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Statin-induced LDL cholesterol response and type 2 diabetes: a bidirectional two-sample Mendelian randomization study

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Abstract

It remains unclear whether the increased risk of new-onset type 2 diabetes (T2D) seen in statin users is due to low LDL-C concentrations, or due to the statin-induced proportional change in LDL-C. In addition, genetic instruments have not been proposed before to examine whether liability to T2D might cause greater proportional statin-induced LDL-C lowering. Using summary-level statistics from the Genomic Investigation of Statin Therapy (GIST, $n_{\max} = 40,914$) and DIAGRAM ($n_{\max} = 159,208$) consortia, we found a positive genetic correlation between LDL-C statin response and T2D using LD score regression ($r_{\text{genetic}} = 0.36$, s.e. = 0.13). However, mendelian randomization analyses did not provide support for statin response having a causal effect on T2D risk (OR 1.00 (95% CI: 0.97, 1.03) per 10% increase in statin response), nor that liability to T2D has a causal effect on statin-induced LDL-C response (0.20% increase in response (95% CI: -0.40, 0.80) per doubling of odds of liability to T2D). Although we found no evidence to suggest that proportional statin response influences T2D risk, a definitive assessment should be made in populations comprised exclusively of statin users, as the presence of nonstatin users in the DIAGRAM dataset may have substantially diluted our effect estimate.

Introduction

3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, also known as statins, have demonstrated consistent benefits to cardiovascular disease (CVD) risk reduction, while being safe and well-tolerated for most people [1]. However, statin treatment has been linked to a modestly increased risk of new-onset type 2 diabetes (T2D), an observation first noted in the JUPITER trial [2], which has since been replicated in large-scale meta-analyses of

randomized controlled trials [3–5]. As promising novel strategies for lowering low-density lipoprotein cholesterol (LDL-C) such as proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors emerge, the safety of lipid-modifying treatments with regard to diabetes risk remains an important question.

In recent years, genetic epidemiology has started to untangle the complex link between LDL-C lowering and T2D risk. For example, analyses of patients with familial hypercholesterolemia have shown that the prevalence of T2D is significantly lower than among unaffected relatives, with variability by underlying mutation type [6]. Furthermore, apparent causal effects on T2D have been shown both for overall genetic predisposition to lower LDL-C concentrations [7–9] as well as for *HMGCR*-, *NPC1L1*-, and *PCSK9*-gene specific (i.e., on target) mechanisms of lowering LDL-C [9–13]. These findings, and recent reanalysis of statin trial data using Egger regression [14], suggest that statin-related dysglycaemia might be mediated largely through LDL-C lowering mechanisms rather than through proposed pleiotropic mechanisms of statins [15].

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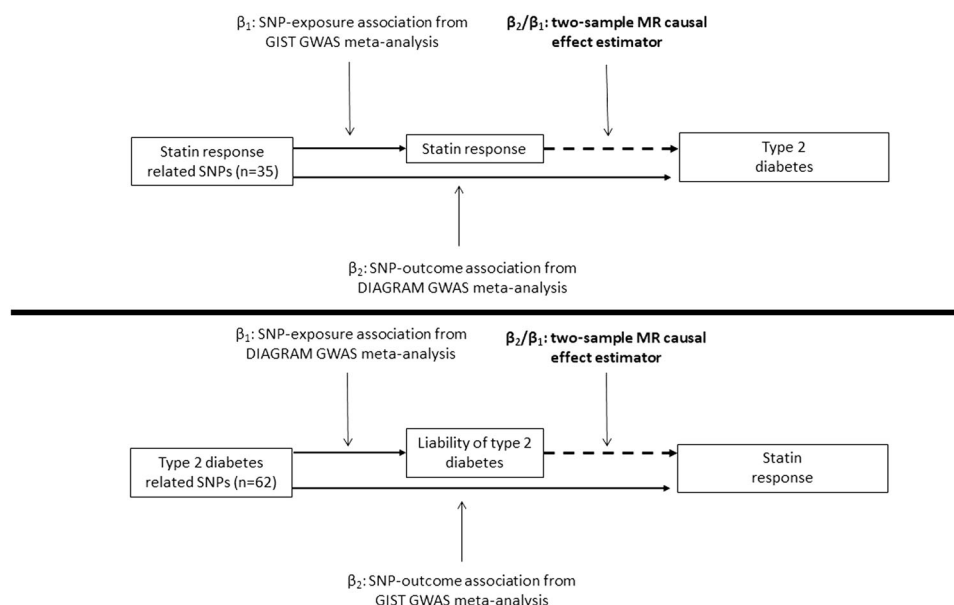


