0.81 to 1.19)	1.00 (0.87 to 1.16)	1.02 (0.88 to 1.19)	1.03 (0.81 to 1.32)	1.06 (0.82 to 1.37)

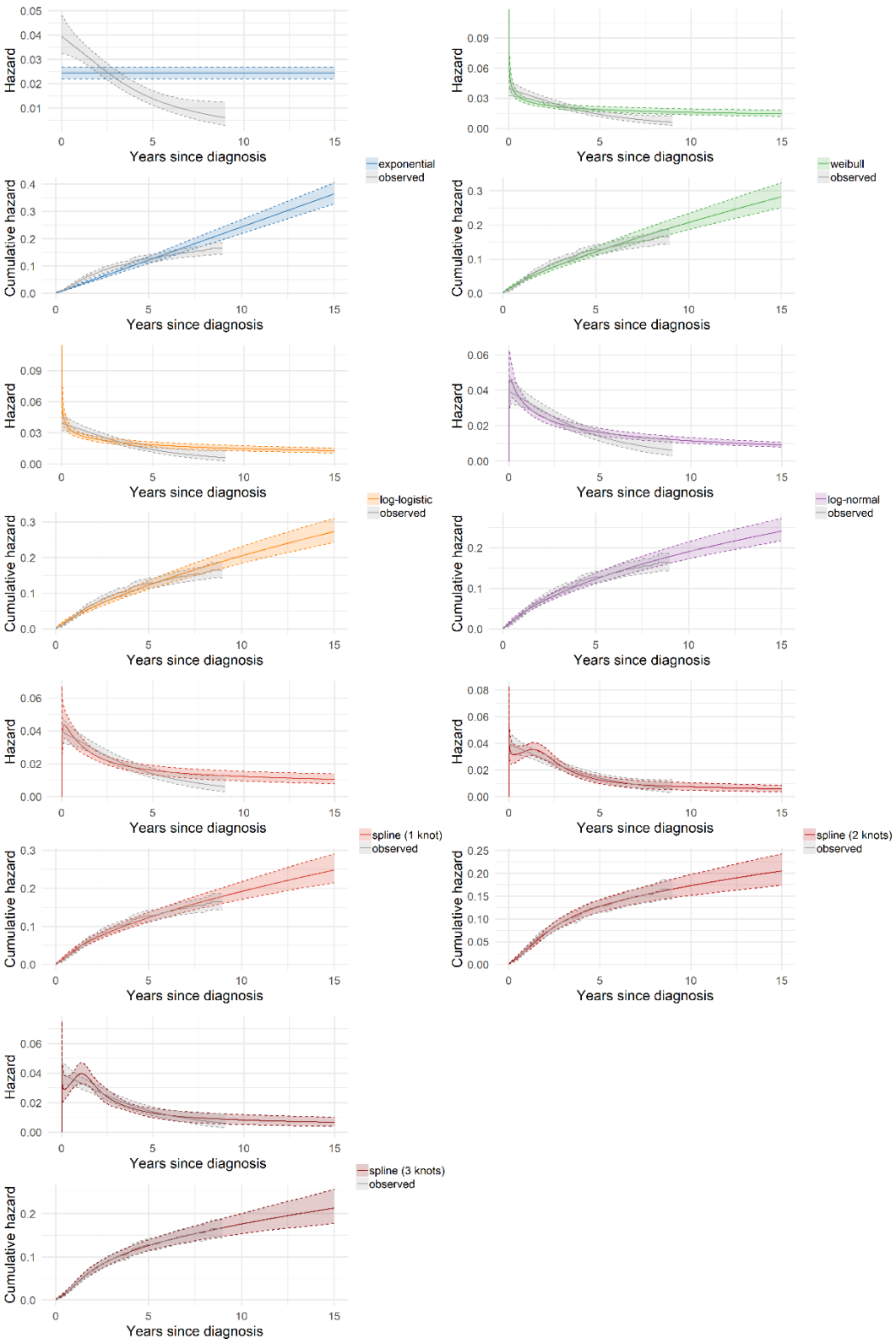
	1st age quartile: 50 to 62		**2nd age quartile: 62 to 69**		**3rd age quartile: 69 to 77**		**4th age quartile: 77 to 105**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
2	1.22 (0.83 to 1.78)	1.10 (0.73 to 1.65)	1.22 (0.97 to 1.54)	1.21 (0.95 to 1.55)	1.00 (0.82 to 1.22)	0.88 (0.71 to 1.10)	0.92 (0.68 to 1.24)	0.98 (0.71 to 1.35)
3+	1.74 (1.03 to 2.92)	1.50 (0.87 to 2.61)	1.12 (0.81 to 1.56)	1.09 (0.77 to 1.55)	1.00 (0.79 to 1.27)	0.84 (0.63 to 1.11)	0.77 (0.55 to 1.08)	0.86 (0.60 to 1.23)
BMI	1.04 (1.01 to 1.08)	1.04 (1.01 to 1.07)	1.03 (1.01 to 1.05)	1.03 (1.01 to 1.05)	1.04 (1.02 to 1.06)	1.03 (1.01 to 1.06)	1.03 (1.00 to 1.07)	1.02 (0.99 to 1.06)
BMI ^2	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	-	-	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)
MEDEA quintile or rural								
1st (least deprived)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd	0.99 (0.66 to 1.50)	0.98 (0.65 to 1.48)	1.03 (0.73 to 1.44)	1.03 (0.73 to 1.45)	1.05 (0.79 to 1.39)	1.02 (0.77 to 1.36)	1.72 (1.09 to 2.71)	1.58 (1.00 to 2.49)

	1st age quartile: 50 to 62		**2nd age quartile: 62 to 69**		**3rd age quartile: 69 to 77**		**4th age quartile: 77 to 105**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
3rd	0.87 (0.58 to 1.30)	0.84 (0.56 to 1.26)	1.05 (0.76 to 1.46)	1.04 (0.75 to 1.44)	1.29 (0.99 to 1.67)	1.25 (0.96 to 1.63)	1.22 (0.76 to 1.96)	1.10 (0.68 to 1.76)
4th	1.07 (0.73 to 1.58)	1.04 (0.71 to 1.53)	1.44 (1.06 to 1.95)	1.41 (1.04 to 1.92)	1.22 (0.94 to 1.59)	1.19 (0.92 to 1.54)	1.57 (1.00 to 2.44)	1.35 (0.86 to 2.11)
5th (most deprived)	1.10 (0.75 to 1.63)	1.05 (0.71 to 1.55)	1.27 (0.92 to 1.77)	1.22 (0.88 to 1.70)	1.18 (0.90 to 1.55)	1.13 (0.86 to 1.49)	1.96 (1.24 to 3.10)	1.72 (1.09 to 2.72)
Rural	0.96 (0.64 to 1.43)	0.93 (0.62 to 1.40)	0.94 (0.67 to 1.31)	0.93 (0.66 to 1.30)	0.68 (0.51 to 0.91)	0.67 (0.50 to 0.89)	1.26 (0.80 to 1.96)	1.15 (0.74 to 1.80)
Smoking status								
Non-smoker	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.15 (0.86 to 1.54)	1.17 (0.85 to 1.60)	0.84 (0.65 to 1.08)	0.93 (0.70 to 1.24)	1.00 (0.82 to 1.22)	1.01 (0.79 to 1.28)	0.92 (0.65 to 1.32)	0.69 (0.47 to 1.02)

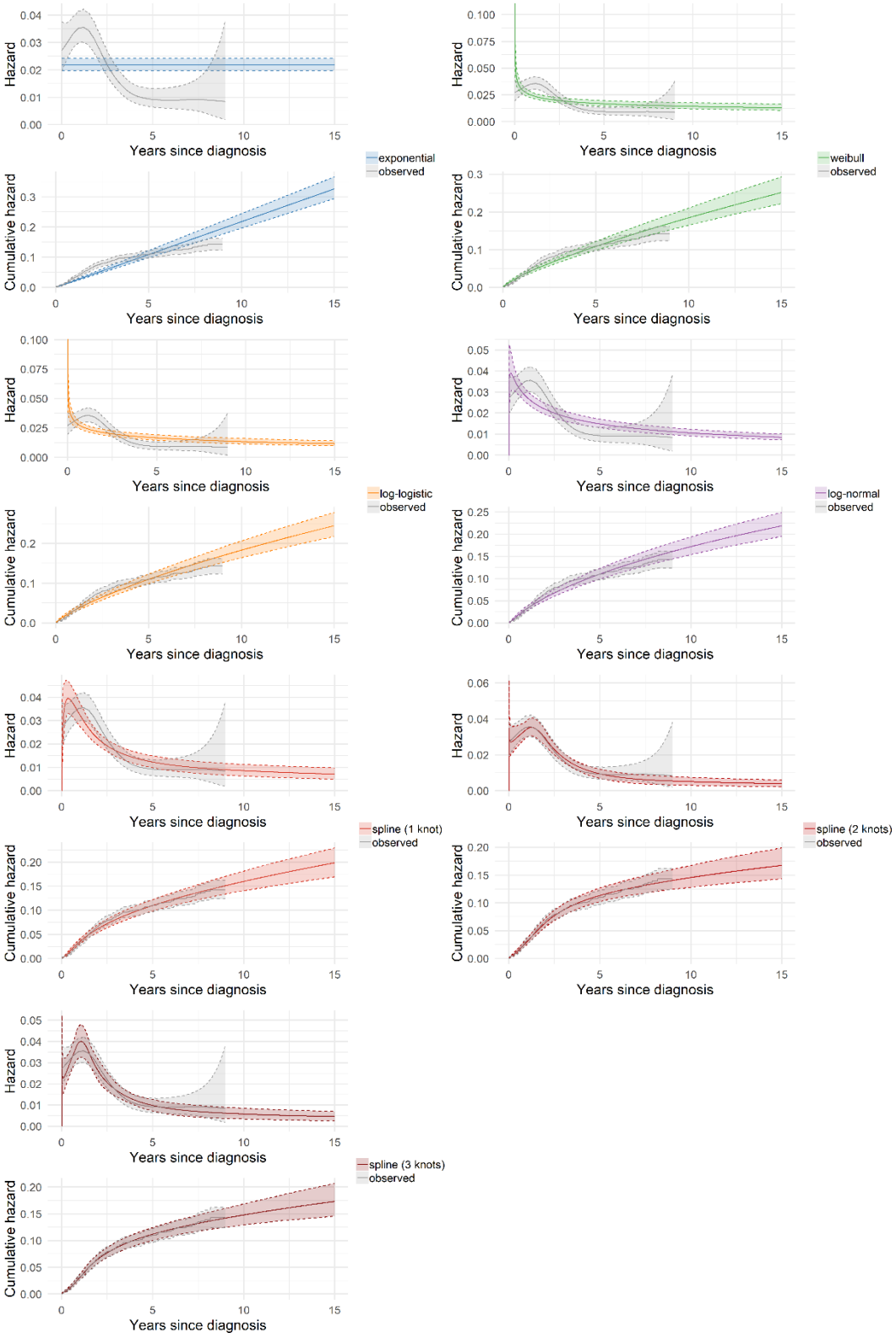
	1st age quartile: 50 to 62		2nd age quartile: 62 to 69		3rd age quartile: 69 to 77		4th age quartile: 77 to 105	
	Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Current smoker	0.89 (0.67 to 1.18)	1.01 (0.75 to 1.37)	0.91 (0.68 to 1.21)	1.01 (0.75 to 1.38)	1.00 (0.75 to 1.33)	0.86 (0.61 to 1.22)	0.70 (0.33 to 1.46)	0.51 (0.24 to 1.08)

MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. BMI: body mass index; PH: proportional hazard, with estimates representing hazard ratios.

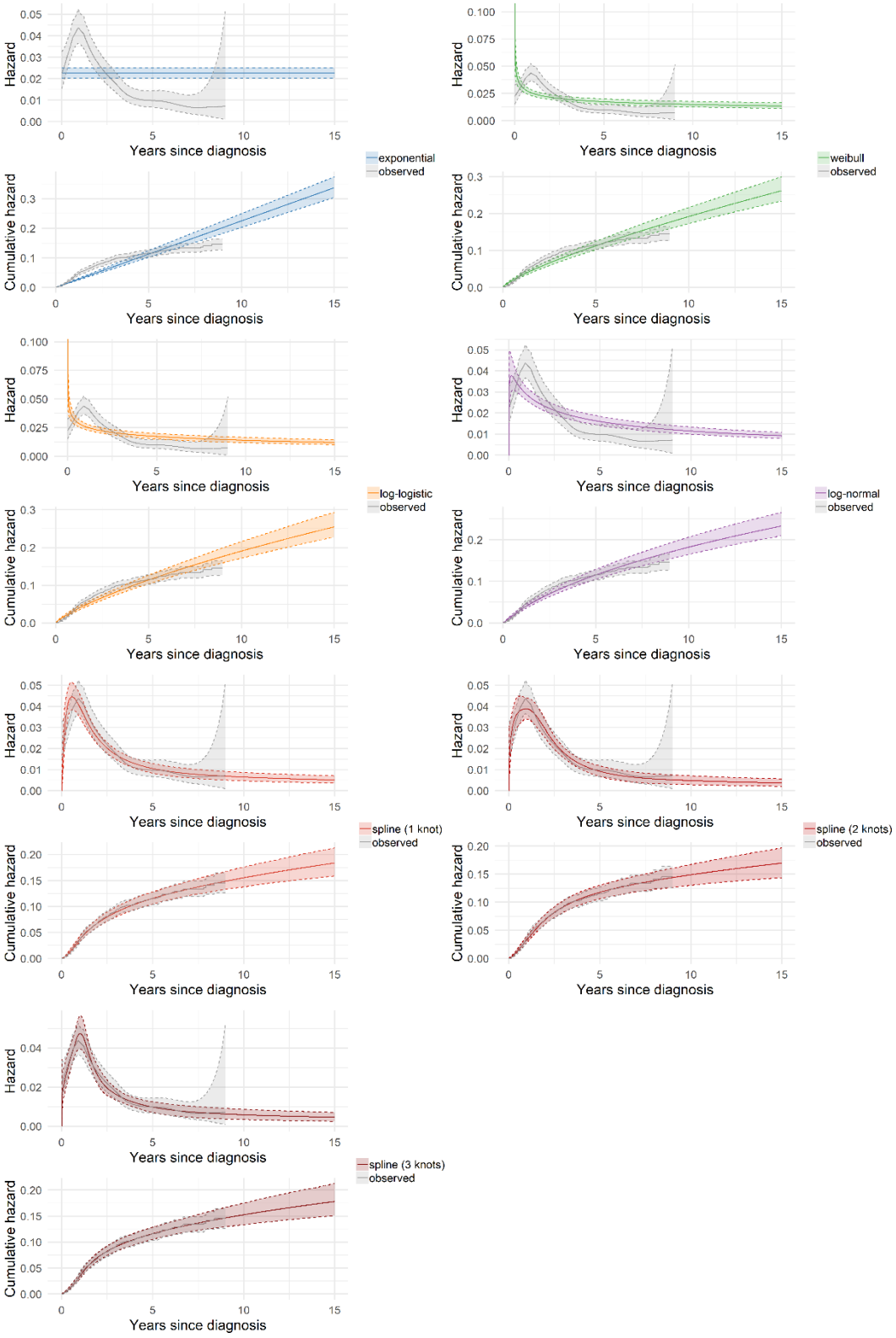
Appendix Figure B.5. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of hip osteoarthritis for 1st age quartile: 50 to 62. The spline-based distribution with 3 knots was chosen.



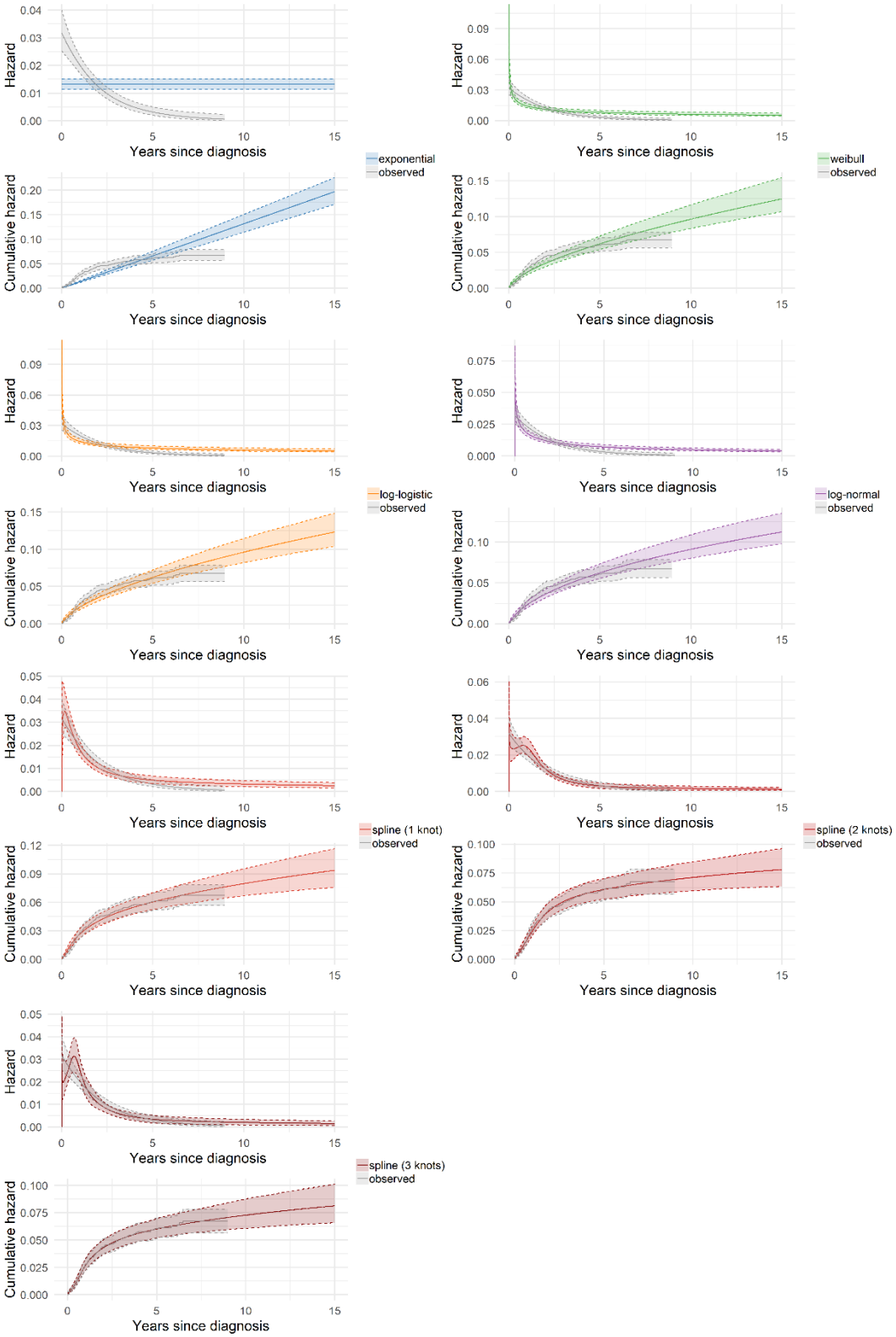
Appendix Figure B.6. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of hip osteoarthritis for 2nd age quartile: 62 to 70. The spline-based distribution with 3 knots was chosen.



Appendix Figure B.7. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of hip osteoarthritis for 3rd age quartile: 70 to 78. The spline-based distribution with 3 knots was chosen.



Appendix Figure B.8. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of hip osteoarthritis for 4th age quartile: 78 to 103. The spline-based distribution with 3 knots was chosen.



