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Association of Statin Use with Increased Risk of Musculoskeletal Conditions: A Retrospective Cohort Study

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Abstract

Introduction—Musculoskeletal conditions, including osteoarthritis (OA), result in tremendous disability and cost. Statins are among the most commonly prescribed medications and their use for primary prevention in many otherwise healthy individuals, including those who are physically active, is increasing. There is conflicting evidence regarding the relationship of statin use and musculoskeletal conditions. Given the rising disability associated with musculoskeletal conditions, understanding predisposing factors, including medication-related exposures, deserves further attention.

Objectives—We examined the association between statin use and the risk of being diagnosed with non-traumatic arthropathies, use-related injury, and undergoing rehabilitation in a cohort with longitudinal follow-up.

Methods—Patients enrolled in a regional military healthcare system between 2003-2012 were evaluated in this retrospective cohort study. A propensity score was generated to match statin-users and nonusers using 115 baseline characteristics. Outcomes included ICD-9 diagnoses codes for Agency for Healthcare Research and Quality disease categories of: non-traumatic arthropathies,

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COMPLIANCE WITH ETHICAL STANDARDS

CONFLICTS OF INTEREST

Una E. Makris, Carlos A. Alvarez, Eric M. Mortensen, Ishak A. Mansi have no conflicts of interest that are directly relevant to the content of this study.

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ETHICAL APPROVAL

Approval was obtained from the Institutional Review Board (IRB) at Brooke Army Medical Center and the VA North Texas Health System.

use-related injury and undergoing rehabilitation. Primary analysis examined the outcomes in statin-users and nonusers after propensity score matching using conditional logistic regression analysis.

Results—Initially, 60,455 patients were identified. We propensity score-matched 6728 statin users with 6728 nonusers (52 years of age, ~47% women). In the propensity score-matched cohort, non-traumatic arthropathies occurred in 59.8% of statin users and 56.0% of nonusers (odds ratio [OR] 1.17, 95% confidence interval [95%CI] 1.09-1.25) and use related injury occurred in 31.9% of statin users and 29.8% of nonusers (OR 1.11, 95%CI 1.03-1.19). There was no difference between statin users and nonusers in undergoing rehabilitation (22.6% among statin users, 21.9% among nonusers, OR 1.04, 95%CI 0.96-1.13).

Conclusion—Statin use was associated with a significant increased risk of non-traumatic arthropathies and use-related injury. Our results provide additional data that can inform patient and clinician conversations about the benefits and risks of statin use.

Keywords

Statin; osteoarthritis; musculoskeletal diseases; use-related injury; observational study

1 INTRODUCTION

Osteoarthritis (OA), one of the most common musculoskeletal conditions, results in tremendous disability and cost at both the personal and societal levels. Similarly, cardiovascular diseases have tremendous morbidity and mortality. Studies are uncovering several potential shared mechanisms between cardiovascular disease and OA. We are still learning more about the multifactorial pathogenesis of musculoskeletal conditions and how metabolic pathways contribute to structural damage and deleterious patient reported outcomes. Statins (hydroxyl-methyl-glutaryl coenzyme A reductase inhibitors) are widely used to prevent cardiovascular disease, and its use is rising.[1] Recent cholesterol management guidelines expanded the recommendations regarding statin use for primary prevention to many otherwise healthy individuals; this often includes individuals who are physically active. However, recommendations are not consistent between expert groups/panels and differ on the populations that should be prescribed statins for primary prevention.[2]

Statins have been shown to have potentially modifying effects in musculoskeletal conditions.[3, 4] Currently, data from observational studies are conflicting[3–7] – there is no consensus on whether statins are protective or deleterious in the development and progression of musculoskeletal conditions. One study noted that statins were associated with a reduction in clinically defined OA.[3] Prompted by data suggesting an association between statin use and a decreased risk of developing OA, there is a current randomized controlled trial (the Osteoarthritis of the Knee Statin (OAKS) study) that seeks to address whether atorvastatin has disease modifying effects in OA by delaying structural and symptomatic progression of knee OA.[8]

Additional research suggests that statin use is *not* associated with improvement in knee pain, function or structural progression of knee OA over four years.[4] Our group reported that statin use, in a different propensity score-matched study of statin users and nonusers, was associated with increased risk of musculoskeletal use-related injury in our primary and secondary analyses and an increased incidence of arthropathies in the secondary analysis only.[9] However, our prior study only included statin users who initiated statins in fiscal year (FY) 2005 and excluded those who initiated statins in subsequent years. It also defined nonusers as those who never used a statin throughout the study period; such a study design of "never-user/user" may exaggerate findings. Additionally, our prior study had a shorter follow up ending in 2010; longer duration of follow-up may reveal adverse events that are slower to develop Given conflicting evidence regarding statin use and the rising disability, societal and personal repercussions associated with both OA, and inconsistency in guidelines for certain populations, understanding predisposing exposures (including medication related) or protective factors deserves further attention.