Fig. 1 Overview of two-sample Mendelian randomization (MR) study on the bidirectional association between statin-induced LDL cholesterol response and type 2 diabetes (T2D). Top panel shows

direction of statin response to T2D, bottom panel liability to T2D to statin response. Layout of figure based upon the work by Taylor et al. (2016) (PMID 27215954).

However, meta-regression approaches modeling heterogeneity among treatment effects from statin trials have produced conflicting results as to whether statin-induced proportional change of LDL-C influences T2D risk [3–5]. Previous Mendelian randomization (MR) studies have been unable to directly answer this question, as genetic instruments solely proxying lifelong lower levels of LDL-C have been utilized. In addition, genetic instruments have not been proposed before to examine whether the greater absolute CVD risk reduction conferred by statin therapy in individuals with T2D could result from greater proportional statin-induced LDL-C lowering. Findings from the largest pharmacogenomic meta-analysis for differential LDL-C response to statin therapy to date by the Genomic Investigation of Statin Therapy (GIST) consortium might be used to investigate these questions. We therefore aimed to use these data to examine the causal direction of the relationship between proportional statin response and T2D using a bidirectional two-sample MR approach.

Methods

To assess the likelihood of a shared etiology between statin response and T2D, which may be the product of a causal relationship, we assessed their genetic correlation using cross-trait linkage disequilibrium (LD) score regression. To detect potential direct causality we performed a bidirectional two-sample MR-analysis, combining summary-level statistics from the GIST [16] and DIABetes Genetics

Replication And Meta-analysis (DIAGRAM) [17] consortia (Fig. 1), to estimate: (1) the causal effect of statin-induced LDL-C response on T2D risk, and (2) the causal effect of liability to T2D on statin-induced LDL-C response. We refer to liability to T2D in this second analysis as it is not possible to determine whether individuals in the GIST dataset have been diagnosed with T2D.

Causal effect of statin-induced LDL-C response on T2D

The GIST consortium's 2014 meta-analysis on statin-induced LDL-C response included up to 18,596 statin-treated subjects in the discovery stage, of whom 9064 (48.7%) were known to have a history of diabetes (type unspecified). The most promising signals ($n = 246$) were taken forward for replication, to be validated in an additional 22,318 statin recipients [16]. Statin response had been defined as the difference between natural log-transformed on- and off-treatment LDL-C levels. Linear regression analyses using this statin response phenotype as dependent variable and genetic variant as independent variable were adjusted for natural log-transformed off-treatment LDL-C level, age, sex, and study-specific covariates including principal components of ancestry. Observational studies had additionally adjusted for statin type-specific equivalent dose in their regression models. The resulting regression coefficient thus approximates the fraction of differential LDL lowering in carriers vs. noncarriers of the SNP. While lead variants for four independent loci (*APOE*, *LPA*, *SLCO1B1*,

SORT1/CELSR2/PSRC1) were presented as the top genome-wide significant hits for statin response in the GIST paper [16], 63 correlated variants attained a p value lower than 5×10^{-5} in a combined meta-analysis of the discovery and replication-stage results.

To assess the effects of these instruments on T2D, we extracted discovery stage summary statistics for these 63 variants from DIAGRAM's 2017 meta-analysis of genome-wide association data from 26,676 T2D case and 132,532 control subjects of European ancestry after imputation using the 1000 Genomes all ancestries reference panel (March, 2012 release) [17]. Contributing studies had performed logistic regression association analysis of T2D against each genetic variant, adjusted for age, sex, and principal components of ancestry. The summary statistics were extracted from the publicly available summary statistics dataset on the DIAGRAM website (<http://www.diagram-consortium.org/>). All variants were available in the DIAGRAM dataset, except two, for which we could not find suitable (i.e., high LD) proxies. We subsequently LD clumped the set of variants using 0.001 as the maximum LD r^2 value to ensure that the remaining instruments were essentially independent. This reduced the set of statin response instruments from 61 to 35 (Supplemental Table 1). We separately examine the effects of the full set of 35 statin response instruments and of the four top hits together. Possible dilution by the presence of nonstatin users in DIAGRAM was explored through simple simulations (Supplementary Note).

