Association of statins with diabetes mellitus and diabetic complications: role of confounders during follow-up

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ABSTRACT

Studies have associated statin use with increased risk of diabetes and diabetic complications. These studies often ensure comparability of statin users and non-users at baseline; however, most studies neglect to consider confounders that occur during follow-up. Failure to consider these confounders, such as new medications or procedures, may result in identification of a spurious association between statins and outcomes. The objective of this study was to examine the association of statins with diabetes mellitus and diabetic complications; and to examine potential confounders during the follow-up period that might affect this relationship. We conducted a retrospective cohort study using Tricare data (from October 1, 2003 to March 31, 2012). We propensity score-matched statin users and non-users on 115 baseline characteristics before starting statins; these characteristics would be potentially associated with the use of statins or the outcomes of interest. Outcomes included the risk of diabetes mellitus and diabetic complications. Out of 60,455 patients (10,910 statin users and 49,545 non-users), we propensity score-matched 6728 statin users to 6728 non-users. Statin users had higher ORs for diabetes (OR 1.34, 95% CI 1.24 to 1.44) and diabetes with complications (OR 1.28, 95% CI 1.16 to 1.42). Adjustment for potential confounders that occurred during the follow-up period did not explain or diminish the association between statins and adverse outcomes. Statin users in comparison to similar non-users were more commonly diagnosed with diabetes and diabetic complications, even after adjustment for potential confounders that occurred during the follow-up period.

Significance of this study

What is already known about this subject?

- Several studies have associated statin use with increased risk of diabetes.
- Some observational studies associated statin use with increased risk of diabetic complications.
- Whereas most observational studies adjust for differences between statin users and non-users at baseline, most neglect to consider confounders that occur during follow-up.

What are the new findings?

- The study successfully matched 6728 statin users with 6728 non-users using propensity score that incorporated 115 baseline characteristics before starting statins.
- Statin users had higher ORs for diabetes (OR 1.34, 95% CI 1.24 to 1.44) and diabetes with complications (OR 1.28, 95% CI 1.16 to 1.42). Adjustment for potential confounders that occurred during the follow-up period did not explain or diminish the association between statin use and adverse outcomes.
- Secondary analyses, including different categories of patients, demonstrated consistent results.

How might these results change the focus of research or clinical practice?

- Further studies, including pragmatic studies and registries with large sample size that extend for long duration are necessary to obtain a more complete assessment of the balance between risks and benefits for statin therapy for primary prevention, especially for low-risk individuals.

INTRODUCTION

Evidence from in vitro studies,[1] meta-analyses of clinical trials,[2 3] studies using Mendelian randomization,[4] and observational studies,[5–8] have indicated that statins increase the risk of incident diabetes. However, the magnitude of this risk varies significantly among studies, ranging from ORs of 1.1 to 4.7.[2 5–9] The effect of statin use on risk of diabetic complications is less certain. Whereas some observational studies noted that statins were associated with higher risk of diabetic complications,[7 10] others associated statins with lower risk of diabetic complications.[11 12]

Additionally, in vitro studies examining the effects of statin on the body and liver fat accumulation associated statins with increased risk of obesity.[13] Observational studies have also noted an association between statin use and lower levels of physical activity,[14] higher caloric

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intake and dietary fat ingestion, and increased body mass index.[15] A study using Mendelian randomization,[4] and a randomized controlled trial (RCT), both noted a similar relationship.[16]

While RCTs are considered to be the 'gold standard' to establish efficacy of interventions or medications, RCTs may underestimate the true incidence of adverse events (AEs) due to their smaller size, shorter duration, and selection bias.[17] Moreover, most statin RCTs did not study the relationship of statin and incident diabetes or diabetic complications. Conversely, observational studies may better identify AEs, but they are limited by the potential presence of unidentified confounders.[18]

High-quality observational studies attempt to identify any potential unrecognized confounders and minimize differences in baseline characteristics of treatment groups. However, during follow-up periods, several factors may be differentially introduced among statin users and non-users that may modify outcomes. For example, statin users, who are more likely to have cardiovascular risk factors or diseases, may receive β-blocker therapy or thiazide diuretics, both of which are known to increase risk of impaired glucose tolerance.[19] Therefore, increased risk of diabetes and diabetic complications may be due to the higher likelihood of statin users to receive these medications, rather than statins themselves. β-blocker medication may be associated with fatigability, which may be surmised to promote less physical activity and consequent obesity.[20] Additionally, statin users (due to their inherent increased risks of cardiovascular diseases) may be more likely to undergo cardiovascular diagnostic or therapeutic procedures, which may be complicated by AEs (such as nephropathy) or result in more frequent follow-up visits leading to ascertainment bias.[17] These AEs may be spuriously associated with statin use. Our hypothesis was that the association between statin use and diabetes and diabetic complications is secondary to medication initiation, undergoing procedures, and ascertainment bias during follow-up, and such associations will significantly diminish or disappear after adjustment for these conditions.

The objectives of this study are to: (1) examine the risk of diabetes and diabetic complications in a cohort of statin users and non-users who had similar access to healthcare and were longitudinally followed within the same healthcare system for a prolonged period; and (2) examine the effects of different potential confounders that may arise during the follow-up period on the higher risk of adverse outcomes associated with statin use.

