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

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Abstract

(word count 250)

Objective: Statins are reported to have a potential beneficial impact 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 Clinical Practice Research Datalink, the UK. 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 and propensity score. Overall, statin use 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).

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Key Messages

- Statins are routinely used in the treatment of cardiovascular diseases, however also might 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 level 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]. However, the possible effect of statins on development and progression of OA remains unclear. One of the earliest studies by Beattie et al[16] reported an increased rate of radiographic hip OA in elderly women. A study by Kadam et al[17] found an association between higher statin dose (the 4th quartile) and reduction in incident OA in people with existing CVD. Statin use associated with radiographic progression of knee OA but not hip OA in a study by Clockaerts et al[18]. However, more recent large studies have not confirmed these findings. For example, statins were associated with radiographic worsening of knee OA over 3 years in a study by Eymard et al[19] but a UK cohort study did not find any association between statin use and incident hand OA[20]. Pooled results from four large Swedish population-based cohorts showed no association between statin use and consultation or surgery for OA of the hip or knee[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]. Some evidence supports a potential beneficial impact of statins on disease activity, attributable to their anti-inflammatory and immunomodulatory properties in rheumatoid arthritis (RA)[24-27]. However,

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)[28]. The accuracy and completeness of the CPRD has been validated by previous studies[29] and many studies have investigated effects of statin on various conditions[30-33]. 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[34], 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

The first statin prescription after a statin-free period of ≥12 months (to prevent prevalent user bias) was identified using drug codes in CPRD[35]. 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[36] (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[32, 33, 37].

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)[38].

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 with 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) [39, 40].

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[41]. ***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[42] 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)[43]. Covariate balance was assessed with standardised mean differences (SMD)[44]. Post-matching SMD <0.1 indicated a good covariate balance between groups[44, 45]. SMD is a validated method to assess whether the PS scores are comparable between treated and untreated 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[45].

Time to event analysis

Cox proportional hazards regression was used to examine 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[42, 46].

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 [47-49]. 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. In total, 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 (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"[50]. We used the PS matched method to minimize "confounding by indication" – an important issue with observational studies examining therapeutic effects[51]. The balanced PS between the groups and the difference between non-PS and PS-matched results suggest 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 association (HR<1). 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"[35]. If we used prevalent exposure, we were unable to define the starting point of the exposure, hence unable to measure time to event outcome. We also accounted for "immortal time bias" by matching index dates between statin-users and non-users[52].

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 report that statins may influence the inflammatory process and disease activity[24, 27]. 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. We hypothesize that if statins work for both cardiovascular events and arthritis-related joint replacement, this might lead to some changes in treatment recommendations.

There are 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 (e.g. BMI). However, from the PS-matched and non PS-matched analyses, we understood the direction of this 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[53]. 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 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. Finally, we were able to obtain good covariate balance between groups by using propensity score matching, however, unknown confounding factors and their potential bias to the study cannot be fully eliminated.

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 joint replacement risk reduction 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
B-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

