Published in final edited form as:

Acad Pediatr. 2017 July ; 17(5): 515–522. doi:10.1016/j.acap.2017.02.006.

Statin Use and the Risk of Type 2 Diabetes Mellitus in Children and Adolescents

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Abstract

Objective—There is increasing evidence of an association between statin use and type 2 diabetes (T2DM) in adults, yet this relationship has never been studied in children or adolescents and may have important implications for assessing risks and benefits of treatment in this population.” We estimated the association between statin use and the risk of T2DM in children with and without a dyslipidemia diagnosis.

Methods—Propensity scores were used to match new users of statins with a minimum 50 percent of days covered (PDC) in the first year of use to up to 10 non-users. Analyses were stratified by a dyslipidemia diagnosis based on recent evidence suggesting a potentially protective effect of familial hypercholesterolemia on T2DM. In sensitivity analyses we varied this period of exclusion and PDC. Cox proportional hazard models compared the hazard of the outcome between the exposed and unexposed patients.

Results—A total of 21,243,305 patients met eligibility criteria, 2,085 (0.01%) of whom met the exposure definition of which 1,046 (50%) had a dyslipidemia diagnosis. Statin use was associated with an increased risk of type 2 diabetes in children without dyslipidemia (HR 1.96, 95% CI 1.20–3.22), but not in children with a dyslipidemia (HR 1.11, 95% CI 0.65–1.90). The results were consistent across variations in the exclusion period and PDC.

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Author Contributions:

NJ, GW and JZ conceived of the study question, NJ conceived of the study design, handled all data manipulation, conducted all analyses and wrote the first draft of the manuscript. GW, JZ, CE and AT reviewed and edited subsequent drafts of the manuscript.

Conflict of Interest: Nina Joyce has worked as a Global Health and Economics Outcome Research fellow for Pfizer, Inc. in a capacity unrelated to the manuscript. The other authors have no conflicts of interest relevant to this article to disclose.

Conclusions—Statin use was associated with an increased likelihood of developing T2DM in children without dyslipidemia. Physicians and patients need to weigh the possible risk of T2DM against the long-term benefits of statin therapy at a young age.

INTRODUCTION

Statin prescribing to children and adolescents is rare, with an estimated incidence of 2.6 new prescriptions per 100,000 person-years.¹ However, the 2008 decision by the American Academy of Pediatrics, followed in 2011 by the National Heart Lung and Blood Institute, to recommend statins as a first line treatment for hyperlipidemia in children age 8 or older has intensified a debate over the risk versus benefits of long-term statin use in youth.^{2, 3} In adults, the side effects associated with statin use are low with approximately 0.1% to 0.2% of all users developing myopathy and less than 1 death due to rhabdomyolysis per 1 million statin prescriptions.⁴ Although studied less extensively, reported rates of side effects in children and adolescents appear to be similar to those found in adults.^{5–8}

Recently, a number of studies in adults suggest that statin use is associated with an increased risk of type 2 diabetes mellitus (T2DM) between 9% and 28%.^{9–14} The putative pathways by which statins may increase the risk of diabetes include impairing insulin secretion, increasing weight-dependent or -independent insulin resistance, and potentially enhanced glucose secretion.^{15,16} Results from these studies prompted the US Food and Drug Administration (FDA) to update statin labeling in 2012 to include a warning for the development of T2DM.¹⁷ Although the increased risk of T2DM can be a counterargument to initiating statin therapy in low risk adults, the benefits in high risk patients for whom statins are indicated most often outweigh the potential side effects, including the risk of T2DM.^{12,18} This calculation may differ in children, however, where the short-term risk of T2DM needs to be weighed against the much longer-term risk of cardiovascular disease.