The objective of this study was to examine the association between statin use and the risk of being diagnosed with non-traumatic arthropathies, use-related injury, and undergoing rehabilitation in a patient cohort with longitudinal follow-up and equal access to healthcare. Our *a priori* hypothesis was that statin use would be associated with musculoskeletal conditions.

2 METHODS

After obtaining approval of the Institutional Review Board (IRB) at Brooke Army Medical Center and the VA North Texas Health System, we used the Military Health System (MHS) Management Analysis and Reporting Tool (M2) to retrieve administrative, clinical, and medication fill data for patients enrolled in the San Antonio Military Multimarket area encompassing the period October 1, 2003 to March 31, 2012. The M2 data include clinical and administrative data of inpatient and outpatient medical encounters within and outside MHS, all dispensed medications, and laboratory investigations performed within MHS.[10] A more detailed description of the methods has previously been published.[11, 12]

Inclusion criteria were ≥ 30-years of age at the start of baseline period (detailed later), at least one medical encounter during the baseline period, and at least one medical encounter during the follow-up period.

Two treatment groups were identified:

1. Statin users: Newly received and continued a statin for at least 120 days. We defined statin new users as those who initiated statin use on or after October 1, 2005– to allow at least two years without using statins since the study start date. Prevalent statin users who received statins prior to October 1, 2005 were excluded. We required that statin users had continued statins for 120 days to improve likelihood that an individual is taking this medication long term and that it was not a one-time prescription that might not have been filled. Additionally, most clinical outcomes of statins, including their beneficial cardiovascular

effects, occurred after several months of statin use. Statin users who used statins for less than 120 days were excluded.

2. Statin nonusers included two groups: Patients who never used statins and statin-users *prior to* being prescribed statins. Including statin users before using statins as nonusers may mitigate immortal time bias and avoid selection bias.[13, 14] Thereafter, we matched treatment groups on baseline period start date and follow-up duration to avoid potential biases resulting from differences in beginning of baseline periods and follow-up duration periods.

2.1 Index date and study periods

The study was divided into two periods: 1) baseline period, which was defined as the two years preceding the index date and was used to describe baseline characteristics; and 2) follow-up period, which started 90 days after the index date and was used to capture outcomes.

Among statin users, the index date was 10 days after the date of first statin use since events occurring in this period are more likely to be due to baseline characteristics than to pharmacological effects of statins. For example, a patient may complain of chest pain suspicious of angina and started on a statin prior to receiving the diagnosis of angina. Among nonusers, the index date was defined as the date marking the end of two years after the first date of any encounter.

The follow-up period started 90 days after the index date; we omitted the first 89 days after index date from outcomes to minimize effects of unrecognized confounders as recommended in prior studies;[15–17] since the pharmacological effects of statins are expected to occur after 3 months at least, therefore, any events that had taken place during this period would most likely represent either a chance or confounders.[15–17]

2.2 Outcomes

We used the Agency for Health Research and Quality Clinical Classifications Software (AHRQ-CCS) disease categories to define our pre-specified outcome groups.[18–23] An outcome was defined as an occurrence of an International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code in inpatient or outpatient settings consistent with diagnostic categories (see Electronic Supplementary Material #1):

1. Non-traumatic arthropathies: Included osteoarthritis (AHRQ-CCS disease category 203) and non-traumatic joint disorders (AHRQ-CCS disease category 204).

2. Use-related injury: Included trauma-related joint disorders and dislocations (AHRQ-CCS disease category 225), and sprains and strains (AHRQ-CCS disease category 232).

3. Undergoing rehabilitation: Included rehabilitation care; fitting of prostheses; and adjustment of devices (AHRQ-CCS disease category 254). We presumed that this category can be considered a surrogate for clinical significance of the former outcomes.