359 **Figure 1. Flow chart of cohort**

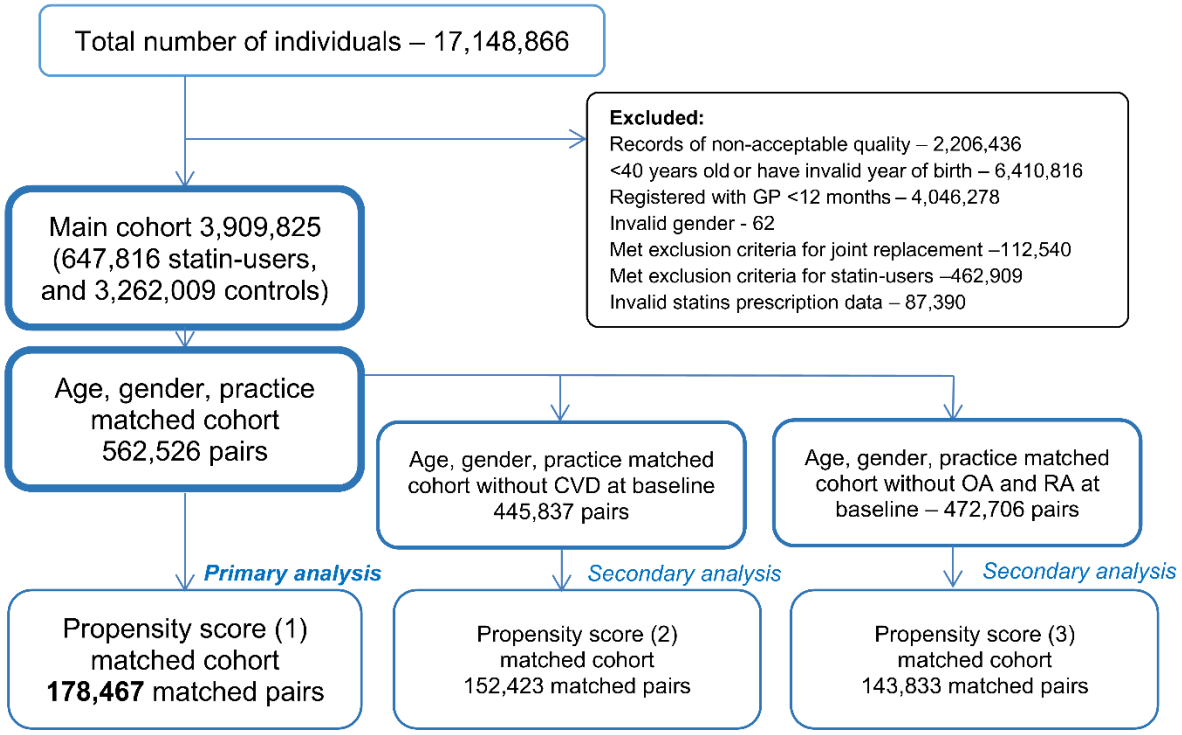

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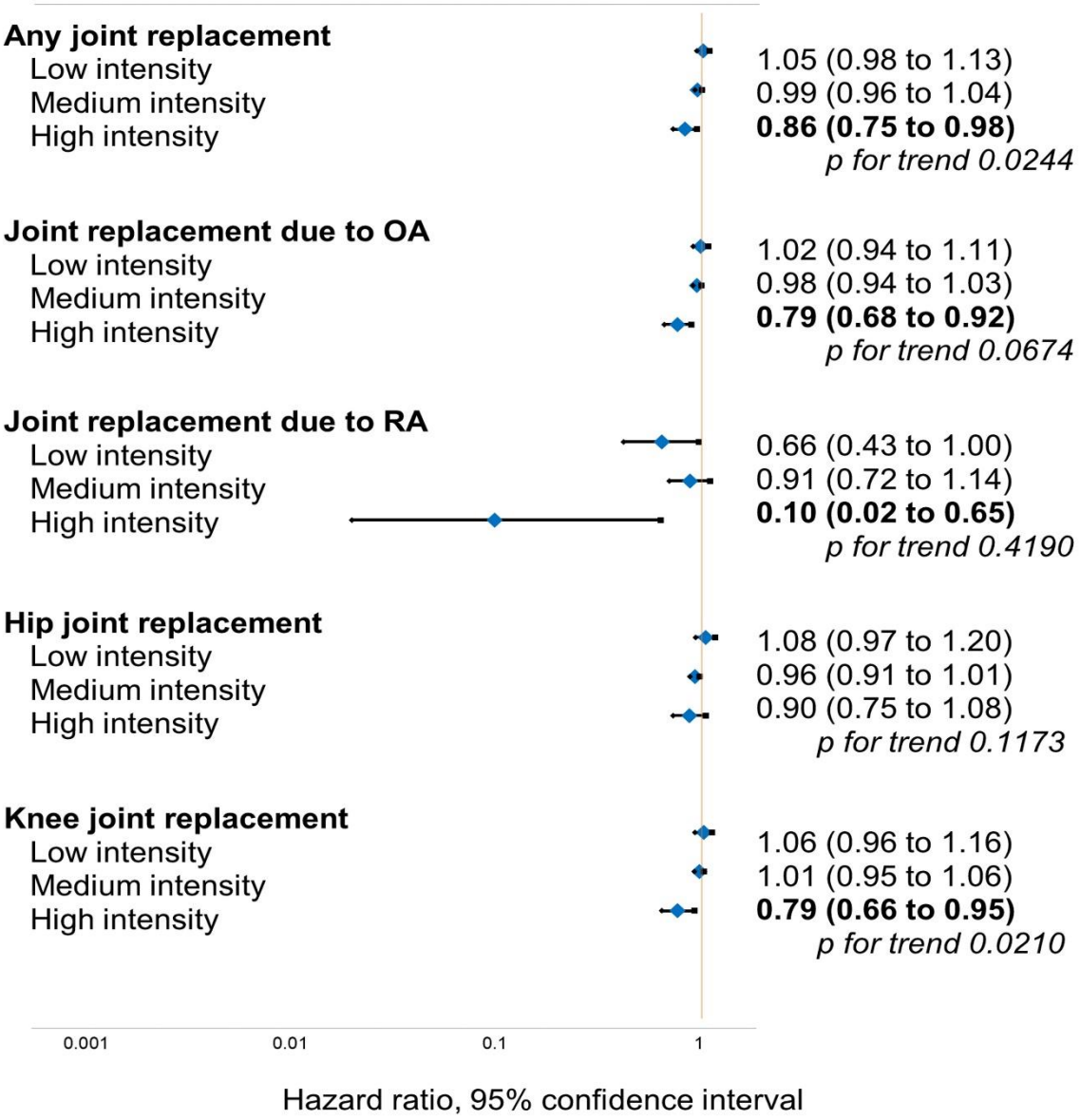
Figure 2. Statin use and joint replacement surgery: dose-response analysis



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.

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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/.

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