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SYSTEMATIC REVIEWS AND META-ANALYSES

Statin use and risk of new-onset diabetes: A meta-analysis of observational studies

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Abstract *Background and aims:* Meta-analyses of randomized control trials investigating the association between incident diabetes and statin use showed an increased risk of new-onset diabetes (NOD) from 9% to 13% associated with statins. However, short follow-up period, unpowered sample size, and lack of pre-specified diagnostic criteria for diabetes detection could be responsible of an underestimation of this risk. We conducted a meta-analysis of published observational studies to evaluate the association between statins use and risk of NOD.
Methods and results: PubMed, EMBASE and MEDLINE databases were searched from inception to June 30, 2016 for cohort and case–control studies with risk of NOD in users vs nonusers, on ≥1000 subjects followed-up for ≥1 year. Two review authors assessed study eligibility and risk of bias and undertook data extraction independently. Pooled estimates were calculated by a random-effects model and between-study heterogeneity was tested and measured by I^2 index. Furthermore, stratified analyses and the evaluation of publication bias were performed. Finally, the meta-analysis included 20 studies, 18 cohort and 2 case–control studies. Overall, NOD risk was higher in statin users than nonusers (RR 1.44; 95% CI 1.31–1.58). High between-study heterogeneity (I^2 = 97%) was found. Estimates for all single statins showed a class effect, from rosuvastatin (RR 1.61; 1.30–1.98) to simvastatin (RR 1.38; 1.19–1.61).
Conclusions: The present meta-analysis confirms and reinforces the evidence of a diabetogenic effect by statins utilization. These observations confirm the need of a rigorous monitoring of patients taking statins, in particular pre-diabetic patients or patients presenting with established risk factors for diabetes.

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Introduction

Statin therapy represents the basis for the management of hypercholesterolemia and prevention of cardiovascular disease [1,2]. Statins are generally safe and well tolerated. However, some studies have reported an association between statin therapy and the risk of new-onset diabetes.

The first trial that evaluated the relationship between statin therapy and incident type 2 diabetes was the West of Scotland Coronary Prevention Study (WOSCOPS), which observed that pravastatin 40 mg/day was associated with a 30% risk reduction for incident diabetes in a high-risk population of men with severe hypercholesterolemia [3]. Since then, several other studies have investigated this relationship, reporting controversial results. In fact, while some studies did not show any apparent effect of statins on the development of new diabetes [3–6], other investigations suggested an increased risk. Among these, the JUPITER (Justification for the Use of Statin in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, in which statin treatment was associated with small but significantly higher levels of glycated hemoglobin and incidence rates of diabetes [7], and an analysis of the WHI (Women's Health Initiative), which reported an increased risk of diabetes mellitus in postmenopausal women taking statins [8]. These findings, together with observations from other clinical trials [9], led to hypothesize that statin therapy might trigger mechanisms leading to the development of diabetes. Several meta-analyses have thus evaluated data from available trials to define whether statin therapy may have a role in the development of type 2 diabetes, and observed an excess risk ranging from 9% up to 13% [10–14]. In particular, the increased risk of incident diabetes seems to be associated with high-intensity statin therapy [13]. A recent meta-analysis [15] showed that statins, as a class, significantly increase the risk of new-onset diabetes by 12% and that atorvastatin 80 mg was associated with the highest risk, followed by rosuvastatin, and simvastatin 80 mg; high dose atorvastatin increased the risk of diabetes even when compared with other statins such as pravastatin, simvastatin or low-dose atorvastatin, in agreement with previous findings.

Despite the risk of incident diabetes is low both in absolute and when compared with the significant reduction of cardiovascular events, the real weight of this risk is still undetermined. In addition, randomized clinical trials (RCTs) have several limitations that might reduce the actual relevance of such increased risk [16]. RCTs in fact, did not include diabetes risk as a primary outcome; as a consequence, they could not reach adequate statistical power and sample size to find an association between statin use and diabetes risk. In addition, the absence of pre-specified criteria for diabetes diagnosis and detection, together with selection bias and dropout from studies, may lead to an underestimation of adverse cases. Finally, the relatively short follow-up period typical of RCTs or the possibility to prematurely terminate the trial once benefits are documented may preclude the detection of a chronic condition such as diabetes [16]. On the other hands, observational studies can be very large and have unlimited duration and follow-up, thus increasing the chance to detect adverse events with low incidence. Aim of the present study was thus to investigate the relationship between statin therapy and risk of incident diabetes by undertaking a meta-analysis of all available observational studies.

Methods

This study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17,18].

Study selection criteria

We evaluated observational studies that reported or allowed to calculate risk of new-onset diabetes (NOD) with statin use.

Studies were included if they met the following criteria: (1) the study examined risk of NOD for statin use *vs* non-use; (2) the study recruited 1000 participants or more; (3) follow-up was at least 1 year; (4) the risk estimate was reported as an odds ratio (OR), hazard ratio (HR) or relative risk (RR); (5) the 95% CI for the risk estimate was included.