The AHRQ-CCS method of development and validation were previously published.[24, 25] The AHRQ-CCS diseases categories were used to estimate the medical expenditure and prevalence of chronic conditions, including musculoskeletal diseases.[26, 27] Using AHRQ-CCS diseases categories, the Healthcare Cost and Utilization Project identified osteoarthritis as the fifth most common principal diagnosis in 2011.[28] Use of ICD-9-CM codes to identify musculoskeletal conditions has been also utilized to describe the epidemiology of osteoarthritis in a population,[29] the prevalence of painful musculoskeletal conditions in Veterans after deployment,[30] and medication adverse events.[9, 31] There is an overall concordance between ICD-9-CM codes for musculoskeletal conditions and Veterans Administration Schedule for Rating Disability (VASRD), which is used by the army to categorize and code permanent disability.[32] The two major subgroups of musculoskeletal conditions in VASRD are “injury” and “diseases”, which together constituted the most common cause for permanent disability in the U. S. army.[32]

2.3 Data and Statistical Analyses

We used a logistic regression model to create a propensity score to match comparison groups on 115 baseline characteristics including personal history, social history, family history, healthcare utilization, baseline period start date, comorbidities, Charlson comorbidity index, [33] use of various classes of medications, and undergoing invasive and noninvasive cardiovascular procedures during the baseline period as well as follow-up duration (see Electronic Supplementary Material #2 and Table 1). After creating a propensity score, we matched treatment groups 1:1 for nearest neighbor with a caliper of 0.01 and tested the balance of covariates using the methods previously described.[34–38]

Primary analysis—We examined odds ratios of outcomes in statin-users and nonusers in the propensity score-matched cohort using conditional logistic regression analysis. We also calculated the number needed to be exposed for one additional person to be harmed.[39]

Secondary and sensitivity analyses—We examined risks of outcomes in the following cohorts using multivariable logistic regression with adjustment for propensity score:

1. Overall cohort: Including all patients who met the study inclusion and exclusion criteria-we performed several analyses:
    a. All statin users vs. nonusers;
    b. All statin users vs. nonusers with additional adjustment for medications use and undergoing revascularization procedures during the follow-up period. We included medication groups that may be associated with increased body weight or musculoskeletal symptoms (systemic corticosteroids, selective serotonin reuptake inhibitors, anti-psychotic, bisphosphonate, hormone replacement therapy, testosterone, warfarin, and cytochrome P450 inhibitors[40]). We also assumed that invasive revascularization procedures (percutaneous coronary intervention, coronary artery bypass surgery, or peripheral revascularization procedure) may result in prolonged bed rest and hospitalization; hence, it may contribute to musculoskeletal symptoms;

c. Statin users who used statins for two years or more vs. nonusers;

d. Statin users who used statins for four years or more vs. nonusers;

e. Statin users who used high-intensity statins for 120 days at least vs. nonusers. Statin intensity was defined as per the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA),[41] with a modification to include simvastatin 80 mg as high-intensity statin;

2. Non-obese cohort: This cohort excluded patients diagnosed with obesity at baseline or at follow-up.

3. Healthy cohort: This cohort excluded patients with any component of the Charlson comorbidity index,[33] cardiovascular disease, or severe chronic disease that may limit survival or physical activity (see Electronic Supplementary Material #3).

4. Musculoskeletal diseases incident cohort: In this analysis, we excluded patients who were diagnosed with any of our outcomes of interest during the baseline period.

5. Statin users cohort: This cohort only included statin users from the overall cohort; in this analysis, we examined risk of outcomes between high-intensity statin users versus moderate/low-intensity statin users.

Baseline characteristics for comparator groups were assessed and standardized differences were reported. Comparisons of the outcomes were considered to be statistically significant at p-values < 0.05. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY).

3 RESULTS

A total of 60,455 patients met the inclusion and exclusion criteria. Statin users in comparison to nonusers were more likely to be men (54% vs. 46%, $p < 0.001$), older (mean age of 53 vs. 45 years old, $p < 0.001$), had higher Charlson comorbidity index (0.87 ± 1.41 vs. 0.37 ± 0.97, $p < 0.001$). Statin users were also taking more prescription medications than nonusers.[11] Among those on a statin, prescriptions for simvastatin (72%) constituted the majority of statins prescribed, followed by atorvastatin (22%), pravastatin (3%), rosuvastatin (2%), and lovastatin or fluvastatin (<1%).

3.1 Propensity score-matched results

We propensity score-matched 6728 statin users with 6728 statin nonusers with no residual differences between treatment groups. Table 1 depicts selected baseline characteristics. Statin users took statins for a median (IQR) of 3.7 (1.9–4.9) years. In the propensity score-matched cohort, 1405 statin users received a high-intensity statin for ≥120 days.

