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USE OF CONTINUOUS EXPOSURE VARIABLES WHEN EXAMINING DOSE-DEPENDENT PHARMACOLOGICAL EFFECTS – APPLICATION TO THE ASSOCIATION BETWEEN EXPOSURE TO HIGHER STATIN DOSES AND THE INCIDENCE OF DIABETES

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ABSTRACT

Background
Many observational studies have found an association between the exposure to statins and the increased risk of diabetes, mostly through the use of intent-to-treat (ITT) like exposure measure (EM). ITT like EM may not adequately reflect the mechanism of action by which statins could cause diabetes.

Objective
To determine if continuous EMs can more accurately reflect the mechanism of action by which statins and incidence of diabetes would be associated than ITT like EM.

Methods
We obtained a cohort of 404,129 diabetes-free incident statin users from the Quebec public drug insurance plan. Patients dispensed with a drug used in the treatment of diabetes or diagnosed with diabetes within 2-years follow-up were defined as cases. Controls were randomly matched to each case on the index date. Three EMs were tested, EM 1: exposure to a high versus low dose statin at baseline (ITT like); EM 2: cumulative standardized statin dose (cSSD) at the index date; and EM 3: cSSD in the 180 days prior to the index date. The optimal EM was selected based upon each model's Akaike's information criterion (AIC). Conditional logistic regressions were used to calculate conditional OR and model AIC.

Results
All three EMs identified an increased risk of diabetes among patients exposed to higher statin doses. Model AIC identified EM 3 as the best EM for this association.

Conclusion
Our results indicate that higher statin doses increase the risk of diabetes but favour a cumulative reversible diabetogenic effect of statins.

Key Words: exposure measures, exposure assessment, drug utilization study

Pharmacoepidemiological studies focus on identifying associations between exposures and outcomes and rely on adequately classifying each individual's drug exposure and outcome statuses. Classification of a patient's exposure status is particularly daunting in the observational setting because a patient's drug profile often varies over time (e.g., multiple doses, intermittent drug use, and frequent switches).

In theory, patients' exposure status should be defined within the relevant time-window, the period during which the drug could plausibly cause the outcome, which is based on the drug's specific mechanism of action.[1,2] Unfortunately, since pharmacoepidemiology often focuses on previously unknown potential side-effects of a drug, the mechanism of action by which the drug could cause the disease can be uncertain. Despite this limit, patients' exposure statuses are often determined by means of the binary intent-to-treat (ITT) approach based on the treatment assignment at the cohort entry date. Appropriate use of the ITT approach depends on patients' persistence to their assigned treatment throughout the study follow-up. Unfortunately, real world drug persistence is far from perfect and use of this exposure classification may substantially bias measures of association.[3]

Patients may use the drugs intermittently and at various doses and frequencies, during the study follow-up. It is therefore impossible to determine under such conditions if the baseline drug exposure status truly reflects the true patient's exposure experience within the relevant time-window.

Rather than using a binary drug dosage variable, the author's think that dose-dependent drug effects may be best defined with the use of continuous variables. Time-dependent exposure not only reflects patients' persistence to the drug, it also incorporates switches in drug dosage throughout patient follow-up and can account for the possibility of the reversibility of the drug's deleterious effect. In situations where the mechanism of action is unknown, it is important to examine the reversibility of this effect by comparing the performance of variables defined under both situations: (1) irreversible effect assumes that once a patient has been exposed, the effect of the consumed medication will persist even after drug he stops taking the drug, and (2) reversible effect where, when following discontinuation of the medication by the patient, the effect of the consumed medication on the patient's risk of event will regress and ultimately disappear over time.

