Supplementary Table 1: Summary of the reports included in the systematic review

Author (year)	Funding	Type of studies included in the review	Methods	Results	Quality
Coleman, et al. (2008)[15]	Not funded	Randomized, placebo-controlled and double-blind trials of statins reporting the incidence of NODM in patients with dyslipidaemia evaluating statin benefits in both primary and secondary prevention of CV events	The MA was performed using the random effects model. The incidence of NODM was treated as a dichotomous variable. Weighted averages were reported as RR with associated 95% CI. Funnel plots and Egger's statistic were used to assess for publication bias. Subgroup and sensitivity analyses were performed to assess whether the use of a specific statin or the exclusion of open-label trials had any effect on the results. Heterogeneity was assessed using I^2 statistic and Cochran Q statistic.	The initial search (from inception to 6 November 2007) yielded 18,669 potential records, and 5 RCTs containing data of 39,791 subjects (follow-up range 2.7–6.0 years) were included in the MA. Daily doses of atorvastatin 10 mg, pravastatin 40 mg, rosuvastatin 10 mg or simvastatin 40 mg were included. This MA concluded that statins did not significantly alter the development of NODM (RR 1.03; 95% CI 0.89–1.19). Subgroup and sensitivity analyses did not significantly change the results. Moderate statistical heterogeneity was observed, and a visual inspection of the funnel plots could not rule out publication bias; however, Egger's weighted regression statistic (p=0.23) suggested that publication bias was less likely.	Critically low
Rajpathak, et al. (2009)[16]	Funded	Randomized, placebo-controlled trials reporting data on the incidence of T2DM during follow-up. Both primary and secondary CV prevention trials were included	The authors performed a hypothesis-testing MA that excluded the initial observations from WOSCOPS and analysis of all available data, including the hypothesis-generating WOSCOPS data. Summary RRs with 95% CIs were computed for each outcome. RRs were defined as the risk of cumulative incidence of diabetes among those who received statins compared with those who received placebo. A random effects model was used for the estimates.	The literature search (from inception to February 2009) initially yielded 568 records, and finally, six trials comprising 57,593 patients were included (statin intervention: n=28,842; placebo: n=28,751) presenting with 2,082 incident T2DM cases. Statins included were 40 mg/day pravastatin, 10 or 20 mg/day rosuvastatin, 40 mg/day simvastatin and 10 mg/day atorvastatin (follow-up range from a median of 1.9 to 5.0 years). In the MA of the hypothesis-testing trials, a small increase in diabetes risk	Critically low

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			Heterogeneity was assessed using Cochran Q statistic based on the pooled RR by Mantel-Haenszel and measured inconsistency. Begg and Mazumdar's funnel plot method was used to assess the publication bias.	(RR 1.13, 95% CI 1.03–1.24; p=0.007) was observed with no evidence of heterogeneity (Q statistic = 4.06 [4 d.f.]; p=0.40, I^2=1.6%). However, this estimate was attenuated and no longer significant when the hypothesis-generating trial was included (RR 1.06, 95% CI 0.93–1.25) and also resulted in significant heterogeneity (Q statistic = 11.8 [5 d.f.]; p=0.03; I^2=57.7%). No evidence of publication bias was found (p=0.15).	
Sattar, et al. (2010)[17]	Not funded	Randomized, placebo- or standard care statin-controlled trials reporting data on the occurrence of incident DM	The authors included only trials with more than 1,000 patients, with identical follow-up in both groups and with a duration of more than 1 year. The I^2 statistic was used to measure heterogeneity. To identify the potential effects of statin therapy on incident DM, they calculated an overall OR with 95% CI using random effects models. A funnel plot and Egger's test were used to test for publication bias.	An initial search from 1994 to 2009 yielded 2,841 potential reports, and finally, they identified 13 statin trials with 91,140 participants. In total, 4,278 patients (statins: n=2,226; control therapy: n=2,052) developed DM during a mean of 4 years. Statin therapy led to a 9% increased risk for incident diabetes (OR 1.09; 95% CI 1.02–1.17), with little heterogeneity between trials (I^2=11%). Meta-regression showed that risk of developing DM with statins was highest in RCTs involving older participants (p=0.019). No publication bias was detected.	Critically low
Preiss, et al. (2011)[18]	Funded	Randomized, end-point statin trials primarily designed to assess the effect of intensive-dose statin treatment compared with moderate-dose therapy on CV outcomes	The authors included trials of 1,000 or more participants exposed to statin therapy with a minimum mean follow-up of 1 year (with identical follow-up in both groups). To identify potential associations of intensive-dose versus	An initial search from 1 January 1996 to 31 March 2011 yielded 1,218 potential records, and finally, they included 5 statin trials with 32,752 participants without DM at baseline. Of these, 2,749 developed DM (intensive-dose group: n=1,449; moderate-dose	Critically low

