Effect of Timing and Duration of Statin Exposure on Risk of Hip or Knee Revision Arthroplasty: A Population-based Cohort Study

Michael J. Cook, Antony K. Sorial, Mark Lunt, Tim N. Board, and Terence W. O'Neill

ABSTRACT. ***Objectives.*** To determine whether the timing and duration of statin exposure following total hip/knee arthroplasty (THA/TKA) influence the risk of revision arthroplasty.

Methods. Subjects from the Clinical Practice Research Datalink, a large population-based clinical database, who had THA/TKA from 1988 to 2016, were included. Propensity score adjusted Cox regression models were used to determine the association between statin exposure and the risk of revision THA/TKA, (1) at any time, and (2) if first exposed 0–1, 1–5, or > 5 years following THA/TKA. We also investigated the effect of duration of statin exposure (< 1, 1–2, 2–3, 3–4, 4–5, > 5 yrs).

Results. The study included 151,305 participants. There were 65,032 (43%) exposed to statins during followup and 3500 (2.3%) had revision arthroplasty. In a propensity score adjusted model, exposure to statins was associated with a reduced risk of revision arthroplasty (HR 0.82, 95% CI 0.75–0.90). Participants first exposed within 1 year and between 1 and 5 years following THA/TKA (vs unexposed) had a reduced risk of revision arthroplasty (HR 0.82, 95% CI 0.74–0.91 and HR 0.76, 95% CI 0.65–0.90, respectively). In relation to duration of statin therapy, participants exposed for more than 5 years in total (vs < 1 yr) had a reduced risk of revision (HR 0.74, 95% CI 0.62–0.88).

Conclusion. Statin therapy initiated up to 5 years following THA/TKA may reduce the risk of revision arthroplasty. (First Release August 1 2019; J Rheumatol 2020;47:441–8; doi:10.3899/jrheum.180574)

Key Indexing Terms:
ARTHROPLASTY HIP REPLACEMENT KNEE REPLACEMENT
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From the Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester; Institute of Genetic Medicine, Newcastle University; The Centre for Hip Surgery, Wrightington Hospital, Wrightington Wigan and Leigh National Health Service (NHS) Foundation Trust, Wigan; UK National Institute for Health Research (NIHR) Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester; Department of Rheumatology, Salford Royal NHS Foundation Trust, Salford, UK.

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M.J. Cook, MSc, Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester; A.K. Sorial, MRCS, Institute of Genetic Medicine, Newcastle University; M. Lunt, PhD, Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester Academic Health Science Centre; T.N. Board, MD, The Centre for Hip Surgery, Wrightington Hospital, Wrightington Wigan and Leigh NHS Foundation Trust; T.W. O'Neill, MD, Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, The University of Manchester, and NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, and Department of Rheumatology, Salford Royal NHS Foundation Trust. M.J. Cook and A.K. Sorial contributed equally to this manuscript. T.W. O'Neill and T.N. Board are joint senior authors.

Address correspondence to Prof. T.W. O'Neill, Arthritis Research UK Centre for Epidemiology, Division of Musculoskeletal and Dermatological Sciences, Stopford Building, The University of Manchester, Oxford Road, Manchester, M13 9PT, UK. E-mail: terence.o'neill@manchester.ac.uk

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Osteoarthritis (OA) is a chronic, painful, and disabling condition associated with significant and increasing economic cost in the UK and globally[1]. Total joint replacement is the definitive treatment for moderate to severe OA of the hip and knee in those who have not responded to medical therapy. The number of total hip/knee arthroplasty (THA/TKA) procedures carried out in the UK is increasing and is predicted to increase further, in part because of demographic changes[2]. The cumulative 5-year probability for revision of primary THA and TKA in the UK is around 2.5%[3]. Revision surgery is more complex, more costly, and has poorer clinical outcomes than primary joint replacement[4]. Therefore, any factors that may help reduce revision rates would help reduce longterm morbidity linked with joint replacement surgery.

There is experimental evidence that statins may have a beneficial effect on bone homeostasis by modulating inflammatory cytokine responses, promoting osteoblast-directed bone formation, and reducing osteoclastic bone resorption[5,6,7]. Animal studies have shown that local and systemic administration of statins following implantation of prosthesis improves osseointegration and increases the mechanical strength of the bone-implant interface within 6 weeks of prosthesis implantation[7,8,9,10,11]. Periprosthetic osteolysis, degradation of bone around the implant, and inhibition of bone formation, leading to aseptic loosening of the implant, is the overall most common indication for revision surgery[12], while instability and infection are common indications for revisions occurring within 5 years of the primary joint replacement[13,14]. An inflammatory response to implant wear-related debris around the joint is the major initiating event in the development of periprosthetic osteolysis[15]. There is some evidence that statins may inhibit this inflammatory reaction by attenuating the production of proinflammatory cytokines[16], and may therefore reduce subsequent periprosthetic osteolysis[17].

