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ORIGINAL RESEARCH ARTICLE

Do Statins Increase the Risk of Esophageal Conditions? Findings from Four Propensity Score-Matched Analyses

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Abstract

Background and Objective Statins are commonly used medications. Whereas some observational studies suggested an association of statin use with Barrett's esophagus and some upper gastrointestinal symptoms, there is a dearth of data on the association of statins and common esophageal conditions such as gastroesophageal reflux disease and esophagitis. The aim of this study is to examine the association of statins with esophageal conditions.

Methods This is a retrospective cohort study using regional military healthcare data (1 October, 2003 to 1 March, 2012). The primary analyses evaluated the odds of: esophagitis; symptoms of esophagitis; gastroesophageal reflux disease/dyspepsia; and esophageal complications of gastroesophageal reflux disease in four propensity score-matched cohorts of statin users and non-users (propensity score-overall, propensity score-healthy, propensity score-women, and propensity score-men cohorts). Secondary and sensitivity analyses were performed.

Results In the propensity score-overall cohort ($n = 12{,}684$), statin users were more likely to be diagnosed with esophagitis (odds ratio 1.11, 95% confidence interval 1.01–1.22) and gastroesophageal reflux disease/dyspepsia (odds ratio 1.18, 95% confidence interval 1.10–1.27) compared with non-users. Similar findings were seen in the propensity score-healthy cohort and in the propensity score-men cohort. In the propensity score-women cohort, the odds of esophagitis was higher among statin users compared with non-users (odds ratio 1.16, 95% confidence interval 1.02–1.32) but other outcomes were not different. In sensitivity analyses, which excluded patients with obesity, statin use was not associated with an increased odds ratio of gastroesophageal reflux disease/dyspepsia.

Conclusion Statin therapy was associated with higher odds of being diagnosed with esophagitis and gastroesophageal reflux disease/dyspepsia. Further study is warranted to elucidate the potential role of statins in these commonly diagnosed esophageal conditions.

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Key Points

This is a retrospective study of 43,438 patients spanning more than 8 years. Four different propensity score-matched cohorts were created and the likelihood of being diagnosed with esophageal conditions among statin users and non-users was examined.

The odds ratios of being diagnosed with esophagitis and gastroesophageal reflux disease/dyspepsia was higher in statin users than in non-users. The number needed to be exposed for an additional patient to be diagnosed with esophagitis is 65 and with gastroesophageal reflux disease/dyspepsia is 24.

Further study is warranted to advise patients and clinicians on the potential role of statins in esophageal conditions.

1 Introduction

Owing to their beneficial effects in lowering the risk of cardiovascular diseases, statins are among the most commonly used medications [1]. Recent guidelines expanded statin use for primary prevention to many otherwise healthy individuals; however, different guidelines differ on the extent of this expansion and the populations that should be prescribed statins for primary prevention [2]. Hence, understanding the risks of adverse events is of paramount importance to balance the benefit–risk ratio, specifically among those with a lower predicted cardiovascular risk [3].

Less well studied is whether statins have a beneficial or adverse impact on esophageal conditions. While esophageal conditions have less impact on morbidity and mortality compared with cardiovascular disease, they may negatively affect quality of life and increase cost of care. Gastroesophageal reflux disease (GERD) affects 30–40% of the US population with an annual healthcare expenditure of US$12 billion and nearly US$50 billion for those with suspected extra-esophageal reflux (chronic cough, asthma, throat symptoms presumed to be GERD related) [4]. Several studies have found that statins are associated with nausea, vomiting [5–8], and dyspepsia [5, 9–11]. Additionally, there have been multiple case reports of statin-induced dysphagia, though mostly related to statin-induced myopathy [12, 13]. Statins have also been associated with a lower risk of Barrett's esophagus [14–16]. Little is known about whether statin use increases the risk of other common gastrointestinal conditions such as GERD and esophagitis.

Given the increasing use of statins for primary prevention in the era of new guidelines, as well as their over-the-counter availability in some countries, it is important to examine the association of statin therapy with esophageal conditions. The objective of this study was to examine the association of statin therapy with esophagitis, symptoms of esophagitis, GERD/dyspepsia, and esophageal complications of GERD.

2 Methods

This retrospective cohort study was approved by the Institutional Review Boards at the Brooke Army Medical Center and VA North Texas Health Care System. We analyzed Tricare data from the San Antonio area military healthcare system from 1 October, 2003 to 1 March, 2012. Tricare is the healthcare program for the US uniformed service members; enrollees include active duty individuals (approximately 17%), participating veterans, and their families. The baseline period (1 October, 2003 to 30 September, 2005) was used to describe baseline characteristics while the follow-up period (1 October, 2005 to 1 March, 2012) was used to assess subsequent outcomes. The Military Health System Management Analysis and Reporting Tool managed by Tricare was used to acquire the data, which included outpatient and inpatient medical records, laboratory data performed within military facilities, medical benefit claims data, and pharmacy data regardless of dispensing pharmacy location or affiliation.

