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RESEARCH ARTICLE

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Statin users have an elevated risk of dysglycemia and new-onset-diabetes

Victoria A. Zigmont[1] | Abigail B. Shoben[2] | Bo Lu[2] | Gail L. Kaye[3] | Steven K. Clinton[4] | Randall E. Harris[1] | Susan E. Olivo-Marston[1]

[1] College of Public Health, Division of Epidemiology, The Ohio State University, Columbus, OH, USA

[2] College of Public Health, Division of Biostatistics, The Ohio State University, Columbus, OH, USA

[3] College of Public Health, Division of Health Promotion, The Ohio State University, Columbus, OH, USA

[4] College of Medicine, Department of Internal Medicine, Division of Medical Oncology, The Ohio State University, Columbus, OH, USA

Correspondence
Victoria A. Zigmont, Southern Connecticut State University, 501 Crescent Street, New Haven, CT 06515, USA.
Email: vzigmont42@gmail.com

Abstract

Objective: Statins are one of the most widely prescribed medications in the United States; however, there is a concern that they are associated with new-onset-diabetes (NOD) development. We sought to understand the risk of dysglycemia and NOD for a cohort of individuals that reflect real-world physician prescribing patterns.

Methods: A retrospective cohort study was conducted among individuals with indications for statin use (n = 7064). To examine elevated glycosylated hemoglobin (>6.0%), logistic regression with inverse probability weighting was used to create balance between incident statin users and nonusers. To evaluate the risk of NOD development, Cox PH models with time varying statin use compared NOD diagnoses among statin users and nonusers.

Results: A higher prevalence of elevated HbA1c (PD = 0.065; 95% CI: 0.002, 0.129, P = 0.045) occurred among nondiabetic incident users of statins. Additionally, statin users had a higher risk of developing NOD (AHR = 2.20; 95% CI: 1.35, 3.58, P = 0.002). Those taking statins for 2 years or longer (AHR = 3.33; 95% CI: 1.84, 6.01, P < 0.001) were at the greatest risk of developing NOD; no differences were observed by statin class or intensity of dose.

Conclusion: As lifestyle programs like the Diabetes Prevention Program are promoted in primary care settings, we hope physicians will integrate and insurers support healthy lifestyle strategies as part of the optimal management of individuals at risk for both NOD and cardiovascular disease. The relationships between statin use and glycemic control should be evaluated in large cohort studies, medical record databases, and mechanistic investigations to inform clinical judgment and treatment.

KEYWORDS

dysglycemia, inverse probability weighting, statin use, survival analysis, type 2 diabetes mellitus

1 | INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States, and roughly 33% of Americans die annually from heart disease or stroke.[1] Statin therapy decreases the occurrence of coronary heart disease (CHD) events (including acute myocardial infarction) by 24% to 37%, independent of baseline heartdisease,[2-4] and is indicated for the primary and secondary

prevention of CVD.[5] Recent estimates from NHANES observed that 27.9% of adults aged 40 to 59 used a cholesterol lowering medication in the previous month, and of these, 83% used a statin.[6]

The JUPITER trial enrolled individuals without diabetes who were free of CVD, but at elevated risk with elevated C-reactive protein (CRP) concentrations, and randomly assigned them to 20-mg rosuvastatin or placebo. Individuals with one or more diabetes risk factors who used statins had a 28% increase in new-onset-diabetes (NOD) (HR = 1.28, 95% CI: 1.07, 1.54) and a moderate increase in median HbA1c levels.[7] The applicability to lower risk individuals is unknown.[7] A meta-analysis of RCTs of statin use and NOD risk found a modest association (HR = 1.09; 95% CI: 1.02, 1.17),[8] and another meta-analysis combined the results from five RCTs and compared intensive and moderate statin use,[9] finding a dose response relationship.

Observational studies of statin use in large cohort studies and retrospective studies using medical records have not consistently aligned with the findings of large RCTs.[10-12] These differences can be attributed to limitations in study design or lack of control for group differences.[13] Statin users may have a higher risk for NOD due to their indications for statin use.[10] This study sought to identify the real-world risk for dysglycemia and NOD among cohort members with indications for statin use who are being seen by physicians in the midwest.

