**Statin use and risk of joint replacement due to osteoarthritis and rheumatoid arthritis: a propensity-score matched longitudinal cohort study**

Aliya Sarmanova (MD, PhD)1,2, Michael Doherty (MA, MD, FRCP)1,

Changfu Kuo (MD, PhD)1,3, Jie Wei (PhD)6,7,

Abhishek Abhishek (MD, PhD)1, Christian Mallen (BMBS, PhD, FRCGP)5,

Chao Zeng (MD, PhD)4,6, Yilun Wang (MD)4, Guanghua Lei\* (MD, PhD)4,8,9,

Weiya Zhang\* (PhD)1

1 Academic Rheumatology Department, Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, UK

2 MRC Integrative Epidemiology Unit, [Bristol Medical School (PHS)](http://www.bristol.ac.uk/population-health-sciences/), University of Bristol, UK

3 Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital, Taoyuan, Taiwan

4Department of Orthopaedics, Xiangya Hospital, Central South University, China

5 Arthritis Research UK Primary Care Centre, Research Institute for Primary Care and Health Sciences, Keele University, UK

6 Division of Rheumatology, Allergy, and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, USA

7 Health Management Center, Xiangya Hospital, Central South University, China

8 Hunan Key Laboratory of Joint Degeneration and Injury, China

9 National Clinical Research Center of Geriatric Disorders, Xiangya Hospital, Central South University, China

\*- joint senior authors

**Emails:**

Dr Aliya Sarmanova: [aliyasarmanova@gmail.com](mailto:aliyasarmanova@gmail.com)

Professor Michael Doherty: [michael.doherty@nottingham.ac.uk](mailto:michael.doherty@nottingham.ac.uk)

Dr Abhishek Abhishek:  [Abhishek.Abhishek@nottingham.ac.uk](mailto:ana.valdes@nottingham.ac.uk)

Professor Christian Mallen: [c.d.mallen@keele.ac.uk](mailto:c.d.mallen@keele.ac.uk)

Dr Changfu Kuo: [zandis@gmail.com](mailto:zandis@gmail.com)

Dr Chao Zeng: [zengchao@csu.edu.cn](mailto:zengchao@csu.edu.cn)

Dr Jie Wei: weij1988@csu.edu.cn

Dr Yilun Wang: yilun\_wang@csu.edu.cn

Professor Guanghua Lei: [lei\_guanghua@csu.edu.cn](mailto:lei_guanghua@csu.edu.cn)

Professor Weiya Zhang: [weiya.zhang@nottingham.ac.uk](mailto:weiya.zhang@nottingham.ac.uk)

**Corresponding authors:**

Guanghua Lei, Department of Orthopaedics, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan, China, E-mail: lei\_guanghua@csu.edu.cn;

**Word count:** 3 304 excluding title page, abstract, references, figures, and tables.

Keywords: osteoarthritis, rheumatoid arthritis, joint replacement, TJR, TKR, statins, cohort study.

# Abstract

(word count 248)

**Objective:** Statins are reported to have a potential benefit on progression of osteoarthritis (OA) and on disease activity in rheumatoid arthritis (RA), but existing evidence is conflicting. Our objective was to examine whether statins associate with reduction of joint replacement due to OA and RA.

**Design:** A propensity score matched cohort study. Settings: Electronic health records from the UK Clinical Practice Research Datalink. Participants: We selected people prescribed statins and people never prescribed statins. Each statin-user was matched to a non-user by age, gender, practice and propensity score for statin prescription. Main outcome measures: knee or hip joint replacement overall, and specifically because of OA or RA. Measurements:The association between statins and risk of joint replacement was assessed using Cox proportional hazard regression. Statin exposure was categorised according to the potency of reducing LDL as low (21-28%) medium (32-38%) or high (42-55%) intensity.

**Results:** 178,467 statin-users were matched with 178,467 non-users by age, gender, practice and propensity score. Overall, statin was not associated with reduced risk of knee or hip replacement (HR 0.99, 95% CI 0.97 to 1.03), unless prescribed at high strength (0.86, 0.75 to 0.98). The reduced risk was only observed for joint replacement due to RA (0.77, 0.63 to 0.94) but not OA (0.97, 0.94 to 1.01).

**Conclusions:** Statins at high intensity may reduce the risk of hip or knee replacement. This effect may be RA specific. Further studies to investigate mechanisms of risk reduction and the impact in people with RA are warranted.

**Registration**

The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) (protocol 12\_020R2AR).

**Primary Funding Source**

National Institute for Health Research and National Natural Science Foundation of China.

# Key Messages

* Statins are routinely used in the treatment of cardiovascular diseases, however they might also be beneficial for other conditions.
* In this study statins at high dose showed reduced risk of hip or knee replacement, particularly in people with rheumatoid arthritis.
* Further studies to investigate mechanisms of risk reduction and the impact in people with RA are warranted.

# Introduction

Joint replacement is one of the major economic burdens for healthcare systems worldwide(1-3). The number of joint replacements performed each year have risen dramatically(4, 5) and are set to continue rising with the aging population(6). Waiting-list audits demonstrate that current surgical provision does not meet healthcare needs(7). Approximately 90% of all joint replacements are performed for osteoarthritis (OA)(6).