Search strategy

PubMed, MEDLINE, and EMBASE were searched from inception to 30 June 2016. The search strategy included keywords and MeSH terms relating to statins and type 2 diabetes.

The keywords included: *"hydroxymethylglutaryl-CoA reductase inhibitors"* or *"statins"*, *"diabetes"*, *"cohort study"* or *"case–control study"*. One of the complete search strings is presented in Supplementals.

We excluded studies published as abstracts. The review was restricted to original articles published in English. We also manually searched bibliographies of included studies as well as existing systematic reviews for any other articles that may be potentially suitable.

Data extraction and evaluation

Two authors independently scanned all titles and abstracts and excluded articles that clearly were not observational studies on the topic. We proceeded to assess full-text versions of potentially relevant articles and conducted more detailed checks against our eligibility criteria. Disagreements were resolved by discussion.

We used preformatted tables (Table 1) to record study design and participant characteristics. Data extracted from observational studies were first author, year of publication, mean age range of participants, median follow-up time, drug exposure, and definition of NOD. We also extracted full adjusted estimates of risk along with 95% confidence intervals.

Table 1 Selected characteristics of 20 observational studies included in the meta-analysis.

First author (Year)	Design	Study duration (year)	NOD definition	Mean age (year)	Exposure	OR/RR/HR (95% CI)	Adjustment
Jick SS (2004)	Nested case–control	11	Diagnosis AND drugs	59.2	Any statin Pravastatin Simvastatin	1.1 (0.8–1.4) 0.7 (0.4–1.2) 1.0 (0.7–1.3)	Body mass index, hypertension, steroid use, smoking and the number of GP visits within 3 years preceding the index date
Culver A (2012)	Cohort	9	Self-reported	63.2	Any statin Simvastatin Fluvastatin Atorvastatin Pravastatin	1.48 (1.38–1.59) 1.41 (1.25–1.61) 1.61 (1.35–1.92) 1.61 (1.26–2.06) 1.63 (1.43–1.87)	Age, race/ethnicity, education, cigarette smoking, BMI, physical activity, alcohol intake, energy intake, family history of diabetes, hormone therapy use, study arms, and self-report of cardiovascular disease at baseline
Danaei G (2012)	Cohort	9	Diagnosis OR drugs	63.2	Any statin Simvastatin Atorvastatin Pravastatin Rosuvastatin Fluvastatin	1.14 (1.09–1.19) 1.14 (1.09–1.20) 1.22 (1.12–1.32) 1.01 (0.84–1.21) 1.11 (0.89–1.38) 1.02 (0.69–1.50)	Gender, townsend deprivation score, age, LDL cholesterol, HDL cholesterol, BMI, systolic blood pressure, alcohol use, doctor visits, referrals, hospitalizations, alcoholism, smoking prevalence, hypertension, antihypertensive use, NSAIDs use, aspirin use, other lipid-lowering drugs use, b-Blockers use, hormone replacement therapy, chronic obstructive pulmonary disease, oral steroids use, inhaled steroids use, atrial fibrillation, depression, antidepressant use, hypothyroidism, osteoporosis, history of transplant, immunosuppression therapy, psoriasis, rheumatoid arthritis, chemotherapy, radiotherapy, chronic pancreatitis
Wang KL (2012)	Cohort	8	Diagnosis AND drugs	63.0	Any statin	1.15 (1.08–1.22)	Unadjusted
Chen CW (2013)	Case-control	2	Diagnosis	61.3	Atorvastatin Rosuvastatin Simvastatin Pravastatin	2.80 (1.74–4.49) 4.69 (2.78–7.92) 4.09 (2.52–6.64) 3.41 (1.66–7.04)	Gender, hypertension, coronary heart disease, diabetes, hyperlipidemia, atrial fibrillation, chronic kidney disease, obesity, peripheral arterial disease, non-statin lipid lowering medications, aspirin, angiotensin-converting enzyme inhibitors, triglyceride-lowering medications, hormone therapy, socioeconomic status, geographic region and urbanization level of residence
Currie O (2013)	Cohort	6	Drugs	NA	Any statin	3.31 (2.56–4.30)	Age, sex, and ethnicity
Izzo R (2013)	Cohort	4.7	Biochemicals AND (diagnosis OR drugs)	58.6	Any statin	1.03 (0.79–1.35)	Age, gender, use of statins before diagnosis of diabetes, duration of hypertension and baseline parameters
Zaharan NL (2013)	Cohort	6/9	Drugs	NA	Any statin Atorvastatin Pravastatin Rosuvastatin Simvastatin Fluvastatin	1.20 (1.17–1.23) 1.25 (1.21–1.28) 1.02 (0.98–1.06) 1.42 (1.33–1.52) 1.14 (1.06–1.23) 1.04 (0.91–1.18)	Gender, age groups, prescriptions of oral corticosteroids, antipsychotics, antihypertensive drugs, medications for ischemic heart disease, anti-obesity and other lipid modifying agents.
Bhattacharya R (2014)	Cohort	2	Diagnosis	NA	Any statin	1.62 (1.25–2.09)	Antidepressants–statins use; presence of depression; life style risk factors – BMI categories, lack of physical activity, smoking status, age groups, gender; race/ethnicity; poverty status, insurance status
Cederberg H (2014)	Cohort	5.9	Biochemicals OR diagnosis OR drugs	57.1	Any statin	1.46 (1.22–1.74)	Age, BMI, waist circumference, physical activity, smoking, alcohol intake, family history of diabetes and beta-blocker and diuretic treatment