Appendix Table B.3. Estimated effect of explanatory factors on cause-specific risk of hip replacement following a diagnosis of hip osteoarthritis

	1st age quartile: 50 to 62		**2nd age quartile: 62 to 70**		**3rd age quartile: 70 to 78**		**4th age quartile: 78 to 103**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Age	1.01 (0.98 to 1.04)	1.01 (0.98 to 1.05)	1.01 (0.96 to 1.06)	1.02 (0.97 to 1.07)	0.98 (0.93 to 1.02)	0.98 (0.94 to 1.03)	0.88 (0.84 to 0.93)	0.89 (0.85 to 0.94)
Age^2	-	-	-	-	-	-	-	-
Gender								
male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
female	0.44 (0.36 to 0.55)	0.46 (0.36 to 0.59)	0.56 (0.45 to 0.70)	0.54 (0.42 to 0.71)	0.73 (0.60 to 0.90)	0.66 (0.51 to 0.85)	1.00 (0.74 to 1.35)	0.93 (0.64 to 1.33)
Charlson								
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

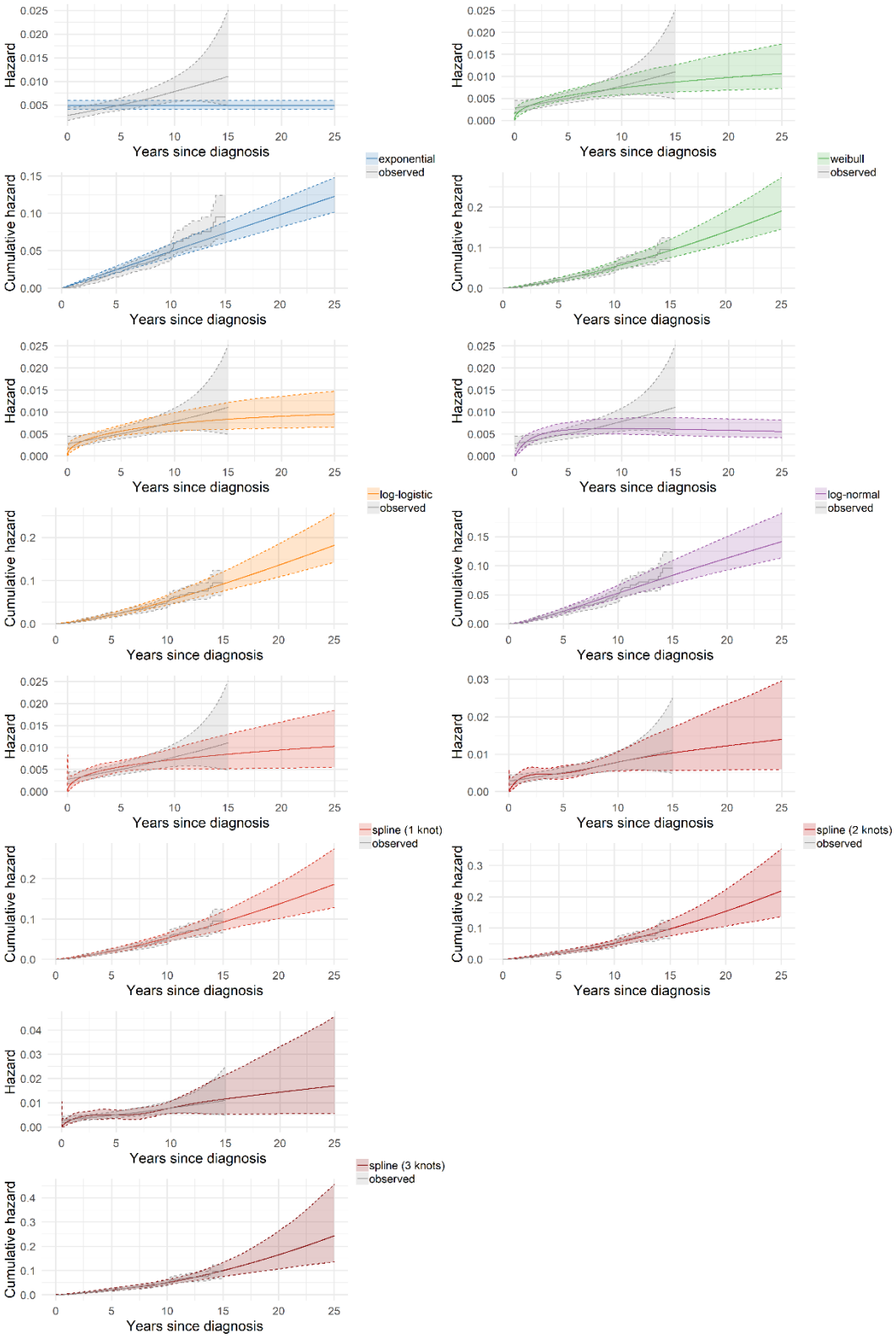
	1st age quartile: 50 to 62		2nd age quartile: 62 to 70		3rd age quartile: 70 to 78		4th age quartile: 78 to 103	
	Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios		Spline-based distribution with 3 knots PH model: hazard ratios	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
1	1.16 (0.91 to 1.49)	1.05 (0.80 to 1.37)	0.93 (0.71 to 1.21)	0.87 (0.65 to 1.15)	0.84 (0.66 to 1.08)	0.82 (0.63 to 1.07)	0.74 (0.51 to 1.06)	0.75 (0.51 to 1.11)
2	0.93 (0.62 to 1.41)	0.88 (0.56 to 1.36)	0.82 (0.56 to 1.21)	0.77 (0.51 to 1.15)	0.89 (0.66 to 1.20)	0.84 (0.61 to 1.16)	1.00 (0.68 to 1.47)	1.00 (0.66 to 1.52)
3+	0.70 (0.33 to 1.49)	0.57 (0.26 to 1.27)	0.87 (0.55 to 1.36)	0.71 (0.44 to 1.16)	0.64 (0.43 to 0.93)	0.58 (0.38 to 0.87)	0.54 (0.34 to 0.86)	0.55 (0.33 to 0.91)
BMI	1.02 (0.98 to 1.05)	1.02 (0.98 to 1.05)	1.00 (0.96 to 1.03)	1.00 (0.96 to 1.04)	1.01 (0.98 to 1.05)	1.02 (0.98 to 1.05)	1.04 (0.99 to 1.09)	1.03 (0.99 to 1.08)
BMI ^2	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)

	1st age quartile: 50 to 62		**2nd age quartile: 62 to 70**		**3rd age quartile: 70 to 78**		**4th age quartile: 78 to 103**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
MEDEA quintile or rural								
1st (least deprived)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd	1.08 (0.70 to 1.66)	1.10 (0.71 to 1.69)	1.11 (0.72 to 1.70)	1.14 (0.74 to 1.76)	1.14 (0.74 to 1.74)	1.15 (0.75 to 1.77)	0.94 (0.56 to 1.59)	0.92 (0.55 to 1.57)
3rd	0.96 (0.63 to 1.46)	1.00 (0.66 to 1.52)	0.85 (0.55 to 1.31)	0.88 (0.57 to 1.37)	0.91 (0.59 to 1.40)	0.90 (0.58 to 1.38)	0.77 (0.44 to 1.34)	0.76 (0.44 to 1.33)
4th	1.00 (0.66 to 1.52)	1.04 (0.68 to 1.59)	0.93 (0.61 to 1.42)	0.97 (0.64 to 1.49)	1.24 (0.82 to 1.86)	1.23 (0.82 to 1.84)	0.88 (0.52 to 1.50)	0.86 (0.51 to 1.47)

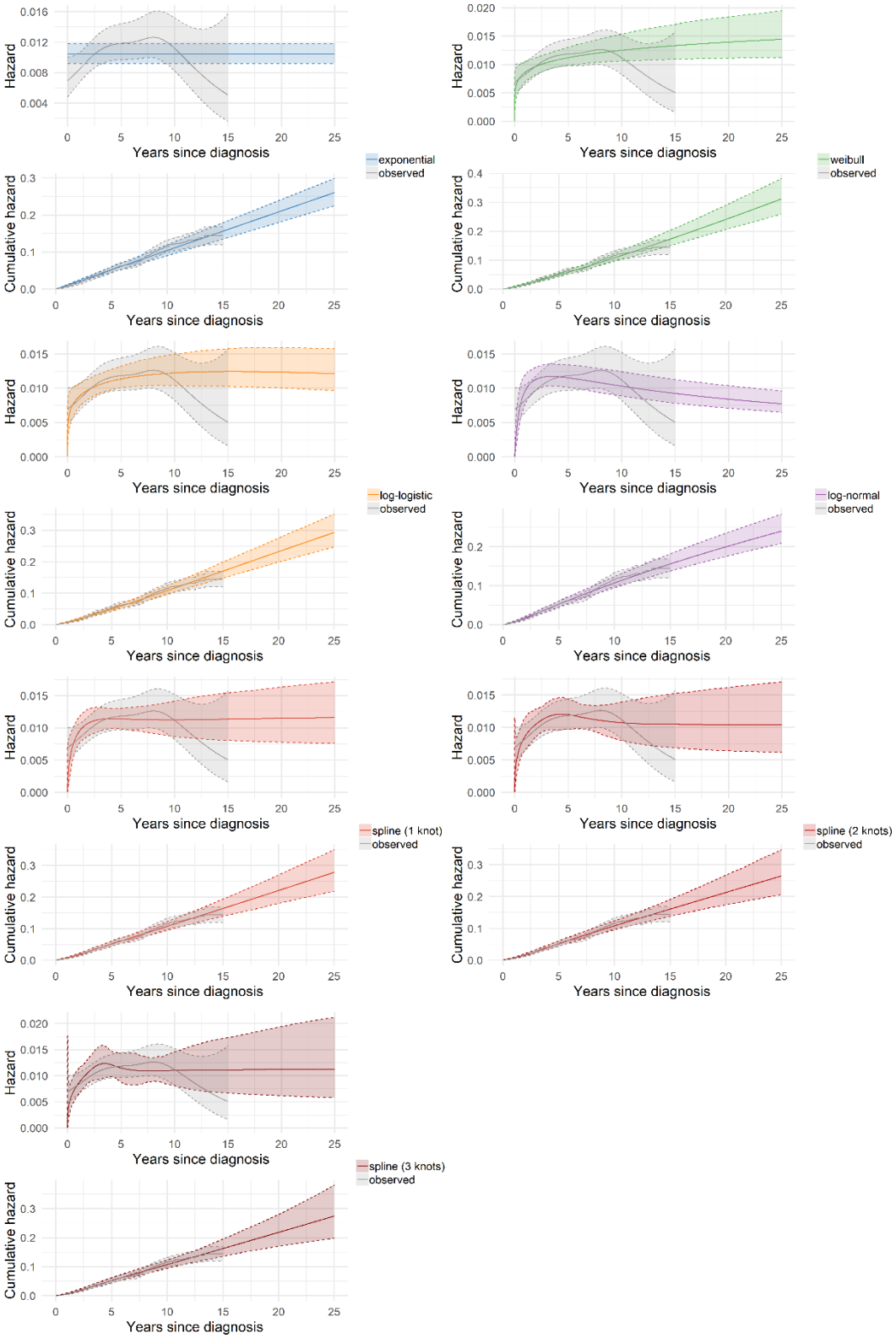
	1st age quartile: 50 to 62		**2nd age quartile: 62 to 70**		**3rd age quartile: 70 to 78**		**4th age quartile: 78 to 103**	
	Spline-based distribution with 3 knots PH model: hazard ratios		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**		**Spline-based distribution with 3 knots PH model: hazard ratios**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
5th (most deprived)	1.09 (0.71 to 1.68)	1.17 (0.76 to 1.81)	0.92 (0.58 to 1.45)	0.96 (0.61 to 1.52)	1.07 (0.69 to 1.66)	1.12 (0.72 to 1.73)	1.07 (0.62 to 1.82)	1.06 (0.62 to 1.83)
Rural	1.11 (0.73 to 1.68)	1.07 (0.71 to 1.62)	0.88 (0.57 to 1.36)	0.88 (0.57 to 1.36)	0.83 (0.54 to 1.28)	0.78 (0.51 to 1.20)	0.64 (0.38 to 1.09)	0.64 (0.38 to 1.09)
Smoking status								
Non-smoker	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.54 (1.15 to 2.07)	1.16 (0.85 to 1.59)	1.29 (0.95 to 1.75)	0.99 (0.70 to 1.39)	1.13 (0.84 to 1.51)	0.96 (0.69 to 1.33)	0.87 (0.53 to 1.45)	0.83 (0.47 to 1.45)
Current smoker	1.37 (1.04 to 1.79)	1.10 (0.82 to 1.46)	1.34 (0.96 to 1.87)	1.05 (0.73 to 1.50)	0.88 (0.53 to 1.45)	0.75 (0.45 to 1.28)	0.74 (0.26 to 2.08)	0.69 (0.24 to 2.03)

MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. BMI: body mass index; PH: proportional hazard, with estimates representing hazard ratios.

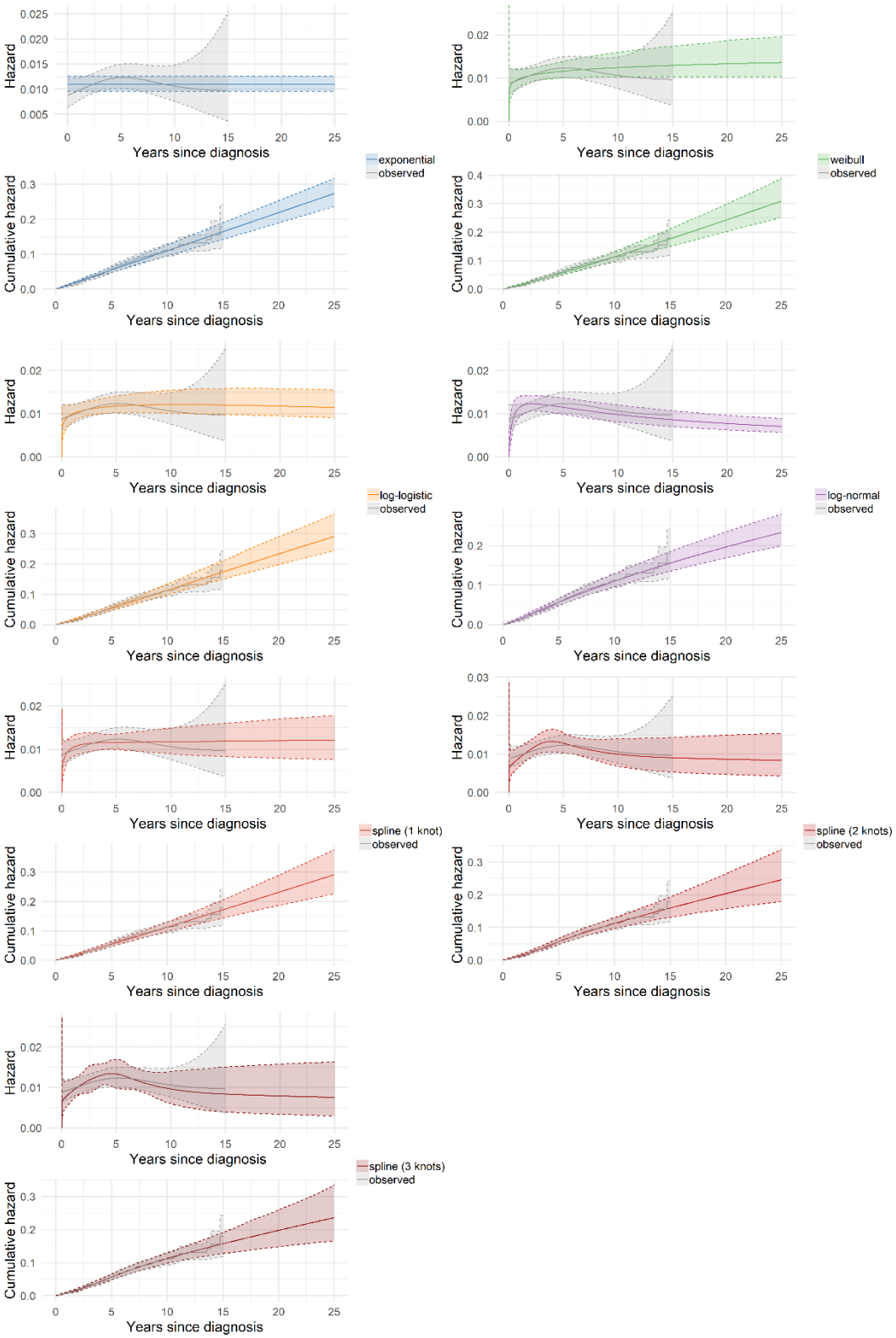
Appendix Figure B.9. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of rheumatoid arthritis for 1st age group: 40 to 54. The Weibull distribution was chosen.



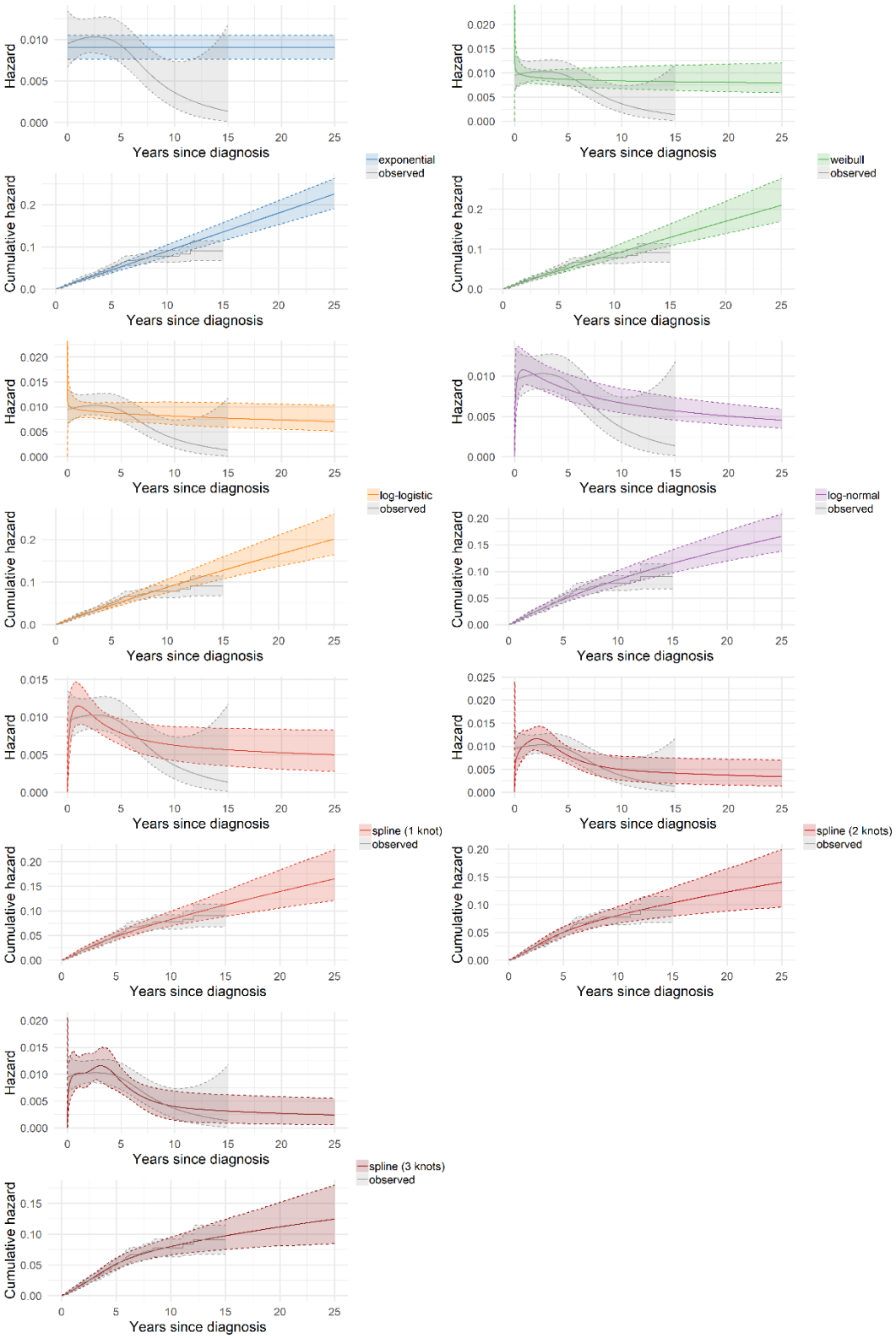
Appendix Figure B.10. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of rheumatoid arthritis for 2nd age group: 54 to 64. The Weibull distribution was chosen.



Appendix Figure B.11. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of rheumatoid arthritis for 3rd age group: 64 to 73. The log-logistic distribution was chosen.



Appendix Figure B.12. Alternative distributions for cause-specific risk of knee replacement following a diagnosis of rheumatoid arthritis for 4th age group: 73 to 99. The log-normal distribution was chosen.



Appendix Table B.4. Estimated effect of explanatory factors on cause-specific risk of knee replacement following a diagnosis of rheumatoid arthritis

	1st age group: 40 to 54 Weibull distribution AFT model: acceleration factors		**2nd age group: 54 to 64 Weibull distribution AFT model: acceleration factors**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Age	0.95 (0.91 to 0.99)	0.95 (0.91 to 0.99)	0.98 (0.94 to 1.01)	0.98 (0.94 to 1.02)	1.02 (0.97 to 1.07)	1.02 (0.97 to 1.08)	0.84 (0.65 to 1.09)	0.84 (0.64 to 1.11)
Age^2							1.01 (1.00 to 1.01)	1.01 (1.00 to 1.02)
Sex								
male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
female	1.19 (0.88 to 1.61)	1.25 (0.90 to 1.74)	0.88 (0.69 to 1.13)	0.89 (0.68 to 1.16)	1.04 (0.79 to 1.37)	1.12 (0.82 to 1.52)	1.08 (0.73 to 1.60)	1.10 (0.70 to 1.73)
Charlson								

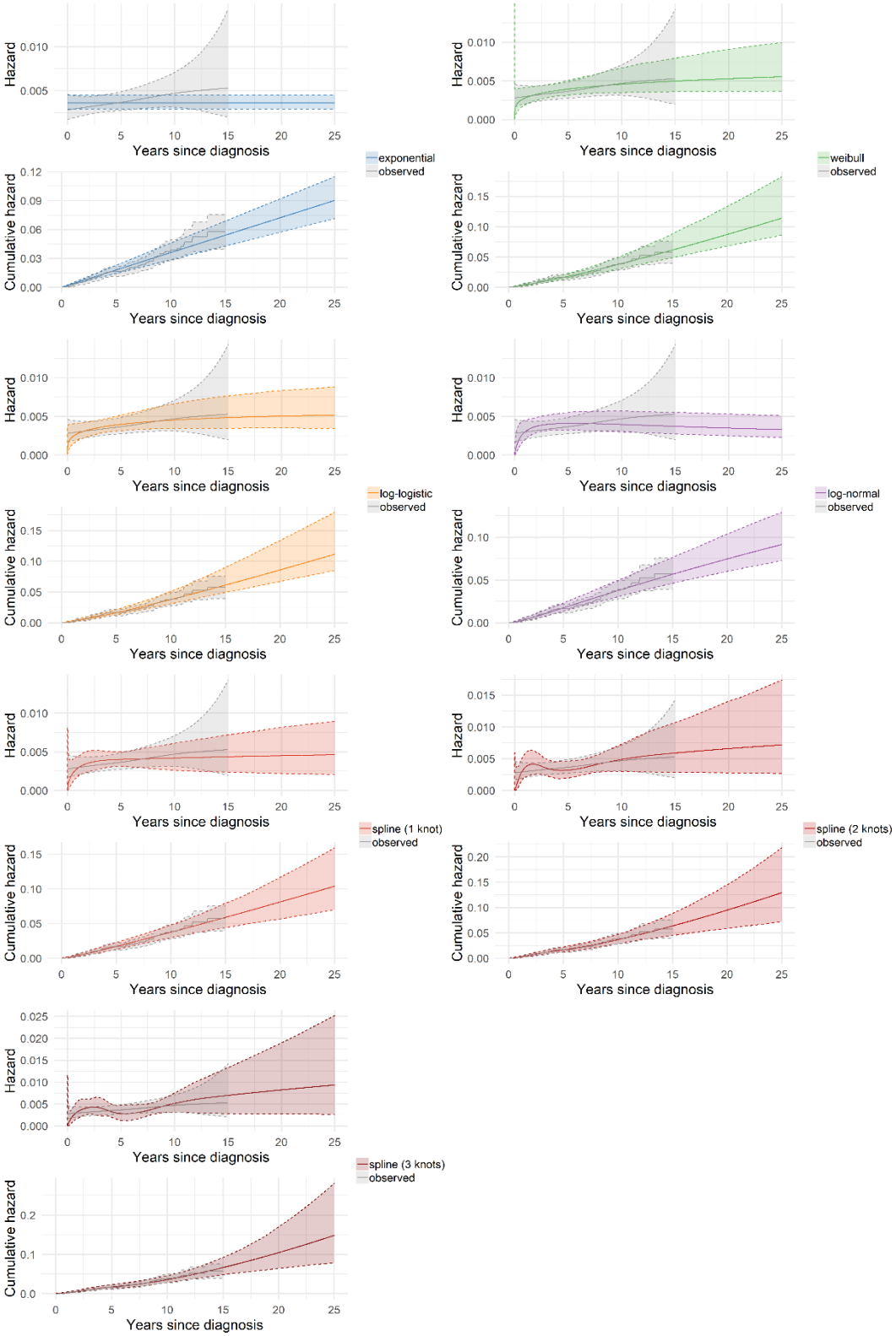
	1st age group: 40 to 54 Weibull distribution AFT model: acceleration factors		**2nd age group: 54 to 64 Weibull distribution AFT model: acceleration factors**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
1+	1.19 (0.58 to 2.45)	1.24 (0.58 to 2.66)	1.27 (0.81 to 2.00)	1.27 (0.79 to 2.04)	1.68 (1.00 to 2.82)	1.72 (0.99 to 2.97)	1.43 (0.82 to 2.49)	1.46 (0.80 to 2.66)
BMI	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)	0.98 (0.96 to 1.01)	0.98 (0.96 to 1.01)	0.99 (0.96 to 1.02)	0.99 (0.96 to 1.02)	0.99 (0.94 to 1.03)	0.99 (0.94 to 1.03)
IMD quintile								
1st (least deprived)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd	1.24 (0.75 to 2.06)	1.23 (0.74 to 2.05)	0.57 (0.39 to 0.84)	0.58 (0.40 to 0.84)	0.84 (0.57 to 1.24)	0.83 (0.56 to 1.23)	0.85 (0.48 to 1.51)	0.82 (0.46 to 1.48)