MATERIALS AND METHODS

After obtaining approval of the Institutional Review Boards at the Brooke Army Medical Center and the North Texas VA Health System, we retrieved administrative data and medication fill histories of inpatient and outpatient medical encounters in the San Antonio Military Multimarket area encompassing the period October 1, 2003 to March 31, 2012 using the Military Health System (MHS) Management Analysis and Reporting Tool (M2), as described in a previous publication.[7] The M2 has been used in administration of healthcare,[21 22] as well as in research.[23–25] The M2 data include the full spectrum of clinical care, regardless of point of care location or affiliation. This encompasses inpatient and outpatient medical encounters within MHS and outside MHS (purchased care), all dispensed medication transaction details, and laboratory investigation performed within MHS.

The study included all subjects enrolled in the system from October 1, 2003 (beginning of fiscal year (FY) 2004) until at least FY 2011, and who were 30 years of age or older, had ≥1 medical encounter during baseline period that would allow a baseline period duration of 2 years, and had ≥1 encounter during the follow-up period.

Treatment groups: Two treatment groups were identified:

1. Statin users: newly received statins on or after of October 1, 2005 and continued to use statins for at least 120 days. The purpose of selecting the date of October 1, 2005 is to allow for at least 2 years of baseline period before starting statin therapy. Statin users who received statins prior to October 1, 2005 (prevalent users), were excluded from the study.
2. Non-users: consisted of two groups: (1) patients who never used statins, and (2) statin users before being prescribed statins. Using this design mitigates immortal time bias.[26] Additionally, counting statin users as non-users—until they started their statins—minimizes confounding by indication.[27]

Index date and study periods

Among statin users, we defined the index date as 10 days after the date of the first statin prescription. This was done to minimize confounding by indication. For example, patients with chest pain might start statins immediately; however, they might not receive a diagnosis code for chest pain for few days after that medical encounter. Among non-users, the index date was defined as the date demarcating 2 years after the first medical encounter.

The study was divided into two periods:

1. Baseline period: used to describe baseline characteristics of treatment groups. The baseline period was defined as the 2 years preceding the index date.
2. Follow-up period: used to describe outcomes. The follow-up period started 90 days after the index date (figure 1). The purpose of omitting the first 89 days after the index date from the outcomes assessment was to minimize confounding by indication, as described in prior studies.[27–29] The clinical effects of statins are expected to occur after at least 3 months; therefore, the events that take place during this run-in period are likely due to pre-existing confounders or chance alone.

Outcomes

An outcome was defined as an occurrence of an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code in inpatient or outpatient settings consistent with prespecified diagnosis groups as defined by the Agency for Health Research and Quality Clinical Classifications Software (AHRQ-CCS);[30] AHRQ-CCS rationale and validation methods were previously published.[31–35] Our outcomes were:

1. Diabetes mellitus: this outcome was defined according to AHRQ-CCS category 49 (diabetes mellitus without complications) excluding V-codes, since V-codes signify pre-existing conditions (see online supplementary appendix A).

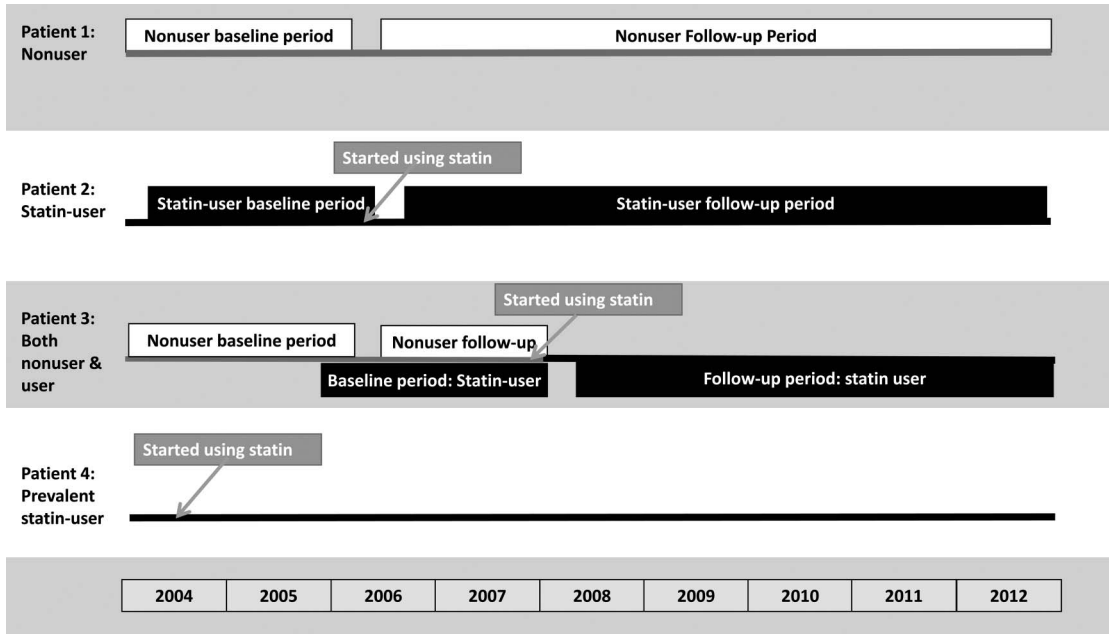

Figure 1 Study design. Patient 1 was counted as a non-user throughout the follow-up period. Patient 2 was counted as statin user throughout the follow-up period. Patient 3 was counted as a non-user until she/he started using a statin toward end of 2007; she/he was counted as a statin user thereafter. Patient 4 started a statin in 2004; therefore, we could not achieve the requisite 2 years of data for the baseline period, so we did not include this patient in the study as either a statin user or a non-user.