2 | MATERIALS AND METHODS

2.1 | Data sources

This study was a retrospective cohort of employees and dependent spouses enrolled in a private insurance plan in the Midwest. Employees who worked ≥32 hours per week were eligible to enroll in the plan. Members were covered for inpatient and outpatient services including ambulatory care, approved specialists, outside referrals, prescription drugs, and laboratory work.

2.2 | Data sources

Data from yearly biometric screening data (collected annually from 2011 to 2014), a health survey (collected in 2014), medical claims data (for medical encounters between 2011 and 2014), and pharmacy claims data (for all outpatient prescriptions from 2009 to 2014) were used for this study. Figure 1 provides a schematic of the study timeline. Blood samples were collected during routine biometric screenings, and the hospital laboratory was used to process the samples (2011-2012). Serum from blood samples was analyzed for lipid content (triglycerides and cholesterol) using Roche Analyzers. The "CardioChek System" (Polymer Technical Systems, Indianapolis, Indiana) was used to obtain total cholesterol, HDL cholesterol, triglycerides, and LDL cholesterol values (2013-2014). Glycosylated hemoglobin (HbA1c) and lipids were measured using blood samples collected via a fingerstick during point of care testing (2013-2014). HbA1c results were obtained using the "Bayer A1C Now" test (Bayer HealthCare LLC, Diabetes Care, Tarrytown, NY), and accuracy and precision were maintained using quality controls.[14] Waist circumference was measured in inches using a flexible tape measure. Weight was measured using a high capacity scale manufactured by Siltec (Bradford, MA), and height was measured using a stadiometer.

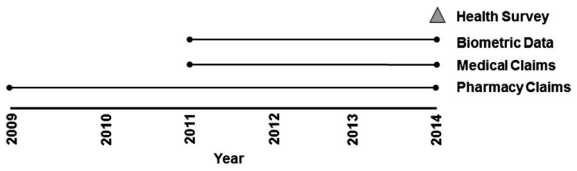

FIGURE 1 Study timeline

2.3 | Study population

Individuals with continuous enrollment in the insurance plan as early as January 2011 and for a minimum of 1 year were eligible for this study. This study limited the population to individuals with indications for statin use based upon ICD-9 diagnosis codes indicating one or more risk factors for CVD (primary prevention) or those who have had a CVD event (secondary prevention) using the primary diagnosis located on medical claims from professional outpatient and inpatient medical encounters.[5] Supplementary Table S1 provides these diagnoses codes. Adults with a type 2 diabetes diagnosis prior to the beginning of the study or during the first 90 days of enrollment in the insurance plan were excluded.

2.4 | Statin exposure

Individuals were classified as statin users if they had two or more filled prescriptions for a statin, and they obtained more than 30 pills during the study. Individuals who initiated statin use prior to January 2011, or within 90 days of enrollment, were classified as prevalent users and were excluded.[15] Incident statin users were defined as those who initiated statin use more than 90 days after enrollment in the insurance plan. Statin users were classified by class and intensity of dose using the 2013 American College of Cardiology and American Heart Association Guidelines.[16]

2.5 | Study outcomes

For the first analysis of this study, which sought to identify the likelihood of dysglycemia related to statin use, individuals' last HbA1c measurement was used as the study outcome. Individuals who had a HbA1c level ≤ 6.0% were compared with those with a value >6.0%, which indicated an elevated risk of prediabetes.[17-19] The cut point of 6.0 is commonly used for dysglycemia in clinical practice,[18] and it has a relatively high sensitivity (76.9%) and specificity (87.3%) compared with other cut points.[19] For the second analysis in this study, we sought to identify the risk of NOD associated with statin use. NOD was measured by using ICD-9 diagnoses codes for type 2 diabetes mellitus that were present on either an inpatient medical claim or at least two claims with a CPT code

for evaluation and management. This algorithm has 86% sensitivity, 97% specificity, and a PPV of 80%.[15]

An ethics committee provided us with IRB approved for this study at both the hospital and the university where the researcher was located. These standards were in line with the US Federal Policy for the Protection of Human Subjects (Office of Human Research Protections).