Macedo AF (2014)	Cohort	20	Diagnosis	62.3	Any statin	1.57 (1.54−1.59)	Adjusted for age, gender, propensity score, post index date diagnosis of hepatic disease and family history of diabetes
Lichtenstein KA (2015)	Cohort	10	Biochemicals OR drugs	40.0	Any statin	1.14 (1.02−1.27)	Age, sex, race/ethnicity, exposure to antiretroviral therapy, prevalent hepatitis C, BMI, and cumulative use of protease inhibitors
Mansi I (2015)	Cohort	10	Diagnosis	53.0	Any statin	1.87 (1.67−2.01)	Propensity score (age, gender, smoking, alcohol-related disorders, substance-related disorders, charlson comorbidity score, overweight/obese, hypertension, acute kidney injury, asthma, gastrointestinal hemorrhage, gastritis/duodenitis, nonspecific chest pain, heart disease not otherwise specified, osteoarthritis, arthropathy, and back disorder, sprains, strains, and trauma-related joint disorders, fracture of bone, osteoporosis, rehabilitation care, fitting of prostheses, and adjustment of devices, number of inpatient admissions, number of outpatient medical encounters, number of encounters for immunization, receive immunization and screening for infectious disease, beta-blocker, diuretic, ACE-Is/ARBs, calcium channel blocker, proton pump inhibitors, aspirin, NSAIDs, bisphosphonates, sedatives, SSRI, antipsychotic, tricyclic anti-depressants, systemic corticosteroids, hormone replacement therapy, testosterone, cytochrome p450, non-statin lipid lowering drugs, oral hypoglycemic, antiplatelet agents (other than aspirin), warfarin)
Radford NB (2015)	Cohort	3	Biochemicals OR drugs OR self-reported	48.2	Any statin	2.04 (1.30−3.22)	Statin use at visit 2, age, gender, chronic renal failure, and metabolic syndrome at index visit
van de Woestijne AP (2015)	Cohort	15	Self-reported (with cross-validation)	59.0	Any statin	1.66 (1.14−2.42)	Age, gender and propensity score (age, sex, localisation of vascular disease, body mass index, HDL-cholesterol, plasma triglycerides, systolic blood pressure, plasma glucose, platelet inhibitors, blood pressure lowering medication, smoking, eGFR and time since inclusion)
Calza L (2016)	Cohort	5.2	Biochemicals OR drugs	44.5	Any statins	1.09 (0.76−1.49)	Age, sex, race, chronic hepatitis C, body mass index, fasting serum concentration of triglycerides, cumulative exposure to combination antiretroviral therapy (cART) and cumulative exposure to specific antiretroviral agents
Castro MR (2016)	Cohort	6	Diagnosis	55.7	Any statins	1.19 (1.05−1.35)	Lipid panel (LDL, HDL, triglycerides), blood pressure, body mass index, the use of hypertension drugs and demographics (age and gender)
Lin ZF (2016)	Cohort	3.1	Diagnosis	65.4	Any statin Atorvastatin Pravastatin Rosuvastatin Simvastatin Fluvastatin	1.27 (1.14−1.41) 1.30 (1.13−1.50) 1.71 (1.12−2.60) 1.42 (1.23−1.64) 1.60 (1.10−2.32) 1.38 (1.07−1.80)	Age, sex, various comorbidities (ischemic heart disease, cerebrovascular disease, heart failure, hypertension, renal disease, hyperlipidemia, liver disease and peripheral vascular disease) and comedication

(*continued on next page*)

Table 1 (*continued*)