Statin users in the propensity score-matched cohort had a higher likelihood of non-traumatic arthropathies (odds ratio (OR) 1.17, 95% confidence intervals (CI) 1.09-1.25), and use

related injury (OR 1.11, 95% CI 1.03-1.19), but not undergoing rehabilitation (OR 1.04, 95% CI 0.96-1.13) (Table 2). The number needed to be exposed to cause one additional person to be harmed was 26 for non-traumatic arthropathies and 45 for use related injury (table 2).

3.2 Secondary analysis

In the overall cohort, statin users had a higher adjusted odds of being diagnosed with non-traumatic arthropathies (OR 1.20, 95% CI 1.13-1.27), and use related injuries (OR 1.13, 95% CI 1.07-1.20). When additionally adjusting for medications and revascularization procedures during follow up, statin users were more likely than nonusers to experience non-traumatic arthropathies (OR 1.17, 95% CI 1.10-1.24), and use related injuries (OR 1.10, 95% CI 1.04-1.17). Statin users for two years or more were more likely to experience non-traumatic arthropathies (OR 1.44, 95% CI 1.35-1.53), use related injuries (OR 1.26, 95% CI 1.19-1.35), and to undergo rehabilitation (OR 1.19, 95% CI 1.11-1.27). Similar results were seen when we restricted statin users to those who took statins for four years or more in comparison to nonusers, as well as high-intensity statin users in comparison to nonusers. In each of the non-obese cohorts, the healthy cohort, or the musculoskeletal conditions incident cohort, statin users in comparison to nonusers had higher odds of nearly all outcomes (Table 3).

To further demonstrate a dose-effect relationship, we compared high intensity statin users to moderate/low intensity statin users (Table 4) and found that high intensity statin users were more likely to experience non-traumatic arthropathies (OR 1.20, 95% CI 1.10-1.32), use related injuries (OR 1.19, 95% CI 1.08-1.32), and undergo rehabilitation (OR 1.68, 95% CI 1.51-1.87).

4 DISCUSSION

Our study supports previous findings that statin use may be associated with increased likelihood of being diagnosed with musculoskeletal conditions,[9, 42, 43] specifically non-traumatic arthropathies and use-related injury. We also found evidence for a dose response to both dosage and duration of statin use and outcomes evaluated, including the use of rehabilitative services.

Our finding of an association of OA diagnosis in statin users even after controlling for multiple factors is in contrast to some recent publications speculating on potential benefits of statins for prevention or amelioration of OA symptoms or denoting evidence emerging from in-vitro studies.[44, 45] A longitudinal study of a cardiovascular disease cohort population using UK national clinical practice data revealed that higher statin dose and larger dose increments were associated with a reduction in clinically defined OA as compared to statin nonusers.[3] However, this study exclusively evaluated a cardiovascular disease cohort and the baseline characteristics of statin users and nonusers were considerably different raising concern for other unmeasured confounders. Both randomized controlled trials and observational studies have their limitations in assessment of statins adverse events, which were discussed in few recent publications. [46–48] Methodology of observational studies may be biased towards beneficial effects of statins due to unrecognized confounders such as

healthy user bias.[49] Additionally, statin use may act as a surrogate marker for having better access to healthcare or higher socioeconomic status.[46] In our study, all patients had equal access and cost of healthcare.

It is conceivable that statins may increase vulnerability to myalgias and contribute to the myopathic component often experienced with musculoskeletal diagnoses. Some studies noted that skeletal muscle biopsies from statin users compared to nonusers had a characteristic pattern on electron microscopy that included breakdown of the T-tubular system and subsarcolemmal rupture, regardless of presence of symptoms and/or serum creatinine kinase elevation.[50, 51] The clinical implications of these findings are not clear, but it may be surmised that such changes may contribute to the increased odds of non-traumatic arthropathies and use-related injury. We are gaining a greater appreciation for other potential pain sources contributing to musculoskeletal pain,[52–55] yet it remains unclear exactly the role for statin use in this pathway.[50, 51] Future studies are warranted to determine where on the mechanistic pathway statin use is contributing to the experience of musculoskeletal pain.