2. Diabetes mellitus with complications: this outcome was defined according to AHRQ-CCS category 50 (see online supplementary appendix A).

AHRQ-CCS category 49 (diabetes without complication) and category 50 (diabetes with complications) have been widely used in clinical research, as well as in examining healthcare usage.[36–42] Accounting for 'diabetes mellitus' and 'diabetes mellitus with complications' using ICD-9 codes is an essential component in computing the Charlson comorbidity score using Deyo *et al*'s[43] method and the Elixhauser comorbidity score;[44] both of them are widely used in clinical research.[45] The sensitivity of ICD-9 codes for diagnosing diabetes without complications in different studies is moderate (77.7% and 78.3%), but its specificity is high (98.4% and 98.9%).[46 47] Similarly, the sensitivity of ICD-9 codes for diagnosing diabetes with complications is moderate (63.6%), but its specificity is high (98.9%).[47]

Data and statistical analyses

We used ICD-9-CM codes to identify comorbidities during baseline period (see online supplementary appendix B), and calculated patients' Charlson comorbidity score using Deyo *et al*'s[43] method. Using propensity scores, we matched statin users to similar non-users using 115 baseline characteristic variables before starting statin therapy among users (see online supplementary table S1); baseline characteristics included age calculated at the beginning of each baseline period, gender, social and family history, healthcare usage, baseline period start date, follow-up duration, comorbidities, medication use, and undergoing invasive and non-invasive cardiovascular procedures at baseline.

We used a logistic regression model to create the propensity score and test the balance of covariates using the routines previously described.[48–52] We performed 1:1 nearest neighbor matching with a caliper of 0.01; hence, each statin user was matched to a non-user with the closest propensity score not exceeding 0.01.

Primary analysis: Risks of outcomes in statin users and non-users in the propensity score-matched cohort were examined using conditional logistic regression analysis. We then created nested, multivariable logistic regression models that incrementally adjusted for several key potential confounders that occurred during the follow-up period including:

1. Administration of medications during the follow-up period that may cause impaired glucose tolerance, diabetes, or obesity (table 1);[53] statin users may be more likely to receive these medications because of a health conscious bias or more exposure to healthcare provider.[17]
2. Undergoing cardiovascular procedures during follow-up period (table 1); non-invasive cardiac procedures may serve as a marker for patient's perceived comorbidities, such as sedentary life or poor dietary habits that may not be reflected directly on a medical diagnosis. Therefore, it can serve to adjust for confounding by indication. Invasive cardiac procedures may be complicated by nephropathy, embolization, or followed by some restrictions on physical activities.
3. Number of inpatient admissions and outpatient encounters during the follow-up period; the more medical visits a patient has, the more likely a new condition like diabetes could be diagnosed (ascertainment bias).[17]

Secondary analyses: Risks of outcomes in the following cohorts were examined using multivariable logistic regression models that incrementally adjusted for the propensity score and the aforementioned potential confounders:

1. Diabetes incident cohort: this cohort excluded patients who had diabetes at baseline and examined risk of diabetes and diabetes with complications at follow-up.

Table 1 Cohort groups and study methods

Cohort description	Covariates included in different analyses	Number of statin non-users	Number of statin users
Primary analysis			
PS-matched cohort			
Pairs of statin users and non-users were matched based on PS	1. Unadjusted model: no adjustment was necessary since treatment groups were fully matched	6728	6728
	2. Adjusted for medications that are associated with obesity or diabetes during the follow-up period*	6728	6728
	3. Adjusted for medications that are associated with obesity or diabetes and undergoing non-invasive cardiac or revascularization procedures during follow-up period†	6728	6728
	4. Adjusted for medications that are associated with obesity or diabetes, undergoing non-invasive cardiac or revascularization procedures, and number of inpatient admissions and outpatients encounters during follow-up period‡	6728	6728
Sensitivity analysis			
PS-matched cohort			
Pairs of statin users and non-users were matched based on PS	Definition of follow-up period was changed to start 360 days after the index date. Unadjusted model: no adjustment was necessary since treatment groups were fully matched.	6728	6728
Secondary analyses			
Diabetes incident cohort			
Excluded patients who had diabetes at baseline	1. PS-adjusted model§	46,810	7852
	2. Fully adjusted model¶	46,810	7852
Diabetes and obesity incident cohort			
Excluded patients who had diabetes or obesity at baseline	1. PS-adjusted model§	41,424	5793
	2. Fully adjusted model¶	41,424	5793
Healthy cohort			
Excluded patients with any Charlson comorbidity index or severe chronic disease	1. PS-adjusted model§	35,783	4563
	2. Fully adjusted model¶	35,783	4563
Non-obese cohort			
Excluded patients with obesity at baseline or at follow-up	1. PS-adjusted model§	29,821	5340
	2. Fully adjusted model¶	29,821	5340
Overall cohort: non-users vs high-intensity statin users			
Compared non-users vs high-intensity statin users in the overall cohort	1. PS-adjusted model§	49,545	2470
	2. Fully adjusted model¶	49,545	2470
Statin users only: high-intensity statin users vs moderate-intensity/low-intensity statin users			
Included all statin users only, comparing outcomes between high-intensity statin users to moderate-intensity/low-intensity statin users	1. PS-adjusted model§	None included	10,910
	2. Fully adjusted model¶	None included	10,910