Two observational studies have suggested that exposure to statins may be associated with a reduced risk of revision of primary arthroplasty[18,19]. A study from Denmark showed that postoperative statin use was associated with an all-cause adjusted relative risk (95% CI) of revision surgery following total hip arthroplasty of 0.34 (0.28–0.41)[18]. However, that study did not take into account time-varying statin exposure, which is likely to have resulted in an overestimation of the effect of statin exposure on the risk of revision. A second study, using data from the Clinical Practice Research Datalink (CPRD) and the Danish National Health System (DNHS), used a number of approaches including a time-dependent model with followup time divided into 2 periods defining exposed and unexposed periods. The periods ran from the time of primary joint surgery until a day before the first postoperative statin prescription (non-exposed), and from the date of the first prescription until the end of followup (exposed). Using this approach, statin exposure was associated with a more modest reduced risk of revision [incidence rate ratio (RR) 0.90, 95% CI 0.85–0.96][19]. These previous observational studies, however, did not consider whether the timing of first statin exposure relative to the primary surgery was significant in influencing the risk of revision. This may be important, because experimental studies, as outlined above, suggest different mechanisms of action that are dependent on the timing of the exposure relative to the primary surgery. If, for example, the effect was to enhance osseointegration, then it is likely that the effect would be observed only in those who received statins in the early postoperative period.

The primary aim of our study was to determine whether the timing of statin exposure influences the risk of revision surgery in patients who have undergone a primary THA/TKA. We also looked at whether duration of therapy affected the risk of revision.

MATERIALS AND METHODS

Study population and setting. The CPRD is a database of anonymized primary care records of over 11.3 million patients (~6.9% of the UK population), and is broadly representative of the UK general population[20]. The CPRD includes demographic details, medication prescriptions, diagnoses, referrals, and hospital admissions with their major outcomes. The CPRD was used to retrospectively identify patients who had undergone a primary THA or TKA from January 1, 1988, to December 31, 2016, for inclusion in this study. Patients who were aged < 40 years, had a history of hip fracture, or who had inflammatory arthritis at the time of primary THA/TKA, were excluded from the analyses. Surgical procedures are recorded in CPRD using Read/OXMIS codes. A list of codes used to identify those with primary THA/TKA, based on a previously published list[21], is shown in Supplementary Table 1 (available from the authors on request).

Ascertainment of outcome. The primary outcome of our study was all-cause revision arthroplasty. A list of Read/OXMIS codes used to identify patients in CPRD who had a revision arthroplasty[22] is given in Supplementary Table 2 (available from the authors on request).

Primary exposure. The primary exposure was statin use from the time of primary arthroplasty, identified using prescription records in the CPRD. In the primary analyses, participants were modeled as continuously exposed from the date of their first statin prescription during followup. Participants were classified as unexposed at a given time if they had not been exposed to statins from the date of their primary THR/TKR up to that time. In a sensitivity analysis, adjustment was made for exposure to statins in the 12 months leading up to the study start date.

Covariates. Following a review of the literature to identify potential confounders, these were included as covariates in the analyses: the year of primary THA/TKA, age, sex, body mass index (BMI), smoking status (never, former, current), alcohol intake (non-drinker, current drinker, ex-drinker), General Practice deprivation score (defined by the Index of Multiple Deprivation), joint replaced (hip or knee), and selected morbidities (Supplementary Table 3, available from the authors on request). Morbidities were identified using Read/OXMIS codes recorded in CPRD.

Statistical analyses. Baseline characteristics for participants exposed/unexposed to statins during the study period were compared using unpaired, 2-tailed T tests for continuous variables, and chi-square tests for categorical variables. Cox regression models were used to estimate the hazard of revision in participants exposed to statins compared to those unexposed to statins during followup. In all Cox models, the index date was the date of the primary THA/TKA. Participants were censored at the date of revision surgery, the date at which their general practitioner (GP) stopped contributing data to the CPRD, the date the participant transferred out of their GP's practice, the date of death, or December 31, 2016 (whichever came first). Participants who had more than 1 primary THA/TKA were censored at the date of their second THA/TKA, because the side of the primary THA/TKA is not recorded in the CPRD and therefore it was not possible to determine which primary surgery the revision related to. Therefore, inferences about, and comparisons of, the hazard of revision at any time relate to participants who were still alive at that time.