First author (Year)	Design	Study duration (year)	NOD definition	Mean age (year)	Exposure	OR/RR/HR (95% CI)	Adjustment
Olotu BS (2016)	Cohort	1.3	Diagnosis	46.3	Any statin	2.07 (1.77–2.42)	Age, sex, hyperlipidemia, obesity, hypertension, use of diabetogenic medications, and Charlson Comorbidity Index score
					Atorvastatin	1.95 (1.62–2.35)	
					Pravastatin	1.40 (1.04–1.87)	
					Rosuvastatin	1.75 (1.19–2.56)	
					Simvastatin	1.79 (1.43–2.24)	
					Fluvastatin	1.95 (1.28–2.96)	
Rha SW (2016)	Cohort	3	Biochemicals OR drugs	60.2	Any statin	1.99 (1.36–2.92)	Male gender, age, history of risk (hypertension, coronary artery disease, coronary spasm, dyslipidemia, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, b blockers, diuretics, nitrates, and statins
					Atorvastatin	2.09 (1.27–3.44)	
					Pravastatin	2.88 (1.50–5.55)	
					Rosuvastatin	2.13 (1.04–4.38)	
					Simvastatin	0.99 (0.49–2.02)	
					Fluvastatin	2.54 (1.03–6.21)	

A quality assessment of included studies was conducted for descriptive purposes and to evaluate potential differences according to quality criteria (Supplemental data). Two authors independently assessed study quality and resolved disagreements by further review and discussion. The methodological quality of the included case–control and cohort studies was evaluated using the validated Newcastle–Ottawa scale [19]. Scores range from zero to 10 stars.

Statistical analysis

We pooled the estimates by using the fixed-effects and random-effects model according to DerSimonian & Laird method [20]. When a significant heterogeneity was found, the results from the random-effects model were presented. Between-study heterogeneity was tested by Cochrane's Q test and measured with the I^2 statistic (the proportion of between-study variability caused by heterogeneity) [21]. A stratified analysis was performed to assess if follow-up length, geographic area and propensity score matching could be the source of between study heterogeneity.

Publication bias was evaluated visually through funnel plot and with the Egger's test [22].

To evaluate to what extent obtained results could be influenced by a single study, an influence analysis was performed by omitting one study at a time.

All tests were considered statistically significant for p-values less than 0.05. The analyses and the corresponding graphical visualization of forest and funnel plots were conducting using R package "metafor" (v 1.9-7).

Results

Overall, 2272 unique papers were retrieved from PUBMED, EMBASE and MEDLINE databases. Based on title/abstract, we selected 43 studies for full-text evaluation; among them, 20 observational studies fulfilling inclusion criteria were included in the final analyses (Fig. 1) [8,16,23–40].

Characteristics of the included studies are shown in Table 1. The years of publication range from 2004 to June 2016; 2 of them were case–control studies [25,35], 18 were cohort studies. The follow-up duration ranged between 2 and 20 years (median 7.2 years). Most of the studies were conducted in Europe (8 studies) and US (7 studies). The quality evaluation based on the Newcastle–Ottawa scale found an average score of 7, with 9 studies having score $\geq$8 (Supplemental Table 1).

Overall, statin users have significantly greater risk of new-onset diabetes compared with non-users (RR 1.44; 95% CI, 1.31–1.58) (Fig. 2). When considering single statins, we observed that users of rosuvastatin and atorvastatin have the greatest increase in diabetes risk, being the relative risk 1.61 (95% CI, 1.30–1.98) in rosuvastatin users and 1.49 (95% CI, 1.31–1.70) in atorvastatin users (Fig. 3). All reported estimates were obtained using the random-effect model since a large between-study heterogeneity