For example, recently, results of a meta-analysis indicated that higher statin doses compared to lower doses increased the risk of diabetes.[4] This association has been examined in several pharmacoepidemiological studies using various EMs, including the dose-dependent and baseline ITT like EM.[5–9] Most studies using the dose-dependent effect of statins found a small positive association between the exposure to higher versus lower statin doses and diabetes (hazard ratios [HR] ranging from HR=1.15 [1.05–1.26][5] to 1.30 [95%CI 1.20–1.40][6] [EM differed between both studies]). Given the small effect sizes obtained in these studies and the potential for important confounding by indication,[10–13] which may not have been fully adjusted for in the analyses,[14] we believe that the noted positive association could have been erroneous and would not have been observed had we used a more appropriate EM.

Since persistence to statins is known to be poor and may have been titrated during follow-up,[8,15–18] we believe that the use of a continuous statin dose variable should be favoured when examining the dose-dependent association between statins and diabetes. Therefore, in order to better assess the association between statins and diabetes, we analyzed the data using both the ITT like approach based on the dose prescribed at the cohort entry date and, since the mechanism of action by which statins could cause diabetes is not known,[19–22] two cumulative statin dose variables, (1) irreversible, and (2) reversible mechanisms.

METHODS

Data Sources

This study was performed using medico-administrative databases from the province of Quebec, Canada. Quebec is the second most populated province in Canada, with more than 8 million inhabitants.[23] A unique identification number is assigned to every individual, and all diagnoses and all health services provided are systematically recorded within the *Régie de l'assurance maladie du Québec* (RAMQ) databases. Pharmaceutical claims are also recorded but only for residents covered by the RAMQ public drug insurance plan. Information was obtained from the Quebec physician's service and claims databases (i.e., RAMQ databases) and the Quebec hospitalization databases (i.e., *Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière* [MED-ECHO] databases), which have previously been validated.[24–27] For this study we used three RAMQ databases (i.e., the Demographic, Medical Services and Claims and

Pharmaceutical databases) and three MED-ECHO databases (i.e. the Hospitalization – Descriptions, Hospitalization – Diagnoses and Hospitalization – Intervention databases). Patient records were linked across all databases by use of the unique identification number. The identification numbers were encrypted to protect patient confidentiality. Access to data was granted by the *Commission d'accès à l'information* and the protocol was approved by the *Centre hospitalier de l'Université de Montréal* ethics' committee.

Cohort Definition

A cohort of new statin users was provided to us by RAMQ, the date of the first dispensation of a statin was defined as the cohort entry date. Patients were considered to have been newly initiated on a statin if they did not have a claim for a statin dispensation in the year prior to the cohort entry date. Eligible patients had: (1) to have been newly initiated on either simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin or rosuvastatin between January 1st 1998 and December 31st 2010, (2) to be covered by the RAMQ public drug insurance plan for at least a year prior to the cohort entry date, and (3) to be at least 40 years of age at the cohort entry date. We excluded every patient: (a) who received any other cholesterol lowering drug dispensation (including niacin, cerivastatin or a combination statin drug) in the year prior to or on the cohort entry date; (b) who received a dispensation for drugs used in the treatment of diabetes (WHO ATC A10)[28] in the year prior or on the cohort entry date; (d) who received a diagnosis of diabetes (ICD-9 code: 250.x; ICD-10 codes: E10.x – E14.x) in the year prior or on the cohort entry date; (e) who were admitted in a long-term care facility in the year prior or on the cohort entry date; or (f) who received >1 statin dispensation at the cohort entry date since it is impossible to identify the order in which they were taken or if they were taken together. Patients who met both inclusion and exclusion criteria were entered within the *Full Cohort*.

All patients included within the *Full Cohort* were followed up to either the end of coverage by the RAMQ public drug insurance plan, incidence of diabetes, date of death, date of admission within a long-term care facility, first dispensation of cerivastatin, 730 days following the cohort entry date, or March 31st 2010, whichever came first.

Study Design

We used a case-control study design nested within the *Full Cohort*. All study data were set-up according to the recommendations by Essebag et al.[29] in order to reproduce the method they describe.