The study population included 30- to 85-year-old individuals who had at least one outpatient visit and at least one prescription medication during the baseline period along with at least one medical encounter during the follow-up period. Patients were enrolled in the system during both the study baseline and follow-up period with no missing data.

Statin users were defined as those who filled a statin prescription for a cumulative period of ≥ 90 days from 1 October, 2004 to 30 September, 2005 while the non-users did not receive a statin throughout the entire study period. The 2013 American College of Cardiology/American Heart Association cholesterol guideline was used to define high-intensity statin use with a modification to include 80 mg of simvastatin in the high-intensity statin use group because this dose was commonly used at the time of the study period but not at the time of the guideline [17].

Using these data, we formed four main cohorts, from which we created four different propensity score (PS)-matched cohorts. Full descriptions of the creation and

performance of these four PS-matched cohorts have been previously published [18–21].

1. *Overall cohort* [18] this cohort included patients who met the study criteria. Statin users in this overall cohort were PS matched to non-users using 82 baseline characteristics including but not limited to demographics, comorbidities as defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM) codes according to the Agency for Healthcare Research and Quality Clinical Classifications Software (AHRQ-CCS) [22], Charlson Comorbidity Index [23], use of 20 classes of medications [24], and healthcare utilization (PS-overall cohort).
2. *Healthy cohort* [19] this cohort included patients from the overall cohort who used statins for primary prevention and were without severe comorbidities as previously published [19]. Therefore, the healthy cohort excluded patients with any Charlson Comorbidity Index element and any cardiovascular diseases or comorbid conditions that might limit life expectancy or physical activity. Statin users in this healthy cohort were PS matched to non-users using 42 baseline characteristics (PS-healthy cohort).
3. *Women cohort* [20] this cohort included only women from the overall cohort. Statin users in this women cohort were PS matched to non-users using 79 baseline characteristics (PS-women cohort).
4. *Men cohort* [21] this cohort included only men from the overall cohort. Statin users in this men cohort were PS matched to non-users using 79 baseline characteristics (PS-men cohort).

Study outcomes were defined using ICD-9-CM codes, as identified by the AHRQ-CCS [22]. The AHRQ-CCS methods of development and validation were previously published [25, 26]. We used the following pre-specified outcomes:

(1) *Esophagitis* Defined by AHRQ-CCS category 9.4.1.1 (ICD-9-CM codes: 53010, 53011, 53012, 53013, 53019). The use of ICD-9-CM codes in identifying esophagitis was noted to have a sensitivity of 46.8%, specificity of 98.8%, and a positive predictive value (PPV) of 94.8% [27].

(2) *Symptoms of esophagitis* Defined by AHRQ-CCS 17.1.6, which included nausea and vomiting (ICD-9-CM codes: 7870, 78701, 78702, 78703, 78704), and AHRQ-CCS 9.12.2, which included dysphagia (ICD-9-CM codes: 78720, 7872, 78721, 78722, 78723, 78724, 78729).

(3) *GERD/dyspepsia* Included GERD (ICD-9-CM codes 7871 [heartburn/pyrosis], 5301, 5302, 5303), and was noted to identify GERD with a sensitivity of 56.1%, specificity of 98.5%, and PPV of 94.8%) [27], dyspepsia (ICD-9-CM code 5368, as used in prior publication) [28], and esophageal reflux (ICD-9-CM codes 53081).

(4) *Esophageal complications of GERD* Defined by selected codes from AHRQ-CCS 9.4.1.2, which included ulcer of esophagus without or with bleeding, stricture and stenosis of esophagus, and Barrett's esophagus (ICD-9-CM codes: 5302, 53020, 53021, 5303, 53085). The use of ICD-9-CM codes in identifying esophageal stricture was noted to have a sensitivity of 50%, specificity of 99.8%, and a PPV of 87.5% [27].

Primary analyses In these analyses, we examined the prevalence and odds of being diagnosed with the outcomes during the follow-up period in the four PS-matched cohorts of statin users and non-users.

Secondary analyses Given the high prevalence of our outcomes of interest in the general population [29–32] and hence their high prevalence at the baseline period in our PS-matched cohorts, we sought to perform secondary analyses in which we excluded all patients who had experienced any esophageal conditions documented during the baseline period from the PS-matched cohorts. Therefore, we created four incident cohorts for our secondary analyses and examined the odds of the outcomes during the follow-up period in each incident cohort, adjusting for the PS as the following: (1) incident PS-overall cohort: excluded patients who experienced any outcome at baseline from the PS-overall cohort; (2) incident PS-healthy cohort: excluded patients who experienced any outcome at baseline from the PS-healthy cohort; (3) incident PS-women cohort: excluded patients who experienced any outcome at baseline from the PS-women cohort; and (4) incident PS-men cohort: excluded patients who experienced any outcome at baseline from the PS-men cohort.