Causal effect of liability to T2D on statin-induced LDL-C response

As candidate genetic instruments for liability of T2D we selected 128 genetic instruments at 113 loci. These 128 variants represent the established loci from the literature before the DIAGRAM's 2017 publication as well as the novel signals detected therein, with 42 being genome-wide significant ($p < 5 \times 10^{-8}$) in this DIAGRAM dataset. Discovery stage regression coefficients and standard errors for a total of 128 single nucleotide polymorphisms (SNPs) at 113 loci were extracted from the publicly available summary statistics dataset on the DIAGRAM website (<http://www.diagram-consortium.org/>).

Next, we extracted summary statistics for the identified T2D liability instruments from GIST's 2014 genome-wide meta-analysis on statin-induced LDL-C response. Of note, none of the identified T2D liability instruments were among those SNPs carried forwards to the replication stage of the GIST meta-analysis. In total, 78 of the 128 instruments were available in the discovery GIST dataset. We subsequently LD clumped the set of variants, again using 0.001 as the maximum LD r^2 value. This reduced the set of instruments from 78 to 62 (including 24 genome-wide

significant instruments), which include 19 proxies with an $r^2 \geq 0.8$ with the original variant in 1000 Genomes European samples (Supplemental Table 2). To tease out possible bias from using weaker instruments, we aimed to examine the combined effects of the T2D liability instruments before and after restricting the analysis to the genome-wide significant instruments.

Sample overlap

Of the studies that contributed to the discovery-stage meta-analysis of GIST, four (Atherosclerosis Risk in Communities Study, Framingham Heart Study, Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) I and II) also contributed to the DIAGRAM meta-analysis. Of the studies contributing to the replication-stage meta-analysis of GIST, one (Rotterdam Study) also contributed to the DIAGRAM meta-analysis. We were unable to precisely determine the overlap between the datasets. However, if we assume that all participants from these five studies contributed to both analyses, up to 5% (with respect to the larger dataset, i.e., DIAGRAM) of overlap may be present for our analyses.

Statistics—LD score regression

A causal relationship between two heritable traits should induce a genetic correlation between these traits. The use of LD score regression to quantify genetic correlation has been described in detail elsewhere [18, 19]. Briefly, under the assumption that biologically relevant variants are uniformly distributed across the genome, genetic variants in high LD with many nearby variants are more likely to tag causal variants, and therefore have larger squared effect size estimates. This can be quantified by each variant's 'LD score': the sum of squared correlations with all nearby variants. Cross-trait LD score regression calculates the cross product of test statistics from different GWAS meta-analyses, and then regresses the cross product on that variant's LD score. In our study, the genome-wide summary-level datasets of both GIST (discovery stage, including only variants with $N > 5000$, and without genome control-correction) and DIAGRAM's 2012 GWAS [20] were thus used to estimate the genetic correlation of statin-induced LDL-C proportional response with T2D using the LD Hub platform (<http://ldsc.broadinstitute.org/ldhub/>) [21]. After QC, 1,039,702 genetic variants which overlapped between the two GWAS datasets were included for this analysis.

Statistics—MR-analysis

Partial F-statistics were calculated per instrument as measure of instrument strength [22]. For each set of instruments

separately (i). statin response-all ($n = 35$), (ii). statin response-restricted ($n = 4$ genome-wide significant instruments), (iii). T2D liability-all ($n = 62$), (iv). T2D liability-restricted ($n = 24$ genome-wide significant instruments) an MR-analysis was performed using an inverse-variance weighted (IVW) linear regression, with instrument-outcome associations as dependent variable, instrument-exposure associations as independent variable, and with the intercept constrained to zero [23]. Estimates of the causal effect of statin response on T2D are presented as odds ratio for T2D per 10% increase in statin response. For examining the effects of liability to T2D on statin response we rescaled effect estimates such that they represent increase in statin response (% extra lowering of LDL-C) per doubling of the odds of liability to T2D in the population, by multiplying the causal estimate by 0.693 (i.e., $\log_e 2$) prior to exponentiating.