CASE DEFINITION

We used the incidence of *de novo* diabetes as the outcome within our study. The index date of all cases, in terms of the follow-up time scale, was defined as the first occurrence of a hospitalization with a principal or secondary diagnosis for diabetes (ICD-9 code 250.x; ICD-10 codes E10.x – E14.x) or the date of the first dispensation for a drug used in the treatment of diabetes (WHO ATC A10), whichever came first.[5]

CONTROLS

We randomly matched each case identified within the *Full Cohort* to 64 controls.[29] Decision to match each case to 64 controls was based on recommendations by Essebag et al.[29] which showed that the results of a nested case-control study using 64 randomly selected controls provided results similar to those from a Cox proportional hazard model using all available data for a fraction of the computational time. In order to be concordant with this approach, all non-cases were eligible to acts as potential controls as long as they were diabetes-free at the time of the case's index date (hereby defined as the control's index date).

Exposure Measure

We tested three distinct EMs, (1) baseline ITT like, (2) cumulative dispensed statin dose under an irreversible effect hypothesis and (3) cumulative dispensed statin dose under a reversible effect hypothesis (graphical representation of the 3-exposure measures is provided in the Supplementary File 1).

Under the baseline ITT like EM, patients initially dispensed to either a daily dose ≥10 mg of rosuvastatin, ≥20 mg of atorvastatin or ≥40 mg of simvastatin on the cohort entry date were considered in the high dose statin group, patients initially dispensed a daily dose <10 mg of rosuvastatin, <20 mg of atorvastatin or <40 mg of simvastatin or who were dispensed any daily dose of either lovastatin, pravastatin or fluvastatin were considered in the low dose statin group. Such a

definition is similar to the definition used within other cNODES projects and by others.[5,30–32]

The 2 cumulative statin EMs assumed a dose-dependent drug class effect.[4,21] Using the World Health Organization Defined Daily Dose (DDD) index,[28] we converted all dispensation received during the study follow-up into an atorvastatin 80 mg DDD (a80-DDD=1) equivalent value.

Exposure under the irreversible effect setting hypothesis was defined as the sum of all a80-DDD dispensed to the patient from the patient's cohort entry date up to his/her index date.

Exposure under the reversible effect setting hypothesis was defined as the sum of all the a80-DDD dispensed to a patient within the 180 days prior to his/her index date.

STATISTICAL ANALYSES

Discrete data are presented as absolute and relative values (*n* [%]) while continuous data are presented as means and standard deviations (means [SD]). Time to statin discontinuation was analyzed using a 50% grace period (i.e., in the event a patient does not receive a new dispensation within a period of time equal to half the length of the last dispensation's duration, that patient was assumed to have had discontinued statin therapy). Patients were assumed to have had discontinued statin therapy if they did not receive a new statin dispensation before the end of the grace period. Multivariate conditional logistic regression models were used to compute conditional odds ratios and 95% confidence intervals (OR [95% CI]) and each model's Akaike's information criterion (AIC).[33] Predetermined potential confounders were forced within each model. These included baseline characteristics (patients' sex, age at the cohort entry date, poverty level status [based on if the patient was receiving a guaranteed income supplement at the cohort entry date or not], year of entry within the cohort [as a categorical variable]), medical resources utilization variables (≥1 hospitalization, ≥5 outpatient visits, ≥5 distinct drugs dispensed to the patient, all within the year prior to the cohort entry date), comorbity variables (history of myocardial infarction, history of stroke, hypertension, hypercholesterolemia, history of peripheral vascular disease, history of congestive heart failure), medical intervention variables (history of coronary artery bypass graft, history of percutaneous coronary intervention) and drug dispensation variables (dispensation of a loop diuretic, calcium blocker, beta-blocker, angiotensin receptor blocker and angiotensin converting enzyme inhibitor). Comorbidities, medical intervention and drug dispensation variables were all assessed in the year prior to the cohort entry date and each was entered as a distinct binary variable (presence vs. absence). The model with the lowest AIC was considered to best fit our data.[34] Relevant differences in AIC were those ≥4 points,[35,36] all models that showed differences in AIC below this cut-off point were considered to fit equally well the data. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Roughly half (404,129 patients [50.5%]) of the 800,551 patients provided to us by RAMQ were selected for inclusion within the *Full Cohort* (Figure 1).