To examine if there is a dose–response relationship, we performed the following analyses: (1) examined the odds of the outcomes in all participants of the overall cohort (not only the PS-matched cohort) of high-intensity statin users compared with non-users, adjusting for the PS; and (2) examined the odds of the outcomes in statin users of the overall cohort comparing high-intensity statin users with low- or moderate-intensity statin users, adjusting for the PS.

Sensitivity analyses We performed the following analyses: (1) non-obese PS-overall cohort: excluded patients diagnosed with overweight/obesity at baseline from the PS-overall cohort; (2) non-obese overall cohort: excluded patients diagnosed with overweight/obesity at baseline or during the follow-up from the overall cohort (not only the

PS-matched cohort); and (3) PS-overall cohort adjusting for the PS and the combined use of aspirin, beta-blockers, and PPI.

Statistical analyses Chi-square analysis for categorical variables and unpaired two-tailed Student *t* test for continuous variables were used to compare baseline characteristics of the groups. Using baseline characteristics, we created the PS using a logistic regression model and performed the nearest number matching to achieve 1:1 matching and balance between groups, as described previously [18–21].

For the primary analyses, the odds ratio (OR) was calculated using conditional logistic regression. For secondary analyses, we used separate logistic regression models for each outcome and adjusted for the PS. Statistical significance was achieved when a two-tailed p value was < 0.05. Stata Version 12 (StataCorp, College Station, TX, USA) and SPSS Version 22 (IBM, Armonk, NY, USA) were used to perform the statistical analyses.

3 Results

A total of 43,438 patients (13,626 were statin users and 29,812 were non-users) fulfilled the study criteria and constituted the overall cohort. In this overall cohort, 38% of statin users were prescribed high-intensity statins. Statin users were older and had more comorbidities (data not shown). Various statins were used: simvastatin (74%), atorvastatin (17%), pravastatin (7%), and rosuvastatin (2%). The mean duration of follow-up was 6.19 years. We matched 6342 pairs of statin users and non-users in the PS-overall cohort who had comparable characteristics at baseline (Table 1). Similarly, we created matched statin users and non-user pairs on all baseline characteristics included in creating the PS for the other three cohorts: PS-healthy cohort (3351 pairs), PS-women cohort (2890 pairs), and PS-men cohort (3302 pairs).

Table 2 lists the prevalence of our outcomes at the baseline of different cohorts. Nearly one fourth of subjects had GERD or dyspepsia, 7% symptoms of esophagitis, approximately 3% had diagnosed esophagitis, and 1% had esophageal complications of GERD.

3.1 Primary Analyses

In the PS-overall cohort, statin users compared with non-users were more likely to be diagnosed with esophagitis (odds ratio [OR] 1.11, 95% confidence interval [CI] 1.01–1.22, $p = 0.03$) as well as GERD/dyspepsia (OR 1.18, 95% CI 1.10–1.27, $p < 0.001$) during the follow-up period. Similar findings were seen in the PS-healthy cohort and the PS-men cohort. Additionally, in the PS-men cohort, statin users compared with non-users were more likely to have esophageal complications of GERD (OR 1.33, 95% CI 1.04–1.70, $p = 0.03$). In the PS-women cohort, the odds of esophagitis was higher among statin users compared with non-users (OR 1.16, 95% CI 1.02–1.32, $p = 0.03$) but other outcomes were not statistically different (Table 3).

3.2 Secondary Analyses

Table 4 depicts our secondary analyses in which we excluded from the PS-matched cohorts patients who experienced esophageal conditions during the baseline (incident cohorts). In the incident PS-overall cohort, statin users were more likely to have a new diagnosis of esophagitis during the follow-up period with borderline significance (OR 1.14, 95% CI 1.00–1.30, $p = 0.05$) and GERD/dyspepsia (OR 1.17, 95% CI 1.07–1.28, $p < 0.001$) compared with non-users. Similarly, in both the incident PS-healthy cohort and the incident PS-women cohort, statin users were more likely to have a new diagnosis of esophagitis and GERD/dyspepsia during the follow-up period compared with non-users. In the incident PS-men cohort, statin users were more likely to have GERD/dyspepsia (OR 1.27, 95% CI 1.13–1.44, $p < 0.001$) compared with non-users.

High-intensity statin users compared with non-users in the overall cohort had a higher odds of GERD/dyspepsia but were less likely to have the esophageal complications of GERD (Table 5). Restricting analysis to statin users only in the overall cohort, high-intensity statin users compared with low- to moderate-intensity statin users had a higher incidence of all outcomes except for esophageal complications of GERD.

3.3 Sensitivity Analyses

Table 6 depicts our sensitivity analyses results. After excluding patients with obesity from the PS-overall cohort, the OR of GERD/dyspepsia was similar among statin users and non-users; however, the OR of esophagitis continued to be increased among statin users. Similar results were found in the non-obese overall cohort.