We undertook analysis of the whole cohort and separately assessed hip and knee arthroplasties. Multiple imputation by chained equations was used to impute missing values of BMI, smoking, and alcohol intake. All covariates included in the fully adjusted model were used in the imputation model, with 10 iterations. Propensity score adjustment was used, however, as the primary method to control for potential confounding by indication[23]. Separate logistic regression models were used to determine the propensity score for first exposure to statins in each of the following time periods: 0–1 years, 1–5 years, > 5 years following primary THA/TKA. The log odds of the propensity score were included in the Cox models, because the propensity

score was not normally distributed. To test whether the association between the log odds of the propensity score and survival was linear, quintiles of the log odds of the propensity score were plotted against log failure rate.

A categorical, time-varying variable was created to indicate the timing of first statin exposure. The time-varying variable had 4 categories: unexposed, first exposed 0–1 years, first exposed 1–5 years, first exposed > 5 years following the primary THA/TKA. Each participant exposed to statins was classified as exposed in the relevant period from the date of their first statin exposure. Each exposed participant appeared in only 1 of the timing categories, determined by the timing of first exposure. The categorical timing variable was entered into a Cox regression model. The referent group comprised participants who were not exposed to statins during followup.

To determine the association between duration of statin exposure and revision risk, the cumulative number of days exposed was calculated for each participant at all failure times (revision dates) in the cohort. The cumulative days exposed was categorized as < 1 year (365 days; referent), 1–2 years, 2–3 years, 3–4 years, 4–5 years, and > 5 years and included as a covariate in a fully adjusted Cox model.

To estimate how robust any observed association between statin exposure and revision risk is to unmeasured or residual confounding, a recently introduced measure, the E-value, was calculated[24]. The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both statin exposure and revision risk to fully explain away any observed effect estimate[24]. All statistical analyses were carried out using STATA version 13 (StataCorp.).

Ethics approval was obtained from the Independent Scientific Advisory Committee for the Medicines and Healthcare Products Regulatory Agency (reference 16_201R).

RESULTS

Subjects. Of the 164,224 people who had a THA/TKA from January 1988 to December 2016, there were 12,919 excluded who had a history of hip fracture, were < 40 years old, or had inflammatory arthritis at the time of primary THA/TKA, leaving 151,305 participants for the analysis (Figure 1). Of those included, 78,594 had a THA and 72,711 had a TKA (Figure 1). The 14th Annual National Joint Registry (NJR) Report included 1.86 million THA/TKA for the period April 1, 2003, to December 31, 2016[3]. The number of participants included in our study who had a THA/TKA in the same