Baseline characteristics of the *Full Cohort* are shown in Table 1. Among patients included within the *Full Cohort*, 264,947 patients (65.6%) were dispensed a low dose statin and 139,182 patients (34.4%) a high dose statin on the cohort entry date. About half of patients (192,964 [47.8%]) were males and the average age was 65.2 years old (SD 11.0).

Most patients did not remain on their initially assigned statin regimen throughout the 2-year follow-up period (Figure 2). At 30-days, one in five patients (20.3%) had already been dispensed at least a different a80-DDD or had discontinued statin therapy, this proportion rose to 63.3% at one year and continued to rise thereafter. When focusing solely on discontinuation of statin therapy, results showed that 18.7% and 58.0% of patients had discontinued statin therapy at 30-days and at 1-year.

We identified a total of 12,978 patients who developed *de novo* diabetes within the 2-years follow-up. Each case was randomly matched to 64 controls that were at risk of developing *de novo* diabetes at the matched case's index date. All 3 EMs (baseline ITT like, cumulative dispensed statin dose under an irreversible effect hypothesis and cumulative dispensed statin dose under a reversible effect hypothesis) were tested within this nested case-control study. Crude and adjusted OR for all 3 EMs are shown in Table 2. Odds of developing diabetes within the 2-years

FIG. 1 Patient flow-chart within the study.

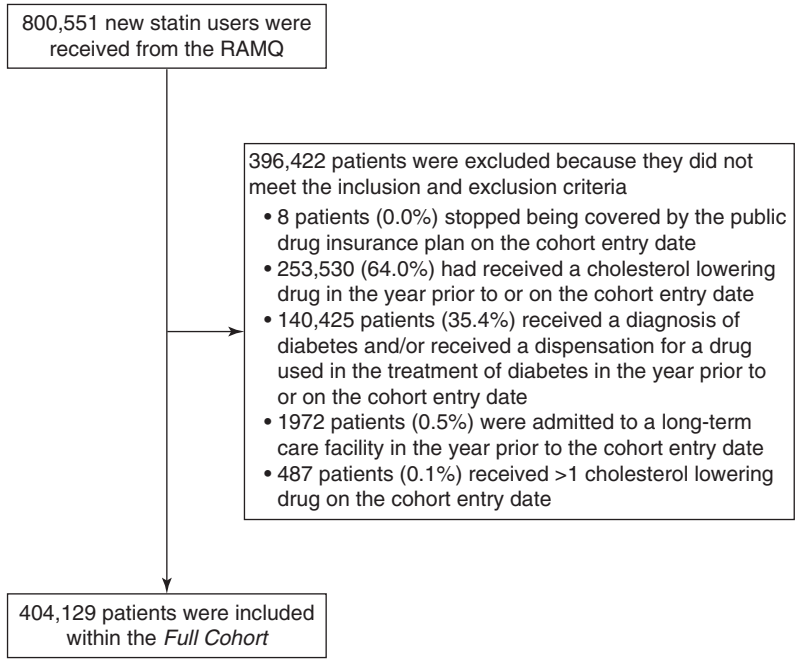


TABLE 1 Baseline Demographic Characteristics and Comorbidity Status of the *Full Cohort*

	Full cohort ***n*** **(%)**
	404,129 (100)
Age, mean (SD)*	65.2 (11.0)
Male sex	192,964 (47.8)
Dispensed a high dose statin*	139,182 (34.4)
At least 5 medical outpatient visits	247,266 (61.2)
Poverty level*	159,379 (39.4)
At least 1 hospitalisation	105,368 (26.1)
Myocardial infarction	33,955 (8.4)
Stroke	12,630 (3.1)
Hypertension	170,213 (42.1)
Dyslipidemia	135,463 (33.5)
Peripheral vascular disease	8784 (2.2)
Congestive heart failure	20,167 (5.0)
Coronary artery bypass graft	6778 (1.7)
Percutaneous coronary intervention	21,831 (5.4)
Dispensation of loop diuretics	26,800 (6.6)
Dispensation of calcium blockers	96,761 (23.9)
Dispensation of beta-blockers	126,816 (31.4)
Dispensation of angiotensin receptor blockers	61,066 (15.1)
Dispensation of angiotensin converting enzyme inhibitors	88,593 (21.9)
At least 5 different drugs dispensed	235,898 (58.4)