*Adjustment for use of medications that are associated with obesity or diabetes (β-blockers, diuretics, systemic corticosteroids, selective serotonin reuptake inhibitors, antipsychotics, hormone replacement therapy, smoking cessation therapy, and cytochrome P450 inhibitors[53]).
†Adjustment for use of medications that are associated with obesity or diabetes and undergoing an non-invasive cardiac procedures (cardiac stress test, echocardiography, and cardiac catheterization) or invasive revascularization procedures (percutaneous coronary intervention, coronary artery bypass graft surgery, and peripheral arterial revascularization procedures).
‡Adjustment for use of medications that are associated with obesity or diabetes, undergoing non-invasive cardiac or revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period.
§Adjusted for PS.
¶Adjusted for PS, medications that are associated with obesity or diabetes, undergoing non-invasive cardiac and revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period.
PS, propensity score.

2. Diabetes and obesity incident cohort: this cohort excluded patients who had diabetes or obesity at baseline and examined risk of diabetes and diabetes with complications at follow-up.
3. Healthy cohort: this cohort excluded patients with any of the following conditions during the baseline period: Charlson comorbidity index > 0.0; diabetes mellitus; valvular, endocardial, pericardial, and myocardial heart diseases; complications of hypertension; acute or chronic ischemic heart diseases; arrhythmia or conduction abnormalities; cerebrovascular diseases; peripheral vascular diseases including aneurysms; chronic obstructive lung diseases or respiratory failure; nephrosis or nephritis; chronic kidney diseases; rheumatoid arthritis or systemic lupus erythematosus; schizophrenia and psychotic disorders; history of suicide attempts; malignancy; and liver diseases (see online supplementary appendix B). Thereafter, we examined risk of diabetes and diabetes with complications at follow-up.

4. Non-obese cohort: this cohort excluded patients with obesity at baseline or at follow-up and examined risk of diabetes and diabetes with complications at follow-up.
5. High-intensity statin users versus non-users in the overall cohort: In this analysis, we only included statin users who used high-intensity statins for 120 days or more and examined risk of diabetes and diabetes with complications at follow-up. Statin intensity was defined following the guidelines of the American College of Cardiology/American Heart Association (ACC/AHA);[54] however, we included simvastatin 80 mg as a high-intensity statin, which was still in use at the time of our study.
6. Statin users cohort: this cohort only included statin users from the overall cohort. In this analysis, we examined risk of diabetes, and diabetes with complications between high-intensity statin users versus moderate-intensity/low-intensity statin users.

Sensitivity analysis: We redefined the follow-up period start date from 90 days after the index date to 360 days after the index date and examined the risk of diabetes and diabetes with complications at follow-up.

Finally, we examined the HR of outcomes in the propensity score-matched cohort using Cox proportional hazard analysis. Time-to-first-occurrence of each outcome was the dependent variable, and statin use as an independent variable. We repeated the analysis with adjustment for medications associated with obesity or diabetes, undergoing revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period (figure 2).

Baseline characteristics for treatment groups were examined using χ^2 for dichotomous variables and Student's t-test for continuous variables. A p value of ≤ 0.05 was used to define statistical significance. Statistical analyses were performed using SPSS V.23 (IBM, Armonk, New York, USA).

RESULTS

A total of 60,455 patients were included (10,910 statin users and 49,545 non-users) in the study. Statin users were older, and were more likely to be men and to have more comorbidities. Additionally, statin users used other classes of medications more frequently. Throughout the study period, simvastatin constituted 71.9% of statin prescriptions, atorvastatin 22.3%, pravastatin 3.4%, rosuvastatin 2.1%, and lovastatin or fluvastatin 0.3% . Among statin users, 2470 (22.6%) used high-intensity statins for ≥120 days.[54]

Our healthy cohort included 4563 statin users (41.8% of statin users) and 35,783 non-users (72.2% of non-users). The non-obese cohort included 5340 statin users (49.0% of statin users) and 29,821 non-users (60.2% of non-users).

Propensity score-matched analysis

We successfully matched 6728 statin users with 6728 non-users based on their propensity scores with no significant residual differences in baseline characteristics between treatment groups (table 2 and online supplementary table S1). In the propensity score-matched cohort, statin users used statins for a mean (SD) cumulative duration of 1261 (650) days, and a median (IQR) of 1357 (683–1800) days. During the study, 1405 (20.9%) statin users received a high-intensity statin for ≥120 days and 4941 (73.4%) received a moderate-intensity statin for ≥120 days. The mean (SD) number of inpatient admissions during the follow-up period for non-users and statin users was 1.96 (4.64) and 1.73 (4.05), respectively (p=0.003); and of outpatient medical encounters was 181 (267) and 193 (261), respectively (p=0.008).

Primary analysis

Statin users in the propensity score-matched cohort had higher ORs for diabetes in comparison to non-users (OR 1.34, 95% CI 1.24 to 1.44) and for diabetes with complications (OR 1.28, 95% CI 1.16 to 1.42; table 3).