Statins are lipid-lowering drugs recommended for primary and secondary prevention of cardiovascular disease (CVD)(8). Statins lower circulating levels of low-density lipoproteins, and have other anti-inflammatory and immune-modulating effects(9-14) that have prompted studies to examine the potential role of statins as structure-modifying treatments for OA(15). Statin use has been associated with an increased risk of development, but not progression, of radiographic hip OA in elderly women (16), and with increased risk of progression of radiographic knee OA (17, 18). Conversely, one study has reported a protective effect of statins on development of knee OA in people with existing CVD (19). However, some more recent large studies have not confirmed these findings (20, 21). In the Osteoarthritis Initiative cohort statin use was not associated with lower risk of pain worsening, incident radiographic knee OA or radiographic symptomatic knee OA unless taken for more than 5 years (22). A recent study in the Clinical Practice Research Datalink (CPRD) found that statin therapy initiated up to 5 years following total hip/knee replacement may reduce the risk of revision arthroplasty(23). Taking into account existing evidence, the possible effect of statins on development and progression of OA remains unclear.

In contrast, more evidence supports a potential benefit of statins on disease activity, attributable to their anti-inflammatory and immunomodulatory properties in rheumatoid arthritis (RA)(24-27). For example, a recent meta-analysis of nine randomized controlled trials found that statin use is associated with significantly decreased C-Reactive protein and improved disease activity score in patients with RA taking atorvastatin for 12 weeks (28). However, a cohort study using the UK primary care database – the QResearch database did not find any benefit of statins on the incidence of RA (29). Whether statins have different effects on joint replacements due to OA and RA has not been examined.

We therefore undertook the present study using a large UK-wide national primary care database to investigate the association between statins and risk of joint replacement due to OA and RA.

# Methods

## Study design

## This was a propensity score matched cohort study.

## Participants

The CPRD is a large, longitudinal population-based, primary care database that includes data on demographics, symptoms, tests, diagnoses, prescriptions and referrals to secondary care routinely collected by UK general practitioners (GPs). By July 2017, it covered 718 GP practices in England, Scotland, Wales, and Northern Ireland with anonymised health data on over 17 million people (26% of the total UK population)(30). The accuracy and completeness of the CPRD has been validated by previous studies(31) and many studies have investigated effects of statin on various conditions(29, 32-34). The study protocol was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) (protocol 12\_020R2AR).

We identified a cohort of patients aged 40 and over, registered with up-to-standard GP practices (i.e. practices that met standardised quality criteria based on the continuity of recording and the number of recorded deaths) for more than 12 months from 1 January 1987 to 31 July 2017. ***Statin-users*** were defined as people who were ever prescribed a statin (two or more prescriptions). ***Non-users*** were defined as people who had never been prescribed statins during the period of current registration.

For statin users ***the index date*** was defined as the date of first statin prescription. Non-users were assigned an index date of their matched statin-users (pairs were matched by year of birth, gender and practice). Patients were followed up from the index date until first joint replacement, death, deregistration, or end of follow-up (31 July 2017) whichever came first.

A flow chart of the selected main cohort included is shown in Figure 1. The main cohort was further refined for a cohort excluding those with existing cardiovascular disease (CVD) in order to estimate the risk of joint replacement in people without CVD as defined by the NICE guidelines(35), i.e., using statin as a primary prevention.

Exclusion criteria were: invalid age or gender records; invalid joint replacement date; joint replacement prior to the first prescription of statin; joint replacement due to hip fracture or infection; revision surgery without a record of a primary joint replacement; invalid statin prescription data (e.g. if the number of tablets in prescription prescribed exceeded 600 or the daily dose exceeded the maximum daily dose for this drug); statin-users who received a single statin prescription only; statin-users prescribed cerivastatin (withdrawn from the market in 2001 due to adverse effects); and statin-users with prescription gaps of more than 90 days (i.e. discontinuation).

## Exposure

Exposure was defined as at least two statin prescriptions. Prior to the first prescription, participants had to had at least 12 month stain-free period to prevent prevalent user bias (36). We prioritised UK approved statins that were available for prescription, including simvastatin, atorvastatin, fluvastatin, rosuvastatin, and pravastatin (simvastatin 10 mg is also available over-the-counter). Statins were categorised as ***low intensity*** (21-28% reduction in low-density lipoprotein), ***medium intensity*** (32-38%) and ***high intensity*** (42-55%) according to their lipid lowering potency(37) (Appendix 1). Median statin intensity was calculated for each year of intake and for the total duration of statin exposure.

***Total duration of statin exposure*** was defined as the continuous use of statin, i.e., no discontinuation of more than 90 days between prescriptions during the follow-up period. This 90-day exposure window has been used in previous studies based on routinely collected data in primary care(29, 34, 38).

***Percentage of days covered (PDC)* *by statins per year*** was estimated as the number of prescriptions multiplied by days of each prescription (considering number of tablets per day or if not specified assuming a dosage of one tablet per day) divided by 365. Switching between statins or to fixed combinations was regarded as a continuation of therapy.

We accounted for overlapping tablet days assuming that the patient had finished the current prescription before starting the refill prescription as shown in Appendix 2 (e.g. the patient was credited for the surplus statin from overlapping refills)(39).

## Outcomes

**The primary outcome** was joint replacement defined as at least one record of total or partial knee joint replacement (KJR) or hip joint replacement (HJR) according to the standard clinical terminology system used in General Practice in the United Kingdom i.e. Read codes. Read codes for KJR and HJR are provided in Appendix 3. If a person had HJR plus KJR, the earlier event was chosen for any joint replacement. We also examined: ***[1] site-specific (hip or knee) joint replacement***; ***[2] joint replacement due to OA* (**Read codes included hip OA, knee OA, generalised OA, other joint OA); ***[3] joint replacement in people due to RA***.

**OA** was defined as present if at least one record of hip OA, knee OA, generalised OA, and OA of other joints was identified during follow-up.