4 Discussion

In this study of 12,684 subjects matched for similar baseline characteristics and followed for a median of 6.2 years, we found that statin use was associated with a higher likelihood of being diagnosed with esophagitis in all four PS-matched cohorts. Statin use was also associated with a higher likelihood of being diagnosed with GERD/dyspepsia in the PS-matched cohorts except for the PS-women cohort, in which the OR showed a trend toward higher

Table 1 Selected baseline characteristics of propensity score (PS)-matched statin users and non-users from the overall cohort and the healthy cohort[a]

Variable	PS-overall cohort			PS-healthy cohort		
	Non-users *n* (%) (*n* = 6342)	Statin users *n* (%) (*n* = 6342)	*p* value	Non-users *N* (%) (*n* = 3351)	Statin users *N* (%) (*n* = 3351)	*p* value
Age (years), mean ± SD	56.0 ± 12.0	55.7 ± 12.4	0.13	53 ± 11.0	53 ± 11.0	0.72
Women	2856 (45.0)	2924 (46.1)	0.23	1285 (38.3)	1314 (39.2)	0.48
Smoking[b]	534 (8.4)	509 (8.0)	0.44	241 (7.2)	237 (7.1)	0.89
Alcohol-related disorders	83 (1.3)	78 (1.2)	0.70	29 (0.9)	31 (0.9)	0.80
Overweight/obesity[c]	993 (15.7)	960 (15.1)	0.43	493 (14.7)	455 (13.6)	0.19
Charlson Comorbidity Index: mean (SD)[d]	0.64 ± 1.23	0.66 ± 1.25	0.29	0	0	
Comorbidities[e]						
Coronary atherosclerosis and other heart disease	277 (4.4)	314 (5.0)	0.10	0	0	
Cerebrovascular disease	128 (2.0)	125 (2.0)	0.90	0	0	
Diabetes mellitus	743 (11.7)	789 (12.4)	0.21	0	0	
Diabetes mellitus with complications	220 (3.5)	247 (3.9)	0.22	0	0	
Acute myocardial infarction	20 (0.3)	25 (0.4)	0.50	0	0	
Hypertension with complications and secondary hypertension	176 (2.8)	181 (2.9)	0.79	0	0	
Asthma	375 (5.9)	366 (5.8)	0.70	102 (3.0)	96 (2.9)	0.71
Aortic and peripheral arterial embolism or thrombosis	12 (0.2)	14 (0.2)	0.85	0	0	
Peripheral and visceral atherosclerosis	153 (2.4)	169 (2.7)	0.37	0	0	
Acute and unspecified renal failure	65 (1.0)	78 (1.2)	0.30	5 (0.1)	5 (0.1)	1.00
Non-specific chest pain	1024 (16.1)	1009 (15.9)	0.74	301 (9.0)	326 (9.7)	0.31
Healthcare utilization						
Number of outpatient visits during baseline period: mean ± SD	31.7 ± 36.8	31.8 ± 40.6	0.84	21.1 ± 22.7	21.1 ± 19.1	0.97
Number of inpatient admissions during baseline period: mean ± SD	0.3 ± 0.8	0.3 ± 0.8	0.75	0.08 ± 0.3	0.08 ± 0.3	0.82
Number of encounters for immunization during baseline period: mean ± SD	0.5 ± 1.6	0.5 ± 3.7	0.75	0.4 ± 1.1	0.42 ± 1.1	0.37
Other medications used during baseline period, *n* (%)						
NSAID	3729 (58.8)	3702 (58.4)	0.64	1911 (57.0)	1926 (57.5)	0.73
PPI	2009 (31.7)	2030 (32.0)	0.70	861 (25.7)	863 (25.8)	0.98
Aspirin	1835 (28.9)	1890 (29.8)	0.28	777 (23.2)	826 (24.6)	0.16
Beta-blocker	1099 (17.3)	1123 (17.7)	0.57	428 (12.8)	459 (13.7)	0.28
SSRI	1059 (16.7)	1067 (16.8)	0.87	441 (13.2)	456 (13.6)	0.62
Calcium channel blocker	987 (15.6)	1001 (15.8)	0.75	384 (11.5)	395 (11.8)	0.70
Non-statin lipid-lowering drug	373 (5.9)	391 (6.2)	0.50	194 (5.8)	217 (6.5)	0.26
Other baseline variables not included in PS matching						
Hiatus hernia[f]	136 (2.1)	132 (2.1)	0.85	37 (1.1)	49 (1.5)	0.23
Combined use of both NSAID and PPI	1305 (20.6)	1343 (21.2)	0.42	558 (16.7)	578 (17.2)	0.54
Combined use of aspirin and beta-blocker	442 (7.0)	428 (6.7)	0.62	138 (4.1)	157 (4.7)	0.28