The clearest indication for statin use in children is heterozygous familial hyperlipidemia (heFH)- a genetic condition resulting in significantly elevated low-density lipoprotein cholesterol (LDL-C). Children with heFH have an increased risk of cardiovascular disease, and left untreated, it is estimated that 50% of males and 30% of females will suffer an acute cardiovascular event before the age of 60.^{19,20} Complicating the risk assessment in children is a recent study reporting a significantly lower prevalence of T2DM among patients with heFH compared to their unaffected relatives, and a randomized controlled trial reporting no increased risk of T2DM in patients with heFH treated with statins.^{21,22} Results from these studies raise the possibility that the gene mutation resulting in FH may also confer protection from T2DM.

Although there is evidence demonstrating an increased risk of diabetes associated with statin use in adults, to our knowledge that link has not been evaluated in children. To fully assess the risk-benefit ratio of statin treatment in childhood, it is necessary to first quantify the risk of T2DM associated with statin treatment in this population. Accordingly, the objective of this study was to estimate the risk of incident T2DM associated with statin use in a commercially insured population of youth ages 8 to 20 with and without diagnosed

dyslipidemia between 2003 and 2014. We hypothesized that, similar to adults, statin use in children would be associated with an increased risk of T2DM.

METHODS

Data source and study cohort

Data for this analysis came from the MarketScan Research Database for calendar years 2003 through 2014. The MarketScan database is a compilation of commercial health insurance claims that includes data on all medical claims for employees and their dependents, and thus does not include information on individuals covered under Medicaid, Medicare or the uninsured. As data are collected from employers, MarketScan contains information on individuals through the duration of the employment with their employer, or until their employer ceases to participate in providing data. We assessed all patients ages 8 to 20 between 2003 and 2014 for inclusion in the study cohort. Eligibility for inclusion in our analysis was defined as no T2DM diagnosis and no dispensings for a statin in the 12-month period following the first date of enrollment after the age of 7 (figure 1, period A).

Statin exposure and follow up time

We employed a new user study design to estimate the effect of statin use on rates of incident T2DM.²³ Though we chose to exclude individuals with a recorded diagnosis of T2DM, we cannot ensure that we are identifying the first T2DM diagnosis for a patient, only that it was the first diagnosis during the period for which we were able to observe them. New statin use was defined as the first (“index”) statin dispensing after a minimum 12 months of no recorded dispensings (figure 1, period A). In our primary analysis we limited our exposed group to patients with a minimum of 50 percent of days covered (PDC) in the 12-month lag-period following the index dispensing (figure 1, period B). The PDC is a commonly used measure of medication adherence in which the total number of days supplied for each prescription are summed and divided by the observation interval, which we defined in our primary analysis as the 12-month lag period. Because we cannot tell if a patient is taking the medication, only that he or she has filled a prescription, our measures may underestimate adherence. However, the PDC has been shown to be a valid measure of adherence in prior studies.²⁴ All patients with less than 12-months of follow up or a T2DM diagnosis during the lag period were excluded from the primary analysis.

We chose to use a 12-month lag-period for several reasons. First, children who are prescribed statins have a higher prevalence of comorbidities associated with an increased risk of diabetes.¹ Consequently, it is likely that some of the early T2DM diagnoses are due to confounding by indication and unrelated to statin exposure. Second, though there is limited consensus on the mechanism by which statins cause diabetes in adults,²⁵ results from the re-analysis of clinical trials in adults suggest that 12 months represents a biologically plausible lag time between exposure and outcome.^{9,10,26} In sensitivity analyses, however, we varied both the duration of the lag-period and the required PDC.

Propensity Score Matching

We calculated year-specific propensity scores as the probability of initiating statin use in a given year conditional on a set of measured covariates listed in table 1. Statin users who did not meet the case criteria of 50 PDC over the 12-month lag period were excluded from the pool of potential unexposed matches, while non-statin users were eligible to be an unexposed match in each year for which they contributed person-time and could serve as an unexposed match in multiple years. PDC was calculated as the sum of the days-supply for dispensings that occurred within the lag period divided by the number of days in the lag period.²¹

Propensity score models included the all variables listed in table 1 as well as interactions between dyslipidemia and each covariate, and an interaction between age and sex. Each comorbidity was defined as present on observing two outpatient claims during a 12-month period or a single inpatient claim and absent otherwise. While comorbidities were considered present if they occurred at any point prior to the index date, prescription dispensings, procedures and measures of health care utilization were assessed in the 12-month baseline period prior to the index statin dispensing for statin users (see supplemental tables 1 and 2 for the ICD-9 codes used to define each comorbidity and the specific drugs included in each drug class).