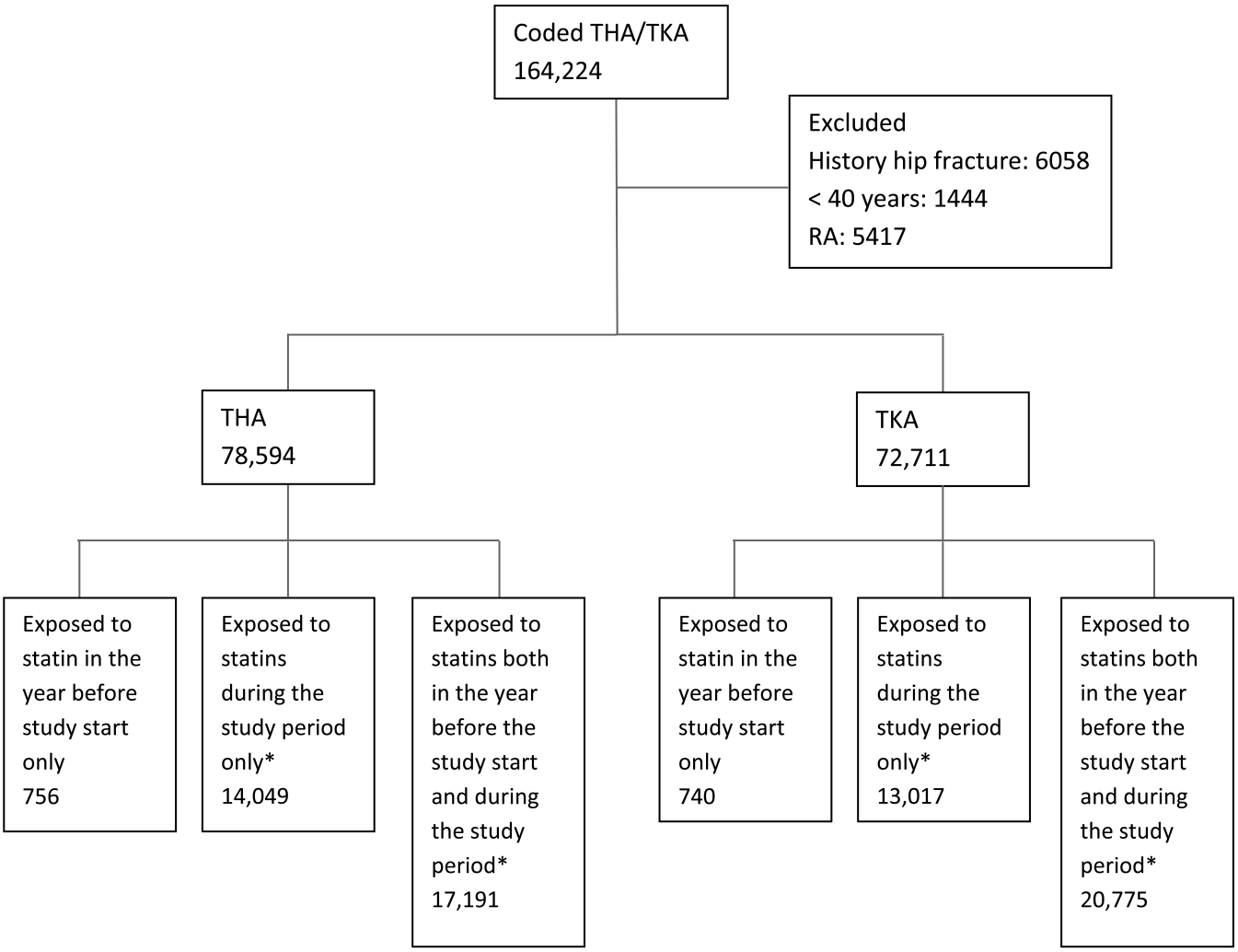

Figure 1. Population flow diagram. * The study period is the time from primary THA/TKA until revision or censoring. THA: total hip arthroplasty; TKA: total knee arthroplasty; RA: rheumatoid arthritis.

period was 116,716, though because there are differences in the geographical areas covered by the NJR and the CPRD during the study period, a direct comparison is not possible. There were 65,032 members of the study cohort (43%) exposed to statins during the followup period, and 3500 participants (2.3% of the study cohort) had revision arthroplasty. The median (interquartile range) followup time was 3.9 (1.1–7.8) years. The mean (SD) age of the study cohort was 69.7 (9.9) years, and 59% of the study participants were female.

Baseline characteristics. Compared to those who were not exposed to statins at baseline, those who were exposed to statins were slightly older (70.3 yrs vs 69.2 yrs) and less likely to be female (53.7% vs 69.2%). They had a higher BMI (29.6 kg/m^2 vs 28.5 kg/m^2), were less likely to have never smoked (46.5% vs 55.7%), were more likely to have never consumed alcohol (19.8% vs 18.9%), and were more likely to be an ex-drinker (2.9% vs 2.1%). In addition, they were more likely to have most of the comorbidities considered and to have used most of the medications considered (Table 1). Baseline characteristics for participants who did/did not have revision arthroplasty are shown in Supplementary Table 3 (available from the authors on request).

Influence of timing of first statin therapy on THA/TKA revision rates. Of those exposed to statins during followup, 852 (1.3%) had revision arthroplasty, compared to 2648 (3.1%) of those not exposed to statins. During the followup period, in the propensity score adjusted model, compared to those who were not exposed to statins, those who were exposed had a reduced HR for revision surgery (hip or knee; HR 0.82, 95% CI 0.75–0.90). Stratified by joint, statin therapy was associated with a reduced HR for hip (HR 0.86, 95% CI 0.76–0.98) and knee (HR 0.76, 95% CI 0.66–0.88) revision surgery. We did not have information on the type of implants used. Metal-on-metal hip implants are linked with a higher risk of revision. We carried out a sensitivity analysis restricted to THA carried out before 2000 and after 2009, when metal-on-metal bearing surfaces were not commonly used. We found statin exposure to be associated with a reduced HR for revision (HR 0.83, 95% CI 0.68–1.00), with an effect size similar to the HR of that observed when including all subjects.