	1st age group: 40 to 54 Weibull distribution AFT model: acceleration factors		**2nd age group: 54 to 64 Weibull distribution AFT model: acceleration factors**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
3rd	0.92 (0.59 to 1.44)	0.92 (0.59 to 1.45)	0.71 (0.48 to 1.05)	0.71 (0.48 to 1.05)	0.94 (0.62 to 1.43)	0.92 (0.60 to 1.40)	0.74 (0.42 to 1.33)	0.72 (0.39 to 1.30)
4th	1.02 (0.64 to 1.63)	0.99 (0.62 to 1.59)	0.63 (0.42 to 0.93)	0.63 (0.42 to 0.94)	1.40 (0.87 to 2.28)	1.36 (0.83 to 2.21)	0.81 (0.44 to 1.47)	0.76 (0.41 to 1.42)
5th (most deprived)	1.01 (0.62 to 1.66)	0.97 (0.58 to 1.61)	0.76 (0.49 to 1.19)	0.75 (0.48 to 1.17)	0.86 (0.54 to 1.35)	0.80 (0.50 to 1.27)	1.10 (0.53 to 2.29)	1.10 (0.51 to 2.36)
Smoking status								
Non-smoker	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.26 (0.75 to 2.12)	1.33 (0.78 to 2.28)	0.99 (0.70 to 1.38)	0.98 (0.69 to 1.38)	1.19 (0.78 to 1.81)	1.20 (0.78 to 1.85)	1.13 (0.64 to 1.99)	1.18 (0.65 to 2.15)

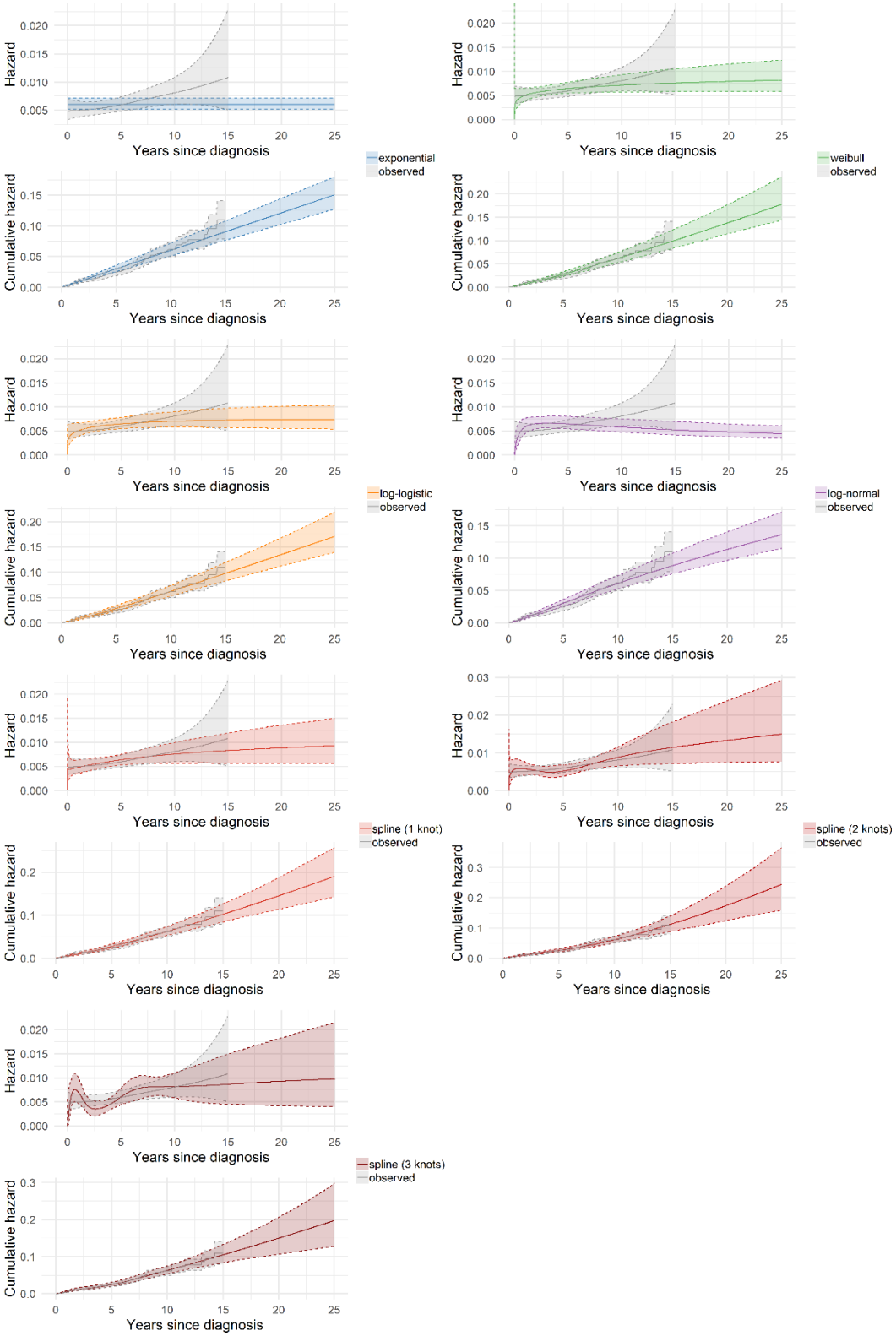
	1st age group: 40 to 54 Weibull distribution AFT model: acceleration factors		**2nd age group: 54 to 64 Weibull distribution AFT model: acceleration factors**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Current smoker	1.30 (0.79 to 2.15)	1.33 (0.79 to 2.24)	1.20 (0.82 to 1.73)	1.18 (0.81 to 1.73)	1.58 (0.95 to 2.62)	1.61 (0.96 to 2.72)	1.34 (0.65 to 2.76)	1.44 (0.68 to 3.08)

BMI: body mass index; IMD: index of multiple deprivation. PH: proportional hazard, with estimates representing hazard ratios. AFT: accelerated failure time, with estimates representing acceleration factors.

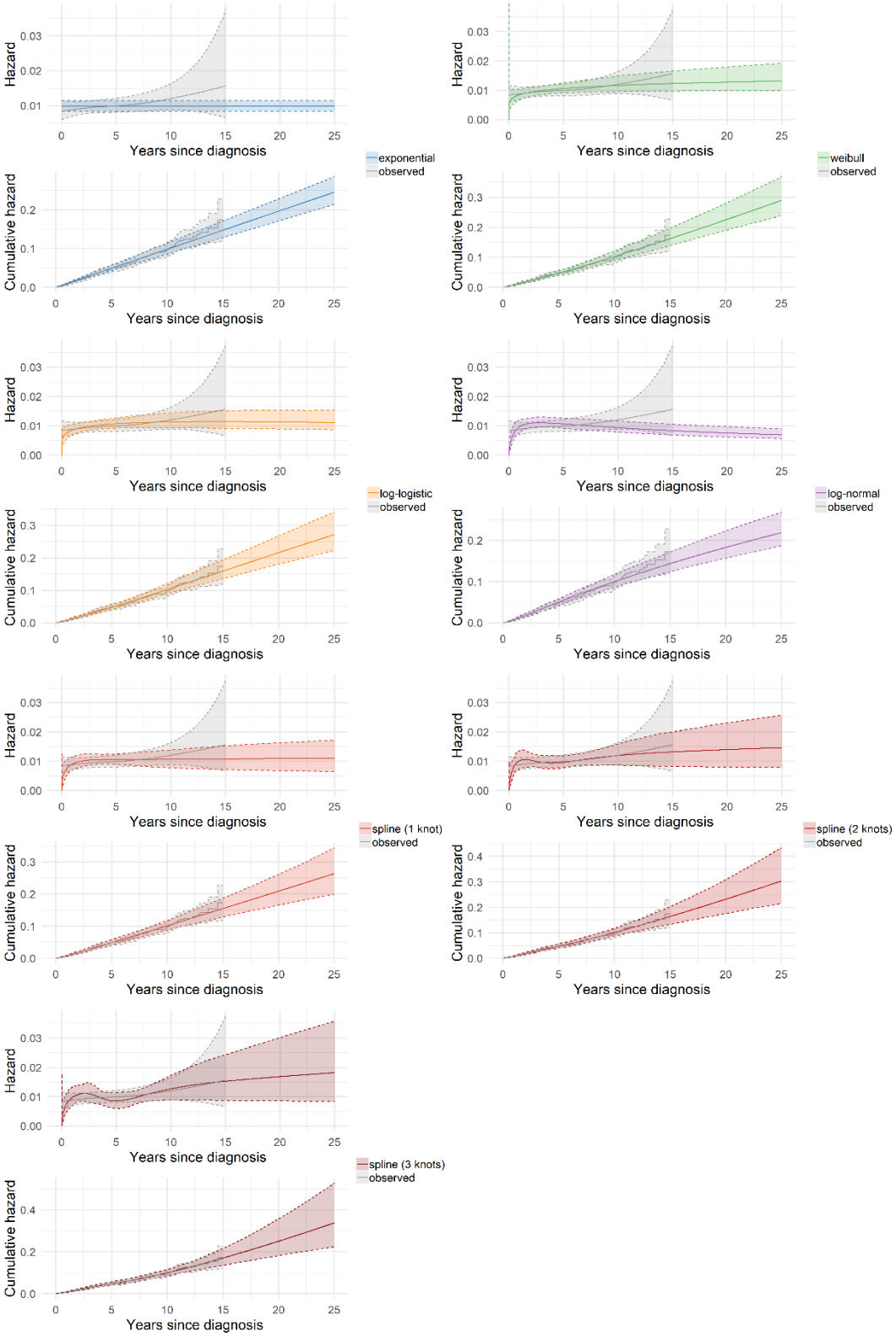
Appendix Figure B.13. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of rheumatoid arthritis for 1st age group: 40 to 54. The spline-based distribution with 3 knots was chosen.



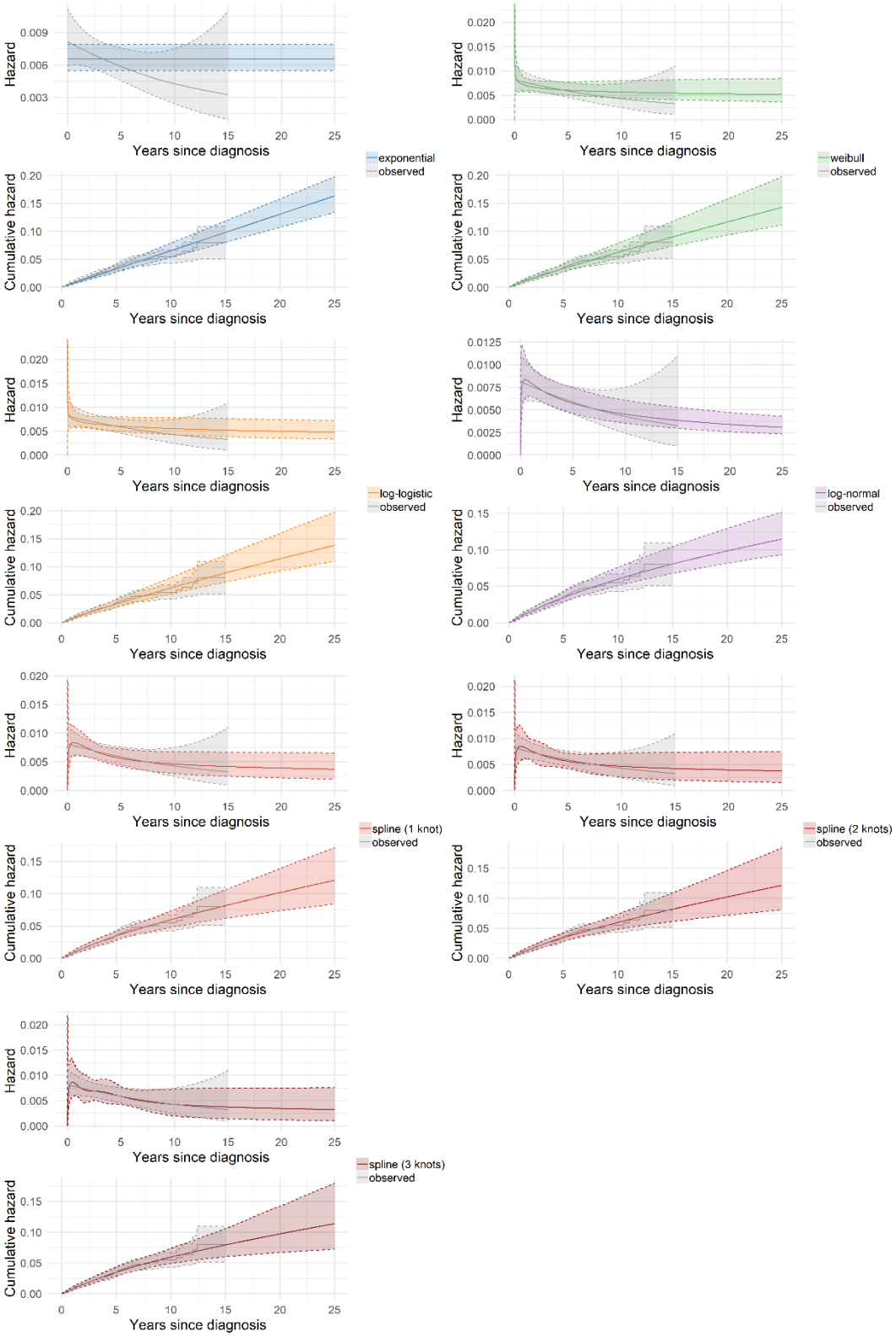
Appendix Figure B.14. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of rheumatoid arthritis for 2nd age group: 54 to 64. The spline-based distribution with 3 knots was distribution was chosen.



Appendix Figure B.15. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of rheumatoid arthritis for 3rd age group: 64 to 73. The log-logistic distribution was chosen.



Appendix Figure B.16. Alternative distributions for cause-specific risk of hip replacement following a diagnosis of rheumatoid arthritis for 4th group: 73 to 99. The log-normal distribution was chosen.



Appendix Table B.5. Estimated effect for explanatory factors on cause-specific risk of hip replacement following a diagnosis of rheumatoid arthritis

	1st age group: 40 to 54 Spline-based distribution with 3 knots PH model: hazard ratios		**2nd age group: 54 to 64 Spline-based distribution with 3 knots PH model: hazard ratios**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Age	1.06 (1.00 to 1.13)	1.06 (1.00 to 1.14)	1.09 (1.03 to 1.16)	1.09 (1.03 to 1.16)	0.97 (0.92 to 1.02)	0.97 (0.92 to 1.02)	1.08 (1.02 to 1.14)	1.09 (1.02 to 1.15)
Sex								
male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
female	0.80 (0.49 to 1.30)	0.80 (0.47 to 1.36)	1.27 (0.87 to 1.85)	1.22 (0.81 to 1.84)	0.70 (0.52 to 0.96)	0.71 (0.51 to 1.00)	0.58 (0.34 to 1.00)	0.53 (0.29 to 0.97)
Charlson								
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

	1st age group: 40 to 54 Spline-based distribution with 3 knots PH model: hazard ratios		**2nd age group: 54 to 64 Spline-based distribution with 3 knots PH model: hazard ratios**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
1+	1.06 (0.39 to 2.91)	1.07 (0.37 to 3.12)	0.89 (0.47 to 1.69)	0.86 (0.44 to 1.70)	1.90 (1.07 to 3.35)	1.89 (1.03 to 3.46)	1.10 (0.58 to 2.10)	1.05 (0.52 to 2.12)
BMI	0.99 (0.94 to 1.04)	0.99 (0.95 to 1.05)	0.99 (0.94 to 1.03)	0.99 (0.94 to 1.03)	0.99 (0.96 to 1.03)	0.99 (0.96 to 1.03)	1.01 (0.95 to 1.06)	1.01 (0.95 to 1.07)
BMI ^2			1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)				
IMD quintile								

	1st age group: 40 to 54 Spline-based distribution with 3 knots PH model: hazard ratios		**2nd age group: 54 to 64 Spline-based distribution with 3 knots PH model: hazard ratios**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
1st (least deprived)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd	1.50 (0.74 to 3.07)	1.46 (0.72 to 3.00)	1.19 (0.72 to 1.98)	1.18 (0.71 to 1.96)	0.62 (0.40 to 0.95)	0.61 (0.39 to 0.94)	0.96 (0.50 to 1.87)	0.94 (0.47 to 1.88)
3rd	0.87 (0.39 to 1.93)	0.84 (0.38 to 1.87)	1.00 (0.58 to 1.71)	1.01 (0.58 to 1.73)	0.67 (0.43 to 1.06)	0.67 (0.43 to 1.06)	1.29 (0.63 to 2.64)	1.29 (0.61 to 2.71)
4th	0.69 (0.29 to 1.64)	0.68 (0.29 to 1.62)	1.01 (0.58 to 1.77)	1.01 (0.57 to 1.77)	0.67 (0.42 to 1.06)	0.66 (0.41 to 1.05)	1.22 (0.59 to 2.51)	1.24 (0.58 to 2.63)

	1st age group: 40 to 54 Spline-based distribution with 3 knots PH model: hazard ratios		**2nd age group: 54 to 64 Spline-based distribution with 3 knots PH model: hazard ratios**		**3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors**		**4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
5th (most deprived)	1.06 (0.47 to 2.38)	1.02 (0.45 to 2.35)	0.80 (0.42 to 1.52)	0.81 (0.43 to 1.56)	1.04 (0.59 to 1.84)	1.03 (0.58 to 1.83)	1.70 (0.69 to 4.19)	1.74 (0.68 to 4.41)
Smoking status								
Non-smoker	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.00 (0.42 to 2.42)	0.96 (0.39 to 2.36)	0.76 (0.44 to 1.32)	0.79 (0.45 to 1.38)	1.03 (0.68 to 1.54)	0.95 (0.63 to 1.45)	1.06 (0.57 to 1.97)	0.96 (0.50 to 1.84)

	1st age group: 40 to 54 Spline-based distribution with 3 knots PH model: hazard ratios		2nd age group: 54 to 64 Spline-based distribution with 3 knots PH model: hazard ratios		3rd age group: 64 to 73 Log-logistic distribution AFT model: acceleration factors		4th group: 73 to 99 Log-normal distribution AFT model: acceleration factors	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Current smoker	1.15 (0.56 to 2.39)	1.16 (0.55 to 2.47)	0.82 (0.49 to 1.36)	0.89 (0.52 to 1.51)	1.23 (0.76 to 1.99)	1.14 (0.70 to 1.87)	1.07 (0.46 to 2.51)	1.06 (0.43 to 2.60)

BMI: body mass index; IMD: index of multiple deprivation. PH: proportional hazard, with estimates representing hazard ratios. PH: proportional hazard, with estimates representing hazard ratios. AFT: accelerated failure time, with estimates representing acceleration factors.