Instrument-outcome associations were plotted against instrument-exposure associations to visualize the resulting regression line from the IVW analysis using the full and restricted sets of instruments. Furthermore, causal effect estimates for the individual instruments (i.e., Wald ratios) were plotted against the inverse of their standard error to facilitate visual detection of possible horizontal pleiotropy (i.e., a direct effect on the outcome rather than via the exposure). We subsequently performed three complementary sensitivity analyses which relax the assumption of no horizontal pleiotropy amongst the genetic variants. First, MR-Egger regression, of which the intercept formally tests for the presence of unbalanced horizontal pleiotropy, and the slope reflects the causal effect estimate after adjusting for this pleiotropy by adding an intercept to the IVW method [24]. Additional approaches that are similarly more robust to potential violations of the instrumental variable assumptions than the conventional (i.e., IVW) MR-analysis were the weighted median-based estimator [25] and the weighted mode-based estimator [26], which respectively use the weighted median of, and the highest density of, the ratio estimates across the individual instruments as estimate of the true causal effect. We additionally tested for heterogeneity in effects estimates by means of Cochran's Q and Rucker's Q' [27, 28]. First-order weights were utilized for this calculation. Finally, as several of the proposed instruments for statin-induced LDL-C response are known to independently associate with fasting LDL-C levels, we performed a multivariable MR-analysis for the analysis of statin response to T2D, adjusted for effects on fasting LDL-C levels [29]. This multivariable analysis included 32 statin response instruments, and 64 instruments for fasting LDL-C concentrations from the Global Lipids Genetics Consortium 2013 GWAS on blood lipid levels [30]. The number of instruments used for the multivariable MR-analysis differ from the other MR analyses due to not all instruments being available in all three GWAS datasets. All MR analyses were carried out in R

version 3.4.2 [31], without correction for multiple testing, using the TwoSampleMR R-package which accompanies the MR-base analytical platform, and the sample code provided by the methodology paper on multivariable MR [29, 32] (code available upon request).

Results

We found a statistically significant positive genetic correlation of statin-induced LDL-C response with T2D (r_{genetic} (s.e.) = 0.36 (0.13), $p = 0.0071$) using LD score regression.

The median F-statistic (25, 75th percentile) was 23.2 (16.3, 37.8) for the full set of statin response instruments, and 18.1 (16.2, 20.9) for the full set of T2D liability instruments. These respectively increased to 44.8 (35.5, 70.7) and 73.1 (38.8, 120.3) for the restricted sets of instruments. As shown in Fig. 2 and the Table 1, we did not find statistical evidence that statin-induced differential LDL-C response has a causal effect on T2D risk, nor that liability to T2D has a causal effect on statin-induced differential LDL-C response. This held true for both the full and restricted sets of instruments, and results from all sensitivity analyses were consistent with these findings. More specifically, our results for the full sets of instruments indicate the OR of T2D is 1.00 (95% CI: 0.97, 1.03) per 10% increase in statin-induced LDL-C response, and that statin-induced LDL-C response is increased by 0.20% (95% CI: -0.40, 0.80) per doubling of the odds of T2D liability. Evidence of unbalanced horizontal pleiotropy was present only for the restricted set of statin response instruments, as indicated by the MR-Egger intercept (intercept (95% CI): 1.04 (1.01, 1.07)) and Fig. 3, but this is likely an artifact of including such a small number of instruments ($n = 4$). Neither Cochran's Q nor Rucker's Q' were suggestive of substantial heterogeneity in the effect estimates. Finally, a multivariable MR-analysis where we adjust for effects of all SNPs on fasting LDL-C did not lead to different conclusions regarding the effect of statin response on T2D risk (OR 1.02 (95% CI: 0.97, 1.07 per 10% increase in statin-induced LDL-C response).

Discussion

Using LD score regression we found a positive genetic correlation of proportional statin response with T2D using genome-wide data, pointing to shared genetic determinants between these traits. However, our bidirectional MR analyses did not provide evidence of direct causal mechanisms of either statin-induced LDL lowering on risk for T2D, nor liability to T2D on statin response. Sensitivity analyses of these MR analyses showed consistent results, suggesting that the issue of horizontal pleiotropy is unlikely to substantially influence our results.