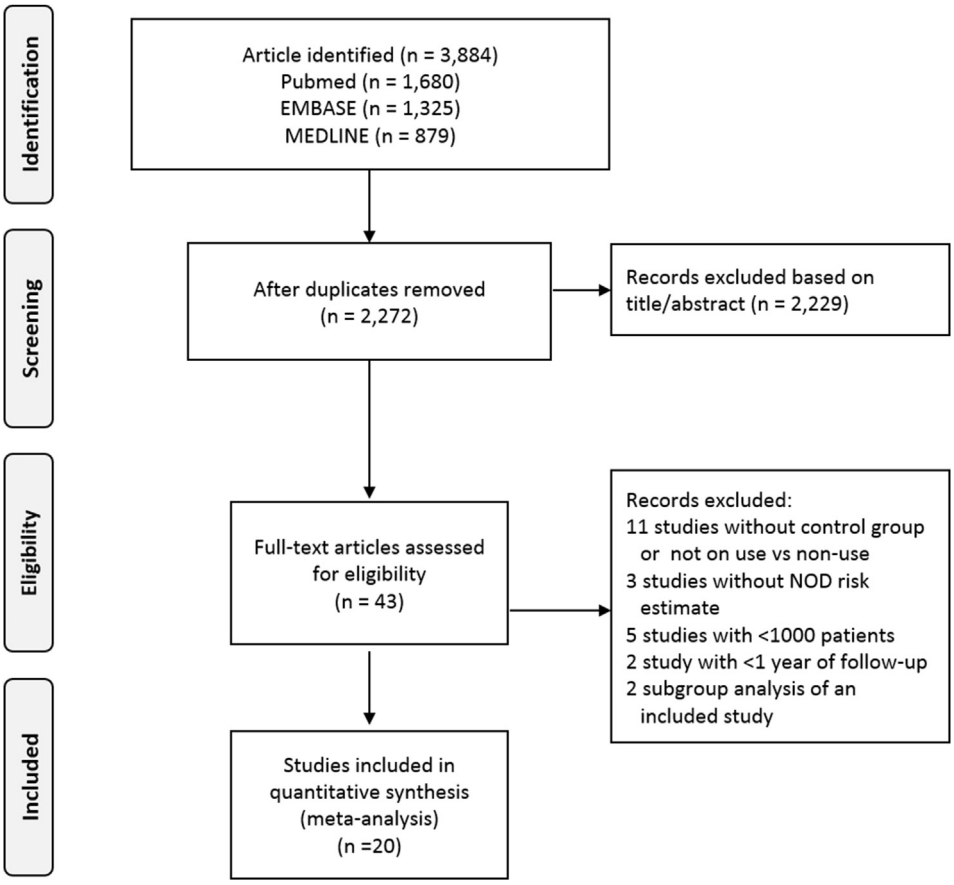

Figure 1 Flow-chart for the selection of eligible observational studies.

was detected in all analyses (the I^2 index was 97% for any statin).

Stratified analysis

Table 2 shows the results of the stratified analysis. Follow-up duration and propensity score matching do no seems to be sources of heterogeneity, since the between strata-specific estimates do not differ (p-values 0.173 and 0.195 respectively). On the contrary, an effect of the country was observed (p-value < 0.001), mainly due to the only study from New Zeland [26], which reported a higher association estimate compared with the other included studies; in fact, omitting this study, the test for the difference between group estimates provides a p-value of 0.197.

Publication bias

Evidence of publication bias was found for atorvastatin (p-value Egger's test $= 0.03$) but not for other statins or for use of any statin (Supplemental Figs. 1 and 2).

Influence analysis

As reported above, the overall pooled estimate is 1.44 (95% CI, 1.31–1.58); when we performed the influence analysis by omitting one study at a time, we did not observe any significant change in the estimate pooled, suggesting that none of the included studies affects substantially the overall estimate (Supplemental Table 3).

Discussion

The results of our study show a 44% increased risk of new-onset diabetes among statin users compared with non-users; the analysis of single statins, indicating an increased risk varying from 38% in simvastatin users up to 61% in rosuvastatin users, suggesting a class effect. A high between-study heterogeneity was observed in our meta-analysis; the influence analysis shows a slight (but not significant) impact of the study of Currie et al. [26], on the pooled estimate for overall statin use. Analyses of influence and publication bias, although showed some evidence that individual papers and selective inclusion might have some effect respectively, do not seem to materially affect our estimates.

Several clinical trials have reported an increased risk of new-onset diabetes in statin users, and meta-analyses of randomized clinical trials have confirmed such a finding [10–15]. In line with this, the present meta-analysis of available observational studies shows that subjects treated with statins are at higher risk of developing diabetes