Exposure in the first 5 years following surgery appeared protective; compared to those who were not exposed to statins, the HR (95% CI) of revision in those first exposed to statins in the periods 0–1, 1–5, and > 5 years after the primary surgery was 0.82 (0.74–0.91), 0.76 (0.65–0.90), and 0.95 (0.76–1.19), respectively, though the CI for the > 5-year category included unity (Table 2). In separate analyses looking at the individual joint sites, the results were similar for those who had had a knee arthroplasty with first exposure in the periods 0–1 and 1–5 years following surgery. That situation was associated with reduced revision risk in the propensity score adjusted model (HR 0.76, 95% CI 0.65–0.89 and 0.71, 95% CI 0.54–0.92, respectively; Table 2). For hips, only first exposure in the period 1–5 years following THA was associated with a statistically significant reduced risk of revision (HR 0.80, 95% CI 0.65–0.99; Table 2). Visual inspection of a plot of quintiles of the log odds of the propensity score and log failure rate for each propensity score model confirmed a linear association.

Propensity score adjustment was used in the primary analysis. Multivariable, fully adjusted models gave similar effect sizes to the propensity score adjusted models, though the CI around the revision risks in the whole cohort (HR 0.86, 95% CI 0.73–1.03) and also hips (HR 0.87, 95% CI 0.68–1.10) included unity.

Influence of duration of statin therapy on THA/TKA revision rates. Compared to participants exposed to statins for a total duration of < 1 year (reference), those exposed for more than a total of 5 years had a reduced risk of revision (HR 0.74, 95% CI 0.62–0.88; Figure 2).

Sensitivity analyses. In total, 39,462 participants were exposed to statins in the year leading up to the study start. Results from sensitivity analyses adjusting for statin exposure in the year leading up to the study start were not significantly different from the main analyses (data not shown). We looked also at those who had contributed data to CPRD from January 1988 for at least 10 years and who had no primary THA/TKA during that time. Among this smaller subset, during the observation period from 1998 to 2016, the HR (95% CI) for revision among those exposed to statins compared to those unexposed was protective, as in the main analysis, though the confidence bounds included unity (0.88, 0.73–1.05).

The E-value (lower 95% CI) for the HR for revision in participants first exposed to statins in the period 0–1 and 1–5 years after THA/TKA, compared to those who were unexposed, in the fully adjusted model was 1.49 (1.37) and 1.64 (1.37), respectively. The E-value represents the necessary minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to explain away the observed association between postoperative statin exposure and revision risk[24].

DISCUSSION

In this analysis of a large, population-based cohort, statin therapy was linked with a reduced risk of revision hip and knee surgery. Timing of first exposure to statin therapy appeared to influence the risk of revision surgery with first exposure within 5 years of surgery being linked with a reduction in risk. There was some evidence that duration of therapy may also be important; compared to those who took therapy for < 1 year, those who were took statin therapy for > 5 years had a reduced risk of revision surgery.

Our results are consistent with 2 previous studies suggesting a protective effect of statin therapy on risk of revision surgery. Thillemann, *et al*, in an analysis of 57,581 THA recorded in the Danish Hip Arthroplasty Register from

Table 1. Participant characteristics at baseline.