**RA** was defined as present if either of two definitions was met, specifically: (1) at least one diagnostic Read code for RA (any group) and at least one appropriate prescription of a DMARD with no alternative indication for the DMARD; or (2) two or more diagnostic Read codes for RA (on different dates) and at least one RA code in group 1 or group 2 with no alternative diagnosis after the final RA code (Appendix 4) (40, 41).

**Secondary** **outcomes: *[1] joint replacement in people without CVD*** i.e. focusing on statin use for primary prevention of CVD.

## Covariates

Patient demographics (e.g. age, sex, practice), comorbidities and relevant medications were identified as covariates. Body mass-index was not included because it caused a large number of missing data, especially in controls. All comorbidities, including those diagnoses used as alternative indications for DMARDS or alternative diagnosis for OA and peripheral joint pain, are defined in Appendix 5. CVD included diseases of the heart and blood vessels caused by atherosclerosis including heart attack, myocardial infarction, coronary or ischaemic heart disease and atherosclerosis (NICE guidelines).

## Statistical analysis

### Propensity score

Each statin-user was matched with non-user by age, gender, practice, and propensity score (PS). We estimated a PS (i.e. probability of being prescribed statin) for each statin user and non-user using multivariable logistic regression.

***PS model for the main cohort*** included age, gender, lifestyle factors (smoking, alcohol dependence), RA (yes/no), RA duration in years, OA (yes/no), OA duration in years, Charlson comorbidity index and individual comorbidities to reduce residual confounding (diabetes mellitus, hypertension, cardiovascular disease, ischaemic stroke and other thromboembolic diseases, peripheral pain, peripheral vascular disease, atrial fibrillation, congestive heart disease, renal disease, valvular heart disease), and other medications used (nitrates, anti-platelets, diuretics, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, DMARDs, oral corticosteroids).

For the sub-cohort (Figure 1) we estimated subgroup-specific PS and re-matched individuals(42). ***PS model for people without CVD*** at baseline included the same set of co-variates as in the PS model for main analysis except for CVD.

PS matching was performed using the “greedy” matching algorithm(43) where a set of X cases was matched to a set of Y controls in a set of X decisions, excluding those who could not be matched. PS distribution before and after matching for the main cohort is shown in Appendix 6. Before PS matching we trimmed at the extreme ends of the PS tail (below the 5th and above the 95th percentile)(44). Covariate balance was assessed with standardised mean differences (SMD)(45). Post-matching SMD <0.1 indicated a good covariate balance between groups(45, 46). SMD is a validated method to assess whether the PS scores are comparable between exposed and unexposed groups. SMD is preferable over significance testing (i.e. p-value) which is influenced by sample size, and over the c-statistic or area under the receiver operating characteristic (ROC) curve(46).

### Time to event analysis

***Cox proportional hazards regression*** was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) between statin users and non-users. For our primary analysis we estimated:

* Non-PS matched HR using multivariable Cox regression, adjusting for all covariates including age, gender, lifestyle factors (smoking, alcohol dependence), RA (plus duration in years), OA (plus duration in years), Charlson comorbidity index (Appendix 7), comorbidities (diabetes mellitus, hypertension, cardiovascular disease, ischaemic stroke and other thromboembolic diseases, peripheral pain, peripheral vascular disease, atrial fibrillation, congestive heart disease, renal disease, valvular heart disease), other medication used (nitrates, anti-platelets, diuretics, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, DMARDs, oral corticosteroids).
* PS matched HR using Cox regression stratified on matched sets with robust standard errors to account for “cluster effect” within matched pairs(43, 47).

***Dose-response analysis*** was performed using linear trends for effect of statin intensity (0 for non-users, 1 for low, 2 for medium and 3 for high intensity).

In addition, competing risk of death was adjusted using the proportional sub-distribution hazard regression (48-50). This was because if a person died before an outcome of interest, it would challenge the assessment of that outcome.

All analyses were performed using SAS statistical software version 9.4

# Role of the Funding Source

The funding source had no role in: the design or conduct of the study; the collection, analysis, or interpretation of the data; or the writing of the report. The corresponding authors had full access to all data in the study and had final responsibility for the decision to submit the manuscript for publication.

# Results

***Cohort description.*** A total of 3,981,838 individuals met our inclusion criteria, of whom 706,943 were statins-users and 178,467 were successfully PS matched to the same number of non-users (PS distribution before and after matching is shown in Appendix 6). After PS-matching, all covariates were balanced between the two groups (Table 1). The number of patients at risk of having joint replacement in each year of follow-up is shown in Appendix 8. The mean age of the matched cohort was 62 (SD ~11, range 40-86) years and 52% were women (Table 1). Mean duration of follow-up was 6.88 (SD 3.98) for statin-users and 6.25 years (SD 3.82) for non-users. The maximum period of follow up was 28 years in both groups.

***Statin prescribing.*** Most statin-users in the PS-matched cohort started treatment with medium intensity statins (73%) and had good adherence (PDC≥80) at baseline and during the first year of follow-up (75% and 63% respectively). 26% of statin-users discontinued treatment during the first 2 years (Table 2).

***Joint replacement.***In non-PS matched analysis statin-users had higher probability of having any joint replacement compared to non-users (HR 1.13, 95% CI 1.10 to 1.16). However, in the PS-matched cohort joint replacement was not associated with statins (0.99, 0.97 to 1.03)) (Table 3). Additional adjustment for the competing risk of death in the PS-matched cohort provided similar results (1.02, 0.98 to 1.05).

In the subgroup analysis, there were no relationships between statins and KJR or HJR, or joint replacement due to OA (Table 3). However, statin-users with RA were less likely to undergo joint replacement compared to non-users with RA (0.77, 0.63 to 0.94).