Comorbidity status, drug dispensations and medical utilization rates were all assessed in the year prior to the cohort entry date.
**At the cohort entry date*

FIG. 2 Time to switching from the initially dispensed statin dosage to a different statin dosage or to discontinuation.

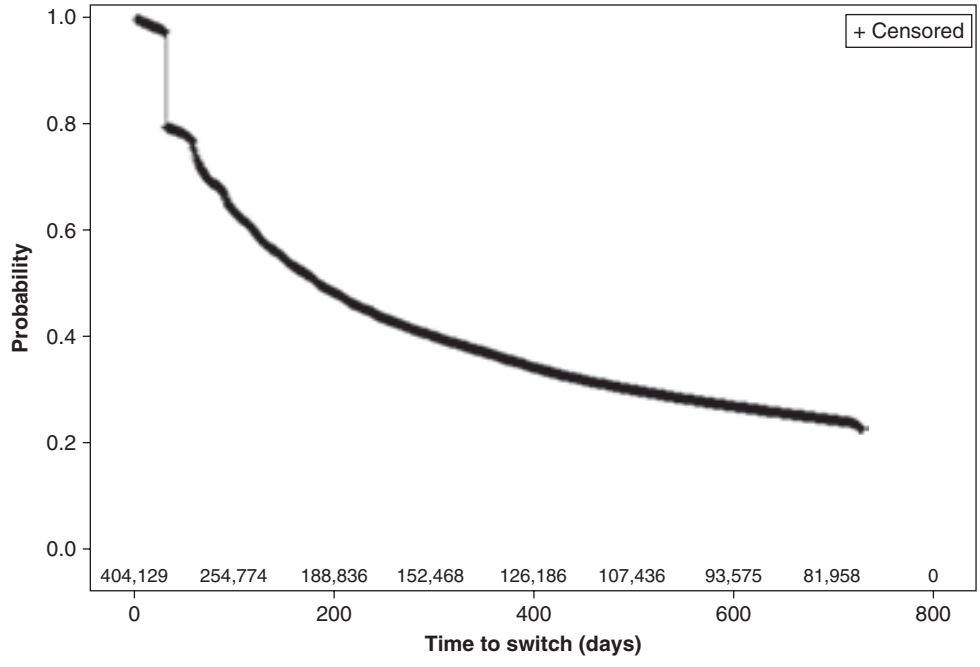


TABLE 2 Crude and Adjusted Conditional Odd Ratios of Developing Diabetes At 2-Years' Follow-Up

Exposure Measure	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted Model AIC
Baseline ITT like	1.300 (1.254 – 1.347)	1.110 (1.068 – 1.154)	105,673
Continuous dose-dependent irreversible effect variable (per 100 a80-DDD dispensed)*	1.224 (1.187 – 1.262)	1.132 (1.093 – 1.172)	105,656
Continuous dose-dependent reversible effect variable (per 100 a80-DDD dispensed)†	1.719 (1.603 – 1.845)	1.422 (1.312 – 1.541)	105,631