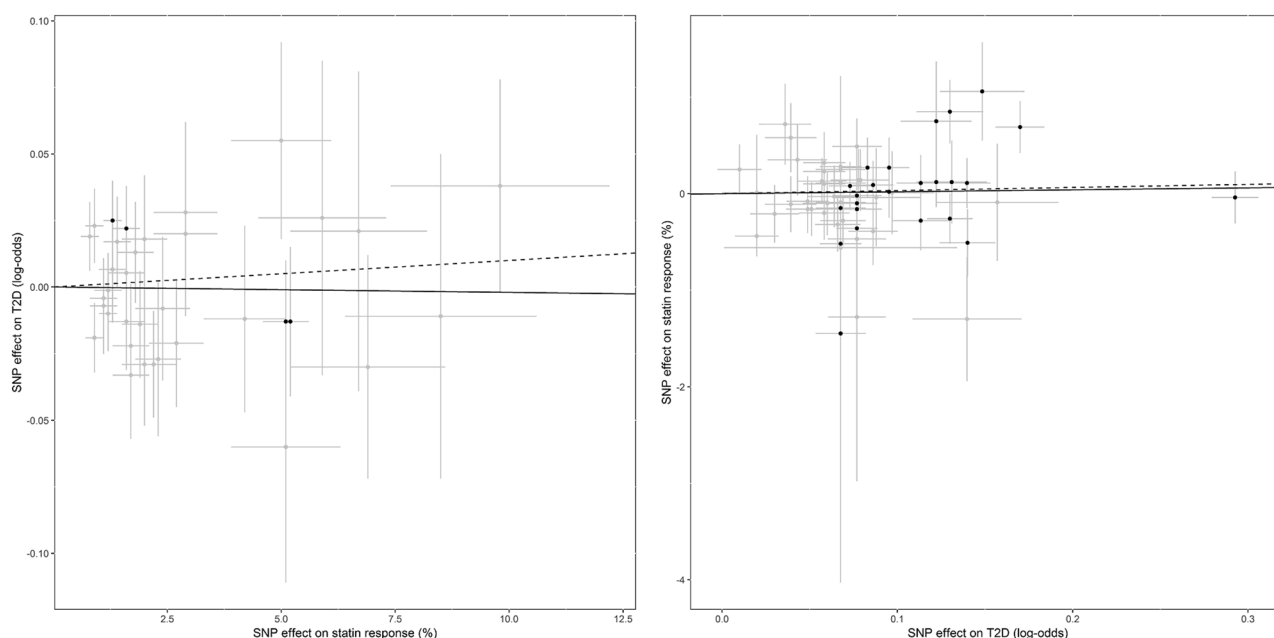


Fig. 2 Scatterplots of per-allele effects. The plots display the instrument-outcome (y-axis) against individual instrument-exposure (x-axis) per-allele effects, shown separately for statin response (left panel) and liability of type 2 diabetes instruments (T2D, right panel).

The filled dots correspond to the restricted lists of variants (see text), while the full set included all dots. The lines correspond to the inverse-variance weighted combined MR estimator, for the restricted (dashed line) and full set of instruments.

Table 1 Mendelian randomization (MR) estimators for the bidirectional association between type 2 diabetes (T2D) and statin-induced LDL-C response.

	Number of instruments	F-statistic, median (25th, 75th percentile)	Estimate (IVW method, 95% CI)	Sensitivity analyses			Tests of heterogeneity		
				Weighted mode estimate (95% CI)	Weighted median estimate (95% CI)	MR-Egger estimate (95% CI)	MR-Egger intercept (95% CI)	Cochrane's Q (p value)	Rucker's Q' (p value)
Statin response → T2D ^a	35	18.1 (16.2, 20.9)	1.00 (0.97, 1.03)	0.99 (0.93, 1.04)	0.98 (0.94, 1.02)	0.99 (0.94, 1.04)	1.02 (0.92, 1.14)	31.0 (0.61)	31.0 (0.57)
	4	73.1 (38.8, 120.3)	1.01 (0.93, 1.09)	0.98 (0.91, 1.05)	0.98 (0.91, 1.05)	0.91 (0.81, 1.01)	1.04 (1.01, 1.07)	3.4 (0.33)	0.2 (0.93)
T2D liability → Statin response ^b	62	23.2 (16.3, 37.8)	0.20 (−0.40, 0.80)	0.11 (−0.95, 1.18)	0.03 (−0.97, 1.02)	0.62 (−0.55, 1.80)	−0.04 (−0.15, 0.06)	65.5 (0.32)	65.3 (0.30)
	24	44.8 (35.5, 70.7)	0.32 (−0.47, 1.12)	0.04 (−1.07, 1.14)	0.08 (−0.99, 1.15)	1.24 (−0.67, 3.15)	−0.12 (−0.36, 0.11)	32.4 (0.09)	32.3 (0.07)