2.6 | Statistical analyses

Covariates of interest at baseline were compared (gender, age, LDL cholesterol, HDL cholesterol, triglycerides, waist circumference, BMI, ethnicity, education level, number of office visits, number of inpatient hospitalizations, and if an individual took a statin for primary or secondary prevention of CVD) for the statin use groups. Normally distributed continuous covariates were compared using t-tests, and categorical covariates were compared using Pearson's Chi square test. Descriptive statistics were compared after weighting to verify that covariate balance was obtained for the two groups. All final models were checked to confirm that the overlap assumption was satisfied and covariate balance were not violated using the overidentification test.[20]

For analysis one, an ordinary logistic regression model incorporating inverse probability of treatment weights was used to evaluate the risk of elevated HbA1c (>42 mmol/mol; >6.0%) among incident statin users compared with nonusers. Statin nonusers were compared with statin users before and after propensity weighting, and then a final model was used with propensity weights to compare statin users with nonusers. Propensity score is the probability of using statins, conditional on individual's pretreatment characteristics. Analyses were repeated to compare moderate intensity statin users with high intensity statin users and lipophilic statin users with hydrophilic statin users.

For analysis two, to evaluate NOD, individuals were followed to the event that occurred first: NOD; termination of enrollment in the insurance plan; or the end of the follow-up period, 31 December 2014. For statin nonusers, cohort entry was defined as the date of enrollment in the insurance plan, and for statin users, it was defined as the date of a second dispensed prescription for a statin. Participants were split between groups if their statin use changed; statin use was defined using a time-dependent variable with the subject unexposed until exposure and exposed after the second dispensed statin prescription.[20,21] The absolute risk of NOD over the study period was calculated separately for statin users and nonusers.

Cox proportional hazards models were used to compute hazard ratios with accompanying 95% confidence intervals for the association between statin use and NOD. The model building process was informed by clinical knowledge and a directed acyclic graph.[22] Clinically meaningful interactions between statin use and demographic characteristics were tested for inclusion during the model building process ($P < .10$). Purposeful selection was used to build the final model ($P < .05$) to adjust for differences between statin users and nonusers.[20] The final model was checked for the assumption of proportional hazards, for model diagnostics and the goodness of fit test.[20] Subgroup analyses examined the effect of duration of use, statin class and intensity of dose on NOD. A sensitivity analysis examined the effect of changing the definition of an incident statin user based on a new prescription 30 or 60 days following enrollment in the study. SAS version 9.4 (Cary, NC: SAS Institute Inc.) and STATA 14 (StataCorp. 2015. College Station, TX) were used for data analyses.

3 | RESULTS

The final study population consisted of 755 incident statin users and 3928 statin nonusers. The flow diagram is provided in Figure 2. For analysis 1, although incident statin users and nonusers differed at baseline, the groups were balanced for all listed covariates after inverse probability weighting (Supplementary Table S2). The average age of statin and nonusers was 46 years old, average BMI at baseline was 30, and the sample was 64% female, 88% white, and 46% college graduates after weighting. LDL-cholesterol was 139, and HDL-cholesterol was 56 for statin users. Hydrophilic statin users were more likely to be female and less likely to be white compared with lipophilic statin users before probability weighting, and the two groups were balanced for all covariates after probability weighting (Supplementary Table S3). Moderate intensity statin users were more likely to be females than high intensity statin users, and the groups were balanced for all covariates after probability weighting (Supplementary Table S4).

The prevalence differences for elevated HbA1c comparing incident statin users to nonusers are shown in Table 1. Incident statin users were 6.5% more likely to have a HbA1c value greater than 42 mmol/mol (>6%) after inverse probability weighting to create balance between the two groups. This association was statistically significant (PD = 0.065, 95% CI: 0.002, 0.129; P = 0.045). Although the magnitude of association for elevated HbA1c between hydrophilic and lipophilic statin users was similar to what was found for incident