Further analysis in the PS-matched cohort demonstrated an overall trend of dose response effect but this was only significant for any joint replacement (p for trend 0.0244) and KJR (p for trend 0.0210) (Figure 2, Appendix 9). However, comparing to non-users, statins at the high intensity had lower risk of any joint replacement (HR 0.86, 95%CI 0.75 to 0.98), joint replacement due to RA (0.10, 0.02 to 0.65) and joint replacement due to OA (0.79, 0.68 to 0.92).

Among people without any diagnosed CVD at baseline (i.e. primary prevention) statin-users had a marginally lower risk of joint replacement compared to non-users (0.96, 0.93 to 1.00).

# Discussion

The key findings of this population-based cohort study are: [1] statin use was associated with reduced joint replacement due to RA but not OA; [2] high intensity statin was associated with reduced joint replacement due to both RA and OA; and [3] a dose response relationship was observed for any joint replacement and knee joint replacement outcomes.

The main results of this study are consistent with results from four large Swedish population-based cohorts (21) that did not find any association between statin use and joint replacement due to OA. We used joint replacement as the primary outcome because it is a hard outcome and well coded in CPRD(6). Using this outcome without the selection of index disease (OA in this case) helps to avoid “index event bias”(51). We used the PS matched method to minimize “confounding by indication” – an important issue with observational studies examining therapeutic effects(52). The balanced PS between the groups suggests that confounding by indication was kept to the minimum according to the known factors. The reduction of HR from non-PS matched to the PS-matched methods suggests that the direction of the confounding by indication is towards a positive (HR>1), not negative (HR<1), association. This means that if a positive association is observed it is likely to be biased/inflated, whereas if a negative association is observed it is likely to be true and to become even more negative should this confounding be fully controlled. This is in line with our knowledge that both OA and RA are associated with CV events, hence patients with OA or RA are more likely to be given statins than those without these conditions. In addition, our further analysis in people without CVD shows that statins were negatively associated with joint replacement although it was just marginal (p=0.05). This suggests that the PS calculation for joint replacement outcome is justified and the protective effect of statin on joint replacement may be independent from CVD. Furthermore, we controlled for other potential biases. For example, we used the incident statin users in this analysis to avoid “bias of prevalent users”, as this gives a full course of the exposure, and to avoid left censorship or truncation (i.e., outcomes occur before baseline) that may be caused by using prevalence users (36, 53). If we used prevalent exposure, we were unable to define the starting point of the statin exposure, hence unable to measure time to event outcome, and unable to control “immortal time bias” by matching index dates between statin-users and non-users (54).

It is well-established that people with RA have an increased CV risk as a result of complex interaction between traditional risk factors (dyslipidaemia, insulin resistance, arterial hypertension, obesity, smoking) and chronic auto-immune inflammation (25). Statin treatment has been reported to reduce CV risk in RA individuals through its angio-protective, lipid-lowering and anti-oxidative effects (24, 26). Moreover, several studies and a recent meta-analysis of nine randomized controlled trials report that statins may influence the inflammatory process and disease activity (24, 27, 28). Our findings on decreased risk of joint replacement due to RA in statin-users could suggest that statins reduce subsequent joint damage and slow the rate of progression to surgery. If statins work for both cardiovascular events and RA-related joint replacement, this might lead to some changes in treatment recommendations. For example, people with RA and CVD (or at higher CV risk) could be given statins for the management of both conditions. However, the small effect of statins on joint replacement due to RA in our study (HR=0.77, 95% CI 0.63 to 0.94) may not be clinically significant on its own but at this early stage we believe that a statistical significance should not be ignored. Given the limitations of this study, further well designed studies are still needed to examine the mechanism of statins in RA. A randomised control trial to assess the efficacy and cost-effectiveness of different treatment regimens of statin with or without other anti-rheumatic drugs in people with RA and cardiovascular diseases (CVDs) or high risk of CVDs is also justified.

There are several potential limitations to this study. Firstly, we could only use data and variables that are recorded in the CPRD. There are many variables that may influence the balance between statin users and non-users, hence confounding by indication cannot be fully removed. For example, BMI was not included because it caused large number of missing data, particularly in the non-exposure group. However, after the PS matching, the two groups were fairly balanced for major confounding factors, suggesting a comparability between groups. In addition, from the PS-matched and non PS-matched analyses, we understood the direction of the unmeasured confounding, which helps us to adequately interpret the findings with negative association. Secondly, OA records in the CPRD reflect physician-diagnosed OA and are likely to follow NICE criteria for clinical OA that focus on symptomatic cases alone(55). Also we could not account for any delay between first symptoms and the diagnosis of OA/RA in primary care. This was one of the reasons why we used joint replacement as our primary outcomes as this is less prone to misclassification bias. Thirdly, our definition of joint replacement due to OA only included hip and knee OA so the results cannot be generalised to other joints affected by OA. Fourthly, cholesterol testing is not routine in the UK general practice, therefore serum cholesterol was not included in the propensity score model. Fifthly, we did not consider variation in statin prescriptions during follow-up, but used a simple continuous measure (no gaps more than 90 days) that may lead to potential imbalance in terms of exposure between statin users and non-users. Moreover, users of high intensity statins particularly in the RA-group were underrepresented in our analysis (Appendix 9) and therefore, a well-designed study with balanced groups is needed to confirm observed dose-response effect

***Conclusion***

In summary, statins may reduce the risk of joint replacement, especially when given at high strength and in people with RA. The evidence in knee replacement is stronger than that in hip replacement. Further studies to investigate mechanisms of statin and its clinical impact in people with RA are warranted.