Table 1 continued

Variable	PS-overall cohort			PS-healthy cohort		
	Non-users *n* (%) (*n* = 6342)	Statin users *n* (%) (*n* = 6342)	*p* value	Non-users *N* (%) (*n* = 3351)	Statin users *N* (%) (*n* = 3351)	*p* value
Combined use of aspirin, beta-blocker, and PPI	191 (3.0)	150 (2.4)	0.03	53 (1.6)	42 (1.3)	0.30

ICD-9-CM International Classification of Diseases, Ninth Revision, Clinical Modification, *NSAID* non-steroidal anti-inflammatory drug, *PPI* proton pump inhibitor, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor

[a]A full description of these cohorts was previously published [18, 19]

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

[c]Diagnosis is based on selected ICD-9-CM diagnosis codes from category 56 of the Agency for Healthcare Research and Quality-Clinical Classification Software (other nutritional; endocrine; and metabolic disorders) related to overweight, obesity and hyperalimentation (codes: 2780, 27800, 27801, 27802, 27803, 2781, 2788, 7831) [10]

[d]Diagnosis is based on ICD-9-CM codes as identified in the Deyo method for applying the Charlson Comorbidity Score

[e]As defined by the Agency for Healthcare Research and Quality-Clinical Classifications Software

[f]Defined by ICD-9-CM codes: 5513, 5523, 5533

Table 2 Prevalence of outcomes during the baseline period in different propensity score (PS)-matched cohorts

Variable	Non-users *n* (%)	Statin users *n* (%)	*p* value
PS-overall cohort (6342 non-users and 6342 statin users)			
Esophagitis	164 (2.6)	182 (2.9)	0.35
Symptoms of esophagitis	447 (7.0)	405 (7.0)	0.15
GERD/dyspepsia	1510 (23.8)	1582 (24.9)	0.14
Esophageal complications of GERD	87 (1.4)	74 (1.2)	0.30
PS-healthy cohort (3351 non-users and 3351 statin users)			
Esophagitis	57 (1.7)	71 (2.1)	0.25
Symptoms of esophagitis	146 (4.4)	140 (4.2)	0.76
GERD/dyspepsia	652 (19.5)	673 (20.1)	0.52
Esophageal complications of GERD	27 (0.8)	28 (0.8)	0.89
PS-women cohort (2890 non-users and 2890 statin users)			
Esophagitis	86 (3.0)	79 (2.7)	0.64
Symptoms of esophagitis	275 (9.5)	266 (9.2)	0.72
GERD/dyspepsia	822 (28.4)	786 (27.2)	0.30
Esophageal complications of GERD	28 (1.0)	29 (1.0)	1.00
PS-men cohort (3302 non-users and 3302 statin users)			
Esophagitis	84 (2.5)	90 (2.7)	0.70
Symptoms of esophagitis	161 (4.9)	134 (4.1)	0.12
GERD/dyspepsia	671 (20.3)	733 (22.2)	0.06
Esophageal complications of GERD	49 (1.5)	51 (1.5)	0.92

GERD gastroesophageal reflux disease, *PS* propensity score

odds. Secondary analyses generally showed similar results. However, sensitivity analyses, which excluded patients with obesity, demonstrated no association of statin use with GERD/dyspepsia but continued to demonstrate a higher OR of esophagitis among statin users. Based on our findings from the PS-overall cohort and using the previously published formula [33], the number needed to be exposed for an additional patient to be diagnosed with esophagitis is 65 and with GERD/dyspepsia is 24. Although the increased odds of these outcomes was modest

Table 3 Outcomes in propensity score (PS)-matched cohorts of statin users vs. non-users (primary analyses)

Outcome variables	Non-users *n* (%)	Statin users *n* (%)	Odds ratio	95% CI	*p* value
PS-overall cohort (6342 non-users and 6342 statin users)					
Esophagitis	1069 (16.9)	1165 (18.4)	1.11	1.01–1.22	0.03
Symptoms of esophagitis	1507 (23.8)	1441 (22.7)	0.94	0.87–1.02	0.17
GERD/dyspepsia	2822 (44.5)	3085 (48.6)	1.18	1.10–1.27	< 0.001
Esophageal complications of GERD	262 (4.1)	242 (3.8)	0.92	0.77–1.10	0.36
PS-healthy cohort (3351 non-users and 3351 statin users)					
Esophagitis	461 (13.8)	539 (16.1)	1.20	1.05–1.38	0.01
Symptoms of esophagitis	551 (16.4)	573 (17.1)	1.05	0.92–1.19	0.47
GERD/dyspepsia	1283 (38.3)	1467 (43.8)	1.26	1.14–1.38	< 0.001
Esophageal complications of GERD	93 (2.8)	113 (3.4)	1.22	0.93–1.62	0.16
PS-women cohort (2890 non-users and 2890 statin users)					
Esophagitis	535 (18.5)	601 (20.8)	1.16	1.02–1.32	0.03
Symptoms of esophagitis	875 (30.3)	860 (29.8)	0.98	0.87–1.09	0.67
GERD/dyspepsia	1473 (51.0)	1544 (53.4)	1.10	1.00–1.22	0.06
Esophageal complications of GERD	124 (4.3)	108 (3.7)	0.87	0.67–1.13	0.28
PS-men cohort (3302 non-users and 3302 statin users)					
Esophagitis	479 (14.5)	548 (16.6)	1.17	1.03–1.34	0.02
Symptoms of esophagitis	570 (17.3)	563 (17.1)	0.99	0.87–1.12	0.82
GERD/dyspepsia	1284 (38.9)	1482 (44.9)	1.28	1.16–1.41	< 0.001
Esophageal complications of GERD	116 (3.5)	152 (4.6)	1.33	1.04–1.70	0.03