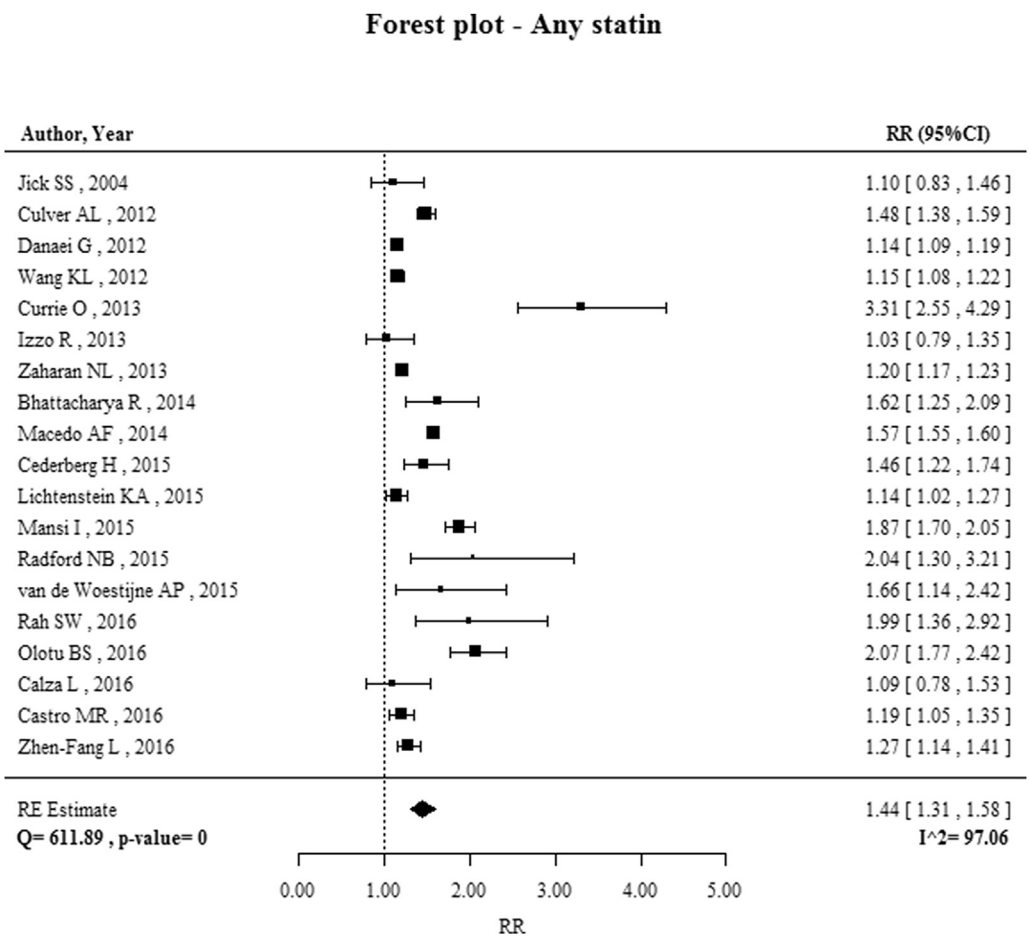

Figure 2 Meta-analysis of risk of new onset diabetes for any statin use vs non use.

compared with patients not treated with statins. The increase of risk results much higher compared with previous meta-analyses of RCTs (44% vs 9–13%) [10,11,13,14,41,42], probably due to the different characteristics of RCTs and observational studies.

Compared with RCTs, observational studies include, in fact, many more subjects followed for a longer time which may result in an increased chance to detect adverse events, in particular those that may require several years to occur or be detected, such as diabetes [16]. Furthermore, the rigorous selection of subjects recruited for an RCT may lead to the exclusion of individuals at higher risk for adverse events [16], and this may result in an underestimation of adverse events, in particular if their incidence is low. In addition, RCTs may have an early stop than planned due to exceeding benefits, as they are designed and powered to detect efficacy, and this may further reduce the chance to detect adverse events.

On the other hand, despite more generalizable than RCTs, due to the lack of subject selection, observational studies may have some limitations. In fact, while in RCTs randomization leads to a comparable distribution of known and unknown factors potentially affecting any observable variable in the compared groups, this is not possible in observational studies due to the absence of randomization, and can result in biases.

A major limitation in the interpretation of results from observational studies is the “indication bias”; in our case, patients treated with statins may be more prone to develop diabetes than those not exposed to statin therapies. Pre-diabetes, i.e. the most important risk factor for type 2 diabetes, is often associated with dyslipidaemia and this increases the chance that subjects with pre-diabetes will be treated with statins; moreover, statin-treated subjects tend to be sicker than non-statin users, and thus they may develop diabetes with higher frequency independently of statin use [43]. Investigators attempted to obtain comparable groups by a range of methods including nested sampling, controlling for potential confounders and propensity score matching. In some studies, risk estimates were adjusted for lipid levels [27,34,39] or propensity score was calculated for matching or adjustment purposes [8,16,25,29,30,34,36–39,44]. For example, Jick et al. [35] limited the study population to untreated and statin treated hyperlipidaemics to minimize the effects of hyperlipidemia itself on the development of diabetes. Also in the study by Corrao et al. [45], the risk of incident diabetes showed a continuous increasing trend with