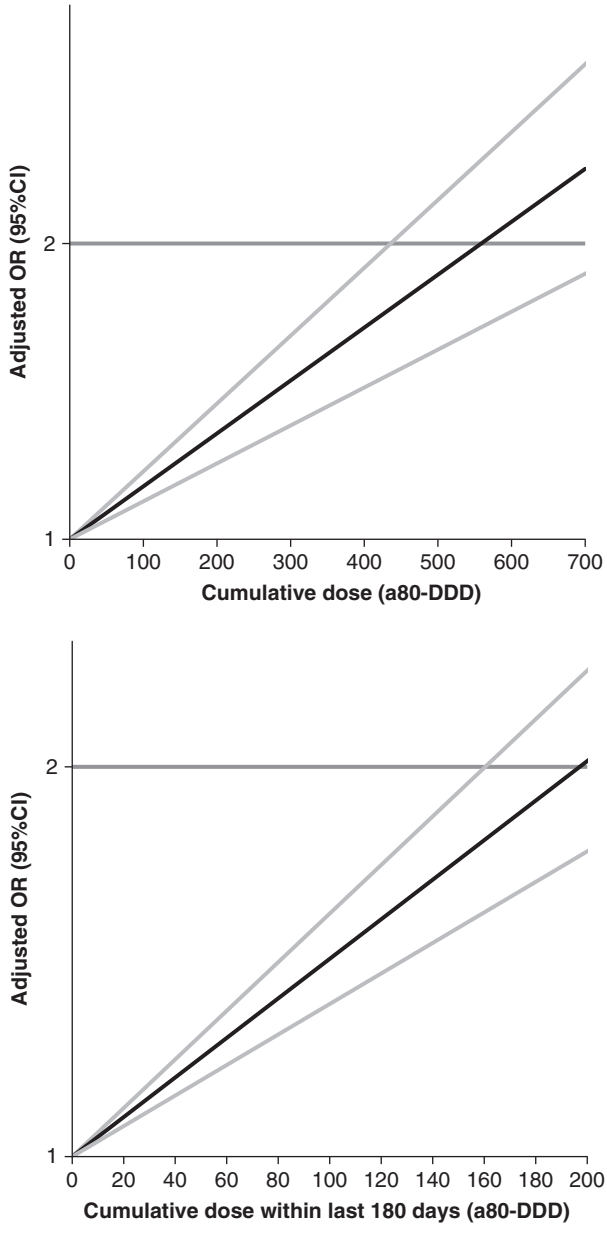
a80-DDD = 80 mg atorvastatin-equivalent defined daily dose; AIC = Akaike's information criterion; CI = confidence interval; ITT = intent to treat; OR = conditional odds ratio.

**Represents the sum of all a80-DDD dispensed to the patients from patients' cohort entry date up to the index date.*

†Represents the sum of all a80-DDD dispensed to patients within the 180 days prior to the index date.

follow-up was higher among patients dispensed a high dose statin versus those dispensed a low dose statin at baseline (baseline ITT like adjusted OR= 1.110 [95%CI 1.068 – 1.154], model AIC=105,673), among patients dispensed higher cumulative statin doses from the cohort entry date up to the index date (irreversible diabetogenic effect hypothesis) (adjusted OR = 1.132 [95%CI 1.093 – 1.172] per 100 a80-DDD dispensed, model AIC=105,656) and among patients dispensed higher cumulative statin doses within the 180 days prior to the index date (adjusted OR = 1.422 [95%CI 1.312 – 1.541] per 100 a80-DDD dispensed, model AIC=105,631). Figure 3 shows the adjusted OR in relation to the cumulative a80-DDD dispensed to patients for both the irreversible (Figure 3A) and reversible (Figure 3B) effects variables. Based on the models' AIC, the cumulative a80-DDD in the 180 days prior to the index date provided the best model fit (reversible diabetogenic effect hypothesis).

FIG. 3 Conditional odds ratios obtained when using (A) a continuous dose-dependent irreversible effect variable and (B) a continuous dose-dependent reversible effect variable.



DISCUSSION

Incidence of diabetes within our cohort of newly initiated statin users was relatively rare (*n*=12,978 [3.2%]). Similar to other published results,[8,15–18] patients' persistence to their initially dispensed statin therapy and to the class as a whole were poor (see Figure 2). Like others, we also found that initiating a patient on a high dose statin (baseline ITT like) was associated with a slightly higher odd of diabetes.[6,8] However, using the continuous dose-dependent exposure variables we found a stronger positive dose-dependent association which, in our view, increases the plausibility that this association might be causal (see Table 2 and Figure 3).