Characteristics	Statin Users, n = 65,032	Statin Non-users, n = 86,273	p[1]
Age, yrs, mean SD	70.3 (8.5)	69.2 (10.8)	< 0.001
Female, n (%)	34,942 (53.7)	54,297 (62.9)	< 0.001
BMI, kg/m^2, mean SD[2]	29.6 (2.4)	28.5 (5.6)	< 0.001
Smoking status[3], n (%)			
Never	28,748 (46.5)	44,016 (55.7)	< 0.001
Former	26,448 (42.8)	26,344 (33.3)	
Current	6601 (10.7)	8661 (11.0)	
Alcohol intake[4], n (%)			
Non-drinker	12,391 (19.8)	14,657 (18.9)	< 0.001
Current drinker	48,394 (77.3)	61,347 (79.0)	
Ex-drinker	1824 (2.9)	1631 (2.1)	
Multiple index of deprivation, decile	5.6 (2.9)	5.5 (2.9)	< 0.0001
Comorbid conditions (diagnosis of/history of), n (%)			
Osteoarthritis	44,577 (68.6)	55,285 (64.1)	< 0.001
Asthma	7830 (12.0)	9683 (11.2)	< 0.001
Malabsorptive syndromes	5525 (8.5)	6568 (7.6)	< 0.001
Hypertension	37,336 (57.4)	29,352 (34.0)	< 0.001
Hyperlipidemia	15,389 (23.7)	4247 (4.9)	< 0.001
Ischemic heart disease	13,411 (20.6)	3817 (4.4)	< 0.001
Stroke	5207 (8.0)	2124 (2.5)	< 0.001
Myocardial infarction	5590 (8.6)	1161 (1.4)	< 0.001
Congestive heart failure	1984 (3.1)	1663 (1.9)	< 0.001
Malignancy	451 (0.7)	631 (0.7)	0.39
COPD	2559 (3.9)	2539 (2.9)	< 0.001
Kidney failure	39 (0.06)	22 (0.03)	< 0.001
Cerebrovascular disease	4512 (6.9)	2123 (2.5)	< 0.001
Peripheral vascular disease	1796 (2.8)	756 (0.88)	< 0.001
Dementia	296 (0.46)	458 (0.53)	0.04
Neoplasm	5336 (8.2)	7034 (8.2)	0.72
Diabetes	10,957 (16.9)	2924 (3.4)	< 0.001
Ulcers	3537 (5.4)	3568 (4.1)	< 0.001
Hemiplegia	134 (0.2)	109 (0.1)	< 0.001
Renal disease	8285 (12.7)	6032 (7.0)	< 0.001
Inflammatory bowel disease	86 (0.1)	142 (0.2)	0.11
Medication			
Proton pump inhibitors	30,594 (47.0)	34,487 (40.0)	< 0.001
Antiarrhythmics	44,502 (68.4)	40,828 (47.3)	< 0.001
Anticonvulsants	5802 (8.9)	6665 (7.7)	< 0.001
Antidepressants	19,226 (29.6)	23,247 (27.0)	< 0.001
Anti-Parkinson drugs	1020 (1.6)	1410 (1.6)	0.31
Thiazide diuretics	28,528 (43.9)	25,205 (29.2)	< 0.001
Anxiolytics	1273 (2.0)	1420 (1.7)	< 0.001
Platelet inhibitors	14,196 (21.8)	7435 (8.6)	< 0.001
Warfarin	4765 (7.3)	3870 (4.5)	< 0.001
ACE inhibitors	13,607 (20.9)	9180 (10.6)	< 0.001
Beta blockers	29,026 (44.6)	21,691 (25.1)	< 0.001
Calcium channel blockers	27,131 (41.7)	19,300 (22.4)	< 0.001
Loop diuretics	13,748 (21.1)	12,688 (14.7)	< 0.001
Nonstatin lipid-lowering drugs	4148 (6.4)	1962 (2.3)	< 0.001
Corticosteroids	26,203 (40.3)	30,778 (35.7)	< 0.001
Oral antidiabetic drugs	1691 (2.6)	381 (0.44)	< 0.001
NSAID	55,429 (85.2)	71,298 (82.6)	< 0.001
Hormone replacement therapy	11,613 (17.9)	16,488 (19.1)	< 0.001
Bisphosphonates	4437 (6.8)	5942 (6.9)	0.62
Calcium/vitamin D	6746 (10.4)	8647 (10.0)	0.03
Selective estrogen receptor modulators	1219 (1.9)	2067 (2.4)	< 0.001

[1] P value from a t test for continuous variables and a chi-square test for categorical variables. [2] Data on BMI available for 72,432 study participants. [3] Data for smoking status available for 140,785 participants. [4] Data on alcohol intake available for 140,244 participants. BMI: body mass index; COPD: chronic obstructive pulmonary disease; ACE inhibitors: angiotensin-converting enzyme inhibitors; NSAID: nonsteroidal antiinflammatory drugs.

Table 2. HR for revision by timing of exposure to statins following primary arthroplasty.