Appendix Table B.6: Cumulative incidence of mortality following a diagnosis of knee or hip osteoarthritis or rheumatoid arthritis

	Knee osteoarthritis (knee replacement as competing risk)	**Hip osteoarthritis (hip replacement as competing risk)**	**Rheumatoid arthritis (knee replacement as competing risk)**	**Rheumatoid arthritis (hip replacement as competing risk)**

	KR/PY	9-year cumulative incidence (% (95% CI))	HR/PY	9-year cumulative incidence (% (95% CI))	KR/PY	15-year cumulative incidence (% (95% CI))	HR/PY	15-year cumulative incidence (% (95% CI))
Total	3,874/ 209,508	19.82% (17.93% to 21.91%)	1,538/ 60,723	22.36% (20.82% to 24.00%)	2,522/ 76,104	43.59% (41.49% to 45.79%)	2,533/ 77,000	43.70% (41.60% to 45.91%)
Age at diagnosis group* (%)								
1st (youngest)	176/ 54,625	3.01% (2.51% to 3.62%)	71/ 14,779	4.99% (3.54% to 7.04%)	129/ 19,371	12.15% (9.63% to 15.32%)	128/ 19,419	11.56% (9.16% to 14.58%)
2nd	324/ 49,643	7.32% (6.21% to 8.64%)	145/ 15,124	8.63% (7.05% to 10.56%)	338/ 22,390	27.41% (23.76% to 31.61%)	344/ 22,917	27.63% (24.03% to 31.76%)
3rd	825/ 56,855	16.28% (14.71% to 18.02%)	366/ 16,491	22.02% (19.31% to 25.10%)	638/ 17,705	52.29% (47.50% to 57.56%)	633/ 17,839	51.98% (47.21% to 57.24%)
4th (oldest)	2,549/ 48,386	55.02% (46.50% to 65.11%)	956/ 14,328	52.27% (47.59% to 57.41%)	1,417/ 16,638	78.93% (75.35% to 82.67%)	1,428/ 16,825	80.02% (76.35% to 83.86%)

	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
Gender								
Male	1,623/ 69,000	22.94% (21.27% to 24.74%)	726/ 23,362	26.49% (23.67% to 29.64%)	918/ 23,541	48.30% (44.69% to 52.19%)	935/ 23,927	48.98% (45.40% to 52.84%)
Female	2,251/ 140,508	18.24% (15.66% to 21.24%)	812/ 37,361	19.51% (17.83% to 21.35%)	1,604/ 52,563	41.36% (38.83% to 44.05%)	1,598/ 53,073	41.20% (38.67% to 43.90%)
Charlson								
0	1,191/ 120,475	12.62% (10.44% to 15.26%)	422/ 32,869	12.21% (10.46% to 14.26%)	2,093/ 68,762	41.77% (39.57% to 44.10%)	2,109/ 69,617	41.96% (39.75% to 44.30%)

	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
1	1,085/ 52,364	23.99% (19.38% to 29.70%)	415/ 14,917	27.08% (23.95% to 30.62%)				
2	735/ 22,691	31.91% (28.43% to 35.81%)	292/ 7,450	34.95% (30.19% to 40.47%)				
3+	863/ 13,978	46.95% (42.30% to 52.11%)	409/ 5,487	55.21% (48.49% to 62.85%)				
1+					429/ 7,342	59.84% (53.25% to 67.25%)	424/ 7,383	59.42% (52.80% to 66.88%)
BMI group (%)								

	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
Normal or underweight (<25)	283/ 9,556	39.40% (21.42% to 72.46%)	170/ 4,361	31.96% (26.89% to 37.98%)	332/ 7,819	42.71% (40.39% to 45.15%)	329/ 7855	42.89% (40.56% to 45.34%)
Overweight (≥25 and <30)	775/ 39,791	24.26% (17.55% to 33.53%)	312/ 13,534	21.04% (18.16% to 24.39%)	99/ 4,496	47.42% (41.90% to 53.68%)	100/ 4,539	46.93% (41.41% to 53.18%)
Obese class I (≥30 and <35)	620/ 37,410	17.69% (15.67% to 19.98%)	203/ 9,630	18.97% (15.61% to 23.04%)	51/ 1,875	35.89% (25.79% to 49.95%)	54/ 1,972	36.75% (26.58% to 50.81%)
Obese class II (≥35 and <40)	223/ 15,260	16.96% (13.55% to 21.24%)	65/ 3,074	16.58% (12.60% to 21.82%)	17/ 950	41.57% (27.40% to 63.08%)	17/ 968	44.57% (29.64% to 67.02%)

	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
Obese class III (≥40)	106/ 6,015	18.26% (12.92% to 25.81%)	19/ 886	24.96% (15.12% to 41.22%)	260/ 8,143	34.53% (15.00% to 79.50%)	260/ 8,197	33.75% (14.57% to 78.20%)
Missing	1,867/ 10,1476	17.75% (16.50% to 19.08%)	769/ 29,238	23.06% (20.75% to 25.62%)	1763/ 52,821	57.69% (47.66% to 69.83%)	1,773/ 53,469	54.99% (45.57% to 66.35%)
IMD/ MEDEA quintile or rural (%)								
1st (least deprived)	337/ 20,180	17.91% (14.11% to 22.72%)	134/ 6946	14.95% (12.27% to 18.20%)	500/ 17,115	44.09% (39.22% to 49.57%)	498/ 17,249	43.30% (38.49% to 48.71%)

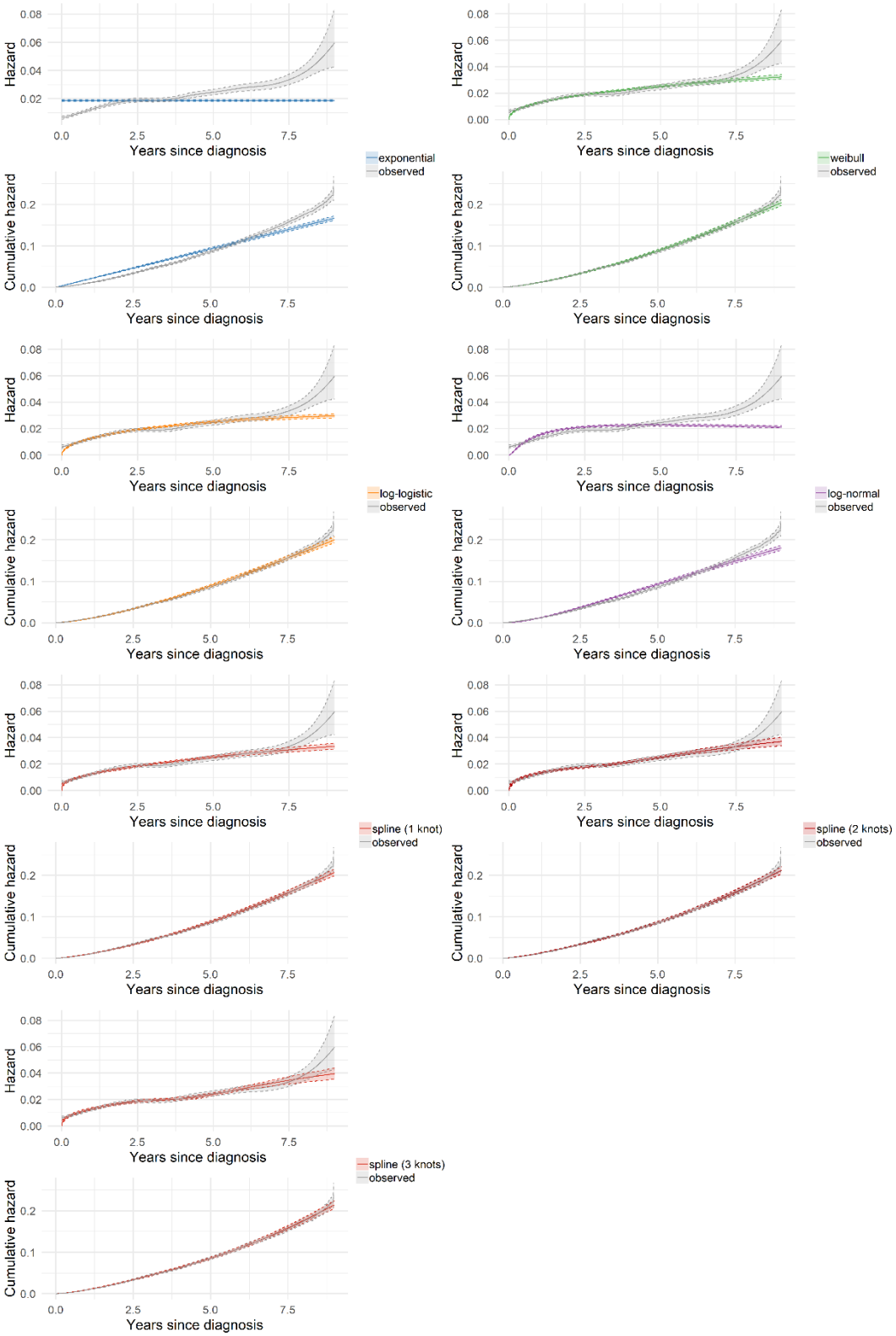
	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
2nd	414/ 30,180	16.06% (13.32% to 19.37%)	162/ 9095	15.20% (12.58% to 18.35%)	545/ 17,223	40.10% (36.13% to 44.51%)	550/ 17,396	41.35% (37.26% to 45.90%)
3rd	481/ 37,924	13.28% (11.65% to 15.13%)	200/ 10565	15.82% (13.27% to 18.86%)	481/ 16,104	41.09% (36.05% to 46.82%)	481/ 16,355	40.13% (35.33% to 45.57%)
4th	500/ 41,932	11.47% (10.12% to 12.99%)	198/ 11088	16.85% (13.96% to 20.34%)	536/ 14,789	46.43% (42.23% to 51.06%)	535/ 14,924	46.34% (42.09% to 51.01%)
5th (most deprived)	422/ 31,745	12.82% (11.29% to 14.54%)	163/ 8,634	16.25% (13.60% to 19.42%)	456/ 10,748	49.18% (44.34% to 54.56%)	465/ 10,938	50.18% (45.17% to 55.76%)

	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
Rural	877/ 39,555	25.32% (18.19% to 35.25%)	344/ 11587	27.38% (22.60% to 33.19%)				
Missing	843/ 7,992	85.51% (72.62% to 100.00%)	337/ 2,807	76.69% (70.99% to 82.85%)	4/ 125	21.78% (9.12% to 52.02%)	4/ 137	21.57% (9.01% to 51.61%)
Smoking status								
Non-smoker	2,395/ 133,845	19.38% (17.09% to 21.99%)	924/ 36,458	23.10% (21.13% to 25.25%)	306/ 11,153	44.39% (35.82% to 55.01%)	308/ 11,220	43.70% (35.63% to 53.59%)
Ex-smoker	538/ 23,815	22.17% (19.38% to 25.37%)	233/ 8,150	25.82% (21.80% to 30.57%)	362/ 10,538	51.71% (42.04% to 63.60%)	362/ 10,548	52.95% (43.13% to 65.00%)

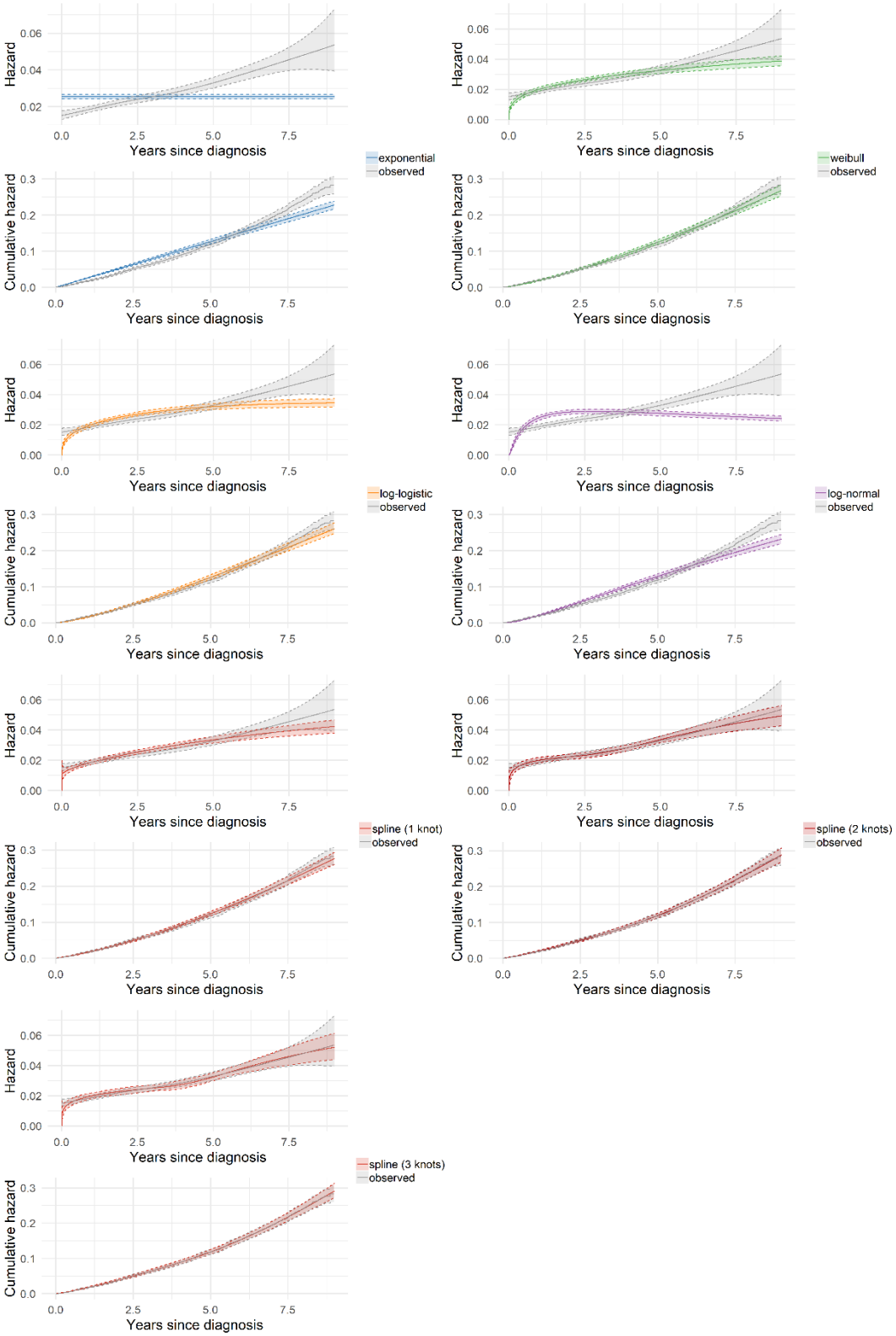
	Knee osteoarthritis (knee replacement as competing risk)		Hip osteoarthritis (hip replacement as competing risk)		Rheumatoid arthritis (knee replacement as competing risk)		Rheumatoid arthritis (hip replacement as competing risk)	
	KR/PY	**9-year cumulative incidence (% (95% CI))**	**HR/PY**	**9-year cumulative incidence (% (95% CI))**	**KR/PY**	**15-year cumulative incidence (% (95% CI))**	**HR/PY**	**15-year cumulative incidence (% (95% CI))**
Current smoker	283/ 17,950	15.60% (12.82% to 18.99%)	137/ 6,393	17.53% (14.45% to 21.28%)	273/ 7,480	47.90% (40.43% to 56.76%)	269/ 7,508	46.02% (38.71% to 54.71%)
Missing	658/ 33,897	20.38% (16.57% to 25.07%)	244/ 9,721	20.86% (17.66% to 24.64%)	1581/ 46,933	42.62% (40.32% to 45.05%)	1594/ 47,724	42.97% (40.64% to 45.42%)

Cumulative incidence of total knee or hip replacement 9 years after a diagnosis of knee or hip osteoarthritis. *Age groups for knee osteoarthritis cohort: 50 to 62, 62 to 69, 69 to 77, 77 to 105; age groups for hip osteoarthritis cohort: 50 to 62, 62 to 70, 70 to 78, 78 to 103; age groups for rheumatoid arthritis cohorts: 40 to 54, 54 to 64, 64 to 73, 73 to 99. MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. BMI: body mass index; CI: confidence interval; HR: hip replacement; KR: knee replacement; OA: osteoarthritis; PY: person years.

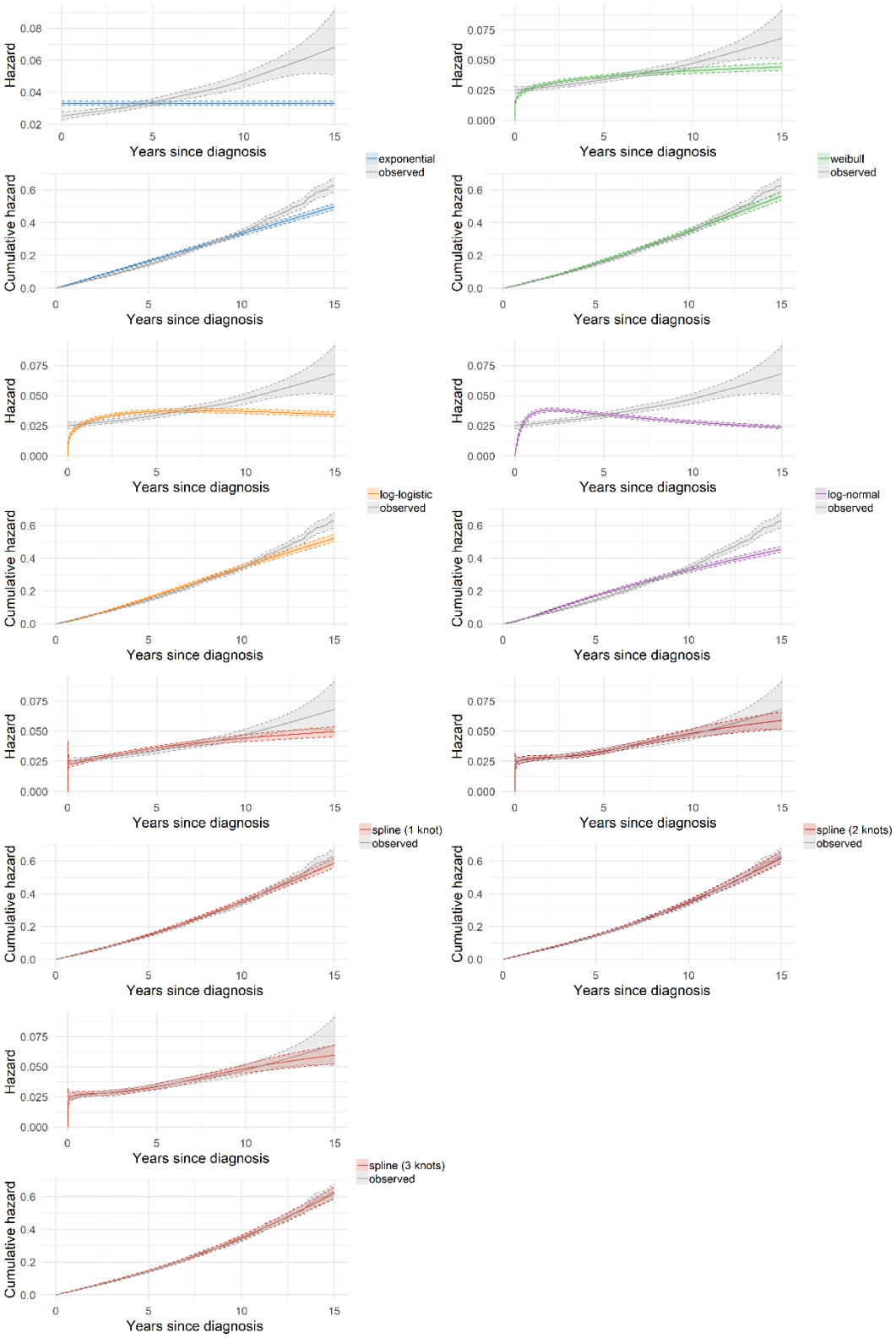
Appendix Figure B.17. Alternative distributions for cause-specific risk of death following a diagnosis of knee osteoarthritis. The spline-based distribution with 3 knots was chosen.



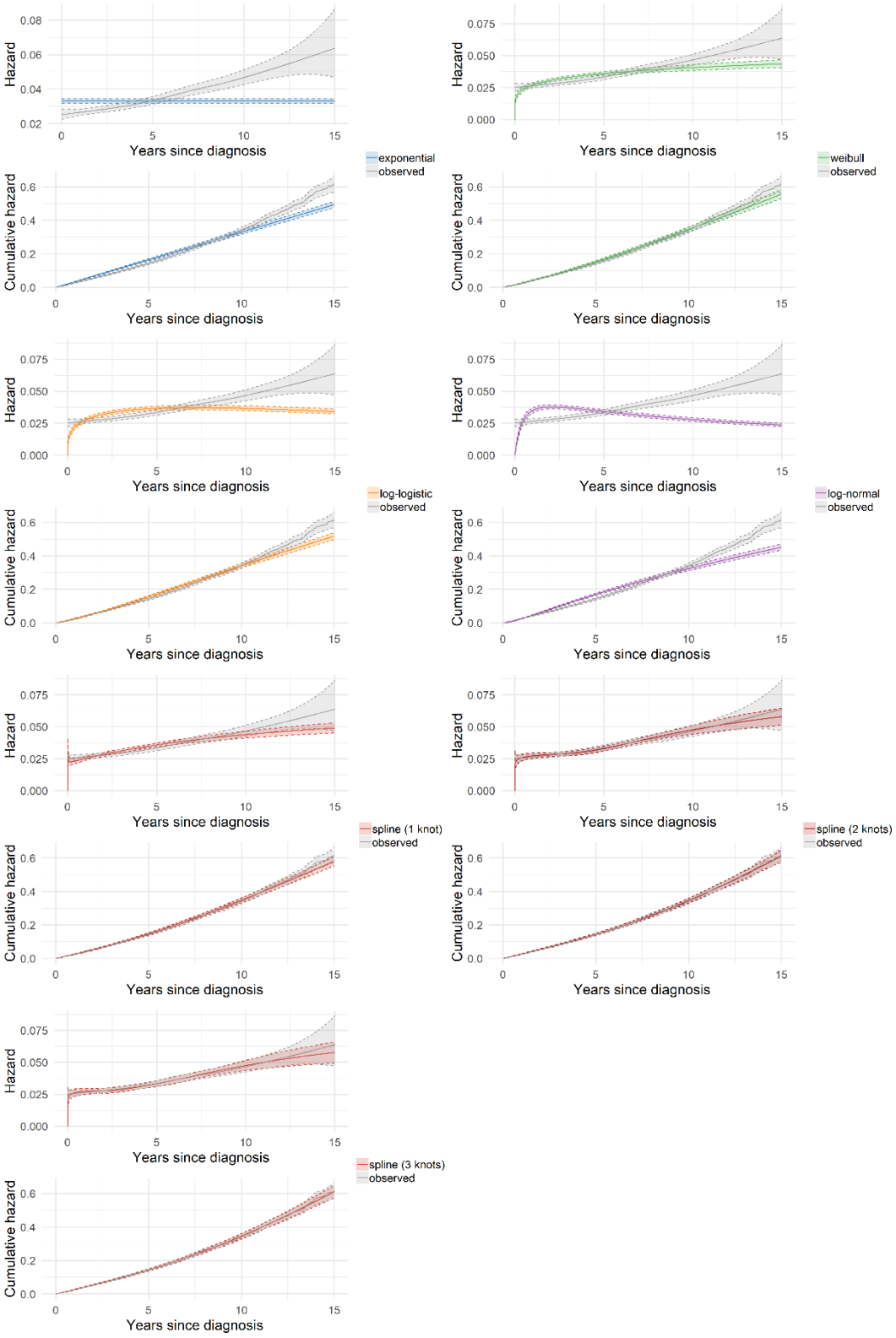
Appendix Figure B.18. Alternative distributions for cause-specific risk of death following a diagnosis of hip osteoarthritis. The spline-based distribution with 3 knots was chosen.