After incremental adjustment for use of other medications associated with obesity or diabetes, undergoing non-invasive cardiac or revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period, statin users had increased risk-adjusted odds of all adverse outcomes compared with non-users (table 3).

Secondary analyses

Table 4 shows that statin users had higher odds of diabetes and diabetes complications in comparison with non-users in all key subgroups analyzed. Among the healthy subgroup, statin users had higher adjusted ORs for diabetes (OR 1.73, 95% CI 1.57 to 1.92) and diabetic complications (OR 2.01, 95% CI 1.59 to 2.53) than non-users. Additionally, those who used high-intensity statins had higher ORs than those who used moderate-intensity/low-intensity statins for all outcomes (table 4).

Sensitivity analyses continued to demonstrate consistent results with our primary and secondary analyses. Finally, HRs for outcomes in the propensity score-matched cohort demonstrated similar results with and without adjustment for potential confounders during follow-up (table 5).

DISCUSSION

This study demonstrates that statin users, in comparison with non-users, have increased risk of diabetes and diabetic complications. This paper intended to dispel three hypotheses that have been suggested to explain this association; namely, potential confounders that arose during the follow-up period, such as,[1] using potentially diabetogenic medications,[2] undergoing cardiovascular procedures (to adjust for confounding by indication), and[3] ascertainment bias. Several secondary analyses using logistic regression analysis and Cox proportional hazard analysis, in different cohorts, demonstrated consistent results. Such consistent results suggest a cause–effect association of statin use and outcomes. Alternatively, it may indicate the presence of a methodological bias, such as unidentified confounders. However, we used several strategies to minimize the chance of the latter; we included in our propensity score 115 variables including demographic data, social and family history, healthcare usage, comorbidities, medication use, and undergoing invasive and non-invasive cardiovascular procedures at baseline. We also adopted several techniques to mitigate any residual confounding by indication. Finally, we performed several secondary analyses to uncover any inconsistency.

The findings of this study are consistent with previous studies which have found higher risk of adverse non-cardiac

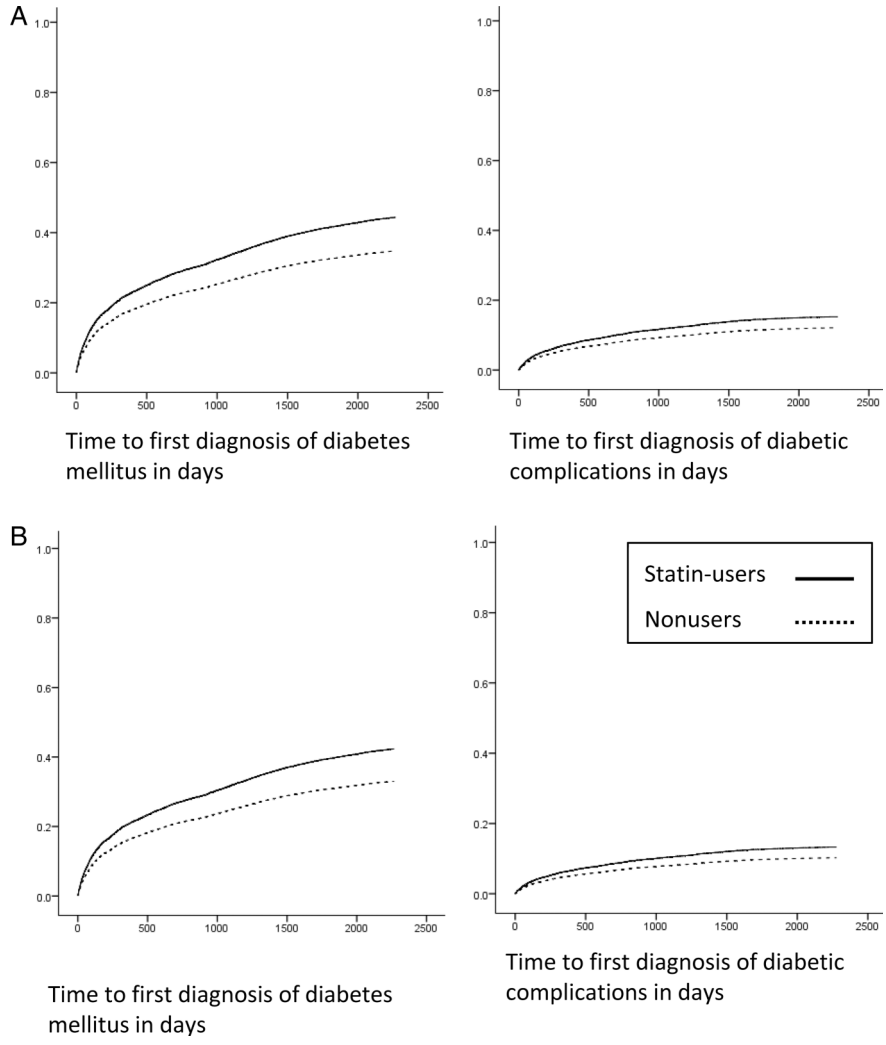

Figure 2 Hazard Ratios of outcomes in statin users in comparison to similar non-users in the propensity-matched cohort during follow-up. (A) Represents unadjusted hazards of outcomes in statin users and non-users. (B) Represents hazards of outcomes in statin users and non-users after adjusting for medications associated with obesity or diabetes, undergoing revascularization procedures, and number of inpatient admissions and outpatients encounters during follow-up period.