**Table 1. Baseline characteristics**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Before PS-matching** | | | **PS-matched** | | |
|  |  | **Statin-users**  (n=562,526) | **Non-users**  (n=562,526) | **SMD** | **Statin-users** (n=178,467) | **Non-users**  (n=178,467) | **SMD** |
| **Index year, n (%)** |  |  |  |  |  |  |  |
| 1989-1999 |  | 30,475 (5.42) | 27,397 (4.87) |  | 7,286 (4.08) | 7,754 (4.34) |  |
| 2000-2009 |  | 408,284 (72.58) | 390,367 (69.40) |  | 123,007 (68.92) | 120,908 (67.75) |  |
| 2010-2017 |  | 123,767 (22.00) | 144,762 (25.73) |  | 48,174 (26.99) | 49,805 (27.91) |  |
| **Socio-demographics** |  |  |  |  |  |  |  |
| Age in years, mean (SD) |  | 63.03 (11.02) | 63.42 (11.11) | 0.036 | 61.91 (10.64) | 62.00 (11.74) | 0.007 |
| Women, n (%) |  | 266,324 (47.34) | 266,324 (47.34) | 0.000 | 89,747 (50.29) | 95,343 (53.42) | 0.063 |
| Smoking, n (%) |  | 313,593 (55.75) | 251,057 (44.63) | **0.224** | 94,190 (52.78) | 96,755 (54.21) | 0.029 |
| Alcohol dependence, n (%) |  | 522 (0.09) | 538 (0.10) |  | 149 (0.08) | 232 (0.13) |  |
| RA, n (%) |  | 5,702 (1.01) | 4,493 (0.80) | 0.023 | 1,906 (1.07) | 2,036 (1.14) | 0.007 |
| Duration (years), mean (SD) |  | 0.09 (1.12) | 0.07 (1.00) | 0.074 | 0.09 (1.13) | 0.10 (1.21) | 0.025 |
| Any OA, n (%) |  | 97,800 (17.39) | 74,482 (13.24) | **0.115** | 28,387 (15.91) | 30,626 (17.16) | 0.034 |
| Duration (years), mean (SD) |  | 1.24 (3.66) | 0.97 (3.35) | 0.077 | 1.12 (3.50) | 1.19 (3.59) | 0.019 |
| **Comorbidities** |  |  |  |  |  |  |  |
| Pain, n (%) |  | 207,424 (36.87) | 156,259 (27.78) | **0.195** | 64,958 (36.40) | 72,305 (40.51) | 0.085 |
| Charlson Index, mean (SD) |  | 0.89 (1.82) | 0.76 (1.79) | 0.074 | 0.80 (1.77) | 0.85 (1.83) | 0.025 |
| Renal, n (%) |  | 31,627 (5.62) | 15,139 (2.69) | **0.147** | 8,582 (4.81) | 8,302 (4.65) | 0.007 |
| Coronary, n (%) |  | 123,781 (22.00) | 15,376 (2.73) | **0.612** | 7,576 (4.25) | 6,907 (3.87) | 0.019 |
| Cerebrovascular disease, n (%) |  | 48,903 (8.69) | 9 291 (1.65) | **0.322** | 5,297 (2.97) | 4,230 (2.37) | 0.037 |
| Peripheral vascular disease, n (%) |  | 23,586 (4.19) | 4,908 (0.87) | **0.213** | 2,838 (1.59) | 2,295 (1.29) | 0.026 |
| Carotid, n (%) |  | 2,106 (0.37) | 210 (0.04) | 0.074 | 107 (0.06) | 55 (0.03) | 0.014 |
| Atrial fibrillation, n (%) |  | 27,506 (4.89) | 13,601 (2.42) | **0.132** | 7,012 (3.93) | 6,726 (3.77) | 0.008 |
| Valvular heart disease, n (%) |  | 1,439 (0.26) | 624 (0.11) | 0.034 | 364 (0.20) | 350 (0.20) | 0.002 |
| Hypertension, n (%) |  | 282,228 (50.17) | 109,389 (19.45) | **0.681** | 71,176 (39.88) | 73,848 (41.38) | 0.030 |
| Diabetes, n (%) |  |  |  |  |  |  |  |
| Without complications |  | 101,978 (18.13) | 10,083 (1.79) | **0.666** | 4,325 (2.42) | 2,785 (1.56) | 0.093 |
| With complications |  | 16,876 (3.00) | 2,308 (0.41) |  | 1,474 (0.83) | 778 (0.44) |  |
| Congestive heart disease, n (%) |  | 17,539 (3.12) | 6,294 (1.12) | **0.139** | 3,112 (1.74) | 2,576 (1.44) | 0.024 |
| **Medication use (n (%))** |  |  |  |  |  |  |  |
| Nitrates |  | 87,410 (15.54) | 6,441 (1.15) | **0.539** | 2,645 (1.48) | 1,895 (1.06) | 0.038 |
| Diuretics |  | 182,956 (32.52) | 73,073 (12.99) | **0.955** | 43,448 (24.35) | 44,962 (25.19) | 0.020 |
| Anti-platelets |  | 244,934 (43.54) | 35,241 (6.26) | **0.955** | 19,129 (10.72) | 16,214 (9.09) | 0.055 |
| DMARDS |  | 6,954 (1.24) | 5,177 (0.92) | 0.031 | 2,136 (1.20) | 2,433 (1.36) | 0.015 |
| Angiotensin converting enzyme inhibitors |  | 200,315 (35.61) | 43,265 (7.69) | **0.721** | 28,112 (15.75) | 27,586 (15.46) | 0.008 |
| AGT antagonists |  | 52,939 (9.41) | 16,843 (2.99) | **0.268** | 11,386 (6.38) | 11,378 (6.38) | 0.001 |
| Β-blockers |  | 170,622 (30.33) | 42,830 (7.61) | **0.479** | 25,180 (14.11) | 27,614 (15.47) | 0.038 |

***Note:*** PS – propensity score, SMD – standardised mean difference, SD – standard deviation, DMARDs – disease-modifying antirheumatic drugs, AGT antagonists - angiotensin II receptor antagonists.

