HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials

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Summary

Background Statins increase the risk of new-onset type 2 diabetes mellitus. We aimed to assess whether this increase in risk is a consequence of inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR), the intended drug target.

Methods We used single nucleotide polymorphisms in the *HMGCR* gene, rs17238484 (for the main analysis) and rs12916 (for a subsidiary analysis) as proxies for HMGCR inhibition by statins. We examined associations of these variants with plasma lipid, glucose, and insulin concentrations; bodyweight; waist circumference; and prevalent and incident type 2 diabetes. Study-specific effect estimates per copy of each LDL-lowering allele were pooled by meta-analysis. These findings were compared with a meta-analysis of new-onset type 2 diabetes and bodyweight change data from randomised trials of statin drugs. The effects of statins in each randomised trial were assessed using meta-analysis.

Findings Data were available for up to 223 463 individuals from 43 genetic studies. Each additional rs17238484-G allele was associated with a mean 0·06 mmol/L (95% CI 0·05–0·07) lower LDL cholesterol and higher body weight (0·30 kg, 0·18–0·43), waist circumference (0·32 cm, 0·16–0·47), plasma insulin concentration (1·62%, 0·53–2·72), and plasma glucose concentration (0·23%, 0·02–0·44). The rs12916 SNP had similar effects on LDL cholesterol, bodyweight, and waist circumference. The rs17238484-G allele seemed to be associated with higher risk of type 2 diabetes (odds ratio [OR] per allele 1·02, 95% CI 1·00–1·05); the rs12916-T allele association was consistent (1·06, 1·03–1·09). In 129 170 individuals in randomised trials, statins lowered LDL cholesterol by 0·92 mmol/L (95% CI 0·18–1·67) at 1-year of follow-up, increased bodyweight by 0·24 kg (95% CI 0·10–0·38 in all trials; 0·33 kg, 95% CI 0·24–0·42 in placebo or standard care controlled trials and –0·15 kg, 95% CI –0·39 to 0·08 in intensive-dose *vs* moderate-dose trials) at a mean of 4·2 years (range 1·9–6·7) of follow-up, and increased the odds of new-onset type 2 diabetes (OR 1·12, 95% CI 1·06–1·18 in all trials; 1·11, 95% CI 1·03–1·20 in placebo or standard care controlled trials and 1·12, 95% CI 1·04–1·22 in intensive-dose *vs* moderate dose trials).

Interpretation The increased risk of type 2 diabetes noted with statins is at least partially explained by HMGCR inhibition.

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Introduction

Statins reduce LDL cholesterol concentration by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), leading to a proportionate reduction in cardiovascular disease (CVD) risk.[1–4] Consequently, statins have become the most widely prescribed drug class: over 25% of US adults aged at least 45 years (30 million individuals) received these drugs from 2005 to 2008[5] and an estimated 56 million might be eligible for statin treatment under new guidelines.[6]

A meta-analysis of randomised controlled trials of statins recently identified a higher risk of type 2 diabetes mellitus from statin treatment compared with placebo or standard care,[7] which was dose related.[8] These findings prompted a US Food and Drug Administration Drug Safety Communication in 2012[9] and a change to statin safety labelling. Subsequently, observational studies have also reported a higher risk of type 2 diabetes with statin treatment compared with individuals not taking statins.[10–12] Although type 2 diabetes is a cardiovascular risk factor, there remains a net benefit of statin treatment for prevention of CVD[3] including among patients with diabetes.[4]

The mechanism underlying the glucose-raising effect of statins is of interest. A potential explanation in observational studies is that statin users adopt a less healthy lifestyle than individuals not taking statins, but this explanation is unlikely in masked treatment trials, which suggests that the effect is pharmacological. However, whether the glucose-raising effect of statins is explained by the same mechanisms as for LDL cholesterol lowering (ie, HMGCR inhibition) or by one of the proposed pleiotropic effects of statins[13,14] (eg, mediated through isoprenoid intermediates and G-protein signalling[15]) is uncertain.