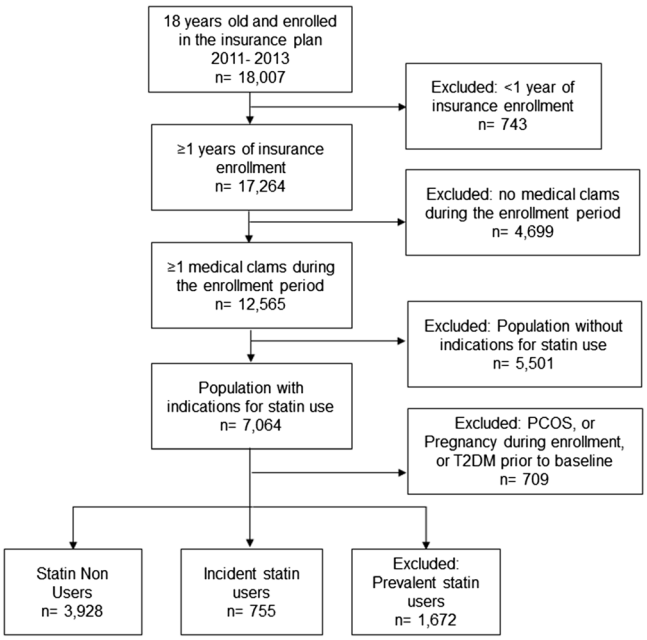

FIGURE 2 Flow diagram

TABLE 1 Prevalence difference of HbA1c greater than 6.0% (42 mmol/mol) for incident statin users and by class, and intensity of use

	Prevalence Difference	95% Confidence Interval	*P*-Value[c]
Statin users compared with non users[a]	0.065	(0.002, 0.129)	**0.045**
Hydrophilic users compared with lipophilic users[b]	0.079	(−0.057, 0.215)	0.256
Moderate intensity users compared with high intensity users[b]	0.060	(−0.061, 0.182)	0.328

[a]Inverse probability weighting adjusted for gender, age, LDL cholesterol level (at baseline), HDL cholesterol level (at baseline), triglyceride level (at baseline), waist circumference prior to initiating a statin, ethnicity, education, use of a statin for primary or secondary prevention of CVD, and number of office visits in the baseline year.

[b]Inverse probability weighting adjusted for gender, ethnicity, and waist circumference prior to initiating a statin.

[c]P-values less than 0.05 have been bolded.

statin users compared with statin nonusers, the association was not statistically significant. Similarly, there was no difference in the prevalence of elevated HbA1c when comparing moderate intensity statin users with high intensity statin users.

Table 2 compares the characteristics of statin users and nonusers in the time to NOD analysis (Analysis 2). Incident statin users used a statin for an average of 574.37 days. During the study period, this population experienced an incidence rate of 6.6% for NOD (310 diagnoses). NOD was most common among statin users (n = 112; 14.8%) compared with nonusers (n = 198; 5.0%).

The characteristics of lipophilic and hydrophilic statin users were similar and are included in Supplementary Table S5. Characteristics for moderate intensity and high intensity statin users were similar and are included in Supplementary Table S6. Participants were followed for a total of 20 112.9 person years. Over the study period, 670 new cases of NOD occurred; 175 were among incident statin users and 495 were among statin nonusers.

Table 3 shows the association between time to NOD among statin user groups. A Cox PH model obtained an incidence rate of type 2 diabetes that was higher among statin users AHR = 2.20 (95% CI: 1.35, 3.58; P = 0.002) after adjustment for baseline characteristics. Figure 3 shows the cumulative hazard of NOD across statin users and nonusers. An increased risk was observed for moderate dose compared with high dose statin use (AHR = 2.14, 95% CI: 0.52, 8.82) and for lipophilic statin users compared with hydrophilic stain users (AHR = 1.03, 95% CI: 0.55, 1.94); however, neither of these associations was statistically significant.