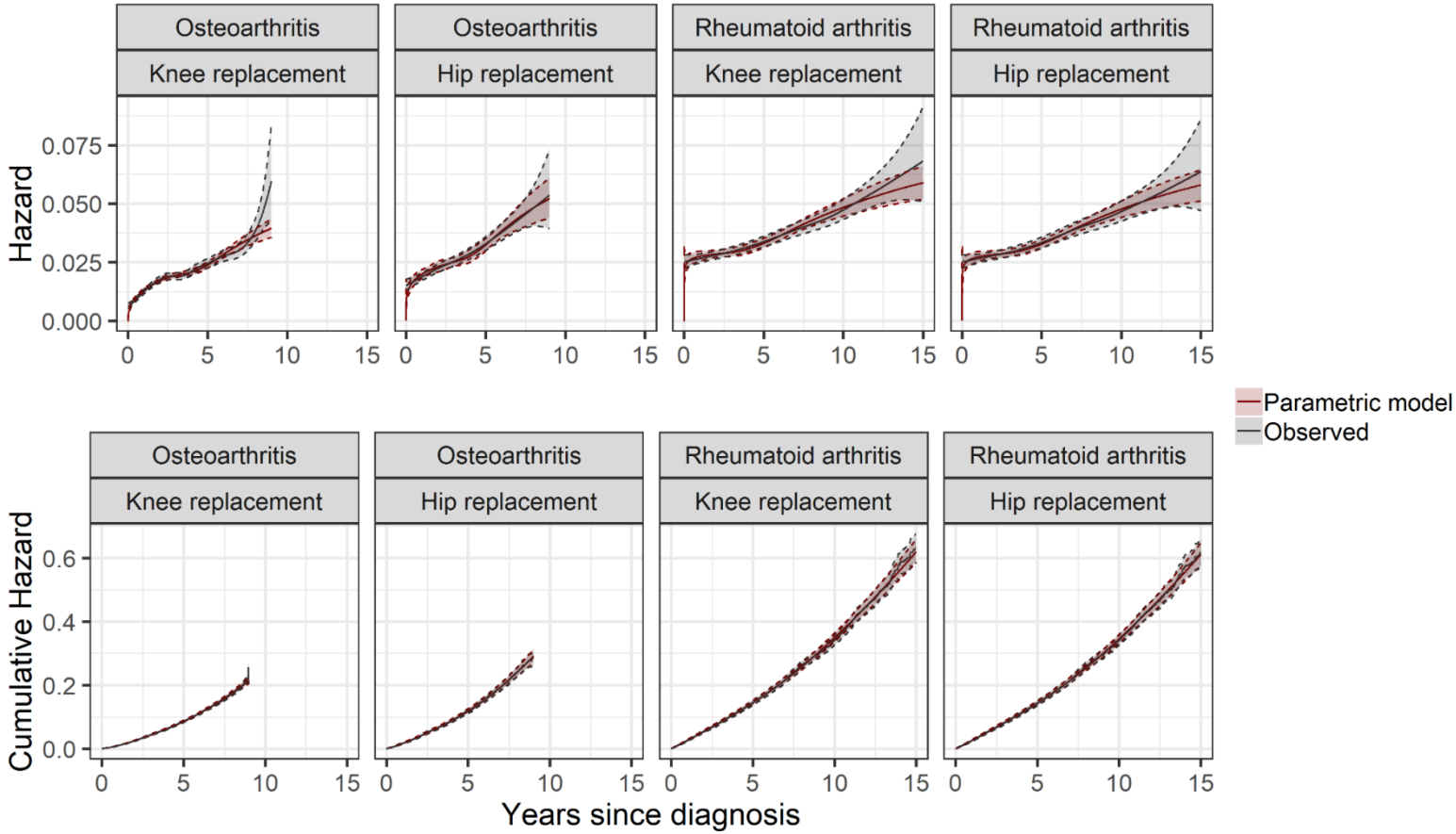
Appendix Figure B.19. Alternative distributions for cause-specific risk of death following a diagnosis of rheumatoid arthritis (censoring at knee replacement). The spline-based distribution with 2 knots was chosen.



Appendix Figure B.20. Alternative distributions for cause-specific risk of death following a diagnosis of rheumatoid arthritis (censoring at hip replacement). The spline-based distribution with 2 knots was chosen.



Appendix Figure B.21: Risks of mortality following a diagnosis of knee or hip osteoarthritis or rheumatoid arthritis with knee or hip replacement as a competing risk. Hazards and cumulative hazards from observed data and intercept-only parametric survival model (spline-based distribution with 3 knots were fitted for those with knee and hip osteoarthritis, spline-based distribution with 2 knots were fitted for those with rheumatoid arthritis)



Appendix Table B.7. Estimated effect of explanatory factors on cause-specific risk of death

	Knee OA		**Hip OA**		**RA**		**RA**	
	Risk of death (knee replacement as competing risk)		**Risk of death (hip replacement as competing risk)**		**Risk of death (knee replacement as competing risk)**		**Risk of death (hip replacement as competing risk)**	
	Spline-based distribution with 3 knots PH		**Spline-based distribution with 3 knots PH**		**Spline-based distribution with 2 knots PH**		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Age	1.12 (1.11 to 1.13)	1.11 (1.11 to 1.12)	1.11 (1.10 to 1.12)	1.10 (1.09 to 1.11)	1.09 (1.09 to 1.10)	1.10 (1.09 to 1.10)	1.09 (1.09 to 1.10)	1.10 (1.09 to 1.10)
Age^2	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)				
Gender								
male	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

	Knee OA		**Hip OA**		**RA**		**RA**	
	Risk of death (knee replacement as competing risk)		**Risk of death (hip replacement as competing risk)**		**Risk of death (knee replacement as competing risk)**		**Risk of death (hip replacement as competing risk)**	
	Spline-based distribution with 3 knots PH		**Spline-based distribution with 3 knots PH**		**Spline-based distribution with 2 knots PH**		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
female	0.68 (0.63 to 0.72)	0.78 (0.72 to 0.84)	0.69 (0.63 to 0.77)	0.69 (0.61 to 0.78)	0.77 (0.71 to 0.84)	0.74 (0.68 to 0.81)	0.76 (0.70 to 0.83)	0.73 (0.67 to 0.80)
Charlson								
0	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
1	2.16 (1.99 to 2.34)	1.67 (1.53 to 1.82)	2.23 (1.95 to 2.56)	1.66 (1.44 to 1.92)				
2	3.50 (3.19 to 3.84)	2.18 (1.98 to 2.41)	3.21 (2.77 to 3.73)	2.17 (1.84 to 2.54)				

	Knee OA		Hip OA		RA		RA	
	Risk of death (knee replacement as competing risk)		Risk of death (hip replacement as competing risk)		Risk of death (knee replacement as competing risk)		Risk of death (hip replacement as competing risk)	
	Spline-based distribution with 3 knots PH		Spline-based distribution with 3 knots PH		Spline-based distribution with 2 knots PH		Spline-based distribution with 2 knots PH	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
3+	7.06 (6.46 to 7.71)	3.42 (3.10 to 3.77)	6.47 (5.65 to 7.43)	3.54 (3.04 to 4.12)				
1+					1.99 (1.79 to 2.21)	1.53 (1.37 to 1.71)	1.97 (1.77 to 2.18)	1.51 (1.35 to 1.69)
BMI	0.97 (0.97 to 0.98)	1.00 (0.99 to 1.01)	0.97 (0.96 to 0.98)	0.98 (0.97 to 1.00)	0.98 (0.97 to 0.99)	0.99 (0.98 to 1.00)	0.98 (0.97 to 0.99)	0.99 (0.98 to 1.00)
BMI ^2	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)	1.00 (1.00 to 1.00)

	Knee OA		**Hip OA**		**RA**		**RA**	
	Risk of death (knee replacement as competing risk)		**Risk of death (hip replacement as competing risk)**		**Risk of death (knee replacement as competing risk)**		**Risk of death (hip replacement as competing risk)**	
	Spline-based distribution with 3 knots PH		**Spline-based distribution with 3 knots PH**		**Spline-based distribution with 2 knots PH**		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
IMD/ MEDEA quintile or rural								
1st (least deprived)	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*
2nd	0.82 (0.71 to 0.95)	0.94 (0.81 to 1.09)	0.93 (0.73 to 1.18)	0.97 (0.77 to 1.22)	1.08 (0.95 to 1.23)	1.05 (0.92 to 1.20)	1.09 (0.96 to 1.24)	1.07 (0.94 to 1.21)
3rd	0.76 (0.66 to 0.88)	0.95 (0.82 to 1.09)	0.99 (0.79 to 1.23)	1.12 (0.90 to 1.40)	1.02 (0.89 to 1.16)	1.04 (0.91 to 1.19)	1.02 (0.89 to 1.16)	1.02 (0.90 to 1.17)

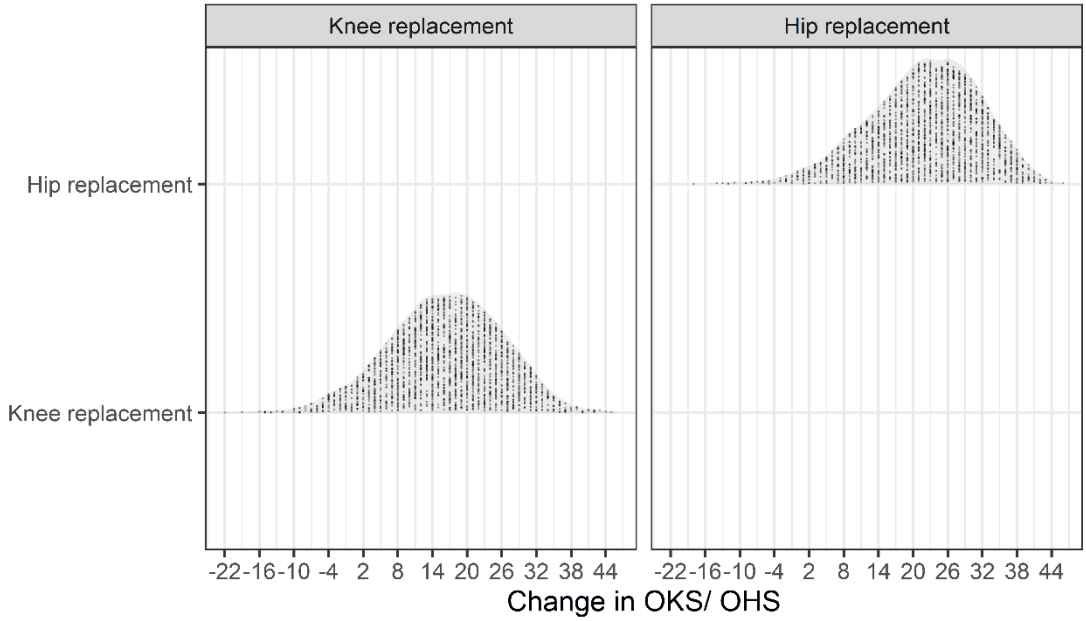
	Knee OA		**Hip OA**		**RA**		**RA**	
	Risk of death (knee replacement as competing risk)		**Risk of death (hip replacement as competing risk)**		**Risk of death (knee replacement as competing risk)**		**Risk of death (hip replacement as competing risk)**	
	Spline-based distribution with 3 knots PH		**Spline-based distribution with 3 knots PH**		**Spline-based distribution with 2 knots PH**		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
4th	0.72 (0.62 to 0.83)	0.87 (0.76 to 1.01)	0.94 (0.75 to 1.17)	1.05 (0.84 to 1.32)	1.24 (1.09 to 1.41)	1.24 (1.08 to 1.41)	1.24 (1.09 to 1.41)	1.25 (1.09 to 1.42)
5th (most deprived)	0.80 (0.69 to 0.93)	1.01 (0.87 to 1.16)	0.98 (0.78 to 1.24)	1.00 (0.79 to 1.26)	1.45 (1.27 to 1.66)	1.63 (1.42 to 1.87)	1.47 (1.29 to 1.68)	1.65 (1.44 to 1.90)
Rural	1.31 (1.15 to 1.49)	1.35 (1.19 to 1.53)	1.52 (1.24 to 1.86)	1.44 (1.18 to 1.76)				
Smoking status								
Non-smoker	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*	*ref*

	Knee OA		Hip OA		RA		RA	
	Risk of death (knee replacement as competing risk)		Risk of death (hip replacement as competing risk)		Risk of death (knee replacement as competing risk)		Risk of death (hip replacement as competing risk)	
	Spline-based distribution with 3 knots PH		Spline-based distribution with 3 knots PH		Spline-based distribution with 2 knots PH		Spline-based distribution with 2 knots PH	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**	**Unadjusted**	**Adjusted**
Ex-smoker	1.28 (1.16 to 1.41)	0.84 (0.74 to 0.95)	1.16 (1.00 to 1.35)	1.07 (0.90 to 1.26)	1.26 (1.09 to 1.45)	1.15 (1.02 to 1.31)	1.27 (1.12 to 1.44)	1.16 (1.02 to 1.31)
Current smoker	1.27 (1.14 to 1.41)	1.66 (1.45 to 1.90)	0.80 (0.66 to 0.97)	1.57 (1.27 to 1.93)	1.31 (1.12 to 1.53)	1.89 (1.63 to 2.18)	1.30 (1.14 to 1.49)	1.86 (1.61 to 2.15)

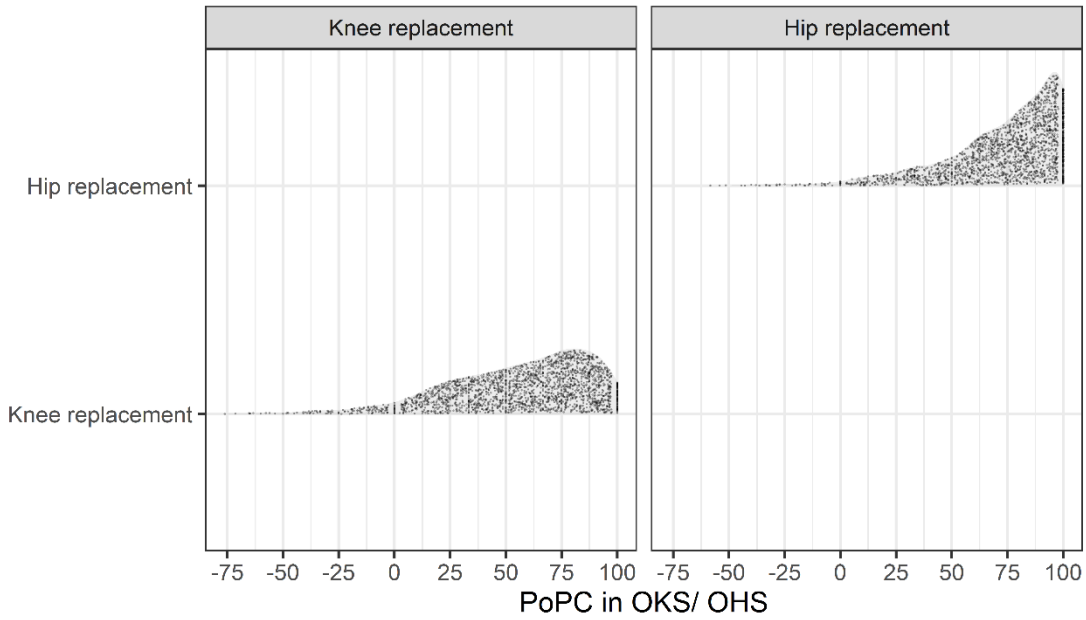
MEDEA is a measure of socioeconomic status developed for Catalonia (Spain), with those living in rural areas having a distinct category. OA: osteoarthritis; RA: rheumatoid arthritis. BMI: body mass index; KR: knee replacement. PH: proportional hazard, with estimates representing hazard ratios.

C.

Appendix Figure C.1. Absolute change in Oxford Knee Score (OKS) and Oxford Hip Score (OHS). Kernel density distributions with points showing observed data.



Appendix Figure C.2. Percentage of potential change (PoPC) achieved in Oxford Knee Score (OKS) and Oxford Hip Score (OHS). Kernel density distributions with points showing observed data.



Appendix Table C.1. Observed OKS for knee replacement cohort and OHS for hip replacement cohort

	Knee replacement cohort (OKS)				**Hip replacement cohort (OHS)**			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
Overall	19 (14 to 24)	37 (29 to 43)	17 (10 to 23)	62 (35 to 81)	17 (12 to 23)	42 (36 to 46)	23 (16 to 29)	81 (61 to 94)
Pre-operative OKS/ OHS**								
1st (worst)	10 (8 to 12)	32 (23 to 39)	22 (13 to 30)	57 (34 to 77)	8 (6 to 10)	38 (30 to 44)	30 (23 to 36)	76 (57 to 89)
2nd	16 (15 to 17)	36 (28 to 42)	20 (11 to 26)	62 (36 to 81)	14 (13 to 15)	42 (35 to 46)	28 (21 to 32)	82 (62 to 94)
3rd	21 (20 to 22)	38 (31 to 43)	17 (10 to 22)	62 (36 to 82)	19 (18 to 21)	43 (38 to 47)	23 (18 to 27)	83 (65 to 96)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
4th (best)	27 (25 to 31)	41 (36 to 45)	12 (7 to 17)	64 (33 to 86)	27 (25 to 30)	44 (39 to 47)	15 (10 to 20)	81 (57 to 96)
Age group*								
1st (youngest)	17 (13 to 23)	36 (26 to 43)	17 (9 to 23)	61 (30 to 81)	17 (12 to 22)	44 (38 to 47)	24 (18 to 30)	85 (67 to 96)
2nd	19 (14 to 25)	38 (30 to 44)	17 (10 to 24)	67 (38 to 84)	18 (12 to 24)	43 (38 to 47)	23 (16 to 30)	84 (67 to 96)
3rd	20 (15 to 25)	38 (30 to 43)	16 (10 to 23)	63 (36 to 82)	18 (13 to 24)	42 (36 to 47)	22 (14 to 28)	79 (59 to 95)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
4th (oldest)	19 (13 to 24)	36 (29 to 42)	15 (10 to 22)	58 (35 to 78)	16 (11 to 23)	40 (33 to 45)	21 (15 to 28)	74 (54 to 89)
Gender								
Male	21 (15 to 26)	38 (30 to 44)	16 (9 to 22)	63 (35 to 85)	19 (13 to 25)	44 (38 to 47)	22 (16 to 28)	84 (65 to 96)
Female	17 (12 to 22)	36 (28 to 42)	17 (10 to 24)	61 (35 to 79)	16 (11 to 22)	41 (35 to 46)	23 (16 to 29)	78 (58 to 92)
Index diagnosis								
OA	19 (14 to 24)	37 (29 to 43)	16 (9 to 23)	62 (35 to 81)	18 (12 to 24)	42 (36 to 46)	23 (16 to 29)	81 (61 to 94)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
RA	15 (10 to 22)	36 (27 to 42)	18 (11 to 24)	59 (33 to 79)	12 (7 to 20)	39 (30 to 44)	24 (15 to 31)	73 (52 to 89)
Charlson score								
0	19 (14 to 25)	38 (30 to 43)	17 (10 to 23)	63 (36 to 83)	18 (13 to 24)	43 (37 to 47)	22 (16 to 29)	82 (62 to 95)
1+	18 (13 to 23)	35 (28 to 42)	16 (9 to 23)	57 (33 to 77)	16 (11 to 22)	41 (33 to 46)	23 (15 to 29)	78 (54 to 92)
BMI group								
Normal or underweight (<25)	21 (16 to 26)	38 (32 to 43)	16 (10 to 22)	62 (37 to 82)	18 (13 to 24)	43 (36 to 46)	22 (17 to 29)	81 (63 to 94)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
Overweight (≥25 and <30)	20 (15 to 25)	38 (30 to 43)	16 (9 to 23)	63 (35 to 82)	18 (13 to 24)	43 (36 to 46)	22 (16 to 28)	82 (62 to 94)
Obese class I (≥30 and <35)	18 (14 to 24)	37 (28 to 42)	17 (9 to 23)	62 (33 to 79)	15 (10 to 22)	41 (35 to 45)	23 (16 to 29)	78 (58 to 90)
Obese class II (≥35 and <40)	16 (12 to 21)	35 (26 to 41)	16 (9 to 22)	53 (30 to 74)	14 (8 to 20)	40 (32 to 44)	24 (16 to 30)	73 (50 to 88)
Obese class III (≥40)	13 (8 to 18)	33 (27 to 40)	20 (13 to 26)	59 (35 to 77)	12 (9 to 16)	39 (34 to 44)	22 (20 to 31)	73 (59 to 88)
Missing	19 (14 to 25)	38 (29 to 44)	16 (10 to 23)	62 (37 to 83)	18 (12 to 24)	43 (36 to 47)	23 (16 to 29)	81 (61 to 95)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
IMD (%)								
1 (least deprived)	20 (15 to 25)	38 (31 to 43)	17 (9 to 23)	62 (35 to 82)	19 (13 to 25)	44 (38 to 47)	22 (16 to 28)	84 (66 to 96)
2	20 (15 to 25)	38 (29 to 44)	16 (10 to 23)	63 (37 to 83)	18 (13 to 24)	42 (37 to 47)	23 (16 to 29)	81 (62 to 96)
3	19 (13 to 25)	38 (30 to 43)	17 (11 to 23)	64 (39 to 81)	17 (12 to 22)	42 (36 to 46)	23 (16 to 29)	80 (60 to 91)
4	17 (12 to 23)	35 (26 to 42)	15 (9 to 23)	54 (28 to 77)	16 (11 to 22)	41 (33 to 46)	22 (15 to 29)	76 (53 to 94)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
5 (most deprived)	16 (12 to 21)	35 (26 to 42)	17 (9 to 24)	60 (30 to 79)	14 (10 to 20)	39 (32 to 45)	24 (15 to 30)	72 (49 to 92)
missing	16 (16 to 16)	44 (44 to 44)	28 (28 to 28)	88 (88 to 88)	11 (11 to 11)	29 (29 to 29)	18 (18 to 18)	49 (49 to 49)
Smoking status (%)								
Non-smoker	18 (13 to 24)	37 (29 to 43)	16 (10 to 23)	61 (36 to 81)	18 (13 to 24)	43 (37 to 46)	22 (15 to 29)	81 (61 to 94)
Ex-smoker	19 (14 to 24)	36 (28 to 43)	16 (9 to 22)	59 (32 to 79)	17 (11 to 22)	42 (35 to 46)	23 (16 to 29)	79 (57 to 93)

	Knee replacement cohort (OKS)				Hip replacement cohort (OHS)			
	Pre-operative Median (IQR)	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**	**Pre-operative Median (IQR)**	**Post-operative Median (IQR)**	**Change Median (IQR)**	**PoPC Median (IQR)**
Current smoker	20 (15 to 24)	37 (29 to 42)	16 (9 to 21)	62 (33 to 80)	16 (11 to 22)	41 (33 to 45)	22 (15 to 29)	79 (52 to 90)
Missing	19 (14 to 24)	38 (29 to 43)	17 (10 to 23)	64 (37 to 82)	18 (12 to 24)	43 (37 to 47)	23 (16 to 29)	81 (63 to 95)

*Age groups for knee replacement cohort: 43 to 64, 64 to 70, 70 to 76, and 76 to 94, age quartile groups for hip replacement cohort: 31 to 63, 63 to 69, 69 to 76, and 76 to 94. ** OKS groups for knee replacement cohort: 2 to 14, 14 to 19, 19 to 24, and 24 to 43, OHS groups for hip replacement cohort: 0 to 12, 12 to 17, 17 to 23, 23 to 44. OA: osteoarthritis. RA: rheumatoid arthritis. IMD: index of multiple deprivation. BMI: body mass index; IQR: interquartile range.