IVW denotes inverse-variance weighted. The different MR estimators can be interpreted as: ^aodds ratio for T2D per 10% increase in proportional statin response, and ^bthe effect on proportional statin response (%) per doubling in the odds of liability to T2D, respectively. A positive statin response value corresponds to an increased LDL cholesterol lowering effect of statin therapy

The findings from the MR analyses suggest that statin-induced proportional change of LDL-C is unlikely to influence T2D risk. If true, this would indicate that it is not the degree of proportional lowering of LDL-C levels in response to statin therapy which increases the risk for diabetes, but the low levels in an absolute sense which may result from this transition. Indeed, results from the JUPITER trial have shown that achieving LDL-C concentrations <30 mg/dl with high-intensity statin therapy was associated with more physician-reported diabetes [33], which was not observed when a threshold of <50 mg/dl was considered [34]. Of further note here is a recent comparison of the risk of T2D in a large electronic health record database between individuals with low and normal LDL-C levels, which

showed that LDL-C levels below 60 mg/dl occurring in absence of statin therapy are also associated with higher T2D risk [35]. Moreover, also in line with our results, researchers using data from 129,170 participants free from T2D at baseline from 20 statin trials did not observe evidence of a clinically relevant association between LDL-C proportional lowering at 1 year and within-trial odds ratios for new-onset T2D (log-odds per 1% reduction in LDL-C: 0.004 (95% CI −0.001, 0.009)) [10].

However, we cannot exclude the possibility that a direct causal effect of statin-induced proportional LDL-C response on T2D may exist, but was (substantially) diluted by the presence of nonstatin users in the DIAGRAM dataset. This is because proposed genetic instruments for pharmacological