outcomes associated with statin use. In a propensity score-matched cohort of healthy subjects (3351 statin users and 3351 non-users) using the same database of the current study (with some difference in inclusion dates), we previously reported that statin users were more likely to be diagnosed with incident diabetes (OR=1.87; 95% CI 1.67 to 2.01) and diabetes complications (OR 2.50; 95% CI 1.88 to 3.32).[7] In contrast to the current study, the definition of statin users in the previously published study limited statin users to those who initiated statins in FY 2005 and excluded those who started statins after FY 2005. Therefore, the baseline period in the previously published study included the period from FY 2003 to FY 2005, and the follow-up period extended from FY 2005 until March 1, 2012. In the current study, we included all new statin users throughout the study period, redefined baseline and follow-up periods accordingly, matched statin users and non-users on index date and follow-up duration, and introduced several measures intended to mitigate any potential biases due to confounding by indication, immortal time bias, and others. Another retrospective study of healthy adults examined effects of short-term statin use (≤1 year) in statin users who used statins as their only prescription medication in comparison to non-users.[10] Statin users had significantly higher odds of developing diabetes (OR=1.93, 95% CI 1.55 to 2.41) and diabetic complications (OR 2.15, 95% CI 1.20 to 3.86).[10] In the current study, restricting the analysis to a healthy subgroup of patients (healthy cohort) resulted in similar odds of diabetes and diabetes with complications (OR 1.73 and 2.01, respectively); this too is consistent with the two prior studies.

Additionally, evidence from in vitro studies, a study involving Mendelian randomization, and observational studies have demonstrated that statin therapy is associated with insulin resistance.[4 55 56] Insulin resistance is associated with increased risk of diabetic complications.[57 58] Most diabetes complications takes years to develop; the mean (SD) of follow-up duration in this study was 4.0 (2.1) years, which is long enough to produce some diabetic complications. However, we cannot exclude that some patients

Table 2 Selected baseline characteristics of statin users and non-users of propensity score-matched cohort

	Non-users (N=6728)	Statin users (N=6728)	Standardized differences
Age in years: mean (SD)	52 (14)	52 (12)	0.002
Female sex: n (%)	3168 (47.1)	3154 (46.9)	−0.004
Healthcare use			
Follow-up duration in days: mean (SD)	1450 (778)	1445 (584)	−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 to end of study	55 (0.8)	58 (0.9)	0.006
Number of inpatient admissions during the baseline period: mean (SD)	0.65 (1.64)	0.62 (1.98)	−0.013
Number of outpatient medical encounters during the baseline period: mean (SD)	66 (105)	65 (86)	−0.014
Social and family history: n (%)			
Smoking*	1816 (27.0)	1821 (27.1)	0.002
Alcohol abuse/dependence	99 (1.5)	92 (1.4)	−0.009
Comorbid conditions/diseases‡: n (%)			
Charlson comorbidity score: mean (SD)§	0.74 (1.33)	0.73 (1.31)	0.003
Obese-overweight	1732 (25.7)	1735 (25.8)	0.001
Thyroid diseases	857 (12.7)	860 (12.8)	0.001
Diabetes mellitus	1321 (19.6)	1354 (20.1)	0.011
Diabetes mellitus with complications	475 (7.1)	487 (7.2)	0.006
Pericarditis, endocarditis, myocarditis	102 (1.5)	108 (1.6)	0.006
Hypertension	3556 (52.9)	3510 (52.2)	−0.014
Myocardial infarction	40 (0.6)	49 (0.7)	0.008
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 (2.7)	−0.001
Peripheral vascular disease	197 (2.9)	186 (2.8)	−0.008
Nephritis and nephrosis	87 (1.3)	88 (1.8)	0.001
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
Schizophrenia and psychosis	42 (0.6)	29 (0.4)	−0.028
Suicide	13 (0.2)	19 (0.3)	0.016
Dementia§	27 (0.4)	24 (0.4)	−0.007
Mild liver disease§	47 (0.7)	41 (0.6)	−0.010
Medications during the baseline period: n (%)			
Smoking cessation medication	181 (2.7)	176 (2.6)	−0.004
β-blocker	976 (14.5)	973 (14.5)	−0.001
Diuretic	1846 (27.4)	1785 (26.5)	−0.20
ACE/ARB	2478 (36.8)	2470 (36.7)	−0.002
Other antihypertensive medication	285 (4.2)	278 (4.1)	−0.005
Oral hypoglycemic	503 (7.5)	489 (7.3)	−0.007
Insulin	166 (2.5)	173 (2.6)	0.006
Proton pump inhibitor	2138 (31.8)	2097 (31.2)	−0.013
Aspirin	1369 (20.3)	1367 (20.3)	−0.001
NSAID	3941 (58.6)	3902 (58.0)	−0.012
SSRI	979 (14.6)	980 (14.6)	<0.001
Antipsychotic	121 (1.8)	117 (1.7)	−0.004
Systemic corticosteroid	671 (10.0)	671 (10.0)	0
Hormone replacement therapy	750 (11.1)	760 (11.3)	0.005
Testosterone	42 (0.6)	43 (0.6)	0.002
Cardiovascular procedures during baseline period: n (%)			
ECG	2308 (34.3)	2258 (33.6)	−0.015
Echocardiography	785 (11.7)	761 (11.3)	−0.010