To investigate the mechanism underlying the glucose-raising effect of statins, we used the mendelian randomisation principle,[16,17] with common variants in the gene encoding a drug target as unconfounded, unbiased proxies for pharmacological action on that target.[18] We identified single nucleotide polymorphisms (SNPs) in the *HMGCR* gene and examined their associations with bodyweight, body-mass index (BMI), waist circumference, plasma insulin and glucose, and risk of type 2 diabetes. Associations with these phenotypes would implicate a mechanism involving HMGCR inhibition. To test the correspondence of genetic and pharmacological effects, we updated a meta-analysis of the effect of statins on type 2 diabetes risk in randomised trials, and added new information on bodyweight.

Methods

Genetic studies

We selected as instruments two SNPs (rs17238484 and rs12916) in the *HMGCR* gene on the basis of genetic associations with LDL cholesterol in the Whitehall II study (n=4678)[19] using the IBC HumanCVD BeadChip (Cardiochip; Illumina, San Diego CA, USA) (appendix).[20] Both were subsequently associated with LDL cholesterol at a genome-wide level of significance,[21] with strong associations in the largest genome-wide study of lipids so far (rs17238484 p=$1·35×10^{-21}$; rs12916 p<$1·00×10^{-30}$).[22] Data were available for the greatest number of individuals for the rs17238484 SNP, and this was used for the principal analysis; a subsidiary analysis used the rs12916 SNP. To investigate potential confounding by linkage disequilibrium between our lead SNPs and others in nearby genes, we assessed the association of the *HMGCR* SNPs with hepatic genome-wide expression data (appendix). If the lead SNPs were in strong linkage disequilibrium with nearby loci, those genes might confound the noted effects of *HMGCR* genotype on measured phenotypes.[23]

In observational population studies (appendix) with genotype data for the rs17238484 SNP (or a proxy in strong linkage disequilibrium, $r^2>0·85$), we included individuals of European descent for whom data were available on one or more phenotype of interest. In a secondary analysis, we included data from a subset of studies with data available on the rs12916 SNP or a suitable proxy.

Biomarkers included in the genetic analysis were total cholesterol, LDL cholesterol, non-HDL cholesterol, bodyweight, BMI, waist and hip circumferences, waist:hip ratio, height, plasma glucose, and plasma insulin (appendix). The primary disease outcome was type 2 diabetes, including prevalent (occurring before study baseline) as well as incident cases (occurring subsequently; appendix). In the mendelian randomisation paradigm, the intervention is the naturally randomised allocation of genotype, which occurs at conception and exerts its effect from that point throughout the lifetime of the individual. Therefore, events prevalent at the time of recruitment to genetic studies are nevertheless incident from the perspective of the time of the genotypic randomisation and can be included in the genetic analysis. Thus, for the genetic analysis, both prevalent and incident cases were included to maximise power.

All studies contributing data to these analyses were approved by their local ethics committees, as described in the published findings of each study (appendix).

Meta-analysis of statin trials

We updated our two previous summary-level meta-analyses[7,8] on the association of statin treatment with incident type 2 diabetes in cardiovascular prevention trials of at least 1000 participants, followed up for at least 1 year. The appendix contains details of the exclusion criteria and trials.

Investigators from 20 eligible trials with data on incident type 2 diabetes were contacted for information on bodyweight change during follow-up by treatment allocation, which was used as a coprimary outcome. 15 trials provided data on bodyweight at baseline and at the last visit attended among individuals free from
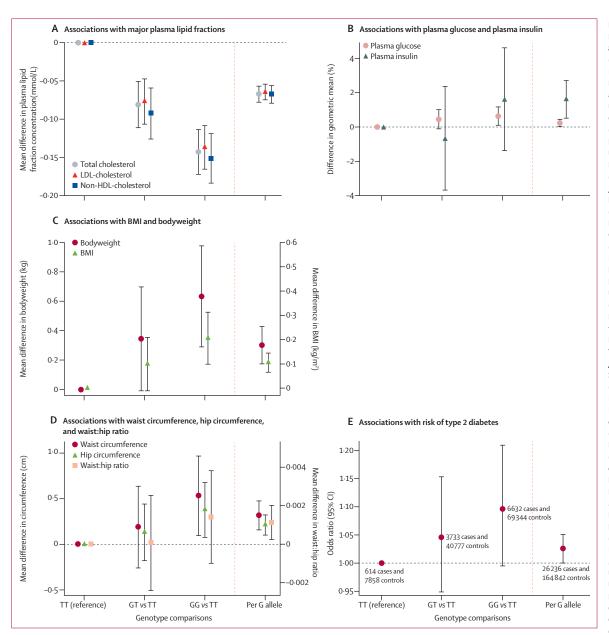
A Associations with major plasma lipid fractions