Exposure	HR (95% CI) for Revision			
	Unadjusted	Adjusted for Year of Primary, Age, and Sex	Fully Adjusted[1]	Propensity Score Adjusted[2]
		Whole Cohort		
Unexposed	Referent	Referent	Referent	Referent
Any Exposure	0.63 (0.58–0.68)	0.81 (0.75–0.88)	0.86 (0.73–1.03)	0.82 (0.75–0.90)
Unexposed	Referent	Referent	Referent	
0–1	0.59 (0.54–0.64)	0.80 (0.73–0.88)	0.82 (0.73–0.92)	0.82 (0.74–0.91)
1–5	0.69 (0.59–0.81)	0.78 (0.66–0.92)	0.78 (0.66–0.92)	0.76 (0.65–0.90)
> 5	0.98 (0.78–1.22)	0.94 (0.75–1.18)	0.93 (0.74–1.17)	0.95 (0.76–1.19)
		Hips[3]		
Unexposed	Referent	Referent	Referent	
Any Exposure	0.66 (0.59–0.73)	0.85 (0.77–0.95)	0.87 (0.68–1.10)	0.86 (0.76–0.98)
Unexposed	Referent	Referent	Referent	
0–1	0.60 (0.53–0.68)	0.84 (0.74–0.96)	0.85 (0.73–0.99)	0.87 (0.75–1.01)
1–5	0.71 (0.58–0.88)	0.82 (0.67–1.02)	0.82 (0.66–1.01)	0.80 (0.65–0.99)
> 5	0.97 (0.74–1.26)	0.96 (0.74–1.25)	0.95 (0.73–1.24)	0.96 (0.73–1.24)
		Knees[4]		
Unexposed	Referent	Referent	Referent	
Any Exposure	0.61 (0.54–0.69)	0.77 (0.68–0.87)	0.78 (0.68–0.90)	0.76 (0.66–0.88)
Unexposed	Referent	Referent	Referent	
0–1	0.59 (0.51–0.67)	0.76 (0.67–0.88)	0.79 (0.67–0.93)	0.76 (0.65–0.89)
1–5	0.67 (0.52–0.87)	0.71 (0.55–0.93)	0.72 (0.55–0.94)	0.71 (0.54–0.92)
> 5	1.03 (0.67–1.56)	0.93 (0.61–1.42)	0.92 (0.60–1.41)	0.98 (0.64–1.49)

Timing of first postoperative statin exposure is measured in years since the primary surgery. Results from a Cox regression model. [1] Adjusted for year of primary TJA, age, sex, body mass index (BMI), smoking status (never, former, current), alcohol intake (non-drinker, current drinker, ex-drinker), General Practice deprivation score (defined by the Index of Multiple Deprivation), joint replaced (hip or knee), diagnosis of osteoarthritis, asthma, malabsorptive syndromes, hypertension, hyperlipidemia, ischemic heart disease, stroke, myocardial infarction, congestive heart failure, malignancy, chronic obstructive pulmonary disease, kidney failure, cerebrovascular disease, peripheral vascular disease, dementia, neoplasm, diabetes, ulcers, hemiplegia, renal disease, inflammatory bowel disease, use of proton pump inhibitors, antiarrhythmics, anticonvulsants, antidepressants, anti-Parkinson drugs, thiazide diuretics, anxiolytics, platelet inhibitors, warfarin, angiotensin-converting enzyme inhibitors, β blockers, calcium channel blockers, loop diuretics, nonstatin lipid-lowering drugs, corticosteroids, insulin, oral antidiabetic drugs, nonsteroidal antiinflammatory drugs, hormone replacement therapy, bisphosphonates, and selective estrogen receptor modulators. [2] Propensity score based on a logistic regression model to predict statin exposure. All variables included in the fully adjusted model were used to calculate the propensity score. [3] Subanalysis of hips is based on 78,594 participants, with 2071 revisions. [4] Subanalysis of knees is based on 72,711 participants, with 1429 revisions. TJA: total joint arthroplasty.

1996 to 2005, suggested that postoperative statin use was associated with an adjusted relative risk of revision (95% CI) of 0.34 (0.28–0.41)[18]. Meanwhile, Lalmohamed, *et al*, used data from the CPRD and the DNHS, with a combined 189,286 THA/TKA recorded from 1998 to 2007[19]. They suggested that, with statin exposure defined in a time-dependent manner, postoperative statin exposure was associated with an adjusted IRR (95% CI) of 0.90 (0.85–0.96)[19]. Differences in study design, duration of followup, and analytic approach may potentially explain the discrepancy in effect size between these 2 studies. Thillemann, *et al* used a time-fixed exposure variable (any postoperative statin exposure) in logistic regression models[18], while Lalmohamed, *et al* used Cox regression with time-dependent statin exposure[19]. However, to our knowledge, there are no data that have looked at the influence of timing of first exposure to statin therapy on the risk of revision.

Laboratory and animal studies have suggested that statins may influence biological processes occurring at different phases following arthroplasty; principally osseointegration, by promoting bone formation[7,8,9,10], and periprosthetic osteolysis, by attenuating the inflammatory response to implant wear-related debris[16]. The fact that in our study statin therapy given more than 1 year following the original surgery was linked with a reduced risk of subsequent revision would suggest that the mechanism by which statins may confer protection is not simply related to an effect on osseointegration, which would typically be complete within 6 months of surgery. Other mechanisms are likely to be involved, including perhaps an effect on loosening (periprosthetic osteolysis) of the implants; our finding that a longer duration of exposure appeared to be protective would be in keeping with this. A small proportion of revisions are due to the occurrence of periprosthetic