Continued

Table 2 Continued

	Non-users (N=6728)	Statin users (N=6728)	Standardized differences
Stress test	625 (9.3)	617 (9.2)	−0.004
Percutaneous coronary intervention	11 (0.2)	19 (0.3)	0.011
Coronary artery bypass graft surgery	3 (0.0)	6 (0.1)	0.004

*Smoking was defined using ICD-9-CM codes: 3051 and V1582.
†Family history of cardiovascular disease was defined using ICD-9-CM codes: V171, V1749, V174, V1741, and V173.
‡Diagnoses were defined in accordance with the AHRQ Clinical Classifications Software disease categories (see online supplementary appendix 2).
§The method by Deyo *et al* was used to calculate the Charlson comorbidity score using administrative data. We also matched the cohort on the 17 components of the Charlson comorbidity score (not all of which are listed in this table).
ARB, angiotensin-receptor blockers; AHRQ, Agency for Health Research and Quality; FY, fiscal year; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; NSAID, non-steroidal anti-inflammatory drugs; SSRI, selective serotonin reuptake inhibitors.

Table 3 Risk of diabetes mellitus and diabetes with complications in the propensity score-matched cohort of statin users and non-users

Variable	Non-users N=6728	Statin users N=6728	OR	95% CI	p value
Unadjusted OR*					
Diabetes mellitus	1977 (29.4)	2406 (35.8)	1.34	1.24 to 1.44	<0.001
Diabetes mellitus with complications	766 (11.4)	952 (14.1)	1.28	1.16 to 1.42	<0.001
Adjusted OR for medications that are associated with obesity or diabetes during the follow-up period†					
Diabetes mellitus			1.35	1.26 to 1.46	<0.001
Diabetes mellitus with complications			1.28	1.16 to 1.42	<0.001
Adjusted OR for medications that are associated with obesity or diabetes and undergoing non-invasive cardiac or revascularization procedures during the follow-up period‡					
Diabetes mellitus			1.33	1.24 to 1.44	<0.001
Diabetes mellitus with complications			1.26	1.14 to 1.40	<0.001
Adjusted OR for medications that are associated with obesity or diabetes, undergoing non-invasive cardiac or revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period§					
Diabetes mellitus			1.35	1.25 to 1.45	<0.001
Diabetes mellitus with complications			1.31	1.18 to 1.45	<0.001
Unadjusted OR* in sensitivity analysis (redefining follow-up period to start 360 days after the index date)					
Diabetes mellitus	1763 (26.2)	2281 (33.9)	1.45	1.34 to 1.56	<0.001
Diabetes mellitus with complications	667 (9.9)	894 (13.3)	1.39	1.25 to 1.55	<0.001

*Unadjusted OR, since patients were balanced for all baseline characteristics.
†Adjusted OR: adjustment for use of medications that are associated with obesity or diabetes (β-blockers, diuretics, systemic corticosteroids, selective serotonin reuptake inhibitors, antipsychotics, hormone replacement therapy, smoking cessation therapy, and cytochrome P450 inhibitors[53]).
‡Adjusted OR: adjustment for use of medications that are associated with obesity or diabetes as listed above and undergoing an non-invasive cardiac procedures (cardiac stress test, echocardiography, and cardiac catheterization) or invasive revascularization procedures (percutaneous coronary intervention, coronary artery bypass graft surgery, and peripheral arterial revascularization procedures).
§Adjusted OR: adjustment for use of medications that are associated with obesity or diabetes as listed above, undergoing non-invasive cardiac or revascularization procedures, and number of inpatient admissions and outpatients encounters during the follow-up period.

may have had undiagnosed diabetes at baseline since recent data indicated that among patients with diabetes, 25% may be undiagnosed.[59]

The collective results of these studies strongly suggest that the increased risk of diabetes among statin users is due to statins themselves, not to their overall increased risk of pre-existing comorbidities, concomitant use of other diabetogenic medicines, confounding by indication, or ascertainment bias. Indeed, a recent editorial noted that the relationship of statin therapy and higher risk of diabetes and obesity is not an incidental finding attributable to unidentified confounders, but rather an 'on-target' effect.[60]

Contrary to these findings, a recent nested case–control study of Danish population,[11] with a median follow-up of 2.7 years, noted that statin users had lower incidence of diabetic retinopathy and diabetic neuropathy, but not diabetic nephropathy. Two other small studies reported that statin use was associated with improvement in diabetic retinopathy.[12 61]

This study has some limitations; despite of their advantage of examining large data set over a prolonged period of time, retrospective cohort studies may suffer from unrecognised confounders. Additionally, the use of ICD-9-CM codes to define some baseline characteristics, such as smoking and obesity, may lack sensitivity. We could not obtain data on body mass index, vital signs, and laboratory investigations; such information would have strengthened our outcomes. The use of ICD-9-CM codes in identifying our outcomes of diabetes and diabetic complications is another limitation, although they have good sensitivity (77.7% or 78.3%) and excellent specificity (95.7% or 98.9%),[46 47] and have been widely used in clinical research and usage reports.[36–42] This likely underestimated the proportion of patients who experienced the outcomes of