Appendix Table C.2. Estimated effects of explanatory factors on post-operative OKS/ OHS

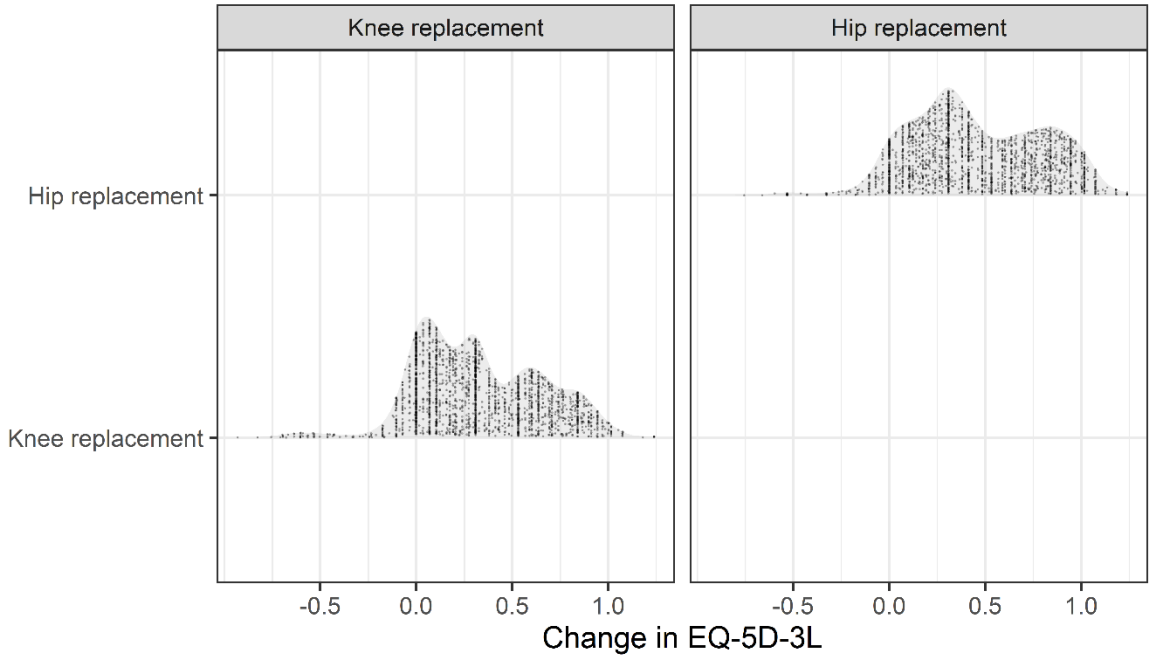
	Knee replacement		**Hip replacement**	
	OKS		**OHS**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Pre-operative score	0.57 (0.45 to 0.69)	0.52 (0.40 to 0.64)	0.80 (0.61 to 0.99)	0.70 (0.52 to 0.88)
Pre-operative score*	-0.16 (-0.30 to -0.02)	-0.17 (-0.31 to -0.03)	-1.41 (-2.08 to -0.75)	-1.38 (-2.03 to -0.73)
Pre-operative score†			3.38 (1.47 to 5.30)	3.36 (1.49 to 5.23)
Age	0.20 (0.10 to 0.30)	0.10 (0.00 to 0.19)	0.01 (-0.06 to 0.08)	-0.05 (-0.12 to 0.02)
Age*	-0.25 (-0.37 to -0.13)	-0.18 (-0.29 to -0.07)	-0.16 (-0.25 to -0.07)	-0.09 (-0.17 to -0.00)
Gender				
Female	*Ref*	*Ref*	*Ref*	*Ref*
Male	1.70 (0.90 to 2.49)	0.33 (-0.45 to 1.11)	2.24 (1.53 to 2.95)	1.48 (0.80 to 2.16)
Diagnosis				
OA	*Ref*	*Ref*	*Ref*	*Ref*
RA	-1.65 (-3.27 to -0.03)	-0.05 (-1.57 to 1.48)	-3.48 (-5.16 to -1.81)	-1.35 (-2.93 to 0.22)
Charlson score				
0	*Ref*	*Ref*	*Ref*	*Ref*

	Knee replacement		**Hip replacement**	
	OKS		**OHS**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
1+	-1.91 (-2.78 to -1.04)	-1.22 (-2.05 to -0.39)	-2.35 (-3.15 to -1.55)	-1.41 (-2.17 to -0.65)
IMD Quintile				
1 (least deprived)	*Ref*	*Ref*	*Ref*	*Ref*
2	-0.33 (-1.47 to 0.80)	0.02 (-1.05 to 1.09)	-0.80 (-1.76 to 0.17)	-0.44 (-1.35 to 0.47)
3	-0.58 (-1.74 to 0.57)	0.14 (-0.95 to 1.24)	-1.82 (-2.80 to -0.84)	-1.16 (-2.09 to -0.23)
4	-3.04 (-4.28 to -1.81)	-1.72 (-2.91 to -0.53)	-3.02 (-4.10 to -1.94)	-2.10 (-3.12 to -1.07)
5 (most deprived)	-3.51 (-5.05 to -1.96)	-1.72 (-3.21 to -0.23)	-4.56 (-6.01 to -3.12)	-3.11 (-4.49 to -1.73)
BMI	-0.29 (-0.38 to -0.19)	-0.16 (-0.26 to -0.06)	-0.20 (-0.29 to -0.11)	-0.16 (-0.25 to -0.07)
Smoking status				
Non-smoker	*Ref*	*Ref*	*Ref*	*Ref*
Ex-smoker	-0.56 (-1.52 to 0.40)	-0.84 (-1.78 to 0.10)	-1.24 (-2.12 to -0.35)	-0.80 (-1.63 to 0.04)

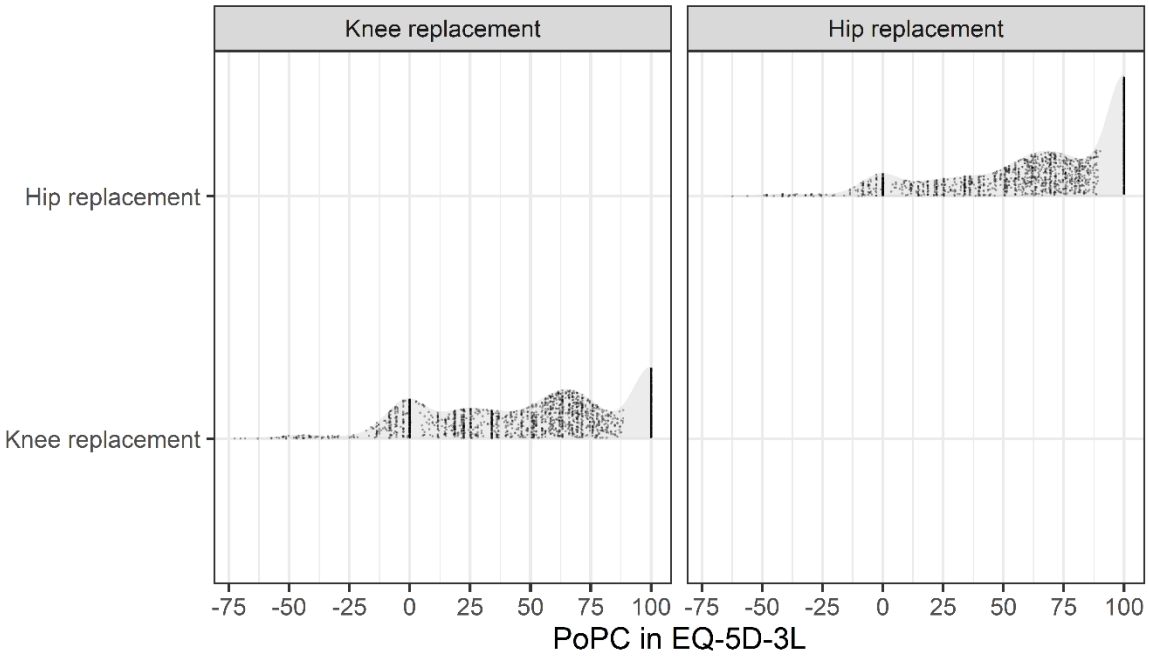
	Knee replacement		Hip replacement	
	OKS		OHS	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Current smoker	-0.19 (-2.06 to 1.68)	-0.53 (-2.36 to 1.30)	-1.66 (-3.09 to -0.22)	-1.75 (-3.15 to -0.35)

Coefficients with 95% confidence intervals in parentheses. TKR: total knee replacement, THR: total hip replacement, OKS: Oxford Knee Score, OHS: Oxford Hip Score, EQ-5D-3L: EuroQol 5-dimension 3-level. Dependent variables were post-operative scores. In unadjusted models only the explanatory factor of interest was included, while multivariable models included all explanatory factors of interest: age, gender (male or female), pre-operative score for the corresponding dependent variable, index diagnosis (rheumatoid arthritis, RA, or osteoarthritis, OA), Charlson score, index of multiple deprivation (IMD) quintile, body mass index, and smoking status. * and † are knot points from restricted cubic splines

Appendix Figure C.3. Absolute change in Euroqol 5-dimension 3-level (EQ-5D-3L) index. Kernel density distributions with points showing observed data.



Appendix Figure C.4. Percentage of potential change (PoPC) achieved in Euroqol 5-dimension 3-level (EQ-5D-3L) index. Kernel density distributions with points showing observed data.


Knee replacement
Hip replacement
Hip replacement
Knee replacement
-75 -50 -25 0 25 50 75 100
-75 -50 -25 0 25 50 75 100
PoPC in EQ-5D-3L

Appendix Table C.3. Observed EQ-5D-3L index for knee and hip replacement cohorts

	Knee replacement cohort				**Hip replacement cohort**			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
Overall	0.59 (0.1 to 0.69)	0.76 (0.66 to 1)	0.31 (0.07 to 0.59)	59.79 (21.08 to 100)	0.52 (0.06 to 0.62)	0.85 (0.69 to 1)	0.41 (0.2 to 0.74)	78.41 (48.78 to 100)
Age group*								
1st (youngest)	0.52 (0.09 to 0.69)	0.71 (0.62 to 0.88)	0.31 (0.07 to 0.57)	58.33 (18.68 to 83.92)	0.52 (0.06 to 0.66)	0.88 (0.69 to 1)	0.41 (0.24 to 0.76)	83.83 (51.36 to 100)
2nd	0.59 (0.09 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.6)	62.2 (22.33 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.41 (0.21 to 0.78)	84.02 (50.61 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
3rd	0.62 (0.16 to 0.69)	0.8 (0.69 to 1)	0.31 (0.07 to 0.6)	61.61 (18.68 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.41 (0.19 to 0.74)	79.1 (48.78 to 100)
4th (oldest)	0.59 (0.1 to 0.69)	0.75 (0.66 to 0.88)	0.27 (0.07 to 0.59)	58.33 (18.68 to 84.46)	0.52 (0.06 to 0.62)	0.81 (0.69 to 1)	0.41 (0.18 to 0.71)	70.41 (39.81 to 100)
Gender								
Male	0.62 (0.16 to 0.69)	0.8 (0.69 to 1)	0.28 (0.07 to 0.53)	58.33 (18.68 to 100)	0.55 (0.06 to 0.69)	0.88 (0.72 to 1)	0.38 (0.21 to 0.73)	88.05 (50.61 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
Female	0.52 (0.09 to 0.69)	0.74 (0.66 to 0.88)	0.31 (0.07 to 0.61)	60.63 (21.49 to 85.44)	0.24 (0.03 to 0.62)	0.81 (0.69 to 1)	0.44 (0.19 to 0.76)	74.21 (46.32 to 100)
Pre-operative EQ-5D-3L index**								
1st (worst)	0 (-0.02 to 0.06)	0.69 (0.55 to 0.8)	0.66 (0.53 to 0.8)	67.3 (56.3 to 78.41)	-0.02 (-0.07 to -0.02)	0.75 (0.59 to 1)	0.82 (0.66 to 1)	76.38 (61.55 to 100)
2nd	0.16 (0.16 to 0.36)	0.73 (0.62 to 1)	0.53 (0.28 to 0.69)	65.63 (44.19 to 100)	0.1 (0.06 to 0.16)	0.85 (0.69 to 1)	0.71 (0.54 to 0.84)	81.33 (65.63 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
3rd	0.62 (0.59 to 0.62)	0.74 (0.62 to 0.88)	0.11 (0 to 0.27)	29.78 (0 to 69.83)	0.59 (0.52 to 0.62)	0.85 (0.69 to 1)	0.26 (0.12 to 0.41)	61.57 (29.14 to 100)
4th (best)	0.69 (0.69 to 0.73)	0.8 (0.69 to 1)	0.11 (0 to 0.31)	33.98 (0 to 100)	0.69 (0.69 to 0.72)	1 (0.8 to 1)	0.24 (0.07 to 0.31)	100 (22.33 to 100)
Diagnosis								
OA	0.59 (0.12 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.59)	60.53 (21.49 to 100)	0.52 (0.06 to 0.66)	0.85 (0.69 to 1)	0.41 (0.2 to 0.74)	79.26 (50.41 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
RA	0.16 (0 to 0.65)	0.69 (0.52 to 0.85)	0.31 (0.07 to 0.6)	54.88 (11.26 to 71.46)	0.06 (-0.07 to 0.59)	0.69 (0.52 to 1)	0.47 (0.13 to 0.76)	69.59 (24.66 to 100)
Charlson score								
0	0.59 (0.16 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.59)	61.61 (22.33 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.41 (0.2 to 0.74)	81.46 (50.61 to 100)
1+	0.59 (0.09 to 0.69)	0.69 (0.62 to 0.88)	0.31 (0.07 to 0.6)	56.3 (18.16 to 82.05)	0.19 (0 to 0.62)	0.8 (0.62 to 1)	0.41 (0.19 to 0.73)	69.59 (39.81 to 100)
BMI group								

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
Normal or underweight (<25)	0.62 (0.16 to 0.69)	0.8 (0.69 to 1)	0.24 (0.07 to 0.43)	57.14 (18.77 to 100)	0.52 (0.06 to 0.62)	0.85 (0.71 to 1)	0.41 (0.26 to 0.8)	77.65 (51.46 to 100)
Overweight (≥25 and <30)	0.62 (0.16 to 0.69)	0.8 (0.69 to 1)	0.27 (0.07 to 0.6)	60.78 (18.68 to 100)	0.52 (0.06 to 0.62)	0.85 (0.69 to 1)	0.41 (0.21 to 0.74)	83.03 (51.34 to 100)
Obese class I (≥30 and <35)	0.59 (0.09 to 0.69)	0.76 (0.66 to 0.88)	0.31 (0.07 to 0.6)	56.3 (22.12 to 83.75)	0.17 (0.01 to 0.62)	0.8 (0.69 to 1)	0.41 (0.16 to 0.71)	71.35 (40.93 to 100)
Obese class II (≥35 and <40)	0.52 (0.09 to 0.69)	0.69 (0.59 to 0.85)	0.31 (0 to 0.56)	54.94 (0 to 77.65)	0.13 (-0.02 to 0.59)	0.73 (0.59 to 1)	0.53 (0.24 to 0.76)	66.12 (50.61 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
Obese class III (≥40)	0.16 (-0.01 to 0.59)	0.69 (0.59 to 0.74)	0.48 (0.12 to 0.65)	59.35 (20.51 to 71.17)	0.09 (-0.02 to 0.59)	0.72 (0.6 to 0.87)	0.37 (0.1 to 0.7)	58.66 (15.3 to 85.62)
Missing	0.59 (0.12 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.6)	62.2 (22.33 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.41 (0.2 to 0.74)	80.32 (49.08 to 100)
IMD (%)								
1 (least deprived)	0.62 (0.16 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.57)	62.12 (22.33 to 100)	0.52 (0.09 to 0.69)	0.88 (0.72 to 1)	0.38 (0.2 to 0.71)	85.04 (51.46 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
2	0.62 (0.16 to 0.69)	0.76 (0.69 to 1)	0.28 (0.07 to 0.57)	59.97 (20.49 to 100)	0.52 (0.06 to 0.62)	0.85 (0.69 to 1)	0.41 (0.2 to 0.76)	80.28 (50.61 to 100)
3	0.59 (0.1 to 0.69)	0.76 (0.66 to 1)	0.31 (0.1 to 0.59)	62.14 (22.33 to 100)	0.52 (0.06 to 0.65)	0.81 (0.69 to 1)	0.41 (0.18 to 0.74)	74.74 (46.32 to 100)
4	0.59 (0.09 to 0.69)	0.73 (0.62 to 0.88)	0.31 (0.07 to 0.6)	54.93 (13.32 to 78.41)	0.2 (0 to 0.62)	0.82 (0.69 to 1)	0.43 (0.22 to 0.79)	74.84 (51.42 to 100)
5 (most deprived)	0.21 (0.06 to 0.62)	0.69 (0.59 to 0.88)	0.33 (0.1 to 0.64)	59.02 (21.49 to 86.09)	0.09 (-0.02 to 0.59)	0.74 (0.59 to 1)	0.48 (0.18 to 0.76)	67.3 (29.62 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
missing	0.16 (0.16 to 0.16)	1 (1 to 1)	0.84 (0.84 to 0.84)	100 (100 to 100)	0.06 (0.06 to 0.06)	0.2 (0.2 to 0.2)	0.15 (0.15 to 0.15)	15.87 (15.87 to 15.87)
Smoking status (%)								
Non-smoker	0.59 (0.09 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.6)	60.82 (22.33 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.41 (0.19 to 0.76)	80.71 (50.61 to 100)
Ex-smoker	0.59 (0.16 to 0.69)	0.73 (0.62 to 0.88)	0.3 (0.07 to 0.53)	54.93 (18.68 to 84.3)	0.26 (0 to 0.62)	0.81 (0.69 to 1)	0.41 (0.21 to 0.73)	71.23 (48.41 to 100)
Current smoker	0.59 (0.16 to 0.69)	0.74 (0.62 to 1)	0.31 (0.1 to 0.53)	58.68 (20.79 to 100)	0.26 (0 to 0.59)	0.8 (0.62 to 1)	0.41 (0.24 to 0.71)	67.57 (40.13 to 100)

	Knee replacement cohort				Hip replacement cohort			
	Pre EQ-5D-3L index	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**	**Pre EQ-5D-3L index**	**Post EQ-5D-3L index**	**Change EQ-5D-3L index**	**PoPC EQ-5D-3L index**
Missing	0.59 (0.1 to 0.69)	0.76 (0.69 to 1)	0.31 (0.07 to 0.6)	62.28 (22.33 to 100)	0.52 (0.06 to 0.69)	0.85 (0.69 to 1)	0.39 (0.2 to 0.74)	81.46 (50.57 to 100)

Age groups for knee replacement cohort: 43 to 64, 64 to 70, 70 to 76, and 76 to 94, age quartile groups for hip replacement cohort: 31 to 63, 63 to 69, 69 to 76, and 76 to 94. **EQ-5d-3L groups for knee replacement cohort: -0.6 to 0.1, 0.1 to 0.6, 0.6 to 0.7, 0.7 to 1.0, EQ-5d-3L groups for hip replacement cohort: -0.6 to 0.1, 0.1 to 0.5, 0.5 to 0.6, 0.6 to 1.0. OA: osteoarthritis. RA: rheumatoid arthritis. IMD: index of multiple deprivation. BMI: body mass index; IQR: interquartile range

Appendix Table C.4. Estimated effects of explanatory factors on post-operative EQ-5D-3L index

	TKR		**THR**	
	EQ-5D-3L index		**EQ-5D-3L index**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Pre-operative score	0.23 (0.20 to 0.26)	0.20 (0.16 to 0.23)	0.88 (0.73 to 1.04)	0.77 (0.62 to 0.93)
Pre-operative score*			-3.27 (-3.98 to -2.56)	-2.92 (-3.62 to -2.21)
Pre-operative score†			5.28 (4.10 to 6.47)	4.69 (3.52 to 5.87)
Age	0.00 (0.00 to 0.01)	0.00 (0.00 to 0.00)	0.00 (-0.00 to 0.00)	-0.00 (-0.00 to 0.00)
Age*	-0.00 (-0.01 to -0.00)	-0.00 (-0.01 to -0.00)	-0.00 (-0.01 to -0.00)	-0.00 (-0.00 to 0.00)
Gender				
Female	*Ref*	*Ref*	*Ref*	*Ref*
Male	0.02 (0.00 to 0.04)	0.00 (-0.02 to 0.02)	0.05 (0.03 to 0.07)	0.02 (0.00 to 0.04)
Diagnosis				
OA	*Ref*	*Ref*	*Ref*	*Ref*
RA	-0.13 (-0.17 to -0.09)	-0.09 (-0.13 to -0.06)	-0.14 (-0.19 to -0.09)	-0.08 (-0.12 to -0.03)
Charlson score				
0	*Ref*	*Ref*	*Ref*	*Ref*

	TKR		THR	
	EQ-5D-3L index		EQ-5D-3L index	
	Unadjusted	Adjusted	Unadjusted	Adjusted
1+	-0.05 (-0.07 to -0.02)	-0.03 (-0.05 to -0.01)	-0.07 (-0.10 to -0.05)	-0.05 (-0.07 to -0.03)
IMD Quintile				
1 (least deprived)	*Ref*	*Ref*	*Ref*	*Ref*
2	-0.00 (-0.03 to 0.03)	0.00 (-0.03 to 0.03)	-0.01 (-0.04 to 0.01)	-0.00 (-0.03 to 0.02)
3	-0.01 (-0.04 to 0.02)	-0.00 (-0.03 to 0.03)	-0.04 (-0.07 to -0.01)	-0.02 (-0.04 to 0.01)
4	-0.05 (-0.08 to -0.02)	-0.03 (-0.06 to -0.00)	-0.05 (-0.08 to -0.02)	-0.02 (-0.05 to 0.01)
5 (most deprived)	-0.08 (-0.12 to -0.04)	-0.04 (-0.08 to -0.00)	-0.14 (-0.18 to -0.10)	-0.09 (-0.13 to -0.05)
BMI	-0.01 (-0.01 to -0.01)	-0.01 (-0.01 to -0.00)	0.00 (-0.01 to 0.01)	-0.00 (-0.01 to 0.01)
			-0.01 (-0.02 to -0.00)	-0.01 (-0.02 to -0.00)
Smoking status				
Non-smoker	*Ref*	*Ref*	*Ref*	*Ref*
Ex-smoker	-0.02 (-0.04 to 0.01)	-0.02 (-0.04 to 0.01)	-0.04 (-0.06 to -0.01)	-0.02 (-0.05 to 0.00)

	TKR		THR	
	EQ-5D-3L index		EQ-5D-3L index	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Current smoker	-0.01 (-0.05 to 0.04)	-0.00 (-0.05 to 0.04)	-0.06 (-0.10 to -0.02)	-0.06 (-0.10 to -0.01)

Coefficients with 95% confidence intervals in parentheses. TKR: total knee replacement, THR: total hip replacement, OKS: Oxford Knee Score, OHS: Oxford Hip Score, EQ-5D-3L: EuroQol 5-dimension 3-level. Dependent variables were post-operative scores. In unadjusted models only the explanatory factor of interest was included, while multivariable models included all explanatory factors of interest: age, gender (male or female), pre-operative score for the corresponding dependent variable, index diagnosis (rheumatoid arthritis, RA, or osteoarthritis, OA), Charlson score, index of multiple deprivation (IMD) quintile, body mass index, and smoking status. * and † are knot points from restricted cubic splines

D.