Another area of great clinical importance is whether and how statin use affects physically active adults. Our results demonstrated that statin users have higher odds of being diagnosed with use-related injury than nonusers. Guidelines and consensus panels recommend exercise and physical activity of varying intensity. The interaction between effects of statins and physical activity is not well studied. Few studies noted that high level of structured physical activity has a protective cardiovascular effects comparable to medications including statins in patients with existing cardiovascular diseases. [56] As for adverse events, most studies focused on effect of statins on musculoskeletal strength and athletic performance with mixed results.[57] However, very few studies examined the risk of use-related injury in association with statin therapy, specifically in physically active individuals. Several studies have noted that statin use was associated with myalgia or increase in serum creatinine kinase level in physically active individuals,[58–60] but the incidence of strain, sprain, and dislocation was not examined. However, in a cross-sectional survey of amateur runners from the Netherlands (4460 subjects), there was no statistically significant difference in OR of exercise-related injuries between statin users and nonusers, although injuries were highly prevalent (38%). [61] Yet, the number of statin users in this study was only 117 subjects and defining baseline characteristics and outcomes was based on an online questionnaire. Given the morbidity and personal/societal burden associated with musculoskeletal use related injuries (i.e. time off work, emergency department visits, adverse effects from treatment) it will be critical to rigorously evaluate the role of statin use in development of these injuries as younger healthy adults are prescribed statins and this population is encouraged to increase physical activity.

One major implication of our research is whether statin use (including dose and duration of use) will result in increased levels of long-term disability among users. Our results show a significant association with ICD-9-CM diagnostic codes; however, the distal outcome, and presumably the more critical outcome, namely subsequent functional impairment and disability, has not been evaluated in this study. However, a prospective study noted that statin users in comparison to nonusers expended less metabolic equivalents, engaged in less moderate physical activity, and exhibited more sedentary behavior.[62] On the other hand, a

recent study showed that older adults who take statins can still benefit from interventions to increase physical activity.[63] This conflicting evidence underscores the tension of prescribing statins in younger physically active populations who may have a lower risk of cardiovascular disease but greater stakes of suffering from musculoskeletal disorders. In fact, data indicate that musculoskeletal disabilities among all US soldiers discharged with permanent disability constitute 71% of all disability conditions.[64] Additional research is timely to understand how to frame conversations around these competing risks (cardiovascular versus musculoskeletal disability), eliciting priorities, and how to act upon these priorities.

This study has several strengths including its longitudinal design that spanned the period from 2003 to 2012; prolonged follow-up allows identifying adverse events that are slower to develop. The study population encompassed enrollees of Tricare prime or plus of the same regional military healthcare area; hence, all enrollees have reasonably similar access and cost of healthcare, which minimizes confounding due to socioeconomic factors.[65] We also intended this study to mitigate several of the limitations common to observational studies, in general, and to our prior study from the same healthcare system, in particular.[9] As we detailed earlier, we counted statin users as nonusers during the period that preceded statin prescription; such design mitigate immortal time bias and avoid selection bias.[13, 14] We also performed several pre-specified secondary analyses that were intended to explore if different unrecognized confounders may have contributed to the association of statins with musculoskeletal conditions. Since some studies suggested a tight association between development of degenerative joint diseases and cardiovascular diseases (in which statins are commonly prescribed),[66, 67] the association of statin with musculoskeletal conditions may represent protopathic bias.[68] Therefore, in addition to including the prevalence of cardiovascular diseases in our propensity score creation, we also included undergoing non-invasive and invasive cardiac procedures. We also performed a secondary analysis, in which we adjusted for undergoing cardiac procedures during the followup period and another secondary analysis, in which we excluded any patient with cardiovascular disease or major comorbidity (healthy cohort). Our results remained consistent; in fact, restricting analysis to the healthy cohort, resulted in stronger association with our outcomes despite a smaller sample size. Additionally, concerns were raised that confounders introduced during the follow-up period (not the baseline period) may introduce bias in results of studies.[72] Therefore, we adjusted for usage of medications that may be related to our outcomes during the follow-up period. To explore if severity of obesity may have acted as a confounder, we performed a secondary analysis in which we excluded patients with obesity at baseline or during follow-up. Such exclusion, did not weaken our findings despite of the smaller sample size. Overall, our results remained consistent regardless of how we divided the cohort, which gives confidence in our findings.

Several limitations of this study also warrant discussion. Despite our effort to mitigate or minimize unrecognized confounders, as detailed earlier, it is impossible to ascertain the absence of unrecognized confounders in retrospective studies despite propensity matching and several secondary analyses. For example, physical activity was not measured and active duty status was not known to us (overall 17% of Tricare enrollees are active duty military). Also, several ICD-9-CM codes for baseline characteristics or statin-associated outcomes