Table 4 Risk of diabetes mellitus and diabetes with complications in statin users in comparison to non-users

Variable	Non-users	Statin users	PS-adjusted model*			Fully adjusted model†		
			OR	95% CI	p value	OR	95% CI	p value
Diabetes incident cohort: excluded patients who had diabetes at baseline								
	N=46,810	N=7852						
Diabetes mellitus	6185 (13.2)	1650 (21.0)	1.44	1.33 to 1.56	<0.001	1.40	1.29 to 1.52	<0.001
Diabetes mellitus with complications	935 (2.0)	290 (3.7)	1.52	1.26 to 2.24	<0.001	1.47	1.23 to 1.76	<0.001
Diabetes and obesity incident cohort: excluded patients who had diabetes or obesity at baseline								
	N=41,424	N=5793						
Diabetes mellitus	4997 (12.1)	1160 (20.0)	1.52	1.39 to 1.67	<0.001	1.47	1.34 to 1.62	<0.001
Diabetes mellitus with complications	731 (1.8)	206 (3.6)	1.71	1.39 to 2.12	<0.001	1.65	1.34 to 2.03	<0.001
Healthy cohort								
	N=35,783	N=4563						
Diabetes mellitus	4210 (11.8)	936 (20.5)	1.73	1.57 to 1.92	<0.001	1.62	1.47 to 1.80	<0.001
Diabetes mellitus with complications	604 (1.7)	155 (3.4)	2.01	1.59 to 2.53	<0.001	1.83	1.46 to 2.30	<0.001
Non-obese cohort: excluded patients with obesity at baseline or follow-up								
	N=29,821	N=5340						
Diabetes mellitus	3382 (11.3)	1550 (29.0)	1.37	1.24 to 1.51	<0.001	1.37	1.24 to 1.52	<0.001
Diabetes mellitus with complications	770 (2.6)	583 (10.9)	1.39	1.18 to 1.65	<0.001	1.46	1.24 to 1.72	<0.001
Overall cohort: non-users vs high-intensity statin users								
	N=49,545	N=2470						
Diabetes mellitus	8165 (16.5)	1119 (45.3)	1.29	1.16 to 1.43	<0.001	1.29	1.15 to 1.43	<0.001
Diabetes mellitus with complications	1934 (3.9)	514 (20.8)	1.16	1.001 to 1.35	0.05	1.19	1.02 to 1.38	0.03
Statin users only: high-intensity statin users vs moderate-intensity/low-intensity statin users								
	Moderate-intensity/low-intensity	High-intensity						
	N=8440	N=2470						
Diabetes mellitus	3146 (37.3)	1119 (45.3)	1.10	1.07 to 1.13	<0.001	1.19	1.08 to 1.31	<0.001
Diabetes mellitus with complications	1236 (14.6)	514 (20.8)	1.13	1.09 to 1.18	<0.001	1.25	1.11 to 1.42	<0.001

*Adjusted for PS.
†Adjusted for: PS, medications that are associated with obesity or diabetes, undergoing non-invasive cardiac and revascularization procedures, and number of inpatient admissions and outpatients encounters during follow-up period.
PS, propensity score.

Table 5 Hazard ratios of diabetes and diabetes with complications in statin users in comparison to non-users in the propensity-matched cohort

	HR (95% CI)	p value
Without adjustments		
Diabetes mellitus	1.28 (1.20 to 1.36)	<0.0001
Diabetes mellitus with complications	1.26 (1.15 to 1.39)	<0.0001
With adjustment for medications associated with obesity or diabetes, undergoing revascularization procedures, and number of inpatient admissions and outpatients encounters during follow-up		
Diabetes mellitus	1.28 (1.21 to 1.36)	<0.0001
Diabetes mellitus with complications	1.30 (1.18 to 1.43)	<0.0001

interest. However, the prevalence of diabetes at end of follow-up period is commensurate with recently reported national trends (~16% of adults 54–64 years of age).[62] Similarly, the lack of laboratory data to support the diagnosis of diabetic complications, such as serum creatinine or albuminuria, is another limitation for the study; hence, further study using laboratory findings in addition to diagnoses codes are warranted. We could not perform a chart review to validate our codes since the Institutional Review Board approved obtaining de-identified data that cannot be linked to medical charts.

Unfortunately, ICD-9-CM codes often do not provide information on severity of illness. It may be presumed that physicians prescribe statins to patients who suffered more severe obesity; therefore, statin users could have been more likely to develop diabetes and diabetic complications. However, restricting the analysis to patients with no comorbidities or no obesity was associated with higher risk of outcomes, and adjusting for many potential confounders during follow-up did not change our findings. Despite all the limitations of using ICD-9-CM codes as a method in identifying baseline characteristics and outcomes, we do not know of any reason for differential ascertainment bias between statin users versus non-users.

In conclusion, statin use was associated with higher risk of diabetes and diabetic complications, which seemed more pronounced in patients with less comorbidities at baseline. Further studies, including pragmatic studies and registries with large sample size that extend for long duration are necessary to obtain a more complete assessment of the balance between risks and benefits for statin therapy for primary prevention, especially for low-risk individuals.

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Association of statins with diabetes mellitus and diabetic complications: role of confounders during follow-up

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