Appendix Table D.1. Cumulative incidence of revisions after knee or hip replacement

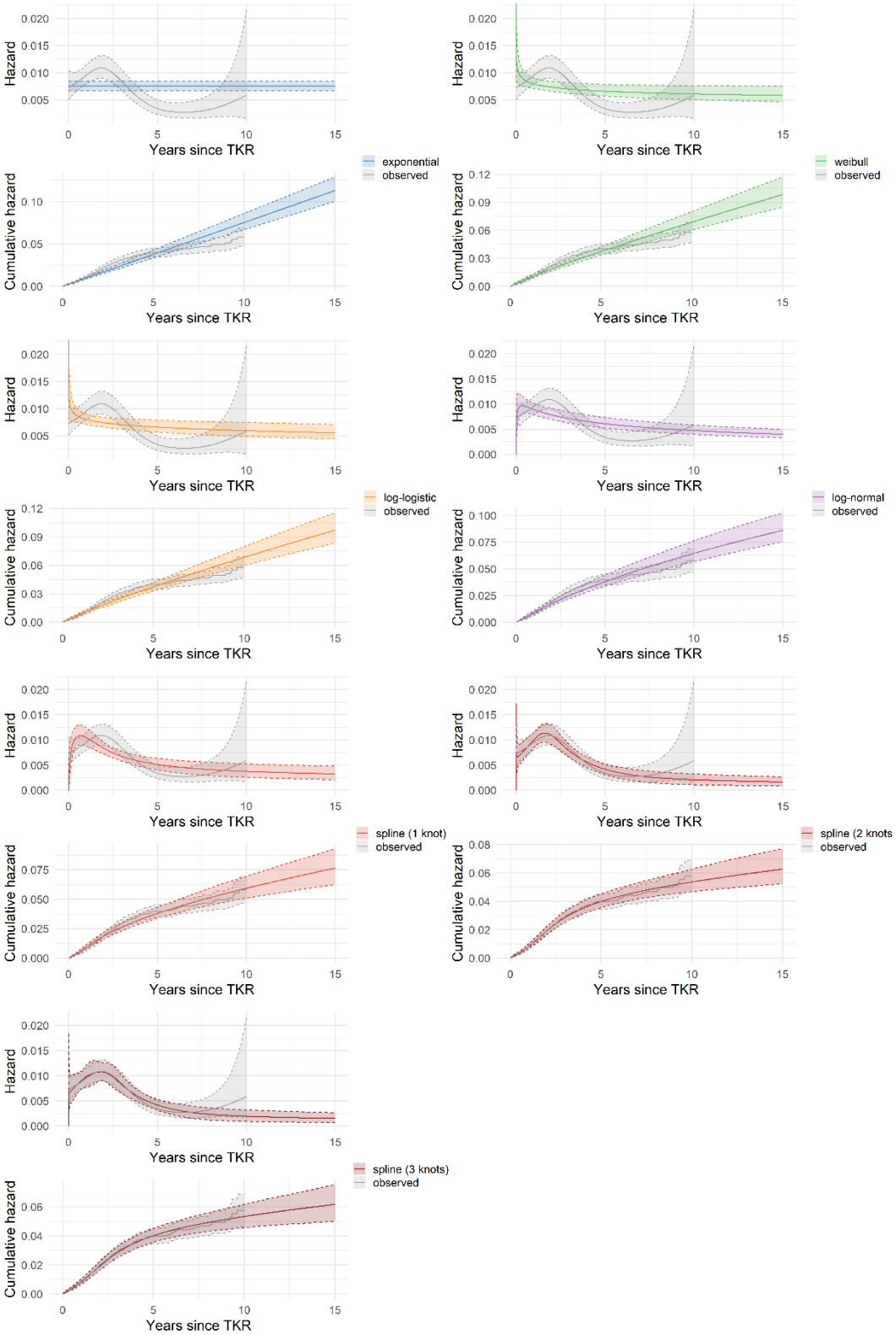
	Knee replacement		**Hip replacement**	
	Revisions /person years	**10-year cumulative incidence (% (95% CI))**	**Revisions/person years**	**10-year cumulative incidence (% (95% CI))**
Total	257/ 34,153	5.12% (4.32% to 6.06%)	248/ 43,151	4.87% (4.20% to 5.65%)
Age group* (%)				
1st (youngest)	101/ 7,914	10.71% (7.89% to 14.54%)	79/ 10,263	6.85% (5.27% to 8.89%)
2nd	68/ 8,462	5.54% (3.97% to 7.74%)	57/ 11,273	4.49% (3.33% to 6.07%)
3rd	55/ 8,545	3.79% (2.83% to 5.08%)	59/ 9,985	5.03% (3.70% to 6.84%)
4th (oldest)	33/ 9,232	1.89% (1.33% to 2.69%)	53/ 11,629	3.56% (2.58% to 4.93%)
Sex				
Male	125/ 19,852	6.06% (4.76% to 7.72%)	132/ 25,213	4.71% (3.82% to 5.80%)
Female	132/ 14,302	4.44% (3.50% to 5.63%)	116/ 17,939	4.99% (4.08% to 6.11%)
Index diagnosis				
OA	240/ 31,257	5.20% (4.37% to 6.18%)	229/ 40,835	4.76% (4.08% to 5.55%)
RA	17/ 2,896	4.26% (2.15% to 8.44%)	19/ 2,316	6.81% (4.08% to 11.35%)

	Knee replacement		Hip replacement	
	Revisions /person years	**10-year cumulative incidence (% (95% CI))**	**Revisions/person years**	**10-year cumulative incidence (% (95% CI))**
Charlson				
0	212/ 27,475	5.36% (4.47% to 6.44%)	201/ 35,887	4.97% (4.23% to 5.85%)
1+	45/ 6679	3.91% (2.72% to 5.61%)	47/ 7264	3.97% (2.87% to 5.49%)
BMI group (%)				
Normal or underweight (<25)	24/ 1,999	6.44% (4.25% to 9.76%)	19/ 3,848	3.69% (2.23% to 6.12%)
Overweight (≥25 and <30)	31/ 5,050	3.69% (2.31% to 5.87%)	40/ 5,759	6.43% (4.32% to 9.55%)
Obese class I (≥30 and <35)	42/ 4,448	6.24% (4.33% to 8.98%)	33/ 3,800	6.20% (4.03% to 9.55%)
Obese class II (≥35 and <40)	23/ 2,188	5.19% (3.42% to 7.87%)	10/ 1,564	5.62% (2.86% to 11.04%)
Obese class III (≥40)	8/ 693	33.36% (9.09% to 100.00%)	5/ 402	5.94% (2.49% to 14.19%)
Missing	129/ 19,775	4.58% (3.66% to 5.73%)	141/ 27,777	4.46% (3.68% to 5.39%)
IMD quintile (%)				
1st (least deprived)	60/ 7,556	5.53% (3.85% to 7.94%)	80/ 10,898	6.92% (5.34% to 8.98%)
2nd	65/ 8,193	4.44% (3.42% to 5.76%)	59/ 11,231	4.17% (3.13% to 5.56%)

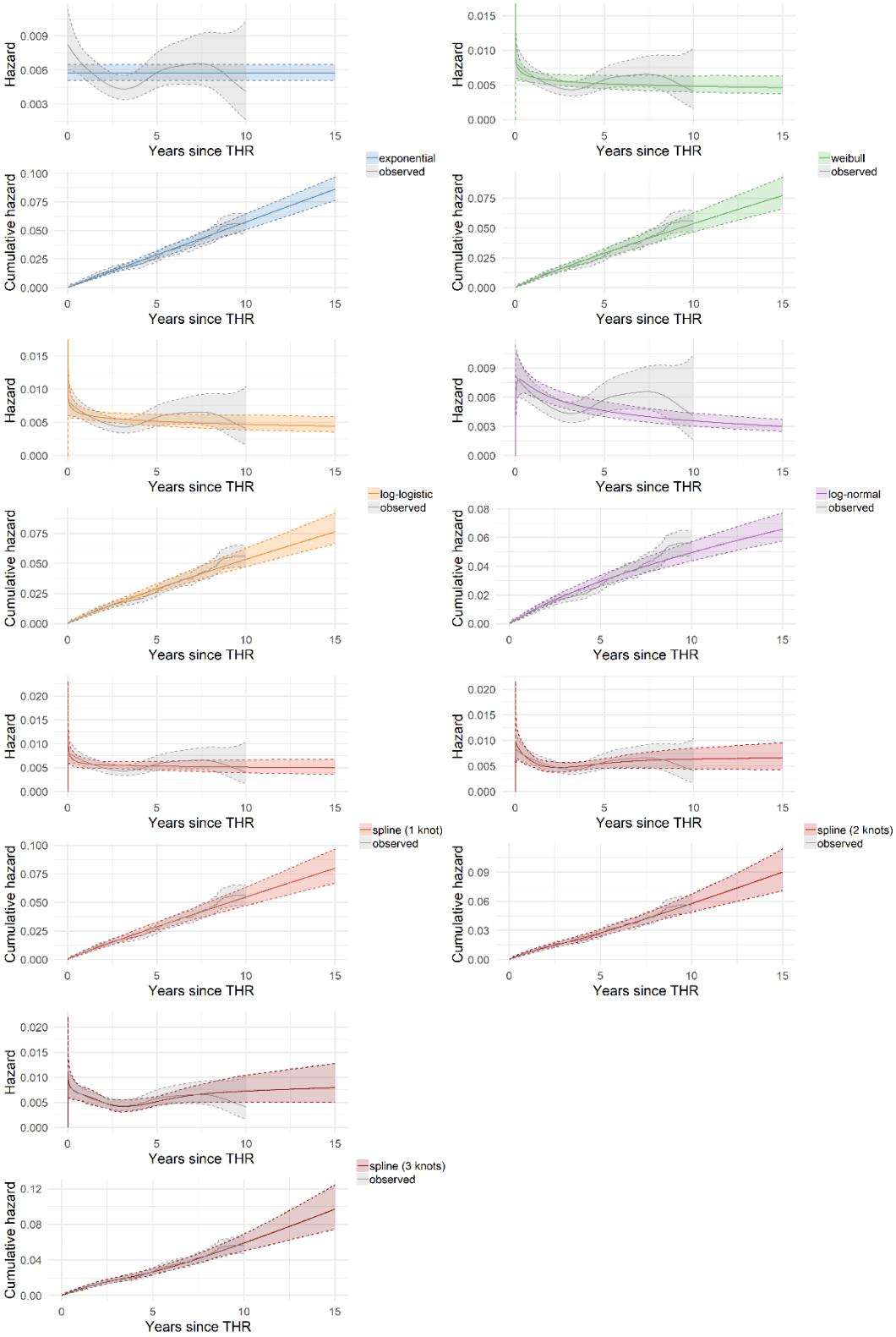
	Knee replacement		Hip replacement	
	Revisions /person years	**10-year cumulative incidence (% (95% CI))**	**Revisions/person years**	**10-year cumulative incidence (% (95% CI))**
3rd	60/ 7,971	6.24% (4.27% to 9.12%)	46/ 9,657	3.64% (2.54% to 5.22%)
4th	54/ 6,699	5.16% (3.59% to 7.41%)	31/ 7,536	3.54% (2.33% to 5.37%)
5th (most deprived)	18/ 3,693	3.45% (2.13% to 5.60%)	32/ 3,816	6.81% (4.56% to 10.16%)
Missing	0/ 41	-	0/ 13	-
Smoking status				
Non-smoker	67/ 8,657	4.68% (3.54% to 6.18%)	54/ 9,387	5.24% (3.75% to 7.34%)
Ex-smoker	68/ 7,230	5.49% (3.88% to 7.77%)	48/ 7,692	4.41% (3.02% to 6.43%)
Current smoker	12/ 1,552	4.26% (2.37% to 7.66%)	13/ 2,479	5.09% (2.43% to 10.66%)
Missing	110/ 16,715	4.90% (3.85% to 6.24%)	133/ 23,594	4.81% (3.98% to 5.81%)

Cumulative incidence of revision procedures 10 years after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. OA refers to knee OA for knee replacement cohorts and hip OA for hip replacement cohorts.

Appendix Figure D.1. Alternative distributions for cause-specific risk of revision after knee replacement. The spline-based distribution with 2 knots was chosen.



Appendix Figure D.2. Alternative distributions for cause-specific risk of revision after hip replacement. The spline-based distribution with 2 knots was chosen.



Appendix Table D.2. Estimated effect of explanatory factors on cause-specific risk of revision after knee and hip replacement

	Revision after knee replacement		**Revision after hip replacement**	
	Spline-based distribution with 2 knots PH		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Age	0.95 (0.94 to 0.97)	0.95 (0.94 to 0.96)	0.98 (0.97 to 0.99)	0.99 (0.97 to 1.00)
Sex				
Male	1.45 (1.13 to 1.85)	1.31 (0.99 to 1.72)	1.24 (0.96 to 1.59)	1.19 (0.91 to 1.57)
Female	*ref*	*ref*	*ref*	*ref*
Index diagnosis				
OA	*ref*	*ref*	*ref*	*ref*
RA	0.77 (0.47 to 1.26)	0.70 (0.41 to 1.18)	1.45 (0.91 to 2.32)	1.49 (0.90 to 2.45)
Charlson				
0	*ref*	*ref*	*ref*	*ref*
1+	0.82 (0.60 to 1.14)	0.88 (0.62 to 1.24)	1.14 (0.83 to 1.57)	1.13 (0.80 to 1.59)
BMI	1.02 (0.99 to 1.05)	0.99 (0.96 to 1.03)	1.03 (1.00 to 1.07)	1.02 (0.99 to 1.06)
IMD				
1st (least deprived)	*ref*	*ref*	*ref*	*ref*
2nd	1.01 (0.69 to 1.46)	1.00 (0.69 to 1.46)	0.72 (0.50 to 1.02)	0.71 (0.50 to 1.02)

	Revision after knee replacement		Revision after hip replacement	
	Spline-based distribution with 2 knots PH		Spline-based distribution with 2 knots PH	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
3rd	0.96 (0.65 to 1.39)	0.93 (0.64 to 1.36)	0.65 (0.44 to 0.95)	0.64 (0.44 to 0.94)
4th	1.04 (0.70 to 1.53)	1.01 (0.69 to 1.50)	0.56 (0.36 to 0.87)	0.55 (0.35 to 0.86)
5th (most deprived)	0.61 (0.35 to 1.07)	0.59 (0.33 to 1.02)	1.14 (0.74 to 1.76)	1.10 (0.71 to 1.71)
Rural				
Smoking status				
Non-smoker	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.20 (0.87 to 1.67)	1.14 (0.81 to 1.60)	1.07 (0.76 to 1.51)	0.86 (0.50 to 1.46)
Current smoker	0.99 (0.55 to 1.78)	0.71 (0.39 to 1.29)	1.02 (0.71 to 1.46)	0.76 (0.44 to 1.32)

OA: osteoarthritis; RA: rheumatoid arthritis; BMI: body mass index; PH: proportional hazard, with estimates representing hazard ratios.

Appendix Table D.3. Cumulative incidence of deaths after knee or hip replacement

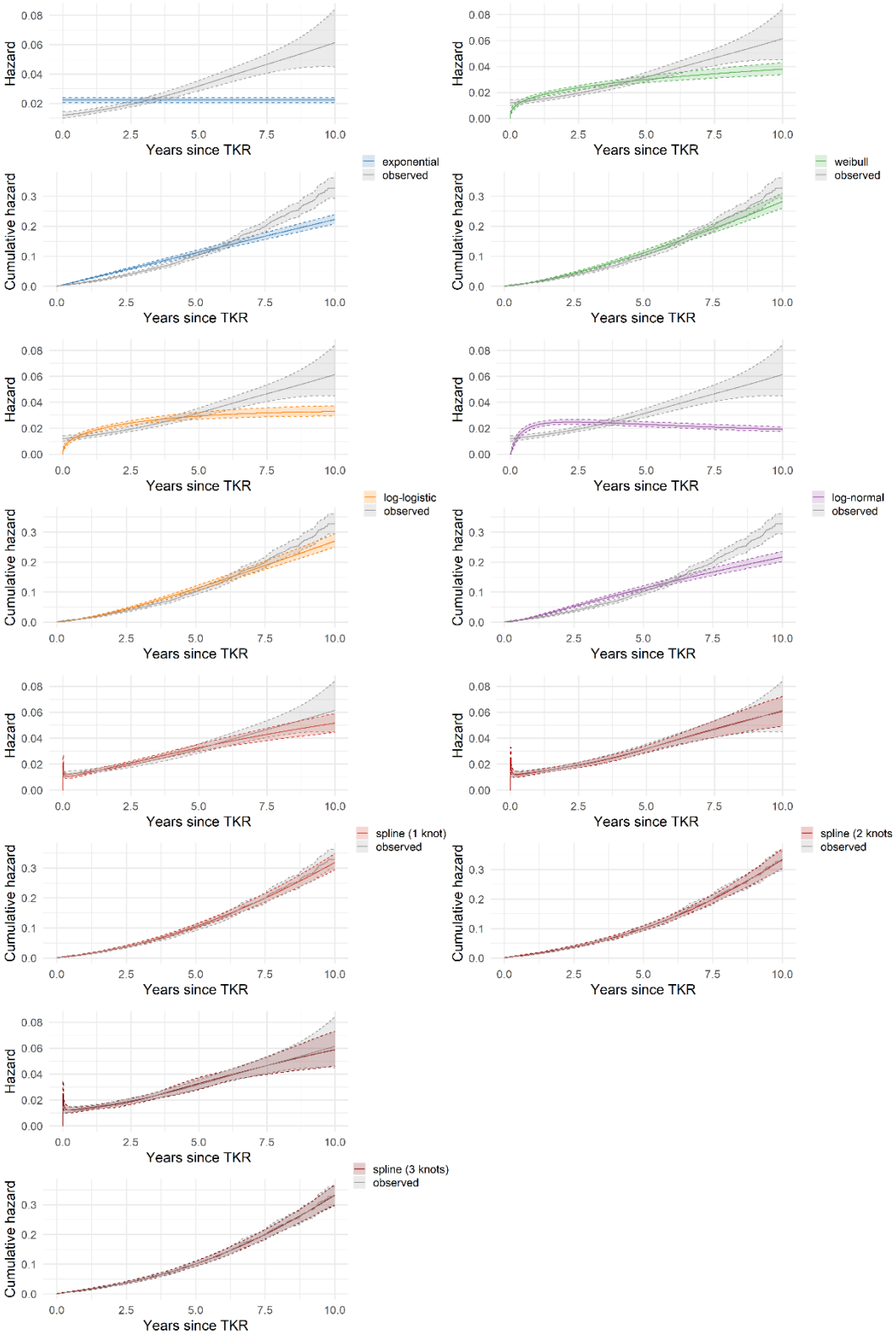
	Knee replacement		**Hip replacement**	
	Deaths/ person years	**10-year cumulative incidence (% (95% CI))**	**Deaths/ person years**	**10-year cumulative incidence (% (95% CI))**
Total	760/ 34,153	27.01% (24.75% to 29.49%)	1,001/ 43,151	24.21% (22.62% to 25.91%)
Age group* (%)				
1st (youngest)	44/ 7,914	7.15% (4.85% to 10.55%)	55/ 10,263	7.27% (5.31% to 9.94%)
2nd	113/ 8,462	19.46% (15.15% to 24.98%)	138/ 11,273	14.92% (12.34% to 18.04%)
3rd	191/ 8,545	25.16% (21.15% to 29.94%)	222/ 9,985	22.46% (19.46% to 25.93%)
4th (oldest)	412/ 9,232	48.44% (43.78% to 53.60%)	586/ 11,629	47.00% (43.46% to 50.84%)
Sex				
Male	358/ 14,302	24.48% (21.72% to 27.58%)	431/ 17,939	24.12% (22.02% to 26.42%)
Female	402/ 19,852	30.61% (26.93% to 34.79%)	570/ 25,213	24.33% (21.98% to 26.92%)
Index diagnosis				
OA	670/ 31,257	26.04% (23.70% to 28.61%)	921/ 40,835	23.68% (22.07% to 25.42%)
RA	90/ 2,896	36.36% (28.82% to 45.87%)	80/ 2,316	33.00% (25.99% to 41.92%)
Charlson				
0	561/ 27,475	24.02% (21.76% to 26.52%)	724/ 35,887	22.11% (20.44% to 23.91%)
1+	199/ 6,679	44.65% (36.97% to 53.92%)	277/ 7,264	35.25% (30.47% to 40.76%)