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			moderate-dose statin therapy with incident DM and CV events, the authors calculated OR and 95% CI from the available data for the number of patients who did not have DM at baseline and those who developed DM during follow-up (using a random effects model). Heterogeneity was assessed using the I^2 statistic. The potential for publication bias was assessed using a funnel plot and Egger's test.	group n=1,300), with a mean follow-up of 4.9 years (SD 1.9). Intensive-dose therapy was associated with a higher risk of developing NODM compared with moderate-dose therapy (OR 1.12, 95% CI 1.04–1.22; I^2=0%). No significant heterogeneity was found (χ^2=2.59; p=0.60; I^2=0% [95% CI 0–79]). There was no evidence of publication bias (p=0.54).	
Cai, et al. (2014)[19]	Funded	RCTs comparing statin therapy with placebo- or standard care-controlled group	RCTs of statins with more than 1,000 participants with a follow-up of at least 2 years were included. The included trials were stratified by the target LDL-C level. To investigate the relationship between target LDL-C level of statin use and NODM, ORs and 95% CIs were used to represent data using random effects models. The I^2 statistic was used to measure heterogeneity. Meta-regression was performed to identify the potential risk factors of statin-induced NODM. Publication bias was assessed by a funnel plot and Egger's test.	An initial search from 1966 to 2012 yielded 2,601 potential records, and finally, 14 trials with a total of 95,102 non-diabetic participants were included. The risks of DM elevated by 33% (OR 1.33, 95% CI 1.14–1.56; I^2=7.7%) and 16% (OR 1.16, 95% CI 1.06–1. 28; I^2=0.0%) when the intensified target LDL-C levels were ≤1.8 mmol/L and 1.8–2.59 mmol/L, respectively. The risk of NODM did not increase when the target LDL-C level was ≥2.59 mmol/L (OR 1.01, 95% CI 0.92–1.10; I^2=0.0%). They found a low heterogeneity (p=0.324; I^2=14.1%). No significant publication bias was reported.	Critically low
Navarese, et al. (2013)[20]	No information provided	RCTs and studies investigating the impact of different types and doses of statins on NODM	RCTs comparing patients treated with high-dose statins versus placebo or with high- versus moderate-dose statins connected in a network with a third comparison (placebo or statin) and	The literature search from November 1994 to October 2012 yielded 29,773 potential records, and finally, 17 RCTs reporting 113,394 patients were identified. Pravastatin 40 mg/day was found to be	Critically low

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			reporting the incidence rates of NODM in both arms. Trials with follow-up of ≤1 year and with <1,000 patients were excluded. An NMA was planned with respect to NODM as an endpoint to compare (1) high-dose statins versus placebo and different high doses of statins, (2) moderate-dose statins versus placebo and different moderate doses of statins, and (3) high-dose versus moderate-dose statins.	associated with the lowest risk for NODM compared with placebo (OR 1.07, 95% credible interval 0.86–1.30). Rosuvastatin 20 mg/day was found to be associated with a 25% increased risk for NODM compared with placebo (OR 1.25, 95% credible interval 0.82–1.90). While atorvastatin 80 mg/day showed an intermediate impact (OR 1.15, 95% credible interval 0.90–1.50). The authors concluded that higher statin doses carried a numerically higher risk for NODM compared with moderate doses.	
Naci, et al. (2013)[21]	No information provided	Open-label and double-blind RCTs comparing one statin with another at any dose or with the control (placebo, diet, or usual care) for adults with, or at risk of developing, CVD. The trials of atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin were included if they had >50 participants per trial arm and they were conducted for at least 4 weeks	The authors systematically reviewed RCTs to evaluate the impact of different statins on subjects with or without CVD. A random effect pairwise MA and NMA were performed to quantify the relative adverse effects of individual statins, including NODM. The heterogeneity was assessed using the I^2 measure. Contour-enhanced funnel plots were used to assess publication bias.	The literature search from 1 January 1985 to 10 March 2013 yielded 19,970 potential records. Finally, 135 trials with 246,955 participants with an average follow-up of 1.3 years were included. Of these, 55 were placebo-controlled trials, and 80 were active-comparator trials. According to the placebo-controlled trials, rosuvastatin resulted in significantly higher odds of DM compared with the control (OR 1.16, 95% CI 1.02–1.31; I^2=0.0%). However, the drug-level NMA did not achieve statistical significance. The authors did not find any statistically significant difference between individual statins in terms of DM incidence (OR, 1.09; 95% credible intervals, 1.02–1.16; I^2=2.8%). No publication bias was reported.	Critically low