**Table 2. Statins characteristics.**

|  |  |
| --- | --- |
| **Variable** | **Measure** |
| N | 178,467 |
| Intensity at start, n (%) |  |
| *Low* | 32,652 (18.30) |
| *Medium* | 130,980 (73.39) |
| *High* | 14,835 (8.31) |
| Total exposure period, days, mean (SD) | 2,024 (1566) |
| Total exposure period, years, n (%) |  |
| *Less than 2 years* | 46,664 (26.15) |
| *3-4 years* | 30,679 (17.19) |
| *5-6 years* | 27,407 (15.36) |
| *7-8 years* | 23,744 (13.30) |
| *9-10 years* | 19,587 (10.98) |
| *>10 years* | 30,386 (17.03) |
| Baseline PDC, mean (SD) | 0.85 (0.24) |
| Baseline PDC *>=80%, n (%)* | 133,664 (74.90) |
| Year 1 PDC (>2 years intake), mean (SD) | 0.76 (0.25) |
| Year 1 PDC*>=80%* (>2 years intake), *n (%)* | 88,700 (62.48) |

***Note:*** SD – standard deviation, PDC – proportion of days covered.

**Table 3. Relation of statin use to joint replacement surgery**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Before PS-matching** | | | | **PS-matched** | | | |
|  | *N of events* | *Person-years* | *Mean follow-up, years (SD)* | *HR (95%CI)\** | *N of events* | *Person-years* | *Mean follow-up, years (SD)* | *HR (95%CI)\*\** |
| **Any joint replacement** | |  |  |  |  |  |  |  |
| *Statin-users* | 21,430 | 3,989,753 | 7.09 (4.07) | **1.13 (1.10 to 1.16)** | 6,490 | 1,229,427 | 6.88 (3.98) | 0.99 (0.97 to 1.03) |
| *Non-users* | 15,910 | 3,607,011 | 6.41 (3.90) | 1 (reference) | 5,691 | 1,115,447 | 6.25 (3.82) | 1 (reference) |
| **Joint replacement due to OA** | | |  |  |  |  |  |  |
| *Statin-users* | 16,263 | 4,013,272 | 7.14 (4.08) | **1.11 (1.08 to 1.15)** | 4,901 | 1,236,347 | 6.92 (3.99) | 0.97 (0.94 to 1.01) |
| *Non-users* | 11,821 | 3,623,933 | 6.44 (3.91) | 1 (reference) | 4,378 | 1,120,856 | 6.28 (3.83) | 1 (reference) |
| **Joint replacement** **due to RA** | | |  |  |  |  |  |  |
| *Statin-users* | 549 | 4,086,522 | 7.27 (4.12) | 0.90 (0.77 to 1.05) | 173 | 1,256,995 | 7.04 (4.03) | **0.77 (0.63 to 0.94)** |
| *Non-users* | 431 | 3,674,882 | 6.53 (3.95) | 1 (reference) | 191 | 1,139,272 | 6.39 (3.88) | 1 (reference) |
| **Hip joint replacement** | |  |  |  |  |  |  |  |
| *Statin-users* | 9,894 | 4,044,099 | 7.19 (4.10) | **1.08 (1.05 to 1.13)** | 3,104 | 1,244,379 | 6.97 (4.01) | 0.98 (0.93 to 1.03) |
| *Non-users* | 8,265 | 3,641,043 | 6.47 (3.92) | 1 (reference) | 2,783 | 1,128,209 | 6.32 (3.85) | 1 (reference) |
| **Knee joint replacement** | |  |  |  |  |  |  |  |
| *Statin-users* | 12,444 | 4,031,130 | 7.17 (4.09) | **1.17 (1.13 to 1.21)** | 3,675 | 1,241,714 | 6.95 (3.99) | 1.00 (0.96 to 1.05) |
| *Non-users* | 8,350 | 3,640,147 | 6.47 (3.92) | 1 (reference) | 3,165 | 1,126,343 | 6.31 (3.85) | 1 (reference) |

Note: PS – propensity score, JR – joint replacement, OA – osteoarthritis, RA – rheumatoid arthritis, SD- standard deviation, hazard ratios (HR) with 95% confidence intervals (CI)

\* - Multivariate Cox regression model adjusted for covariates included in the PS-model (age, gender, smoking, alcohol consumption, RA (plus duration in years), OA (plus duration in years), Charlson comorbidity index, comorbidities (diabetes mellitus, hypertension, cardiovascular disease, ischaemic stroke and other thromboembolic diseases, peripheral pain, peripheral vascular disease, atrial fibrillation, congestive heart disease, renal disease, valvular heart disease), other medication used (nitrates, antiplatelets, diuretics, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, DMARDs, oral corticosteroids)

\*\* - Cox regression model stratified on PS matched sets with robust standard errors to account for “cluster effect” and subpopulation differences

**Figure 1. Flow chart of cohort**

**Figure 2. Statin use and joint replacement surgery: dose-response analysis**

Note: Dose-response analysis was performed using Cox regression and compared people taking low, medium and high intensity statins with non-users (reference category). Statin exposure was categorised as low (21-28% reduction in low-density lipoprotein cholesterol), medium (32-38%) and high (42-55%) intensity.