	Knee replacement		Hip replacement	
	Deaths/ person years	**10-year cumulative incidence (% (95% CI))**	**Deaths/ person years**	**10-year cumulative incidence (% (95% CI))**
BMI group (%)				
Normal or underweight (<25)	69/ 1,999	31.36% (23.80% to 41.33%)	129/ 3848	32.61% (26.54% to 40.07%)
Overweight (≥25 and <30)	98/ 5,050	33.73% (26.09% to 43.62%)	138/ 5759	27.19% (22.16% to 33.37%)
Obese class I (≥30 and <35)	71/ 4,448	20.77% (14.90% to 28.96%)	76/ 3800	26.65% (20.14% to 35.27%)
Obese class II (≥35 and <40)	32/ 2,188	19.48% (12.02% to 31.55%)	29/ 1564	22.86% (15.21% to 34.37%)
Obese class III (≥40)	6/ 693	12.93% (4.73% to 35.33%)	5/ 402	10.63% (3.58% to 31.57%)
Missing	484/ 19,775	27.42% (24.77% to 30.37%)	624/ 27777	22.87% (21.06% to 24.84%)
IMD quintile (%)				
1st (least deprived)	170/ 7,556	27.62% (22.88% to 33.33%)	224/ 10,898	22.02% (19.05% to 25.45%)
2nd	179/ 8,193	27.03% (22.55% to 32.41%)	244/ 11,231	23.48% (20.43% to 27.00%)
3rd	162/ 7,971	25.89% (21.47% to 31.24%)	222/ 9,657	23.12% (20.04% to 26.68%)
4th	142/ 6,699	23.53% (19.11% to 28.97%)	201/ 7,536	28.02% (24.14% to 32.53%)
5th (most deprived)	106/ 3,693	34.81% (28.07% to 43.16%)	110/ 3,816	27.78% (22.76% to 33.91%)
Missing	1/41	11.11% (1.75% to 70.51%)	0/ 13	-

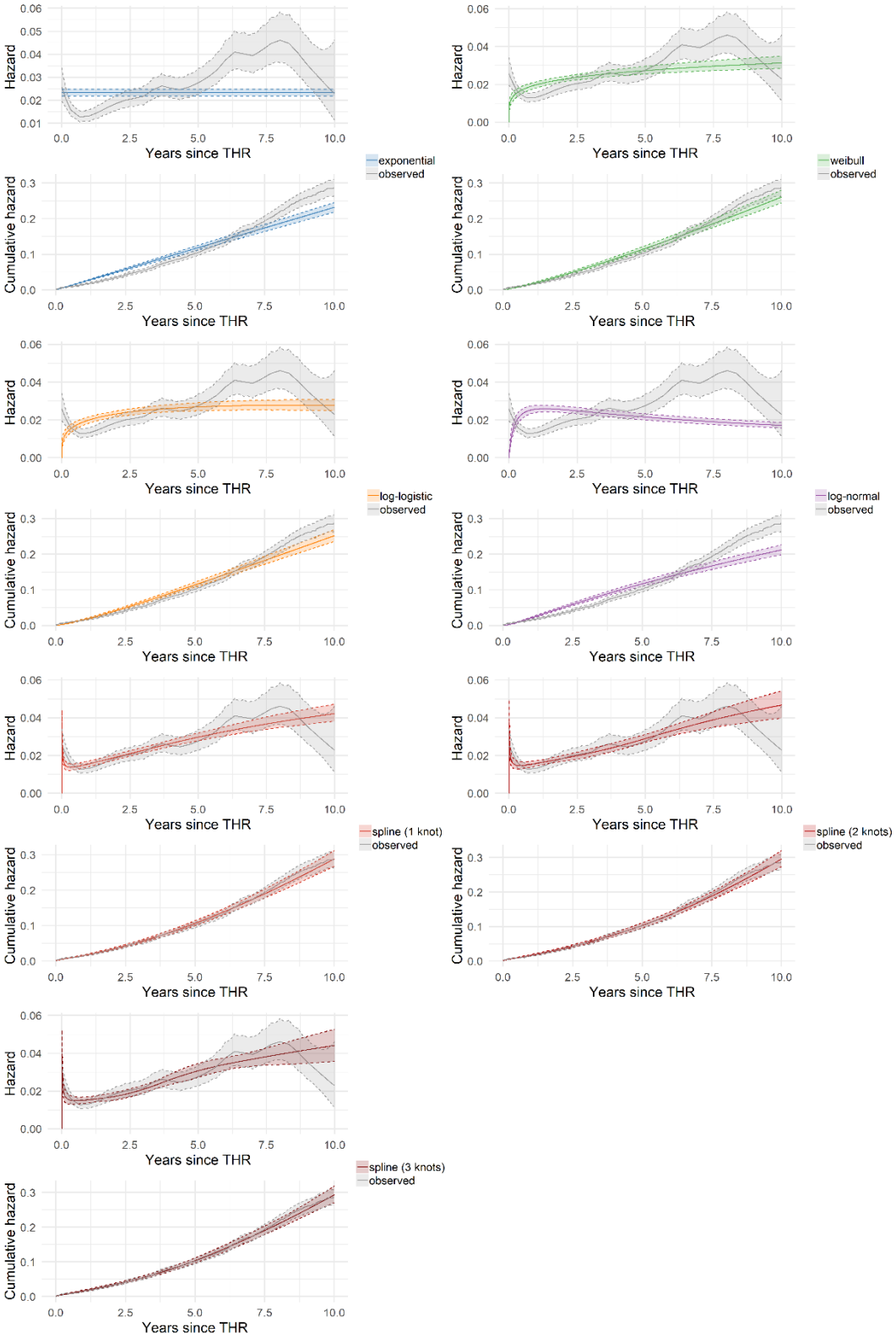
	Knee replacement		Hip replacement	
	Deaths/ person years	**10-year cumulative incidence (% (95% CI))**	**Deaths/ person years**	**10-year cumulative incidence (% (95% CI))**
Smoking status				
Non-smoker	143/ 8,657	20.21% (16.11% to 25.37%)	167/ 9,387	20.35% (16.64% to 24.89%)
Ex-smoker	192/ 7,230	34.51% (26.98% to 44.15%)	224/ 7,692	34.58% (29.31% to 40.79%)
Current smoker	41/ 1,552	40.18% (28.25% to 57.15%)	55/ 2,479	26.14% (17.38% to 39.30%)
Missing	384/ 16,715	27.02% (24.21% to 30.16%)	555/ 23,594	23.43% (21.53% to 25.49%)

Cumulative incidence of mortality 10 years after a knee or hip replacement. *Age groups for knee replacement cohort: <64, 64 to 71, 71 to 77, 77+, age groups for hip replacement cohort: <62, 62 to 70, 70 to 76, 76+. BMI: body mass index; CI: confidence interval; OA: osteoarthritis; RA: rheumatoid arthritis. Osteoarthritis refers to knee osteoarthritis for knee replacement cohorts and hip osteoarthritis for hip replacement cohorts.

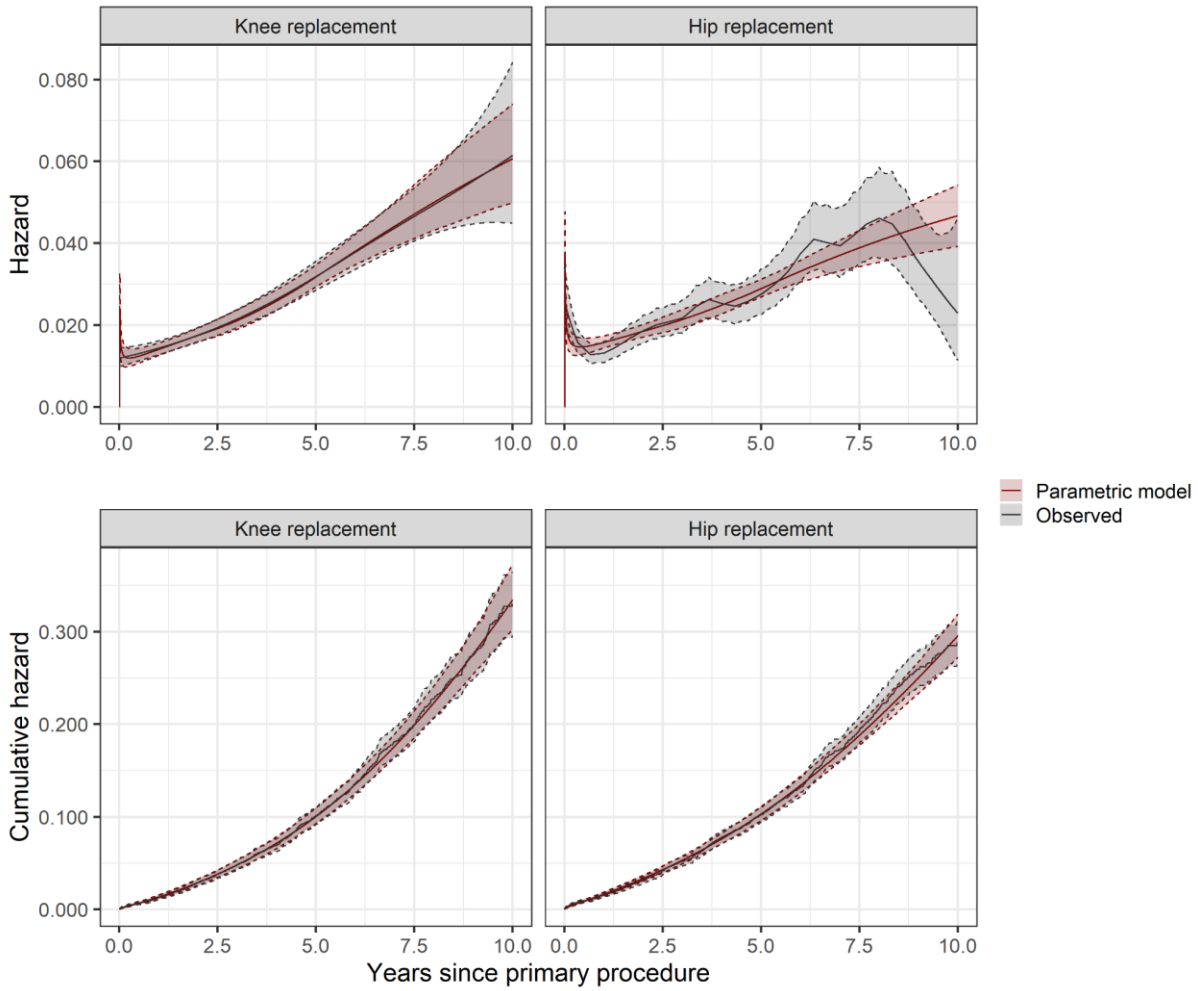
Appendix Figure D.3. Alternative distributions for cause-specific risk of death after knee replacement. The spline-based distribution with 2 knots was chosen.



Appendix Figure D.4. Alternative distributions for cause-specific risk of death after hip replacement. The spline-based distribution with 2 knots was chosen.



Appendix Figure D.5. Risks of mortality after a knee or hip replacement. Hazards and cumulative hazards for each age strata from observed data and intercept-only parametric survival models (both of which were fitted with spline-based distributions with 2 knots).



Appendix Table D.4. Estimated effect of explanatory factors on cause-specific risk of death after knee and hip replacement

	Death after knee replacement		**Death after hip replacement**	
	Spline-based distribution with 2 knots PH		**Spline-based distribution with 2 knots PH**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Age	1.10 (1.08 to 1.11)	1.10 (1.09 to 1.11)	1.10 (1.09 to 1.10)	1.10 (1.09 to 1.11)
Sex				
Male	1.26 (1.09 to 1.46)	1.26 (1.07 to 1.48)	1.06 (0.94 to 1.20)	1.27 (1.11 to 1.46)
Female	*ref*	*ref*	*ref*	*ref*
Index diagnosis				
OA	*ref*	*ref*	*ref*	*ref*
RA	1.43 (1.15 to 1.78)	1.63 (1.29 to 2.07)	1.55 (1.24 to 1.95)	1.64 (1.29 to 2.10)
Charlson				
0	*ref*	*ref*	*ref*	*ref*
1+	1.62 (1.38 to 1.91)	1.45 (1.22 to 1.73)	2.05 (1.78 to 2.36)	1.67 (1.44 to 1.95)
BMI	0.94 (0.92 to 0.96)	0.98 (0.96 to 1.00)	0.94 (0.92 to 0.96)	0.98 (0.96 to 1.00)
IMD				
1st (least deprived)	*ref*	*ref*	*ref*	*ref*
2nd	0.96 (0.77 to 1.20)	0.95 (0.76 to 1.19)	1.05 (0.87 to 1.27)	0.98 (0.81 to 1.19)

	Death after knee replacement		Death after hip replacement	
	Spline-based distribution with 2 knots PH		Spline-based distribution with 2 knots PH	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
3rd	0.89 (0.71 to 1.12)	0.92 (0.73 to 1.15)	1.11 (0.92 to 1.36)	1.04 (0.86 to 1.27)
4th	0.91 (0.72 to 1.15)	0.98 (0.77 to 1.24)	1.30 (1.06 to 1.59)	1.21 (0.99 to 1.48)
5th (most deprived)	1.28 (0.99 to 1.65)	1.36 (1.05 to 1.76)	1.40 (1.10 to 1.78)	1.27 (1.00 to 1.63)
Smoking status				
Non-smoker	*ref*	*ref*	*ref*	*ref*
Ex-smoker	1.67 (1.39 to 2.01)	1.56 (1.28 to 1.91)	1.60 (1.34 to 1.90)	1.44 (1.20 to 1.73)
Current smoker	1.49 (1.07 to 2.06)	2.20 (1.57 to 3.08)	1.18 (0.90 to 1.55)	1.81 (1.37 to 2.40)

OA: osteoarthritis; RA: rheumatoid arthritis; BMI: body mass index; PH: proportional hazard, with estimates representing hazard ratios.

E.

Appendix Table E.1. Estimated procedures and procedure costs for csDMARDs and TNFi for various relative risks (RRs). Results for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis, where effect of treatment effect ends after 5 years

	Current practice			**TNFI**		
	Primary procedures	**Revision procedures**	**Procedure costs (£)**	**Primary procedures**	**Revision procedures**	**Procedure costs (£)**
Knee replacement						
RR: 0.6	264 (194 to 358)	24 (16 to 34)	1,156,303 (841,837 to 1,598,661)	239 (174 to 325)	20 (14 to 28)	998,653 (722,976 to 1,382,854)
RR: 0.8	264 (194 to 358)	24 (16 to 34)	1,156,303 (841,837 to 1,598,661)	251 (184 to 341)	22 (15 to 31)	1,078,024 (785,066 to 1,492,932)
RR: 1.2	264 (194 to 358)	24 (16 to 34)	1,156,303 (841,837 to 1,598,661)	276 (204 to 372)	25 (18 to 36)	1,233,503 (896,138 to 1,711,558)
RR: 1.4	264 (194 to 358)	24 (16 to 34)	1,156,303 (841,837 to 1,598,661)	289 (213 to 388)	27 (19 to 38)	1,309,635 (952,100 to 1,807,766)
Hip replacement						

	Current practice			TNFI		
	Primary procedures	**Revision procedures**	**Procedure costs (£)**	**Primary procedures**	**Revision procedures**	**Procedure costs (£)**
RR: 0.6	163 (107 to 248)	11 (7 to 17)	736,734 (480,435 to 1,132,016)	148 (98 to 225)	9 (6 to 15)	642,393 (419,633 to 993,333)
RR: 0.8	163 (107 to 248)	11 (7 to 17)	736,734 (480,435 to 1,132,016)	155 (102 to 236)	10 (6 to 16)	689,735 (450,037 to 1,066,234)
RR: 1.2	163 (107 to 248)	11 (7 to 17)	736,734 (480,435 to 1,132,016)	170 (112 to 259)	12 (7 to 18)	783,393 (510,620 to 1,197,789)
RR: 1.4	163 (107 to 248)	11 (7 to 17)	736,734 (480,435 to 1,132,016)	178 (117 to 269)	12 (8 to 19)	829,712 (540,640 to 1,263,575)

Appendix Table E.2. Estimated incremental effect of TNFi, relative to csDMARDs, on procedures and procedure costs for various relative risks (RRs). Results for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis, where effect of treatment effect ends after 5 years

	Incremental effect of TNFi		
	Primary procedures avoided	**Revision procedures avoided**	**Procedure costs avoided (£)**

	Incremental effect of TNFi		
	Primary procedures avoided	**Revision procedures avoided**	**Procedure costs avoided (£)**
Knee replacement			
RR: 0.6	25 (18 to 33)	4 (2 to 5)	157,651 (111,281 to 211,849)
RR: 0.8	13 (9 to 16)	2 (1 to 2)	78,279 (55,377 to 104,865)
RR: 1.2	-12 (-16 to -9)	-2 (-2 to -1)	-77,199 (-102,781 to -54,854)
RR: 1.4	-25 (-32 to -18)	-3 (-5 to -2)	-153,331 (-203,512 to -109,206)
Hip replacement			
RR: 0.6	15 (10 to 21)	2 (1 to 2)	94,342 (60,777 to 139,141)
RR: 0.8	7 (5 to 11)	1 (0 to 1)	46,999 (30,321 to 69,191)
RR: 1.2	-7 (-11 to -5)	-1 (-1 to 0)	-46,658 (-68,438 to -30,185)
RR: 1.4	-15 (-21 to -10)	-2 (-2 to -1)	-92,978 (-136,130 to -60,236)

Appendix Table E.3. Estimated procedures and procedure costs for effect estimates from the literature. Results for base case analysis for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis.

Studies and analysis performed	**Estimated effect of TNFi***	**Primary procedures avoided**	**Revision procedures avoided**	**Procedure costs saved**
Knee replacement				
BSBR-RA: PS matched	1.11 (0.84 to 1.47)	-24 (-81 to 10)	-2 (-8 to 1)	-107,518 (-381928 to 46237)
BSBR-RA (age<60): PS matched	0.90 (0.59 to 1.38)	22 (-63 to 57)	2 (-6 to 5)	100,778 (-293,402 to 260,503)
BSBR-RA (age>=60): PS matched	1.31 (0.87 to 1.99)	-64 (-147 to -10)	-6 (-15 to -1)	-294,456 (-685,353 to -46,928)
CPRD: ITS	0.66	80	7	358,399
Hip replacement				
BSBR-RA: PS matched	0.86 (0.6 to 1.22)	21 (-22 to 46)	1 (-2 to 3)	95,458 (-102,121 to 214,117)
BSBR-RA (age<60): PS matched	1.47 (0.75 to 2.91)	-65 (-216 to -14)	-5 (-16 to -1)	-303,965 (-1,031,128 to -66,836)

Studies and analysis performed	Estimated effect of TNFi*	Primary procedures avoided	Revision procedures avoided	Procedure costs saved
BSBR-RA (age>=60): PS matched	0.60 (0.41 to 0.87)	61 (25 to 101)	4 (2 to 7)	279,096 (115,514 to 476,581)
CPRD: ITS	1.17	-24	-2	-111,375

*Hazard ratio from PS matched analyses and relative risks from interrupted time-series analyses. Only deterministic estimates were available from ITS analyses. BSRBR-RA: British Society for Rheumatology Biologics Register for rheumatoid arthritis; PS: propensity score; CPRD: Clinical Practice Research Datalink; ITS: interrupted time-series.

Appendix Table E.4. Estimated procedures and procedure costs for effect estimates from the literature. Results for base case analysis for the study cohort of 1,000 individuals with average profile of those diagnosed with rheumatoid arthritis.

		Current practice			**TNFI**		
Studies and analysis performed	**Estimated effect***	**Primary procedures**	**Revision procedures**	**Procedure costs**	**Primary procedures**	**Revision procedures**	**Procedure costs**
Knee replacement							
BSBR-RA: PS matched	1.11 (0.84 to 1.47)	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	287 (206 to 412)	26 (19 to 38)	1,263,821 (907,825 to 1,858,864)
BSBR-RA (age<60): PS matched	0.9 (0.59 to 1.38)	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	242 (162 to 370)	21 (14 to 34)	1055525 (703,777 to 1,667,593)

		Current practice			TNFI		
Studies and analysis performed	**Estimated effect***	**Primary procedures**	**Revision procedures**	**Procedure costs**	**Primary procedures**	**Revision procedures**	**Procedure costs**
BSBR-RA (age>=60): PS matched	1.31 (0.87 to 1.99)	264 (194 to 349)	24 (17 to 32)	1,156,303 (852,506 to 1,561,720)	328 (225 to 442)	30 (20 to 44)	1,450,760 (996,380 to 2,010,079)
CPRD: ITS	0.66	264	24	115,6303	184	16	797,904
Hip replacement							
BSBR-RA: PS matched	0.86 (0.6 to 1.22)	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	142 (93 to 247)	9 (6 to 17)	641276 (421,337 to 1,137,527)
BSBR-RA (age<60): PS matched	1.47 (0.75 to 2.91)	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	228 (141 to 430)	15 (9 to 30)	1,040,699 (634,723 to 1,995,440)

		Current practice			TNFI		
Studies and analysis performed	**Estimated effect***	**Primary procedures**	**Revision procedures**	**Procedure costs**	**Primary procedures**	**Revision procedures**	**Procedure costs**
BSBR-RA (age>=60): PS matched	0.6 (0.41 to 0.87)	163 (112 to 249)	11 (7 to 17)	736,734 (508,299 to 1,145,048)	102 (62 to 167)	7 (4 to 11)	457,639 (282,456 to 757,496)
CPRD: ITS	1.17	163	11	736,734	187	12	848,110

*Hazard ratio from PS matched analyses and relative risks from interrupted time-series analyses. Only deterministic estimates were available from ITS analyses. BSRBR-RA: British Society for Rheumatology Biologics Register for rheumatoid arthritis; PS: propensity score; CPRD: Clinical Practice Research Datalink (CPRD)]; ITS: interrupted time-series

Appendix Table E.5. Estimates for representative cohorts of 100 individuals with a BMI of 40, but otherwise average profile, where weight loss was mitigated after 5 years

Pathway	Knee replacements	Revisions	Bariatric surgery costs	Knee replacement and revision costs	Total cost	Incremental cost per knee replacement avoided
Current practice	32.9 (27.0 to 39.6)	2.8 (2.3 to 3.4)		162,443 (135,317 to 195,234)	162,443 (135,317 to 195,233)	
Bariatric surgery	30.0 (24.4 to 36.3)	2.5 (2.0 to 3.0)	428,969 (413,064 to 445,933)	144,755 (118,695 to 172,537)	573723 (542,062 to 605,720)	
Difference	-2.8 (-1.3 to -4.8)	-0.3 (-0.1 to -0.6)	428,968 (413,064 to 445,933)	-17,688 (-7,830 to -30,326)	411,279 (391,736 to 431,128)	145,286

*Average profile: a non-smoking 69-year-old woman in the fourth MEDEA quintile, with a Charlson score of 0.

F.

Appendix Figure F.1.Threshold prices for improvements in risk of revision or in quality of life if unrevised after knee and hip replacement at different cost-effectiveness (CE) thresholds