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Finegold, et al. (2014)[22]	Not funded	RCTs comparing statin with placebo. They included (1) double-blinded RCTs comparing statins with placebo for CV prevention, and (2) RCTs reporting information on the side effects in the statin and placebo groups separately	The authors reported adverse events (including NODM), all-cause mortality, fatal or nonfatal MI, and fatal or nonfatal cerebrovascular accidents (stroke). Withdrawals and serious adverse events were also recorded. MA was performed using a random effects model due to trial heterogeneity (assessed using I^2 statistic).	The literature search from inception to December 2012 identified 62 full-text articles, and finally, 14 primary prevention RCTs with 46,262 subjects and 15 secondary prevention RCTs with 37,618 subjects were included in the final analysis. Among the 14 primary prevention trials, statin therapy increased absolute risk of developing DM by 0.5% (95% CI 0.1–1.0%; p=0.012), meanwhile reducing death by a similar extent (0.5%, 95% CI -0.9 to -0.2%; p=0.003). The authors observed that the development of NODM was significantly higher on statins than on placebo (1 in 5 of new cases were actually caused by statins) and that higher doses produced a more detectable effect. High heterogeneity was observed.	Critically low
Swerdlow, et al. (2015)[23]	Not funded	The authors selected two SNPs (rs17238484 and rs12916) in the *HMGCR* gene on the basis of genetic associations with LDL-C in the Whitehall II study (n=4,678) using the Illumina Care iSelect Human Cardiovascular Disease chip (Cardiochip; Illumina, San Diego, CA, USA). To test the correspondence of genetic and pharmacological effects, the authors	The authors used SNP in the *HMGCR* gene, rs17238484 (for the main analysis) and rs12916 (for a subsidiary analysis), as proxies for *HMGCR* inhibition by statins. Associations of these variants with plasma lipid, glucose and insulin concentrations; bodyweight; waist circumference; and prevalent and NODM were assessed. Study-specific effects were pooled by MA, whose findings were compared with a MA of NODM and bodyweight change data from statins RCTs. They assessed the associations of	A total of 43 genetic studies were included containing data from 223,463 individuals. The rs17238484-G allele seemed to be linked with a higher risk of developing NODM (OR per allele 1.02, 95% CI 1.00–1.05; p=0.09); the rs12916-T allele association was found to be consistent (OR per allele 1.06, 95% CI 1.03–1.09). In 129,170 individuals free from T2DM with a mean of 4.2 years of follow-up from 20 RCTs, statins increased the odds of NODM (all trials: OR 1.12, 95% CI 1.06–1.18; placebo- or standard care-controlled	Critically low

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		updated an MA on the effect of statins on DM risk in RCTs and added new information on bodyweight	the rs17238484 and rs12916 SNPs with DM. They combined within-study estimates using fixed-effects and random effects models, with heterogeneity assessed by the I^2 statistic.	trials: OR 1.11, 95% CI 1.03–1.20; intensive-dose versus moderate-dose trials: OR 1.12, 95% CI 1.04–1.22). No significant heterogeneity was observed.	
Teng, et al. (2015)[24]	Not funded	RCTs comparing any statins with placebo or standard of care for primary prevention of CVD in subjects aged ≥65 years. This MA included statin-induced NODM as a secondary parameter in the safety evaluation	A MA of the outcomes was performed using a random effects model. The results were represented as RRs with corresponding 95% CI. Statistical heterogeneity between trials was evaluated using the chi-square test at a significance level of $p<0.1$ and I^2 statistic.	A literature search was performed on RCTs published from 1 March 2009 to 31 August 2014 on statins for the prevention of CV events. The initial search yielded 1,549 records, and a total of eight trials (n=25,952) were found to be eligible for MA. Statins significantly reduced the risks of composite MACE (RR 0.82, 95% CI 0.74–0.92), nonfatal MI (RR 0.75, 95% CI 0.59–0.94) and total MI (RR 0.74, 95% CI 0.61–0.90). No significant differences were observed in myalgia (RR 0.88, 95% CI 0.69–1.13), elevation of hepatic transaminases (RR 0.98, 95% CI 0.71–1.34), NODM (RR 1.07, 95% CI 0.77–1.48), serious adverse events (RR 1.00, 95% CI 0.97–1.04), and discontinuation due to adverse events (RR 1.10, 95% CI 0.85–1.42).	Low
Vallejo-Vaz et al. (2015)[25]	Funded	RCTs comparing pitavastatin (statin) with placebo that included participants without DM and reported on FBG, HbA1c or NODM with at least 12 weeks of follow-up	The association of pitavastatin with the outcomes were estimated using a random effects model. Heterogeneity was assessed using the I^2 statistic and sensitivity and subgroup analyses, and publication bias was assessed with funnel plots and Egger's and Harbord tests. The effect of pitavastatin therapy (versus control) on FBG	An initial literature search from inception to November 2014 yielded 998 records, and finally, 15 studies with 4,815 patients free from diabetes (3,236 allocated to pitavastatin and 1,579 to control) were included. No significant differences were observed for FBG, HbA1c and NODM (RR 0.70, 95% CI 0.30–1.61). No publication bias was observed. Also,	Critically low