To parallel this approach in the pool of potential unexposed matches, an index date was randomly selected in each year based on the distribution of index statin dates among the cases. Comorbidities, drug dispensings and health care utilization was measured prior to the index date as it was for the exposed population. Exposed patients were then matched, with replacement, to up to 10 unexposed patients in each year within a 0.01 caliper of the propensity score. Unexposed matches were randomly selected when more than 10 were available for a given exposed patient. We compared the distribution of covariates between the exposed and unexposed patients using the standardized differences, and considered a standardized difference between -0.1 and 0.1 to be well balanced.^{27,28}

Diabetes

We based our definition of T2DM on two separate algorithms for identifying T2DM in pediatric populations, with a modification to the minimum time period required between claims.^{29,30} Specifically, a new diagnosis for T2DM was identified if any of the following were observed: 1) two outpatient claims in a 24-month period, at least one of which was for T2DM due to evidence that T2DM can be mistakenly coded or difficult to distinguish from type I in pediatric populations.^{16,17}; 2) an inpatient claim with a primary diagnosis of T2DM; 3) a single outpatient claim for T2DM and a dispensing for an oral hypoglycemic or insulin preparation within 120 days; 4) two prescriptions for an oral hypoglycemic or insulin preparation and a claim for a diabetes-related procedure within one year. Patients with a diagnosis of polycystic ovarian syndrome and T1DM were excluded according to the methods detailed in Cooper, et al.³⁰

Analysis

Analyses were run separately for patients with and without a recorded diagnosis of dyslipidemia (ICD-9 code 272.x). Crude incidence of T2DM was calculated as the number of cases of T2DM divided by the sum of the follow up time for the cases and controls separately. The relative risk of T2DM was estimated using hazard ratios from conditional Cox proportional-hazard models which were stratified by the matched pair to ensure equal follow up time within each matched set. Time-to-event was measured from the first day after the end of the lag period to the outcome or censoring (figure 1, period C), and all patients were administratively censored on December 31st, 2014. Estimates were considered statistically significant at a two-sided $p < 0.05$. All analyses were conducted using SAS 9.4 (Cary, NC).

Sensitivity Analyses

To examine the influence of duration and degree of statin exposure on our estimate, we considered lag periods of 6 and 9 months in addition to the 12-month lag period used in the main analysis and redefined statin users as those with at least 75 PDC.

In order to test the robustness of our results to variable definitions, first we modified our definition of T2DM to require that both outpatient claims be for T2DM. Second, we adjusted for the presence of outpatient visits during the lag period to account for measures of health care utilization after the initial statin dispensing. Lastly, only heFH, and no other cause of dyslipidemia, has been suggested as protective against T2DM. Thus, we limited the stratification to only patients with only a claim for pure-hypercholesterolemia (ICD-9 272.0) which includes heFH.