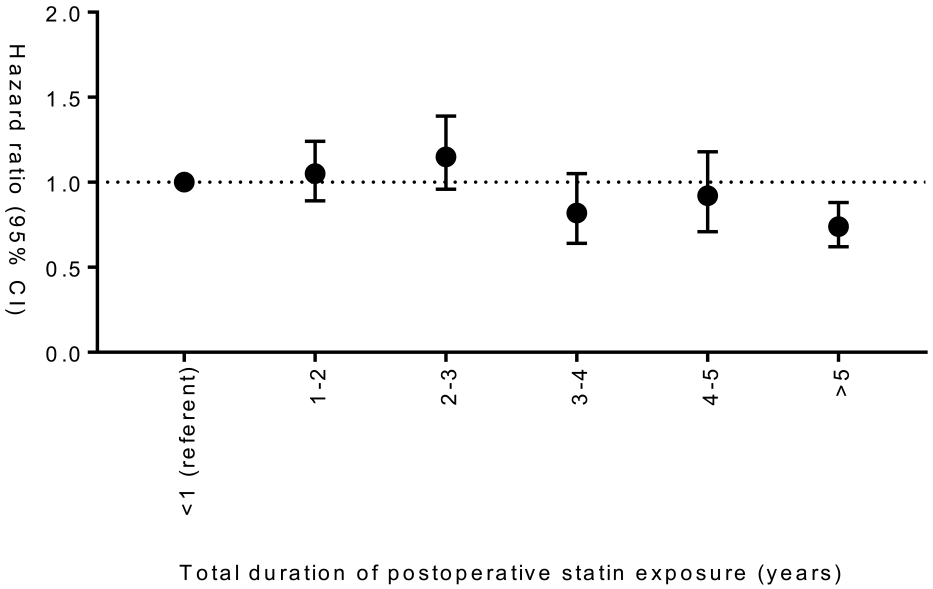

Figure 2. Risk of revision by duration of exposure. Association between total duration of postoperative statin exposure and risk of revision. Exposed for < 1 year is the referent group. Results from a fully adjusted Cox regression model.

fractures, and it is possible that statin therapy may reduce these events. However, because we did not have information about the indications for revision surgery, we cannot confirm this.

Given the increasing number of THA/TKA carried out globally and the increased costs and poorer clinical outcomes associated with revision surgery[4], if the results of our study are confirmed, statins may provide an approach to reducing the risk of revision surgery in patients undergoing primary THA/TKA. However, further research is required to confirm the findings and identify potential mechanisms by which statins are linked to a reduced risk. Although statin therapy is effective and safe in the context of cardiovascular disease prevention, statin therapy is not without risks, which should also be considered[25].

Strengths of our study include a large, representative sample of UK patients with detailed longitudinal prescription data from primary care records, as well as detailed demographic and morbidity data[20]. The results should be interpreted with reference to potential limitations, including, as with all observational studies, the possibility that unmeasured or residual confounding may have influenced our results. However, a review of the literature was carried out to identify putative confounders, which were accounted for in propensity score adjusted analysis[23]. Further, sensitivity analyses showed that any unmeasured confounding would need to be substantial to explain away the observed associations. Improvements in surgical techniques have reduced revision rates during the study period (1988–2016). However, the general decrease in revision rates over time is not likely to have influenced the relationship between statin exposure and revision risk, because improvements in surgical techniques are unrelated to statin use. Data were not available in CPRD about which joint (left/right) each primary THA/TKA relates to. It was therefore necessary to censor participants with bilateral THA/TKA at the time of the second primary operation, because any subsequent revision could not be accurately linked to the correct primary. The effect of this, however, would be to tend to reduce the likelihood of finding a significant association between statin therapy and risk of revision. We cannot exclude misclassification due to the occurrence of joint replacement surgery prior to a subject contributing data to the CPRD who subsequently had a second joint replacement surgery on the contralateral side and then a revision. The observed revision rate in our study (2.3%) was, however, broadly similar to that reported by the NJR (2.4% in the first 5 years following primary hip replacement and 2.6% in the first 5 years following TKA)[3]. Other factors that may influence revision rates, such as implant design and fixation type, were not available in the CPRD.

Our analysis of data from the CPRD revealed that statin therapy was linked with a reduced risk of revision hip and knee surgery. Timing of first exposure to statin therapy appeared to influence the risk of revision surgery, with first exposure within 5 years of surgery being linked with a reduction in risk. The mechanism by which statin therapy is linked with a reduced risk of revision surgery is unknown, though does not appear to be related solely to an effect on osseointegration of the primary prosthesis.

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