We examined if the elevated risk for NOD was due to differences in the duration of exposure. The results from the full Cox PH regression are shown for the adjusted and unadjusted models in Supplementary Table S7. Those using statins for 2 or more years had elevated risk of NOD development (AHR = 3.33 (95% CI: 1.84, 6.01)). Those using statins for less than 2 years did not have a statistically significant increase in the risk of NOD. When comparing these hazard ratios, there is evidence of a trend in increasing risk for increased duration of statin exposure. Those who used statins for 2 or more years had a higher likelihood for NOD based on their characteristics at baseline compared with the other duration groups (Supplementary Table S8). These individuals were older, more likely

TABLE 2 Characteristics of incident statin users and statin nonusers

	Statin Nonusers		Incident Statin Users		
	n = 3928		n = 755		*P*-Value[c]
Time using statins (days)	0	0	574.37	369.48	**<0.001**
Age (mean, sd)	45.83	10.53	49.17	9.58	**<0.001**
Gender (n, (%))					**<0.001**
Women	2434	(62.0)	386	(51.1)	
Men	1494	(38.0)	369	(48.9)	
Ethnicity (n, (%))					0.782
White	2336	(82.8)	463	(83.6)	
Black	360	(12.8)	65	(11.7)	
Other	125	(4.4)	26	(4.7)	
Education level (n, (%))					0.647
HS graduate or less	215	(10.7)	49	(12.7)	
Some college	529	(26.2)	102	(26.4)	
College graduate	921	(45.6)	16	(43.1)	
Post graduate	354	(17.5)	69	(17.8)	
First waist circumference [a] *(mean, sd)*	37.91	6.91	38.91	5.93	**0.004**
First BMI [A.] *(mean, sd)*	30.60	7.12	31.01	6.45	0.230
First LDL-C [A.] *(mean, sd)*	128.43	78.45	176.27	116.96	**<0.001**
First HDL-C [A.] *(mean, sd)*	55.78	17.12	51.37	15.78	**<0.001**
First triglyceride level [a] *(mean, sd)*	134.60	84.22	177.90	120.06	**<0.001**
Waist circumference (n, (%))					0.761
High risk	1567	(54.2)	248	(55.0)	
Not high risk	1323	(45.8)	203	(45.0)	
Total number of CVD diagnoses (mean, sd)	6.63	4.06	7.29	5.17	**<0.001**
Type of prevention (n, (%))					
Primary prevention	3796	(96.6)	718	(95.1)	**0.038**
Secondary prevention	132	(3.4)	37	(4.9)	
Number of office visits [b] *(mean, sd)*	7.58	11.05	7.02	8.62	0.185

[a]First LDL, first HDL, first triglyceride level, first waist circumference, and first BMI refers to the LDL, triglyceride, waist circumference, or BMI measurement prior to statin exposure. For statin nonusers, the first recorded measurement was used.

[b]Variable was measured in the baseline year (2011).

[c]P-values less than 0.05 have been bolded.

TABLE 3 Unadjusted and adjusted hazard ratios of statin use and risk of type 2 diabetes

	Unadjusted			Adjusted		
Comparison	**HR**	**95% CI**	***P*-value[d]**	**AHR**	**95% CI**	***P*-value[d]**
Statin users compared with nonusers[a]	2.49	(1.59, 3.91)	**<0.001**	2.20	(1.35, 3.58)	**0.002**
Moderate intensity users compared with high intensity users[b]	2.19	(0.53, 8.98)	0.276	2.14	(0.52, 8.82)	0.291
Lipophilic users compared with hydrophilic users[c]	1.14	(0.62, 2.12)	0.677	1.03	(0.55, 1.94)	0.922

[a]Model compared statin users with statin nonusers. n = 1486. The HRs were estimated from Cox PH models, adjusting for age, number of office visits in the baseline year, triglyceride level, BMI, HDL-cholesterol level, LDL-cholesterol level, risk level of waist circumference, gender, primary or secondary prevention, education level, and ethnicity.

[b]Model compared moderate dose statin users with high dose statin users. n = 449. The HRs were estimated from Cox PH models, adjusting for age, gender, first BMI, first HDL, and risk level of waist circumference.

[c]Model compared lipophilic statin users with hydrophilic statin users. n = 449. The HRs were estimated from Cox PH models, adjusting for age, gender, first BMI, first HDL, and risk level of waist circumference.

[d]P-values less than 0.05 have been bolded.