RESULTS

Characteristics of the study cohort

Between 2003 and 2014 there were a total of 21,243,305 children aged 8 and 20 years who met the eligibility criteria, of whom 6,926 (0.03%) had a new statin dispensing and 52,249 (0.25%) had a new diagnosis of T2DM. Among new statin users, 2,085 (30%) met the exposure definition of a minimum 50 PDC over a 12-month lag period with no T2DM diagnoses during the lag period, 1,046 (50%) of which had a prior diagnosis for dyslipidemia. After matching new statin users to non-users on their propensity for treatment, there were 869 treated and 8,524 untreated patients with a recorded diagnosis of dyslipidemia, and 848 treated and 8,432 untreated patients without a recorded diagnosis of dyslipidemia (table 1). Approximately 80% of all treated patients were successfully matched to untreated patients (supplemental table 3). Patient characteristics were similar in patients with and without dyslipidemia, with the exception of anti-hypertensive agents which were less common in patients without a dyslipidemia diagnosis and chronic kidney disease and corticosteroids which were more common. The standardized differences between the exposed and unexposed patients were between -0.1 and 0.1 for all covariates (table 1). In sensitivity analyses, covariate distributions and comparisons were similar across all variations of the lag period and PDC (supplemental tables 4–6).

Relative Risk of Diabetes

Among patients without dyslipidemia, 23 developed T2DM in the treated group (100 events per 10,000 person-years) versus 149 who developed T2DM (62 events per 10,000 person-years) in the untreated groups. In Cox proportional hazards models, patients receiving prescriptions for statins had a statistically significant higher relative risk of developing T2DM (HR 1.96, 95% CI 1.20–3.22). Among patients with dyslipidemia, 17 developed T2DM (101 events per 10,000 person years) in the treated group versus 146 who developed T2DM (74 events per 10,000 person years) in the untreated group, yielding a hazard ratio for T2DM that was not statistically significant (HR 1.11, 95% CI 0.65–1.90) (table 2).

Results were similar in sensitivity analyses varying the lag period and PDC for patients with and without a diagnosis of dyslipidemia, with the exception of 75 PDC across a 12-month and 9-month lag period in which relative risks were elevated but not statistically significant in patients without dyslipidemia (table 3).

Additional Sensitivity Analyses

We tested the robustness of our estimates to analytic choices. Specifically, a more conservative definition of T2DM, a more specific definition of dyslipidemia targeted at identifying those with likely heFH, and statistical adjustment for outpatient utilization during the lag period did not materially alter the results (figure 2).

DISCUSSION

In a cohort of privately insured youth ages 8 to 20 years we found that statin use was associated with incident T2DM among children without a prior recorded diagnosis for dyslipidemia. In patients with a recorded diagnosis for dyslipidemia, statins were not significantly associated with incidence of T2DM. Our results were broadly consistent across sensitivity analyses varying the PDC as well as the lag period between the index dispensing and the start of follow up. Similarly, our results were largely consistent when we used more sensitive definitions of dyslipidemia and T2DM, as well as analyses in which we adjusted for the number of outpatient visits during the lag period.

In our primary analyses of children without a prior diagnosis of dyslipidemia we found a higher relative risk of T2DM associated with statin use than has been found in randomized controlled trials or observational studies in adults.^{9–11,31,32} Statin prescribing in childhood is rare and a 2014 survey of physicians suggested there may be hesitation to prescribe statins even to children who meet the guideline recommendations for treatment.³³ Consequently, our cohort represents a specific, and as evident from the high rates of comorbidities, higher risk segment of the population. Thus, to the extent that there are heterogeneous effects of statins on the risk of T2DM, our estimates may reflect one end of the distribution of effects seen in clinical trials. In fact, stratified analyses of clinical trials have found that increased risk of T2DM is limited to patients with a higher baseline risk of T2DM. For example, the JUPITER trial found a 28% higher risk of T2DM in patients with at least one risk factor for diabetes, but no higher risk in patients without any baseline risk factors.⁹ Similarly, a reanalysis of the Treating to New Targets (TNT) trial and the Incremental Decrease in

Clinical Endpoints through Aggressive Lipid Lowering (IDEA) trial, found a 20% increased risk of T2DM in patients with pre-diabetes, but not in patients without pre-diabetes.²⁶ Thus, given the high prevalence of risk factors for T2DM in our cohort it is possible that the higher risk of T2DM observed in our analysis may reflect higher baseline risk of T2DM among the unique subpopulation of children with a minimum level of statin use.