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			and HbA1c at the end of follow-up was estimated as mean differences and corresponding 95% CI. The effect on NODM was estimated using RR with 95% CI.	no significant differences were found whether the authors considered a short-term (12 weeks) or a longer follow-up (32 to 120 weeks). Interestingly, a trend towards a favourable effect of pitavastatin compared with other statins or placebo was observed over longer durations of follow-up.	
Thakker, et al. (2016)[26]	Not funded	RCTs showing mixed results regarding the association of statins and DM were included in this NMA	OR with 95% CI were used as a measure of association between the treatment used and the outcomes. Initially, the authors performed conventional pairwise meta-analyses for all the outcomes and comparisons (using a random effects model) and, later, an NMA for the incidence of NODM. The heterogeneity was assessed by visual inspection of the forest plots and by the I^2 statistic. A meta-regression was also performed to explore the source of heterogeneity.	A literature search (between August 2010 and June 2014) found pre-2010 studies from the bibliography of previously published MA. 29 trials in which 163,039 participants had been randomized were included (141,863 were non-diabetic). The direct MA showed that statins significantly increased the likelihood of developing DM by 12% (pooled OR 1.12; 95% CI 1.05–1.21; I^2=36%; p=0.002; 18 RCTs). In the NMA, atorvastatin 80 mg was found to be associated with the highest risk of developing DM (OR 1.34, 95% CI 1.14–1.57) followed by rosuvastatin (OR 1.17, 95% CI 1.02–1.35). High-dose atorvastatin increased the odds of developing DM even compared with pravastatin, simvastatin and low-dose atorvastatin in the NMA.	Low
Rahal, et al. (2016)[27]	Not funded	End-point RCTs of statins	RCTs with more than 1,000 participants and a minimum of 1 year of follow-up were included. A random effects model was applied to calculate the OR of the incidence of NODM with statin therapy and with different statins. Cochran Q	A literature search from inception to August 2015 yielded 3,349 relevant records, and finally, 14 studies with a total of 94,943 participants were included. A total of 2,392 subjects in the statin group and 2,167 in the placebo group developed	Critically low

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			was used to assess the heterogeneity between the included trials. Publication bias was assessed using funnel plots constructed based on the standard error by log OR.	NODM groups during a 4-year follow-up. The OR of NODM incidence with overall statin therapy was significantly higher compared with placebo (OR 1.11, 95% CI 1.0–1.2; p=0.007). No significant heterogeneity was observed (Q statistic = 19.463, p=0.109, I^2=33.20). Subgroup analysis revealed that only atorvastatin (OR 1.29, 95% CI 1.0–1.6; p=0.042) and rosuvastatin (OR 1.17, 95% CI 1.0–1.3; p=0.01) were significantly associated with the risk of NODM.	
Casula, et al. (2017)[28]	Not funded	Observational studies evaluating the association between statin use and the risk of NODM were included in the MA. The following inclusion criteria were used: (1) studies examining the risk of NODM for statin use versus non-users; (2) ≥1,000 participants; (3) follow-up of ≥1 year; (4) the risk estimate reported as OR, HR or relative risk; (5) 95% CI included for the risk estimate	Estimates were pooled using the fixed effects and random effects models. Heterogeneity was assessed by Cochrane's Q test and measured with the I^2 statistic. A stratified analysis was also performed to assess if follow-up length, geographic area and propensity score matching contribute to heterogeneity. Publication bias was evaluated using a funnel plot and Egger's test.	A literature search was performed on studies fulfilling the inclusion criteria published from inception to 30 June 2016. Overall, 2,272 records were retrieved, and finally, 18 cohort and 2 case-control studies were included in the MA. NODM risk was found to be higher in statin users than non-users (relative risk 1.44, 95% CI 1.31–1.58). High heterogeneity (I^2=97%) was observed. A class effect was observed regarding NODM risk, from rosuvastatin (relative risk 1.61, 95% CI 1.30–1.98) to simvastatin (relative risk 138, 95% CI 1.19–1.61).	Low
Wang, et al. (2017)[29]	Funded	RCTs evaluating the association of reduction in LDL-C with statin therapy and the risk of NODM. They excluded the studies if they	The authors calculated an overall OR using a random effects model as the primary outcome (a fixed effects model was employed as a part of the sensitivity analysis). Meta-regression	A literature search of studies published from inception until May 2016 yielded 5,039 studies, from which 14 trials (n=95,102 participants free from diabetes) were included in the MA. Eight trials	Low