To our knowledge, prior to our work, only a single study tested a continuous dose-dependent variable.[7] However, that study only compared statin users to non-statin users and they did not examine a potential reversible drug effect.

As mentioned previously, the mechanism of action by which statins could cause diabetes is currently unknown. Despite this fact, several potential mechanisms have been proposed: (1) statins could increase insulin resistance, (2) reduce glucose absorption by cells, (3) reduce insulin secretion, and (4) increase the apoptosis rate of β-cells.[21,37] Although we cannot claim that any of these proposed mechanisms are true, none of these would impose an irreversible or reversible effect. As such, we chose to examine both within our study.

In the context of the dose-dependent diabetogenic effect of statins, it would appear that a reversible effect is actually more likely since the association is stronger and the model shows better fit.[34] This dose-dependent reversible diabetogenic effect seems plausible since it takes into consideration both the dose-dependent effect of statins as well as patients' general persistence to this class of drugs. While not confirming this proposed mechanism of action, prior results have shown that at least one of the four proposed mechanism (i.e., that statins could increase insulin resistance) could be reversible.[38,39]

The main strength of our study is that we tested multiple EMs, which accounted for both the poor persistence to statins and dose variations during follow-up. Therefore, our results provide clues on the true mechanism of action by which statins could cause diabetes.

A second strength is the fact that our study was conducted within a very large cohort of incident statin users which compensated for the relative rarity of the outcome.

Our study has limitations. *First*, we chose to explore only two time-windows with an arbitrarily defined wash out period (reversible effect time-window = 6 months) because the mechanism of action by which statins could cause diabetes is unknown.[19–22]

Second, we chose to use a nested case-control study with random control sampling instead of using a time-varying exposure variable within a Cox proportional-hazards model. We had originally considered conducting this study using the latter option; however, at the time of conducting this study, we were unable to do so due to limitations with the computer systems we were using. As such, in order to approximate the Cox proportional-hazards model, we decide to the use the method proposed by Essebag et al. with the maximal number of controls used within their paper.[29]

Finally, we could not define the patients' real date of onset of diabetes within our dataset. It has been known that type 2 diabetes may be present for several years prior to its diagnosis.[40] Some patients could have had diabetes prior to the cohort entry date, but were identified as cases only following their entry within the cohort. Similarly, as the RAMQ database does not provide information regarding biochemical testing, we cannot exclude the possibility that some diabetes-free patients included within our study were known to be in a prediabetes state, and as such, to be at a higher risk of developing diabetes than truly diabetes-free patients.[41] However, although classification errors regarding the outcome may be present within this study, there is no reason to believe that the presence of unknown diabetes or of prediabetes might have a channelling effect on the type and total amount of statins taken by the patients. In spite of this, seeing as we cannot identify these patients, we cannot fully eliminate the risk of this potential bias.

In conclusion, our results support the usefulness of a drug utilization study to assess drug persistence and drug utilization patterns before selecting the design of the etiological study. In the case of statins, the use of a baseline ITT like EM may be inappropriate because of the poor persistence to the initially assigned statin treatment and multiple drug titrations during follow-up, while the use of a dose-dependent definition addresses these gaps. This issue is common and may arise in studies of many other treatments' adverse events. When the mechanism of action is unknown, the use of an appropriate time-window of exposure should be preferred to a fixed over time dichotomous EM. By using what we believe to be most appropriate EM among the three we tested, we obtained a stronger association between statin use and risk of diabetes than what had been previously identified.

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Supplementary Figure 1. Graphical representation of (A) a hypothetical patient's drug dispensation data as well as the (B) baseline intent-to-treat like, (C) continuous dose-dependent irreversible and (D) continuous dose-dependent reversible exposure measures associated with the hypothetical drug dispensation data.