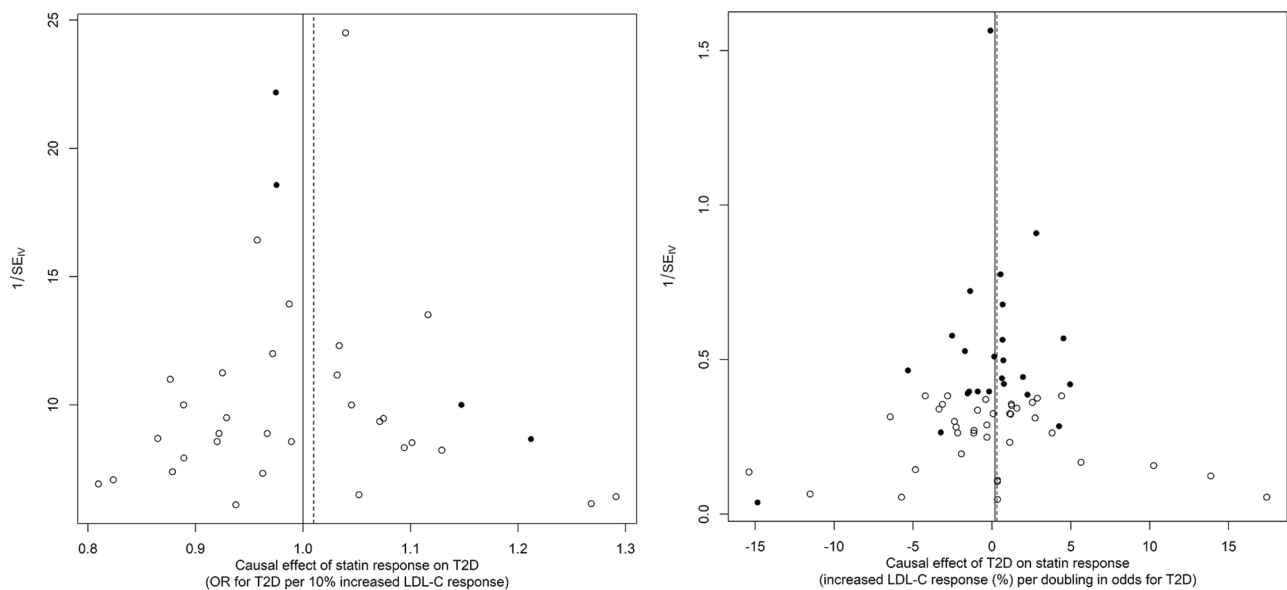


Fig. 3 Funnel plots of individual causal effect estimates. Data presented as funnel plots of Wald ratios for statin response on type 2 diabetes (T2D, left panel), and liability to T2D on statin response (right panel). The black dots correspond to the restricted lists of variants (see

text), while the full set included all dots. The lines correspond to the inverse-variance weighted combined MR estimator, for the restricted (dashed) and full set of instruments.

response phenotypes can only exert their effect in the presence of (i.e., are conditional on) drug usage. More intuitively, if this type of instrument were to associate with an outcome in a population which includes no relevant drug users, this must reflect an alternative pathway unrelated to that specific drug response (i.e., horizontal pleiotropy), or at least a shared genetic etiology between the two traits. Therefore, assessment of any causal effect of instruments derived from pharmacogenetic studies should ideally also be examined in populations composed solely of individuals using the drug of interest. An analogous dilemma has been described in the context of smoking heaviness, where an SNP which strongly predicts cigarettes per day was detected in a GWAS sample including daily smokers, and found to exert an effect only after a person has become an established smoker [36, 37]. Due to our use of summary statistics, we were unable to stratify our analyses on statin use. In addition, it was not possible to weight for the prevalence of statin use, as this is unknown for the DIAGRAM consortium, where statin use is additionally likely to be differential by case/control status. Therefore, given our null results, it is more appropriate to conclude that our MR analyses did not provide evidence for a shared genetic etiology between statin-induced proportional LDL-C response and T2D.

Furthermore, our observation that liability to T2D does not associate with LDL-C response resulting from statin treatment is consistent with previous studies showing that, while individuals with T2D are likely to gain greater clinical benefit from statin therapy in terms of absolute CVD risk reduction, this does not result from differential lowering of

their LDL-C concentrations when compared with non-diabetics [38].

An alternative noncausal explanation for the genetic correlation, which does suggest the presence of (some form of) directionally consistent pleiotropy, may be that both traits are independently influenced by the same underlying biological pathway [39]. Similar observations have been made in the field of neuropsychiatric diseases, where patterns of genetic correlation often reflect shared biological processes rather than causal relationships [40]. More generally, caution has been advised against treating LD score regression results as a singular assessment of causality, amongst others due to its lack of validation against some known causal relationships [41].

While an important strength of our analyses is the use of large-scale GWAS data, increasing the power of our investigations for both directions of causality, we purposely included instruments which did not attain genome-wide significance in their corresponding GWAS to increase the number of instruments. Though instrument-exposure associations will have been estimated with less precision for the weaker (i.e., sub-threshold) instruments, we considered this issue analogous to possible misspecification of weights in allele scores, which causal estimates have been shown to be generally robust to [42]. However, we cannot exclude the possibility of weak instrument bias, particularly for the full set of T2D liability instruments, which included several instruments with an individual F-statistic below 10 [22]. Given the relatively small overlap between the GWAS datasets, it is likely that any weak instrument bias would be towards the null [43]. However, the

analysis using the restricted list of strong instruments reassuringly showed similar results.

In conclusion, our results suggest that liability to T2D is unlikely to influence LDL-C response to a statin, but provided some evidence of a shared genetic etiology between statin-induced LDL-C response and T2D. Future studies should make a definitive assessment of direct causal effects of statin-induced proportional LDL-C response on T2D in populations of statin users.

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Conflict of interest BMP serves on the Steering Committee of the Yale Open Data Access Project funded by Johnson & Johnson. DIC received research support for independent genetic analysis in JUPITER from AstraZeneca. RMK serves on the Merck Global Atherosclerosis Advisory Board. The remaining authors declare no conflict of interest.

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