A recent study found a lower prevalence of T2DM among people with heFH as compared to their unaffected relatives, raising the possibility that the genetic mutation causing heFH may also confer some protection against the development of T2DM. Given the statistically significant associations we observed among patients without dyslipidemia, it is possible that the weaker association we observed in the population with dyslipidemia result from such a protective effect. Yet, caution is warranted in this interpretation as the biological mechanisms by which statins increase the risk of T2DM or heFH lowers the risk of T2DM are not well understood. Additionally, the potential for differential ascertainment of the outcome cannot be ruled out. Patients with a diagnosed condition such as dyslipidemia may have greater contact with the health care system due to increased monitoring, resulting in an increased probability of detecting the outcome. However, rates of health care utilization prior to the index date were included in the propensity model and sensitivity analyses in which we adjusted for the number of outpatient visits during the lag period did not substantially alter our results.

Although to our knowledge this is the first study of the effect of statin use on the risk of diabetes in children, these results need to be interpreted in light of several additional limitations. First, statin use in this population is very low¹ and while results in the group with a diagnosis of dyslipidemia were not significant, point estimates were consistently greater than one. Thus, it is possible that there is a lower, but still positive, risk in patients with dyslipidemia that we did not have the power to detect.

Second, the potential for misclassification of comorbidities cannot be discounted. Our measures of comorbidity status are generated for the purposes of reimbursement, not research. As a result, conditions that have little effect on reimbursement, such as obesity and a family history of diabetes or cardiovascular disease may be undercoded. If the prevalence of this type of misclassification differs with respect to exposure, estimates may be biased. Though measured covariates were balanced across exposure status, suggesting that these substantial risk factors for diabetes were unlikely to bias our estimates, there is still potential for bias due to additional confounders unmeasurable in claims data.

Third, our results may not be generalizable outside of our specific population. We were unable to find matches for 20% of our exposed population. However, while our estimate may be less generalizable, our strict matching criteria result in a more precise estimate. Additionally, our findings reflect associations in a commercially insured population which may be healthier and less obese than the uninsured or publicly insured populations. Further, because we cannot measure race and ethnicity in our data, our results may be an underestimate for racial and ethnic minorities, such as African American's and Latinos, for whom the prevalence of T2DM is higher.³⁴

Lastly, because there is no ICD-9 code for heFH in specific, it is possible that some individuals with a diagnosis for dyslipidemia do not have heFH. However, if heFH is protective against T2DM then misclassification would result in an overestimate of the effect in children with dyslipidemia. Similarly, if children without dyslipidemia truly do have heFH then our estimates in this group would be an underestimate. Thus, given the significantly positive effect we found in children without dyslipidemia and the non-significant effect we found in children with dyslipidemia, misclassification would most likely alter the magnitude of our effect estimates but would be less likely to alter their interpretation. Moreover, sensitivity analyses limiting dyslipidemia to patients with the ICD-9 code 272.0 for “pure hypercholesterolemia”, which includes heFH, did not significantly alter our estimates.

The 2009 AAP and 2011 NHLBI guidelines were updated to reflect developments in the understanding of atherosclerosis in childhood. Yet critics of these recommendations charge that without additional research on the side effects of long-term statin use in children, the guideline updates were premature and risked causing an “epidemic” of treatment and concomitant side effects.^{3,35,36} Our findings contribute to this discussion by suggesting that there may be an increased risk of T2DM associated with statin use in children among those without a recorded diagnosis of dyslipidemia- a group for whom many experts would suggest statin use should be the last option. The clinical implications of our finding that there was no apparent increase in risk of T2DM in children with dyslipidemia diagnosis, however, needs to be interpreted with caution and replication of our results in larger database would be beneficial in verifying the validity of our findings. Physicians and patients need to weigh the possible risk of T2DM against the long-term benefits of statin therapy at a young age, and when statins are prescribed, patients should be closely monitored for evidence of T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Nina Joyce had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

We acknowledge and appreciate the help of Andrew Zullo, PharmD in assisting in the identification and definition of drug classes.