# ARTICLE INFORMATION

**Ethics approval:** We used a fully anonymised data set from the General Practice Research Database. We did not obtain participant's consent because the participant data were taken from the fully anonymised data set and no participant's identity details were revealed. There was no need for participant consent. This study was approved by the Independent Scientific Advisory Committee (ISAC) for Medicines and Healthcare Products Regulatory Agency (MHRA) database research (protocol 12\_020R2AR).

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

**Acknowledgements:** This work was financially supported by the National Natural Science Foundation of China (81772413, 81702207, 81702206). CM is funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands, the NIHR School for Primary Care Research and an NIHR Research Professorship in General Practice (NIHR-RP-2014-04-026). The views expressed are those of the authors and not necessarily those of the National Health Service, NIHR or Department of Health and Social Care.

**Role of the Funder/Sponsor:** The sponsor did not participate in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript and the decision to submit the manuscript for publication.

**Disclaimer:** The opinions, results and conclusions reported in this article are those of the authors and are independent from the funding sources.

**Authors' contributions:** WZ, MD, GL, CZ, JW, CK, AA, YW, CM and AS made substantial contributions to the conception and design of the study. All authors contributed to the writing and editing of the study protocol. AS and WZ conducted the data cleaning, and data analysis. All authors contributed to the interpretation of results. AS wrote the first draft. WZ has full access to the data and takes responsibility for the content and guarantees the integrity and accuracy of the work undertaken. All authors have read, provided critical feedback on intellectual content and approved the final manuscript.

**Data sharing statement:** Owing to ethical restrictions, data are not available for sharing. Anyone who would like to use CPRD data will need to first submit an application to the Independent Scientific Advisory Committee (ISAC) of the Medicines and Healthcare products Regulatory Agency (MHRA) http://www.cprd.com/ISAC/.

# References

1. NICE. Osteoarthritis: the care and management of osteoarthritis [Available from: <https://www.nice.org.uk/guidance/cg177/documents/osteoarthritis-update-final-scope2>.

2. National Joint Registry for England W, Northern Ireland and the Isle of Man. 14th annual Report 2017. 2017.

3. England MaN. NHS National Tariff Payment System 2016/17. Annex A: 2016/17 national prices and national tariff workbook 2017 [Available from: <https://www.gov.uk/government/publications/nhs-national-tariff-payment-system-201617>.

4. Singh JA. Epidemiology of knee and hip arthroplasty: a systematic review. Open Orthop J. 2011;5:80-5.

5. Inacio MCS, Paxton EW, Graves SE, Namba RS, Nemes S. Projected increase in total knee arthroplasty in the United States - an alternative projection model. Osteoarthritis and cartilage. 2017;25(11):1797-803.

6. 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. The Journal of bone and joint surgery British volume. 2010;92(1):130-5.

7. Dixon T, Shaw M, Ebrahim S, Dieppe P. Trends in hip and knee joint replacement: socioeconomic inequalities and projections of need. Ann Rheum Dis. 2004;63(7):825-30.

8. Rabar S, Harker M, O'Flynn N, Wierzbicki AS, Guideline Development G. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ. 2014;349:g4356.

9. Abeles AM, Pillinger MH. Statins as antiinflammatory and immunomodulatory agents: a future in rheumatologic therapy? Arthritis and rheumatism. 2006;54(2):393-407.

10. Gilbert R, Al-Janabi A, Tomkins-Netzer O, Lightman S. Statins as anti-inflammatory agents: A potential therapeutic role in sight-threatening non-infectious uveitis. Porto Biomedical Journal. 2017;2(2):33-9.

11. Lazzerini PE, Capecchi PL, Selvi E, Lorenzini S, Bisogno S, Baldari CT, et al. Statins and the joint: multiple targets for a global protection? Semin Arthritis Rheum. 2011;40(5):430-46.

12. Bauer DC. HMG CoA reductase inhibitors and the skeleton: a comprehensive review. Osteoporos Int. 2003;14(4):273-82.

13. Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM, Verhaar JA, Van GF, Van Meurs JB, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. Ann Rheum Dis. 2011.

14. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med. 2005;352(1):29-38.

15. Conaghan PG. The effects of statins on osteoarthritis structural progression: another glimpse of the Holy Grail? Ann Rheum Dis. 2012;71(5):633-4.

16. Beattie MS, Lane NE, Hung YY, Nevitt MC. Association of statin use and development and progression of hip osteoarthritis in elderly women. The Journal of rheumatology. 2005;32(1):106-10.

17. Clockaerts S, Van Osch GJ, Bastiaansen-Jenniskens YM, Verhaar JA, Van Glabbeek F, Van Meurs JB, et al. Statin use is associated with reduced incidence and progression of knee osteoarthritis in the Rotterdam study. Ann Rheum Dis. 2012;71(5):642-7.

18. Eymard F, Parsons C, Edwards MH, Petit-Dop F, Reginster JY, Bruyere O, et al. Statin use and knee osteoarthritis progression: Results from a post-hoc analysis of the SEKOIA trial. Joint, bone, spine : revue du rhumatisme. 2018;85(5):609-14.

19. Kadam UT, Blagojevic M, Belcher J. Statin use and clinical osteoarthritis in the general population: a longitudinal study. J Gen Intern Med. 2013;28(7):943-9.

20. Burkard T, Hugle T, Layton JB, Glynn RJ, Bloechliger M, Frey N, et al. Risk of Incident Osteoarthritis of the Hand in Statin Initiators: A Sequential Cohort Study. Arthritis Care Res (Hoboken). 2018;70(12):1795-805.

21. Michaelsson K, Lohmander LS, Turkiewicz A, Wolk A, Nilsson P, Englund M. Association between statin use and consultation or surgery for osteoarthritis of the hip or knee: a pooled analysis of four cohort studies. Osteoarthritis and cartilage. 2017;25(11):1804-13.