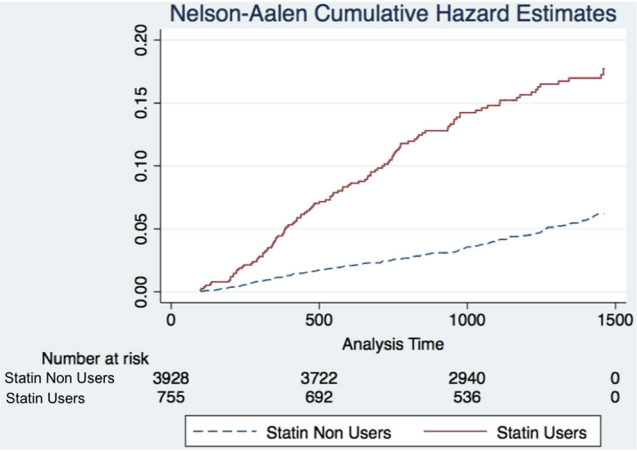

FIGURE 3 Nelson-Aalen cumulative hazard estimates for time to T2DM diagnoses among incident statin users and statin nonusers. Statin nonusers (n = 3928) had a higher rate of T2DM compared with statin nonusers (n = 755). Additionally, the proportional hazard assumption does not appear to be graphically violated. The graph has been cut off at time 1470 days.

to be female, and had more office visits at baseline compared with those using statins for shorter periods of time.

4 | DISCUSSION

This study observed a dose-dependent relationship between NOD across the duration of statin use,[23] which is suggestive of a causal relationship. Those with 2 or more years of statin use had the highest risk of NOD. Individuals using statins for the longest period of time may tolerate the treatment better than those who had effects early in treatment and discontinued their use. Thus, individuals who switch off statin therapy are prevented from developing NOD. The risk of developing NOD among statin users was 2.2 times greater than among nonusers after adjusting for confounding factors. This finding is consistent with other RCTs,[24] meta-analyses of RCTs,[8,25] and the WHI cohort.[13]

This study found an elevated prevalence of dysglycemia and NOD for statin users compared with nonusers. A possible reason for this finding is statins reduce *coenzyme Q10* (CoQ10) biosynthesis in the liver causing mitochondrial dysfunction and energy depletion thereby reducing glucose signaling and transport and causing insulin resistance.[26] Our findings of dysglycemia for statin users compared with nonusers are similar to Liew et al's study of hypertensive individuals; HbA1c was elevated among the entire group of statin users (AOR = 1.29, 95% CI: 1.01, 1.65).[27] However, when this association was stratified by type 2 diabetes status, the association only remained among individuals without diabetes (AOR = 1.21, 95% CI 1.01, 1.44, $P = .037$).[27] The study was underpowered to compare individuals without type 2 diabetes and the participants in this study were older than the ones in this study.

This study did not find an association between elevated prevalence of dysglycemia or risk of NOD when examining statin class or intensity of dose. Our comparisons by statin class focused on comparing incident hydrophilic statin users to incident lipophilic statin users; a similar study focusing on healthy patients taking statins also found similar results of no elevated risk for NOD.[28] A network analysis also found no differences in the risk of NOD when comparing these two groups (OR: 1.05; 95% CI: 0.9, 1.23).[29] The smaller number of individuals in the groups evaluating statin users by class and intensity explains the low precision in confidence intervals and thus drawing conclusions regarding possible differences for specific statins is premature. The occurrence of NOD was similar for hydrophilic users (n = 27, 14.3%) and lipophilic users (n = 85, 15.0%). Heterogeneity was present in statin class. Lipophilic statin users most frequently took simvastatin (58.8%) or atorvastatin (38.9%), and the majority of hydrophilic statin users took pravastatin (63.8%). Previous studies of lipophilic and hydrophilic statins and elevated HbA1c have had mixed findings. Atorvastatin and not pravastatin use was associated with increased HbA1c levels after an average 9.7 months of use ($P < .0001$) among individuals with hyperlipidemia.[30]