Funding Sources:

This work was supported by the Reagan-Udall Foundation for the FDA, project RUF-IMEDS-SA- 0022. Dr. Joyce’s time was supported by an individual pre-doctoral fellowship from the American Heart Association-Founders Affiliate and by the National Institute of Mental Health of the National Institutes of Health under Award Number T32MH019733. Dr. Zachariah’s time was supported by a NHLBI K23 award- HL111335. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Reagan-Udall foundation

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What's New

There was an increased risk of Diabetes Type II (T2DM) associated with statin use in children and adolescents without a diagnosis of dyslipidemia, but no increased risk in children and adolescents with dyslipidemia.

Figure 1.
Study timeline

Figure 2.

Risk of diabetes type II among children according to the presence of a dyslipidemia diagnosis prior to the index dispensing by alternate definitions of the T2DM, dyslipidemia and adjustment for the number of outpatient visits during the lag period.

Characteristics of study population after matching patients with a minimum 50 percent of days covered (PDC) in the 12-month period after the index dispensing to patients with no statin use stratified by the presence of a dyslipidemia diagnosis

Table 1

	No Dyslipidemia				Dyslipidemia			
	Statin Users		Non-users		Statin Users		Non-users	
	N	%	N	%	N	%	N	%
N	848	–	8,432	–	869	–	8,524	–
Demographics								
Female	371	43.8%	3,494	41.0%	426	49.0%	4,272	50.0%
mean age (sd)	16	(3.1)	16	(16.5)	17	(3.1)	17	(3.1)
Diagnosed conditions								
Obesity	34	4.0%	331	4.0%	48	5.5%	438	5.0%
Hypertension Metabolic Syndrome	91	10.7%	885	10.0%	68	7.8%	573	7.0%
Asthma	10	1.2%	106	1.0%	9	1.0%	96	1.0%
Chronic Kidney Disease	56	6.6%	550	7.0%	59	6.8%	590	7.0%
Depression	45	5.3%	398	5.0%	14	1.6%	91	1.0%
ADHD	50	5.9%	517	6.0%	63	7.2%	537	6.0%
Bipolar	62	7.3%	600	7.0%	64	7.4%	593	7.0%
Schizophrenia	50	5.9%	484	6.0%	47	5.4%	410	5.0%
Medications Dispensed	7	0.8%	52	1.0%	4	0.5%	27	0.0%
Anti-hypertensive	365	43.0%	3,690	44.0%	164	18.9%	1,388	16.0%
Anti-asthmatic	240	28.3%	2,359	28.0%	205	23.6%	1,937	23.0%
Corticosteroids	350	41.3%	3,387	40.0%	301	34.6%	2,869	34.0%
Vitamin-D	69	8.1%	624	7.0%	44	5.1%	411	5.0%
Anti-depressant	238	28.1%	2,361	28.0%	217	25.0%	1,937	23.0%
Antipsychotic	102	12.0%	956	11.0%	74	8.5%	609	7.0%
Stimulants	164	19.3%	1,717	20.0%	155	17.8%	1,405	16.0%
Lithium	24	2.8%	251	3.0%	7	0.8%	60	1.0%
Benzodiazapine	189	22.3%	1,800	21.0%	138	15.9%	1,190	14.0%