Author (year)	Funding	Type of studies included in the review	Methods	Results	Quality
		were not randomized, if the studies enrolled 1,000 or fewer participants and that had taken a treatment for less than 1 year. Also, the trials done in patients, with organ transplants or HIV or those receiving haemodialysis, were excluded. Trials lacking data on NODM, endpoint LDL-C or reductions in LDL-C were also excluded	analyses were also performed to investigate the potential sources of heterogeneity. Summary ORs with 95% CIs were initially calculated for the trials with intensive LDL-C-lowering therapy, and then the trials were stratified according to their relative reductions in LDL-C (10–20%; >20–30%; > 30–40%; and >40–50%). For each LDL-C reduction range, OR was calculated. I^2 statistic was used to assess the statistical heterogeneity between trials. A fail-safe number and Egger's test for a funnel plot were used to assess publication bias.	with target LDL-C levels of ≤100 mg/dL or an LDL-C reduction of at least 30% were extracted. The overall risk of incident diabetes was increased by 11% (OR 1.11; 95% CI 1.03–1.20). The intensive-lowering statin group showed an 18% increase in the likelihood of developing DM (OR 1.18; 95% CI 1.10–1.28). The risks of incident DM were 13% (OR 1.13; 95% CI 1.01–1.26) and 29% (OR 1.29; 95% CI 1.13–1.47) in the subgroups with 30–40% and 40–50% reductions in LDL-C, respectively. They found that over 4 years of statin therapy there were one additional case of DM per 137 users with a 30–40% relative reduction in LDL-C and one per 108 statin users with a 40–50% relative reduction in LDL-C. No significant heterogeneity or publication bias (p=0.56 with Egger's test), were observed. Results of the fixed-effects model which was conducted to perform sensitivity analysis of the intensive LDL-C-lowering statin therapy were similar to those of the random effects model, indicating that the generated data had a good stability.	
Kamran, et al. (2018)[30]	Funded	The authors included research studies reporting on associations between NODM and statin use	The authors performed a MA and represented the results as OR (95% CI). The Mantel-Haenszel method was used for calculating a weighted, pooled OR and 95% CI. A	A literature search of studies from 1 July 2006 to 30 June 2016 yielded 1,354 potential records, and finally, 11 studies with 236,864 subjects (statin group: n=56,053; control group: n=180,811) were	Critically low

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		among CV and kidney disease cohorts	heterogeneity statistic was incorporated to calculate the summary OR under the random effects model (DerSimonian and Laird). Both fixed and random effects were reported.	included in the MA. In the statin group, 4,732 subjects developed DM, while 10,447 subjects in the control group developed DM (fixed effects model: pooled OR 1.6; 95% CI 1.55–1.68; random effects model: pooled OR 1.92, 95% CI 1.64–2.25; p<0.001) suggesting a significant positive association between statin use and development of NODM. High heterogeneity was observed (Q statistic=103.5; p<0.001).	

CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; d.f =degrees of freedom; DM = diabetes mellitus; FBG = fasting blood glucose; Hb, haemoglobin; LDL-C = low-density lipoprotein - cholesterol; MA = meta-analysis; MACE = major adverse cardiovascular events; MI = myocardial infarction; NMA= network meta-analysis; NODM = new-onset diabetes mellitus; OR = odds ratio; RCT = randomized controlled trials; RR= risk ratio; SD = standard deviation; SNP, single nucleotide polymorphism; T2DM = type2 diabetes mellitus, WOSCOPS = West of Scotland Coronary Prevention Study.