may lack sensitivity or specificity. While the *ICD-9-CM* codes used in AHRQ-CCS groups have been previously validated and widely used,[19–23] some studies show that ICD-9-CM codes for soft-tissue disorders may lack specificity when compared with actual medical record review.[73] However, other studies have shown good overall concordance between ICD-9-CM codes for musculoskeletal conditions and permanent disability, as detailed earlier.[32] As of yet, statin-associated AEs have no validated diagnostic codes. We did not perform chart review to validate our codes since our IRB approved obtaining de-identified data that could not be linked to the medical record. Despite the known limitations of using ICD-9-CM codes, we cannot think of any reason for differential ascertainment bias between statin users versus nonusers. The use of pharmacy data to account for medication use assumes, but cannot guarantee, that patients are compliant with/taking the medications. The median duration of statin use was 3.7 years; this long duration of dispensing medication may be considered a surrogate marker for actual medication use. Finally, given our participants were Tricare enrollees (includes active duty military (approximately 17% of Tricare enrollees), Veterans, and their families), these results many not be generalizable to a more sedentary population or one with less exposure to strenuous physical activity.

5 CONCLUSION

Our findings that statin use is associated with increased likelihood of musculoskeletal diagnoses including non-traumatic arthropathies (including OA), use-related injury, as well as use of rehabilitative services, have potentially significant implications for clinical practice. These data challenge several existing studies implicating a protective effect of statins on musculoskeletal conditions. We propose that clinicians should consider the risk of musculoskeletal adverse events (specifically for those at the higher spectrum of risk such as athletes and active duty soldiers) when considering starting statins for primary prevention. Further research, particularly in physically active individuals, is needed to obtain a more complete description of the potential unintended consequences of long term statin therapy, hence, enabling a patient-centered approach and informed decision making about treatment. [74]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- In this retrospective cohort study, we examined the association between statin use and the risk of being diagnosed with non-traumatic arthropathies, use-related injury, and undergoing rehabilitation in a cohort with longitudinal follow-up.
- A propensity score was generated to match statin-users and nonusers using 115 baseline characteristics.
- We successfully matched 6728 statin users with 6728 nonusers. In the primary analysis, statin users had a higher odds of non-traumatic arthropathies, use related injury, but not undergoing rehabilitation. Secondary analysis demonstrated similar findings and also showed increased odds of undergoing rehabilitation.
- Our results provide additional data that inform patient and clinician conversations about statin benefits and risks, specifically among those at lower spectrum of cardiovascular risks, those healthy physically active individuals or those prone to musculoskeletal conditions.

Table 1

Selected baseline characteristics (overall propensity score-matched cohort) of statin users and nonusers[a]

	Nonusers (n=6728)	Statin users (n=6728)	Standardized difference
Age in years: mean (SD)	52 (14)	52 (14)	0.002
Female sex: n (%)	3168 (47.1)	3154 (46.9)	−0.004
Health care use			
Follow-up duration in years: mean (SD)	4.0 (2.1)	4.0 (1.6)	−0.009
Baseline period start date: n (%)			
FY 2004-2006	5181 (77.0)	5166 (76.8%)	
FY 2007-2009	1492 (22.2)	1504 (22.4%)	
FY 2009-end of study	55 (0.8)	58 (0.9)	0.006
Number of inpatient admission during baseline period: mean (SD)	0.65 (1.64)	0.62 (1.98)	−0.013
Number of outpatient medical encounters during baseline period: mean (SD)	66 (105)	65 (86)	−0.0.14
Number of inpatient procedures during baseline period mean (SD)	0.51 (1.34)	0.48 (1.76)	−0.021
Number of outpatient procedures during baseline period: mean (SD)	40 (93)	39 (70)	−0.012
Social history: n (%)			
Smoking[b]	1816 (27.0)	1821 (27.1)	0.002
Alcohol abuse/dependence	99 (1.5)	92 (1.4)	−0.009
Comorbid condition/disease: n(%)[c]			
Charlson comorbidity score: mean (SD)[d]	0.74 (1.33)	0.73 (1.31)	0.003
Obesity-overweight	1732 (25.7)	1735 (25.8)	0.001
Diabetes mellitus	1321 (19.6)	1354 (20.1)	0.011
Diabetes mellitus with complications	475 (7.1)	487 (7.2)	0.006
Cataract	1016 (15.1)	1015 (15.1)	<0.001
Valvular heart disease	519 (7.7)	501 (7.4)	−0.009
Hypertension	3556 (52.9)	3510 (52.2)	−0.014
Coronary artery disease	418 (6.2)	439 (6.5)	0.010
Cardiac dysrhythmias	823 (12.2)	759 (11.3)	−0.028
Congestive heart failure	142 (2.1)	129 (1.9)	−0.012
Cerebrovascular disease	186 (2.8)	185 (2.8)	−0.008
Chronic obstructive pulmonary disease and bronchiectasis	722(10.7)	729 (10.8)	0.003
Chronic kidney disease	113 (1.7)	121 (1.8)	0.006
Rheumatoid arthritis	104 (1.5)	110 (1.6)	0.007
Systemic lupus erythematosus	77 (1.1)	72 (1.1)	−0.007
Osteoarthritis and other non-traumatic joint disorder	2714 (40.3)	2653 (39.4)	−0.018
Spondylosis, intervertebral disc disorders, other back problems: n(%)	2020 (30.0)	1992 (29.6)	0.014
Use-related joint disorders (dislocations, sprains and strains)	1363 (20.3)	1368 (20.3)	0.002
Osteoporosis	299 (4.4)	285 (4.2)	−0.010
Rehabilitation care, fitting of prostheses, and adjustment of devices	1193 (17.7)	1179 (17.5))	−0.006
Schizophrenia and psychosis	42 (0.6)	29 (0.4)	−0.028
Medications during baseline period			