CI confidence interval, *GERD* gastroesophageal reflux disease, *PS* propensity score

(approximately 10–30%), the high prevalence of these conditions in the general population would result in a large number of patients experiencing adverse esophageal conditions as a result of statins.

Our study demonstrated that statin use was associated with an increased likelihood to be diagnosed with esophagitis in almost all analyses. Among review papers and studies assessing the clinical safety of statins, esophagitis is not usually listed as one of the studied side effects of statin use [5, 9, 34–36]. However, few studies examined the risk of reflux esophagitis in selected populations and noted that statins may play a neutral or beneficial role. For instance, in a case-controlled study that identified 146 reflux esophagitis cases from endoscopic examinees in a cardiovascular center, statin use was not associated with reflux esophagitis (OR 0.8, 95% CI 0.5–1.4) [37]. In contrast, in a cross-sectional study of 1744 consecutive outpatients who underwent an upper gastrointestinal endoscopy [38], a multivariate analysis showed a significantly lower OR of reflux esophagitis among statin users (OR 0.42, 95% CI 0.18–0.96) [38]. The difference in the results of these two studies from ours may be attributed to their smaller sizes, patient selectivity, and the confounders adjusted for in their models.

Although our primary and secondary analyses demonstrated an association of statin use with GERD/dyspepsia, this association was lost in sensitivity analyses, which excluded patients with obesity. The use of ICD-9-CM codes to identify overweight/obesity cannot determine its severity. Therefore, statin association with GERD/dyspepsia may be the result of confounding from the difference in the severity of obesity between the treatment groups. However, the association of statin and GERD/dyspepsia may not the result of confounding and may reflect a more complex relationship because the prevalence of GERD/dyspepsia during the baseline period in all of the four PS-matched cohorts was similar. Several recent studies noted an association between statin use with obesity [19, 39, 40], and increased caloric and fat intake [41, 42]. Hence, it may be surmised that the association of statin use with GERD/dyspepsia may be conducted through the effect of statins on obesity and increased fat intake.

Some studies noted that statin use was associated with dyspepsia [10, 11]. In a systematic review, one of the most common statin-associated upper gastrointestinal symptoms included dyspepsia [10]. Other meta-analyses of simvastatin and atorvastatin clinical trials noted that dyspepsia was among the most common adverse events, occurring in 0.5–6.0% [5, 9, 43]. However, as much as 92% of these patients in some studies concomitantly received bile acid sequestrants. Additionally, a dyspepsia diagnosis in a clinical trial is most likely a self-reported symptom. In

Table 4 Odds of developing new esophageal conditions in incident cohorts of statin users vs. non-users (secondary analyses)

Outcome variables	Non-users *n* (%)	Statin users *n* (%)	Adjusted odds ratio[a]	95% CI	*p* value
Incident PS-overall cohort (4595 non-users and 4530 statin users)					
Esophagitis	463 (10.1)	516 (11.4)	1.14	1.00–1.30	0.05
Symptoms of esophagitis	848 (18.5)	828 (18.3)	0.98	0.88–1.09	0.70
GERD/dyspepsia	1410 (30.7)	1544 (34.3)	1.17	1.07–1.28	<0.001
Esophageal complications of GERD	92 (2.0)	96 (2.1)	1.04	0.78–1.39	0.77
Incident PS-healthy cohort (2609 non-users and 2583 statin users)					
Esophagitis	218 (8.4)	274 (10.6)	1.30	1.08–1.57	0.01
Symptoms of esophagitis	362 (13.92)	368 (14.2)	1.03	0.88–1.21	0.70
GERD/dyspepsia	707 (27.1)	824 (31.9)	1.26	1.12–1.42	<0.001
Esophageal complications of GERD	38 (1.5)	54 (2.1)	1.45	0.95–2.20	0.09
Incident PS-women cohort (1937 non-users and 1963 statin users)					
Esophagitis	216 (11.2)	262 (13.3)	1.23	1.01–1.49	0.04
Symptoms of esophagitis	463 (23.9)	484 (24.7)	1.04	0.90–1.21	0.58
GERD/dyspepsia	694 (35.8)	766 (39.0)	1.15	1.01–1.31	0.04
Esophageal complications of GERD	38 (2.0)	49 (2.5)	1.30	0.85–2.00	0.23
Incident PS-men cohort (2523 non-users and 2481 statin users)					
Esophagitis	216 (8.6)	250 (10.1)	1.19	0.98–1.44	0.08
Symptoms of esophagitis	342 (13.6)	350 (14.1)	1.03	0.88–1.21	0.71
GERD/dyspepsia	667 (26.4)	783 (31.6)	1.27	1.13–1.44	<0.001
Esophageal complications of GERD	43 (1.7)	51 (2.1)	1.18	0.78–1.78	0.43