	No Dyslipidemia						Dyslipidemia					
	Statin Users			Non-users			Statin Users			Non-users		
	N	%	N	%	N	%	N	%	N	%	N	%
Procedures												
Diabetes Screening	286	33.7%	2,989	35.0%		0.04	304	35.0%	2,885	34.0%		0.02
Lipid Panel	624	73.6%	6,348	75.0%		0.04	813	93.6%	7,954	93.0%		0.01
Health Care Utilization Outpatient visits												
0	47	5.5%	511	6.0%		0.02	5	0.6%	27	0.0%		0.04
1-3	210	24.8%	2,238	27.0%		0.04	158	18.2%	1,788	21.0%		-0.07
4-5	114	13.4%	1,051	12.0%		0.03	160	18.4%	1,564	18.0%		0.00
>6	477	56.3%	4,632	55.0%		0.03	546	62.8%	5,145	60.0%		0.05
Inpatient Visits												
0	707	83.4%	7,183	85.0%		0.05	814	93.7%	8,079	95.0%		-0.05
1-2	96	11.3%	846	10.0%		0.04	50	5.8%	416	5.0%		0.04
>3	45	5.3%	403	5.0%		0.02	5	0.6%	29	0.0%		0.03
Drug Dispensing												
0	17	2.0%	180	2.0%		0.01	20	2.3%	192	2.0%		0.00
1-3	222	26.2%	2,339	28.0%		0.04	256	29.5%	2,761	32.0%		-0.06
4-5	80	9.4%	821	10.0%		0.01	96	11.0%	971	11.0%		-0.01
>6	529	62.4%	5,092	60.0%		0.04	497	57.2%	4,600	54.0%		0.06

Hazard ratios of diabetes associated with statin use by the presence of a dyslipidemia diagnosis among statin users with a minimum 50 PDC in the first 12-months after an index dispensings

Table 2

Dyslipidemia	Exposure	Person Years (PY)	Events	Rate per 10 ⁴ PY	Hazard Ratio	95% CI	p-value
No Dyslipidemia	Non-users	23,648	149	62.26		[reference]	
	>50 PDC	2,097	23	100.64	1.96	(1.20–3.22)	0.007
Dyslipidemia	Non-users	19,884	146	73.98		[reference]	
	>50 PDC	2,018	17	101.39	1.11	(0.65–1.90)	0.703

Table 3

Hazard ratios of diabetes associated with statin use by the presence of a dyslipidemia diagnosis, the lag time between the index dispensing and the start of follow up, and the percent of days covered (PDC) during the lag period

Lag period	Statin Use	Person Years (PY)	Events	Rate per 10 ⁴ PY	Hazard Ratio	(95% CI)	p-value
12 months	Non-users	23,648	149	63.01		[reference]	
	>50 PDC	2,097	23	109.69	1.96	(1.20–3.22)	0.007
	Non-users	14,295	89	62.26		[reference]	
	>75 PDC	1,292	13	100.64	1.45	(0.74–2.85)	0.276
9 Months	Non-users	32,131	180	56.02		[reference]	
	>50 PDC	2,838	27	95.14	1.63	(1.03–2.59)	0.036
	Non-users	22,172	132	59.53		[reference]	
	>75 PDC	1,974	20	101.34	1.50	(0.87–2.59)	0.141
12 months	Non-users	50,252	251	49.95		[reference]	
	>50 PDC	4,353	37	85.01	1.88	(1.27–2.79)	0.002
	Non-users	31,497	173	62.26		[reference]	
	>75 PDC	2,751	27	100.64	2.30	(1.46–3.63)	0.000
9 Months	Non-users	19,884	146	73.43		[reference]	
	>50 PDC	2,018	17	84.25	1.11	(0.65–1.90)	0.703
	Non-users	12,435	92	73.98		[reference]	
	>75 PDC	1,282	13	101.39	1.64	(0.87–3.08)	0.127
6 Months	Non-users	25,442	178	69.96		[reference]	
	>50 PDC	2,512	17	67.67	0.99	(0.59–1.67)	0.982
	Non-users	17,618	133	75.49		[reference]	
	>75 PDC	1,784	17	95.27	1.26	(0.73–2.17)	0.415
Dyslipidemia	Non-users	34,537	282	81.65		[reference]	
	>50 PDC	3,358	32	95.30	1.19	(0.80–1.75)	0.392
	Non-users	22,711	182	73.98		[reference]	
	>75 PDC	2,281	20	101.39	1.03	(0.63–1.67)	0.918