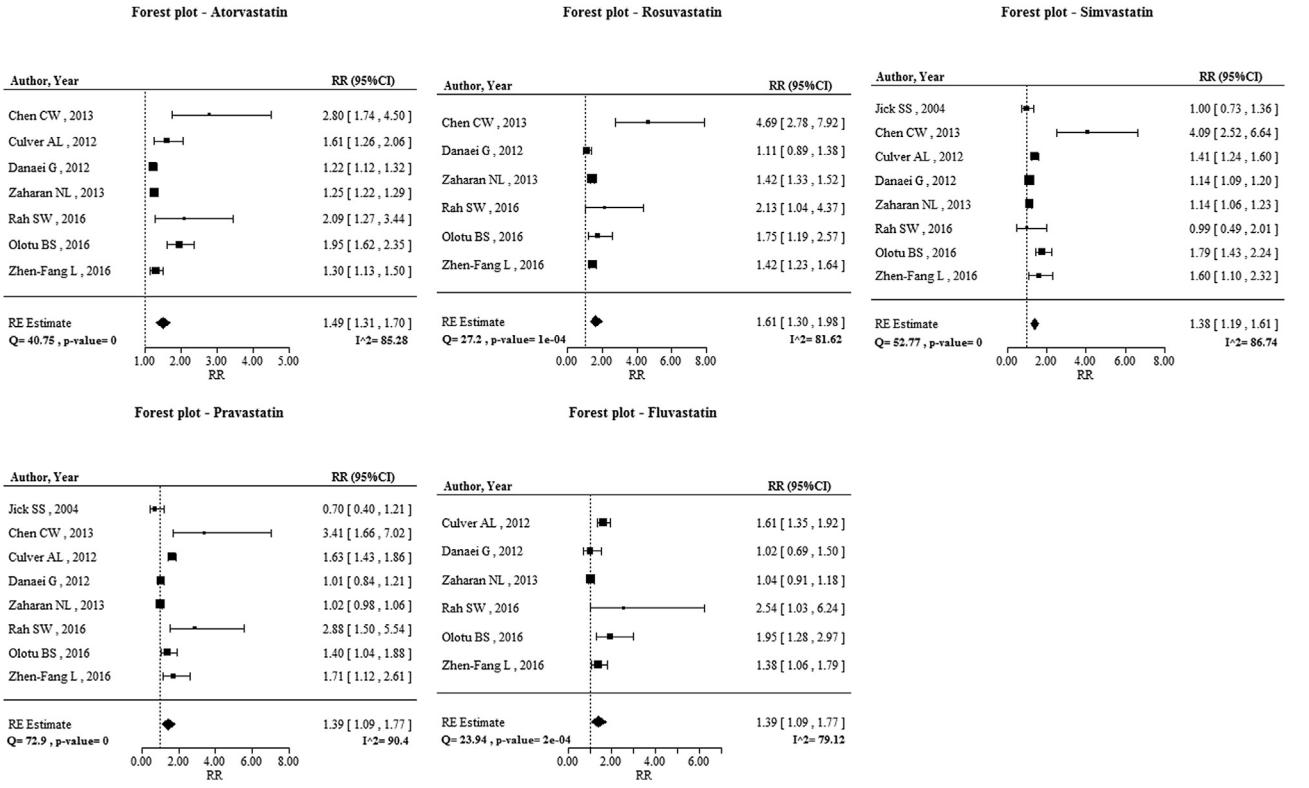

Figure 3 Meta-analysis of risk of new onset diabetes for specific statin use vs non use.

increasing levels of adherence, compared to dyslipidemic patients with low adherence, supporting the role of the drug, in addition to the underlying disease. This finding is further supported by several randomized clinical trials in which an increased diabetes risk among statin users was observed, and randomization is particularly efficient in controlling for selection bias and confounding.

Another potential bias in observational studies is the detection bias, which occurs when a phenomenon is more likely to be observed for a particular set of study subjects. In our case, we can speculate that people prescribed a therapy are more likely to be clinically evaluated, thus increasing their chance of being diagnosed with diabetes. Despite this, in the studies in which adjustment or stratification by frequency of cholesterol tests and outpatient visits was performed the increase in NOD risk was still present [35,45,46]. In addition, patients prescribed statins have a higher risk of new-onset diabetes compared with patients prescribed diclofenac, suggesting that in these two groups of patients, having the same chance to be clinically evaluated, the increased NOD risk can be attributed to statins [26]; moreover, when patients treated with statins were evaluated for the incidence of peptic ulcer, considered as a negative outcome control for statin treatment, a null association was observed, as expected, suggesting that the observed increase of NOD risk was not due to bias [27,46].

In our meta-analysis, we observed little publication bias for atorvastatin. In particular it seems that studies reporting a statistically significant increased risk of new-onset diabetes are more likely published. Since the effect of publication bias was detected exclusively for this statin, it is possible that the effect of atorvastatin may have been overestimated, but it is also reasonable that atorvastatin increases the NOD risk similarly to other statins.

Several studies were performed to identify the biological mechanisms explaining the diabetogenic effect of statins. As first, the inhibition of the statin target 3-hydroxy-methylglutaryl-CoA reductase (HMGCR) seems to play a role [47]. In fact, the analysis of the single nucleotide polymorphism (SNP) rs17238484 in the *HMGCR* gene showed that the rs17238484-G allele was associated with lower LDL-C levels, higher plasma levels of insulin and glucose, greater waist and hip circumference and increased body weight [47]; another SNP, rs12916, showed similar associations with these parameters [47]. Thus, both SNPs seem to be associated with increased risk of diabetes, independently of statin therapy use. In agreement with this observation, statin treatment in randomized trials is associated with bodyweight gain and increased risk of incident diabetes [47].

Besides, the LDL-C-lowering effect of statins may itself increase the risk of diabetes among statin users. In fact, low LDL-C levels are associated with an increased risk of developing new diabetes in subjects not treated with lipid-modifying therapies [48], and this finding is supported by several independent observations. As first, despite at clinical level dyslipidemia is associated with hyperglycemia and insulin resistance, the genetic predisposition to dyslipidemia is associated with lower levels of diabetes-

Table 2 Stratified analyses based on duration of follow-up, on geographic areas and propensity score matching.