	Nonusers (n=6728)	Statin users (n=6728)	Standardized difference
Smoking cessation medications	181 (2.7)	176 (2.6)	−0.004
Diuretic	1846 (27.4)	1785 (26.5)	−0.20
ACE/ARB	2478 (36.8)	2470 (36.7)	−0.002
Calcium channel blocker	906 (14.5)	973 (14.5)	−0.001
Oral hypoglycemic	503 (7.5)	489 (7.3)	−0.007
Insulins	166 (2.5)	173 (2.6)	0.006
Aspirin	1369 (20.3)	1367 (20.3)	−0.001
NSAID	3941 (58.6)	3902 (58.0)	−0.012
Bisphosphonate	483 (7.2)	452 (6.7)	−0.019
SSRI	979 (14.6)	980 (14.6)	<0.001
Systemic corticosteroid	671 (10.0)	671 (10.0)	0
Hormone replacement therapy	750 (11.1)	760 (11.3)	0.005
Cardiovascular procedures during baseline period			
Electrocardiography	2308 (34.3)	2258 (33.6)	−0.015
Echocardiography	785 (11.7)	761 (11.3)	−0.010
Stress test	625 (9.3)	617 (9.2)	−0.004
Cardiac catheterization	96 (1.4)	107 (1.6)	0.007
Percutaneous coronary intervention	11 (0.2)	19 (0.3)	0.011
Coronary artery bypass graft surgery	3 (0.0)	6 (0.1)	0.004
Peripheral arterial revascularization procedures	9 (0.1)	9 (0.1)	<0.001

Abbreviations: ACE/ARB: angiotensin-receptor blockers & angiotensin converting enzyme inhibitors; NSAID: non-steroidal anti-inflammatory drugs; SD: standard deviation; SSRI: selective serotonin reuptake inhibitors

[a] Complete description of all baseline characteristics was previously published[11]

[b] Smoking as defined using ICD-9-CM codes: 3051 and V1582.

[c] Diagnoses as defined by the Agency for Health Research and Quality (AHRQ) Clinical Classifications Software disease categories (Appendix A).

[d] Using Deyo et al method in calculating Charlson comorbidity score using administrative data.

Table 2

Risk of outcomes in statin users in comparison to nonusers in the overall propensity score-matched cohort

Outcome	Nonusers N= 6728 n (%)	Statin users N= 6728 n (%)	Odds ratio	95% CI	*p* value	NNEH
Non-traumatic arthropathies	3767 (56.0%)	4026 (59.8%)	1.17	1.09-1.25	<0.001	26
Use related injury	2002 (29.8%)	2145 (31.9%)	1.11	1.03-1.19	0.01	45
Undergoing rehabilitation	1476 (21.9%)	1519 (22.6%)	1.04	0.96-1.13	0.37	

NNEH: the number needed to be exposed for one additional person to be harmed [39]