In this study, NOD occurrence was similar for high dose (n = 7, 12.7%) and moderate dose statin users (n = 105, 15%). Heterogeneity was also present in statin doses in this study. High intensity users almost exclusively took atorvastatin (94.5%), and moderate intensity

users took atorvastatin (37.9%), simvastatin (31.7%), pravastatin (18.2%), or rosuvastatin (10.3%). A meta-analysis of five large RCTs investigated the impact of statin intensity on NOD[9] among a population taking statins for the secondary prevention of CVD (these patients have all had a previous cardiovascular event). High intensity statin users in these trials took either atorvastatin, or simvastatin and moderate intensity users took pravastatin, simvastatin, or atorvastatin. Similar to our findings, several (n = 4) of these large trials found no overall association, but once the meta-analysis compared the effect estimates, the pooled estimate for NOD comparing high intensity with moderate intensity statin use was statistically significant (RR = 1.12, 95% CI: 1.04, 1.22).[9] This is in contrast to the population in this study who were taking statins for the primary prevention of CVD, and who were on average 10 years younger. Another study examined NOD among a "healthy cohort" of statin users and found a higher risk among high intensity compared with moderate intensity statin users (AOR = 1.5; 95% CI:1.30, 1.73); however, the population was also older than the population in this study. These age differences may make our population less susceptible to the development of NOD.

This study had several limitations. Information about mail away prescriptions were unavailable. Individuals who filled a new prescription for statins 90 days into the study or later were classified as incident statin users. A sensitivity analysis changing this definition did not modify our results. We did not directly measure patient's adherence to their prescribed class and dose of statin, which may be a reason why we did not observe any differences in NOD risk for statin class or intensity of doses; future studies should incorporate this into their research. The availability of biometric screening values for all participants regardless of disease status prevented detection bias or preferential data collection on sick individuals seeking medical care. This study examined short-term statin use (3.7 years or less); therefore, these findings do not represent longer term or lifetime statin exposure that is common in Americans. It is possible that unmeasured confounding factors may influence the results of this study. Prediabetes status was unavailable at the start of the study; however, patients were excluded prior to inclusion in the cohort if they were diagnosed with diabetes at baseline. We were also unable to take into account other prescription medication use, and several health behavior variables including smoking and alcohol use. The generalizability of this study is limited to insured individuals who are routinely monitored by a health care provider. A strength of this study is the use of pharmacy data to accurately measure statin class and intensity of dose, assuming individuals filling their prescriptions take their medications. To address this, statin users were required to fill their medication more than twice during the study period to be classified as a statin user; 85% of incident statin users took their medication for 6 months or longer. We however were unable to measure compliance, and it is possible that some patients did not take their medications as prescribed due to side effects. We expect that physicians were aware of the FDA's formal consumer advisory report released in January 2014 to caution individuals and physicians about the dysglycemic effects of statins.[31] This event may have influenced physician prescribing by motivating physicians to re-consider their statin prescribing practices and increase the monitoring of statin users. Study strengths included a large population (approximately 5000 individuals) with data to describe all health care use during the study. The use of an observational study reflects "real-world" physician care patterns and individual risk factors. Biometric measurements provided the ability to adjust for pre-statin use values, and the survey data allowed for the incorporation of clinically meaningful demographic factors.

The United States is faced with a rise in obesity prevalence and a sedentary lifestyle that predisposes individuals to metabolic syndrome. Although statin use clearly reduces cardiovascular events and mortality, the potential to increase the risk of NOD and its complications has significant implications for patient care.[32] Optimal health requires a multimodality approach and an awareness of potential risks and benefits of pharmaceuticals and an awareness of how additional interventions such as diet, physical activity, and weight management can be incorporated into a treatment plan to minimize toxicity from pharmaceuticals. As lifestyle programs like the Diabetes Prevention Program are promoted in primary care settings, we hope physicians will integrate and insurers support healthy lifestyle strategies as part of the optimal management of patients at risk for both NOD and CVD.

CONFLICT OF INTEREST

No author has any conflict of interest to disclose. All authors have seen and approved the final version of this manuscript. The manuscript has not been previously published nor is not being considered for publication elsewhere. We have no funding to disclose.

AUTHOR CONTRIBUTIONS

V.Z. wrote the manuscript, conducted the analysis, and researched data; S.O.M., R.H., G.K., and S.C. reviewed/edited the manuscript; and A.S. and B.L. contributed to the methods and reviewed/edited the manuscript.

ORCID

Victoria A. Zigmont https://orcid.org/0000-0002-3747-4328

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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