Strata	N	Q	Q p-value	I^2	RR (95% CI)	p-value
Overall	19	611.89	<0.0001	0.971	1.44 (1.31−1.58)	
Length of follow-up						
<7.2 years	10	88.845	<0.0001	0.899	1.58 (1.3−1.94)	0.173
≥7.2 years	9	522.19	<0.0001	0.985	1.34 (1.18−1.52)	
Country						
Asia	4	11.723	0.0084	0.744	1.32 (1.12−1.56)	<0.0001
Europe	8	433.93	<0.0001	0.984	1.27 (1.09−1.47)	
USA	7	77.404	<0.0001	0.923	1.55 (1.3−1.85)	
NZL	1	–	–	–	3.31 (2.55−4.29)	
PS matching (cohort studies only)						
No	13	159.51	<0.0001	0.925	1.43 (1.29−1.59)	0.195
Yes	6	30.895	<0.0001	0.871	1.61 (1.39−1.86)	

N: number of studies included in each stratum, Q and Q p-value: value of the Q statistics and corresponding p-value of the test, I^2: value of the I^2 index, RR (95% CI): value of the stratum-specific relative risk estimate and corresponding 95% confidence interval, p-value: p-value of the test for between-strata difference in the estimates.

related parameters, including fasting plasma glucose, glycated hemoglobin and HOMA-IR, suggesting pleiotropic effects of lipid genes on these parameters independent of blood lipid levels [49]. In addition, genetically higher circulating LDL-C levels are associated with a lower risk of diabetes, as shown by either the analysis of SNPs on genes related to lipid metabolism [50] or by the observation of a lower prevalence of type 2 diabetes among patients with familial hypercholesterolemia compared with unaffected relatives [51], as well as in FH patients with LDLR negative mutations compared with FH patients with LDLR defective mutations [51].

Other mechanisms may however contribute to the new-onset diabetes induced by statins [52]. Several in vitro studies suggest that statin treatment may be detrimental for pancreatic ß-cell function. In fact, statins dose-dependently induce ß-cell damage and smooth muscle cell insulin resistance [53], reduce glucose transporter 4 (GLUT4) expression, a transporter responsible for the uptake of glucose in peripheral cells [53−55], reduce insulin signal transduction [54,56,57], inhibit adipocyte differentiation, thus leading to accumulation of cells unable to secrete insulin-sensitizing hormone and to insulin resistance [54], and reduce pancreatic ß-cell function [58−60]. By inhibiting the cholesterol synthesis pathway, statins also inhibit the synthesis of several other products that are relevant for normal cell functions, such as those involved in glucose homeostasis [52]. Additional mechanisms, such as the link between statin treatment and specific microRNAs involved in the reduction of insulin secretion, are currently being investigated [52].

The results obtained in this meta-analysis could be suggestive of a class effect of statins. However, in this context, pitavastatin, which was not included in our meta-analysis due to the lack of available studies, seems to have a neutral or even beneficial effect on glucose homeostasis, as suggested by a recent meta-analysis of 15 randomized controlled clinical trials which reported that pitavastatin therapy was not associated with increased fasting blood glucose, HbA1c or new-onset diabetes in non-diabetic patients [61]. However, most of the included trials (11 out of 15) had a too short follow-up (12-weeks), although no significant differences in outcomes were observed between short-term and longer-term (32−120 weeks) treatments [61]. In fact, the CAPITAIN study and a sub-analysis of the LIVES study, with follow-ups of 6 months and 104 weeks, respectively, did not report an increased risk of incident diabetes [62,63]. The preliminary results of the J-PREDICT study, designed to specifically address this question, showed a reduced diabetes incidence rate in the pitavastatin group compared with the only lifestyle modification group after 5-year therapy [64]. These results seem to suggest that the diabetogenic effect of statins might not be a class effect, although a long-term evaluation of the diabetogenic effect of pitavastatin is still missing.

In summary, our meta-analysis of observational studies confirms and reinforces the evidence that statins possess diabetogenic properties. Authors from the Cholesterol Treatment Trialists' (CTT) Collaboration re-evaluated the risk-benefit balance of statin therapy from a cardiovascular perspective [65], considering the evidence from randomized trials that each 1 mmol/L reduction in LDL-cholesterol with a statin produces a proportional reduction of about 25% in the rate of major vascular events and, on the other hand, the excess risk of cardiovascular events derived from the increased incidence of statins-associated diabetes, whose clinical relevance and consequence are still unclear. Their conclusions confirm the favorable risk-benefit ratio of these drugs, due to the large reduction in cardiovascular risk, even greater in high-risk patients, such as those with pre-existing diabetes and despite the possible adverse impact of the incident diabetes due to statin therapy [65]. Although the estimates need to be updated with the higher risk from observational studies, we should consider that the diabetic patient is not only characterized by an increased cardiovascular risk, but also by other complications, the need for drugs, and worse quality of life. These aspects are difficult to quantify, but might result in a clinical and economic impact. These observations confirm the need of a rigorous monitoring of patients taking statins, in particular pre-diabetic patients or patients presenting with established risk factors for diabetes.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.numecd.2017.03.001.

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