Table 3

Risk of outcomes in statin users in comparison to nonusers in secondary analysis

Outcome	Statin Nonusers N=49,545	Statin users N=10,910	Adjusted Odds ratio	95% CI	*p* value
Overall cohort adjusting for propensity score (Statin Nonusers = 49,545; Statin users = 10,910)					
Non-traumatic arthropathies	27,712 (55.9%)	6233 (57.1%)	1.20	1.13-1.27	<0.001
Use related injury	18,028 (36.4%)	3081 (28.2%)	1.13	1.07-1.20	<0.001
Undergoing rehabilitation	12,212 (24.6%)	2297 (21.1%)	1.06	0.99-1.13	0.08
Overall cohort adjusting for medications usage and undergoing cardiac procedures during follow-up period, and propensity score[a] (Nonusers = 49,545; Statin users = 10,910)					
Non-traumatic arthropathies	27,712 (55.9%)	6233 (57.1%)	1.17	1.10-1.24	<0.001
Use related injury	18,028 (36.4%)	3081 (28.2%)	1.10	1.04-1.17	0.002
Undergoing rehabilitation	12,212 (24.6%)	2297 (21.1%)	1.01	0.95-1.08	0.71
Overall cohort evaluating patients exposed to statin therapy for 2 years or more vs. nonusers adjusted for propensity score (Nonusers = 49,545; 2- year Statin users = 7007)					
Non-traumatic arthropathies	27,712 (55.9%)	4504 (64.3%)	1.44	1.35-1.53	<0.001
Use related injury	18,028 (36.4%)	2335 (33.3%)	1.26	1.19-1.35	<0.001
Undergoing rehabilitation	12,212 (24.6%)	1735 (24.8%)	1.19	1.11-1.27	<0.001
Overall cohort evaluating patients exposed to statin therapy for 4 years or more vs. nonusers adjusted for propensity score (Nonusers = 49,545; 4-year Statin users = 3427)					
Non-traumatic arthropathies	27,712 (55.9%)	2337 (68.2%)	1.65	1.52-1.78	<0.001
Use related injury	18,028 (36.4%)	1289 (37.6%)	1.38	1.27-1.49	<0.001
Undergoing rehabilitation	12,212 (24.6%)	941 (27.5%)	1.30	1.19-1.41	<0.001
Overall cohort evaluating high-intensity statin users vs. nonusers adjusted for propensity score (Nonusers = 49,545; High-intensity Statin users = 2470)					
Non-traumatic arthropathies	27,712 (55.9%)	1477 (59.8%)	1.20	1.09-1.33	<0.001
Use related injury	18,028 (36.4%)	740 (30.0%)	1.34	1.21-1.49	<0.001
Undergoing rehabilitation	12,212 (24.6%)	683 (27.7%)	1.56	1.40-1.74	<0.001
Cohort of non-obese statin users vs. non-obese statin nonusers adjusted for propensity score (Nonusers = 29,821; Statin users = 5340)					
Non-traumatic arthropathies	14,971 (50.2%)	2777 (52.0%)	1.21	1.12-1.31	<0.001
Use related injury	9451 (31.7%)	1234 (23.1%)	1.13	1.04-1.24	0.005
Undergoing rehabilitation	6024 (20.2%)	875 (16.4%)	1.02	0.92-1.12	0.76
Healthy cohort of statin users vs. healthy nonusers of statin therapy adjusted for propensity score (Nonusers = 35,783; Statin users = 4563)					
Non-traumatic arthropathies	18,913 (52.9%)	2419 (53.0%)	1.39	1.29-1.50	<0.001
Use related injury	12,923 (36.1%)	1307 (28.6%)	1.25	1.15-1.35	<0.001
Undergoing rehabilitation	8397 (23.5%)	847 (18.6%)	1.21	1.11-1.33	<0.001

Outcome	Statin Nonusers N=49,545	Statin users N=10,910	Adjusted Odds ratio	95% CI	*p* value
Musculoskeletal diseases incident cohort adjusted for propensity score (Statin nonusers = 25,802; Statin users = 4592)					
Non-traumatic arthropathies	11,661 (45.2%)	1933 (42.1%)	1.17	1.07-1.27	<0.001
Use related injury	7386 (28.6%)	936 (20.4)	1.20	1.09-1.33	<0.001
Undergoing rehabilitation	4445 (17.2%)	680 (14.8%)	1.15	1.03-1.29	0.02

[a]medications adjusted for included: cytochrome P450 inhibitors, selective serotonin reuptake inhibitors, corticosteroids, antipsychotics, bisphosphonates, hormone replacement therapy, testosterone, and warfarin

Table 4

High-intensity statin users vs. moderate/low intensity statin therapy adjusted for propensity score

	Moderate/low Intensity statin users N= 8440 n (%)	High-Intensity Statin users N= 2470 n (%)	Adjusted Odds ratio	95% CI	*p* value
Outcome					
Non-traumatic arthropathies	4756 (56.4%)	1477 (59.8%)	1.20	1.10-1.32	<0.001
Use related injury	2341 (27.7%)	740 (30.0%)	1.19	1.08-1.32	0.001
Undergoing rehabilitation	1614 (19.1%)	683 (27.7%)	1.68	1.51-1.87	<0.001

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