22. Veronese N, Koyanagi A, Stubbs B, Cooper C, Guglielmi G, Rizzoli R, et al. Statin use and knee osteoarthritis outcomes: A longitudinal cohort study. Arthritis Care Res (Hoboken). 2018.

23. Cook MJ, Sorial AK, Lunt M, Board TN, O'Neill TW. Effect of timing and duration of statin exposure on risk of hip or knee revision arthroplasty: a population-based cohort study. The Journal of rheumatology. 2019.

24. Soulaidopoulos S, Nikiphorou E, Dimitroulas T, Kitas GD. The Role of Statins in Disease Modification and Cardiovascular Risk in Rheumatoid Arthritis. Front Med (Lausanne). 2018;5:24.

25. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524-9.

26. Danninger K, Hoppe UC, Pieringer H. Do statins reduce the cardiovascular risk in patients with rheumatoid arthritis? International journal of rheumatic diseases. 2014;17(6):606-11.

27. Xing B, Yin YF, Zhao LD, Wang L, Zheng WJ, Chen H, et al. Effect of 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitor on disease activity in patients with rheumatoid arthritis: a meta-analysis. Medicine (Baltimore). 2015;94(8):e572.

28. Li GM, Zhao J, Li B, Zhang XF, Ma JX, Ma XL, et al. The anti-inflammatory effects of statins on patients with rheumatoid arthritis: A systemic review and meta-analysis of 15 randomized controlled trials. Autoimmunity reviews. 2018;17(3):215-25.

29. Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. BMJ. 2010;340:c2197.

30. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology. 2015;44(3):827-36.

31. Jick SS, Kaye JA, Vasilakis-Scaramozza C, Garcia Rodriguez LA, Ruigomez A, Meier CR, et al. Validity of the general practice research database. Pharmacotherapy. 2003;23(5):686-9.

32. Meier CR, Schlienger RG, Kraenzlin ME, Schlegel B, Jick H. HMG-CoA reductase inhibitors and the risk of fractures. Jama. 2000;283(24):3205-10.

33. van Staa TP, Wegman S, de Vries F, Leufkens B, Cooper C. Use of statins and risk of fractures. Jama. 2001;285(14):1850-5.

34. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. BMJ. 2016;353:i3305.

35. National Institute for Health and Care Excellence (2016). Cardiovascular disease: risk assessment and reduction, including lipid modification. Clinical guideline [CG181]. <https://www.nice.org.uk/guidance/cg181/chapter/Introduction> accessed 26 Sept 2018.

36. Danaei G, Tavakkoli M, Hernan MA. Bias in observational studies of prevalent users: lessons for comparative effectiveness research from a meta-analysis of statins. American journal of epidemiology. 2012;175(4):250-62.

37. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326(7404):1423.

38. Gardarsdottir H, Souverein PC, Egberts TC, Heerdink ER. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. Journal of clinical epidemiology. 2010;63(4):422-7.

39. Stacy Wang, Zhongwen Huang, Traubenberg S, editors. Measuring Medication Adherence with Simple Drug Use and Medication Switching SAS Global Forum 2013 2013.

40. 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 and rheumatism. 2008;59(9):1314-21.

41. Muller S, Hider SL, Raza K, Stack RJ, Hayward RA, Mallen CD. An algorithm to identify rheumatoid arthritis in primary care: a Clinical Practice Research Datalink study. BMJ Open. 2015;5(12):e009309.

42. Wang SV, He M, Jin Y, Wyss R, Shin H, Ma Y, et al. A review of the performance of different methods for propensity score matched subgroup analyses and a summary of their application in peer-reviewed research studies. Pharmacoepidemiol Drug Saf. 2017;26(12):1507-12.

43. Faries DE, Obenchain R, Haro JM, Leon AC. Analysis of observational health care data using SAS: SAS Institute; 2014.

44. Sturmer T, Rothman KJ, Avorn J, Glynn RJ. Treatment effects in the presence of unmeasured confounding: dealing with observations in the tails of the propensity score distribution--a simulation study. American journal of epidemiology. 2010;172(7):843-54.

45. Nguyen TL, Collins GS, Spence J, Daures JP, Devereaux PJ, Landais P, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. BMC Med Res Methodol. 2017;17(1):78.

46. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28(25):3083-107.

47. Shinozaki T, Mansournia MA, Matsuyama Y. On hazard ratio estimators by proportional hazards models in matched-pair cohort studies. Emerg Themes Epidemiol. 2017;14:6.

48. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.

49. Kohl M, Plischke M, Leffondré K, Heinze G. PSHREG: A SAS macro for proportional and nonproportional subdistribution hazards regression. Computer methods and programs in biomedicine. 2015;118(2):218-33.

50. Nunes JP. Statins in primary prevention: impact on mortality. A meta-analysis study. Minerva cardioangiologica. 2017;65(5):531-8.

51. Dahabreh IJ, Kent DM. Index event bias as an explanation for the paradoxes of recurrence risk research. Jama. 2011;305(8):822-3.

52. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate Behav Res. 2011;46(3):399-424.

53. Vandenbroucke J, Pearce N. Point: incident exposures, prevalent exposures, and causal inference: does limiting studies to persons who are followed from first exposure onward damage epidemiology? American journal of epidemiology. 2015;182(10):826-33.

54. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. BMJ. 2010;340:b5087.

55. Osteoarthritis: Care and management in adults. NICE guidelines [CG177] 2014 [updated February 2014. Available from: <http://www.nice.org.uk/guidance/cg177/chapter/1-recommendations>.