CI confidence interval, *GERD* gastroesophageal reflux disease, *PS* propensity score

[a]Adjusted for PS

Table 5 Odds of esophageal conditions in high-intensity statin users (secondary analyses)

Outcome variables	Non-users *n* (%) ($n = 29{,}812$)	High-intensity statin users *n* (%) ($n = 5214$)	Adjusted odds ratio[a]	95% CI	*p* value
Overall cohort: high-intensity statin users vs. non-users					
Esophagitis	3505 (11.8)	1134 (21.7)	1.04	0.93–1.16	0.47
Symptoms of esophagitis	5896 (19.8)	1631 (31.3)	1.06	0.97–1.17	0.21
GERD/dyspepsia	9684 (32.5)	2987 (57.3)	1.11	1.02–1.21	0.02
Esophageal complications of GERD	628 (2.1)	292 (5.6)	0.80	0.65–0.99	0.04

Outcome variables	Low- to moderate-intensity statin users *n* (%) ($n = 8412$)	High-intensity statin users *n* (%) ($n = 5214$)	Adjusted odds ratio	95% CI	*p* value
Statin users in the overall cohort: high-intensity vs. low- to moderate-intensity statins					
Esophagitis	1583 (18.8)	1134 (21.7)	1.15	1.05–1.25	0.002
Symptoms of esophagitis	2269 (27)	1631 (31.3)	1.09	1.01–1.18	0.03
GERD/dyspepsia	4342 (51.6)	2987 (57.3)	1.15	1.07–1.23	<0.001
Esophageal complications of GERD	421 (5.0)	292 (5.6)	1.00	0.85–1.17	0.98

CI confidence interval, *GERD* gastroesophageal reflux disease

[a]Adjusted for propensity score

Table 6 Odds of developing esophageal conditions in sub-cohorts of statin users vs. non-users (sensitivity analyses)

Outcome variables	Non-users *n* (%)	Statin users *n* (%)	Adjusted odds ratio[a]	95% CI	*p* value
Non-obese PS-Overall cohort (5349 non-users and 5382 statin users)					
Esophagitis	879 (16.4)	982 (18.2)	1.13	1.02–1.25	0.02
Symptoms of esophagitis	1261 (23.6)	1207 (22.4)	0.91	0.79–1.07	0.25
GERD/dyspepsia	2315 (43.3)	2589 (48.1)	1.07	0.98–1.17	0.13
Esophageal complications of GERD	222 (4.2)	208 (3.9)	0.92	0.76–1.12	0.40
Non-obese overall cohort (17,484 non-users and 7124 statin users)					
Esophagitis	1751 (10.0)	1368 (19.2)	1.19	1.06–1.32	0.004
Symptoms of esophagitis	3159 (18.1)	2083 (29.2)	0.95	0.81–1.11	0.48
GERD/dyspepsia	4919 (28.1)	3733 (52.4)	1.09	0.99–1.21	0.09
Esophageal complications of GERD	340 (1.9)	403 (5.7)	1.07	0.86–1.34	0.53
PS-overall cohort adjusting for PS and the combined use of aspirin, beta-blocker, and PPI (6342 non-users and 6342 statin users)					
Esophagitis	1069 (16.9)	1165 (18.4)	1.12	1.02–1.23	0.01
Symptoms of esophagitis	1507 (23.8)	1441 (22.7)	0.91	0.79–1.05	0.19
GERD/dyspepsia	2822 (44.5)	3085 (48.6)	1.09	0.999–1.18	0.052
Esophageal complications of GERD	262 (4.1)	242 (3.8)	0.93	0.78–1.11	0.40

CI confidence interval, *GERD* gastroesophageal reflux disease, *PPI* proton pump inhibitor, *PS* propensity score

[a]Adjusted for PS

contrast, a randomized controlled trial of lovastatin did not show an increased risk of dyspepsia among statin users (1.9% of the 1663 patients given placebo vs. 1.3% of the 1645 patients given lovastatin) [44]. Whereas, in our study, the odds of being diagnosed with GERD/dyspepsia was higher in statin users in comparison to non-users, the odds of esophageal complications of GERD, which included ulcer, stricture and stenosis of esophagus, and Barrett's esophagus, was not increased in our study. In fact, the OR of complications of GERD in high-intensity statin users in comparison to non-users was lower (OR 0.80, 95% CI 0.65–0.99). Several studies noted that statins were associated with a significantly lower odds ratio of Barrett's esophagus and odds of Barrett's segment ≥ 3 cm [14, 15]. In a meta-analysis of pooled data (1098 Barrett's, 2085 controls), statin use was significantly associated with a reduced risk of Barrett's esophagus [16].

Some in-vitro and animal studies may provide biologic plausibility for our findings. Statins increase endothelial nitric oxide production [45]; nitric oxide is an inhibitory neurotransmitter in the gastrointestinal tract, including the esophagus, hence, it may cause GERD [46, 47]. In an animal model, simvastatin potentiated the local oxidative stress and inhibited DNA synthesis resulting in a three-fold increase in ulcerated lesion size in the gastric mucosa [48]. In contrast, statins were thought to have a protective effect on the mucosa through inducing cyclooxygenase-2 gene expression and prostaglandin [37, 49].

In our study, although statin use was associated with an increased odds of being diagnosed with esophagitis, statin use was not associated with symptoms of esophagitis, which included nausea and vomiting. There are conflicting data among various studies in both the occurrence and the severity of nausea and vomiting associated with statin use. Reported incidences of nausea and vomiting among statin users in different studies ranged from 0.0 to 10.5% [5, 6, 8, 50]. Some studies reported that these symptoms did not differ significantly in statin users from the placebo group [43, 51]. Some studies reported that nausea was among the adverse events most often leading to the withdrawal of atorvastatin-treated patients [6], whereas others reported that these symptoms were mild and transient and that most patients continued statin use [10]. It should be noted that patients in randomized controlled trials were also placed on restrictive diets, which may have contributed to some of these symptoms.

Further research including prospective observational studies and pragmatic studies is warranted to confirm our findings because of the potential widespread clinical implications. Clinicians and patients should be aware of these potential gastrointestinal adverse risks and factor these into the decision to use statins for primary prevention, especially among patients at a lower risk of cardiovascular diseases and a higher risk for developing esophageal conditions. The increased number of statin-treated patients that would result in additional esophagitis

should be factored in overall statin cost-effectiveness analyses, as these esophageal conditions are costly (even if not life threatening). Studies have shown that the presence of upper gastrointestinal symptoms in patients with other diseases significantly increased healthcare utilization as reflected in higher rates of hospital admission, outpatient visits, and endoscopic procedures [28]. Therefore, examining the impact of widespread use of statins is important both for cost effectiveness as well as for patient safety.

Our study has several strengths. To our knowledge, our study is the largest to examine the odds of being diagnosed with esophageal conditions in statin users compared with non-users. The study spanned 8 years and captured all events regardless of the point-of-care location or affiliation. We used four different PS-matched analyses, examined our outcomes in a healthy cohort to minimize confounders, and examined the odds of our outcomes in separate men and women cohorts because some reports suggested sex-based differences in the risks of esophageal diseases [52, 53].

Several limitations are worth noting. Because of its retrospective design, the study may suffer from unidentified confounders. We have adopted several techniques to minimize such confounding such as including a wide array of baseline characteristics, using four different PS-matched cohorts, and performing several secondary and sensitivity analyses. However, unidentified confounders may still exist. For example, obesity is associated with both GERD and cardiovascular diseases; statins are preferentially prescribed to patients with cardiovascular diseases. Hence, a spurious association between statin use and GERD may be noted. However, we also used a PS-healthy cohort in whom there was no cardiovascular diseases or severe comorbidities at baseline; the association of statins and esophageal conditions was more pronounced in this cohort. The ICD-9-CM codes have variable sensitivity and specificity for various outcomes; selected ICD-9-CM codes have high specificity, but lower sensitivity, which may underestimate the prevalence and magnitude of the association. Although we used pre-specified outcomes based on AHRQ-CCS and a literature review, as we detailed earlier, these outcomes may overlap in their definitions or may not be very specific for the diagnosis. For example, "symptoms of esophagitis" included nausea, vomiting, and dysphagia, which are not specific for esophagitis and dyspepsia, which may occur with esophagitis, was included in a different outcome (GERD/dyspepsia). The use of pharmacy data to reflect medication use assumes patient compliance. Additionally, simvastatin was the most commonly used statin in our study, this pattern may differ from current statin utilization trends. Although we accounted for many baseline characteristics and created different PS-matched groups to avoid incidental findings from analyzing large databases, unrecognized confounders may still exist. Some of the upper gastrointestinal symptoms are more subjective complaints than others; therefore, there is an inherent variability and subjectivity to coding the symptoms and there may be variation in the extent of physician reporting and coding certain conditions.

5 Conclusion

Our findings suggest that long-term statin therapy is associated with esophagitis and possibly GERD/dyspepsia. With the increasing use of statins and the pressure to become available over the counter, further study is warranted to advise patients and clinicians on the potential role of statins in these commonly diagnosed group of esophageal conditions.

Compliance with Ethical Standards

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