Total cholesterol
LDL-cholesterol
Non-HDL-cholesterol

B Associations with plasma glucose and plasma insulin

Plasma glucose
Plasma insulin

C Associations with BMI and bodyweight

Bodyweight
BMI

D Associations with waist circumference, hip circumference, and waist:hip ratio

Waist circumference
Hip circumference
Waist:hip ratio

E Associations with risk of type 2 diabetes

614 cases and 7858 controls

3733 cases and 40777 controls

6632 cases and 69344 controls

26236 cases and 164842 controls

Figure 1: Association of rs17238484 genotype with type-2 diabetes-related traits
Association of the rs17238484 genotype with (A) major plasma lipids fractions; (B) plasma glucose and insulin; (C) BMI and bodyweight; (D) waist and hip circumference and waist:hip ratio; and (E) risk of type 2 diabetes. Bars are 95% CIs. BMI=body-mass index.

type 2 diabetes at baseline. Two trials (ALLHAT[24] and A to Z[25]) did not measure bodyweight sequentially, and bodyweight data were unavailable from the remaining three trials (appendix). Data were also analysed separately for participants not experiencing any primary cardiovascular outcome (according to trial-specific definitions) to exclude the possibility that the effect of statin treatment on bodyweight was limited to participants experiencing cardiovascular events.

Changes in LDL cholesterol in each treatment group at 1 year were available from the Cholesterol Treatment Trialists' Collaboration meta-analysis for 18 trials,[1] whereas data for mean changes in LDL cholesterol during two trials were taken from the primary publications.[26,27] Information about plasma glucose and insulin concentrations, BMI, waist circumference, and waist:hip ratio was unavailable from the trials.

Statistical analysis
For the genetic studies, we assessed study-specific associations of rs17238484 and rs12916 with each continuous trait using univariate linear regression models.

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Plasma glucose and insulin were analysed on the natural logarithmic scale because of their skewed distributions, and we present proportional differences in geometric means per allele. The rs17238484-G allele and rs12916-T allele were each associated with lower LDL cholesterol concentration and were designated the effect alleles, to facilitate direct comparison with statin treatment.

We assessed associations of the rs17238484 and rs12916 SNPs with type 2 diabetes risk using univariate logistic regression models to estimate the odds ratio (OR) per LDL-lowering allele. We combined within-study estimates using fixed-effects and random-effects meta-analyses, with heterogeneity quantified by the I^2 statistic.[28] Heterogeneity between subgroups was assessed using meta-regression. All genetic analyses were done using a prespecified routine in Stata version 12.1, which was translated for use in SPSS, SAS, and R where necessary.

To corroborate our genetic findings, we examined the associations of the two lead SNPs in a large genome-wide association study of BMI,[29] a Metabochip analysis of plasma insulin,[30] and a genome-wide association and Metabochip analysis of type 2 diabetes.[31]

In the meta-analysis of statin trial data, we synthesised within-trial ORs for type 2 diabetes during follow-up in participants free from type 2 diabetes at baseline and within-trial mean differences in bodyweight change between treatment groups, calculated as the difference from baseline to final visit, using random-effects and fixed-effects meta-analyses. We undertook meta-regression analyses of the associations of new-onset type 2 diabetes and bodyweight change with change in LDL cholesterol at 1 year and with follow-up duration. We assessed inter-study heterogeneity using the I^2 statistic and used Stata version 10.1 for trial-related analyses.

Role of the funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit for publication. DIS, DP, ADH, and NS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 38 Cardiochip SNPs within 55 kb of the *HMGCR* gene, seven met prespecified criteria for instrument selection (appendix), of which all but the two selected, rs17238484 and rs12916, were in strong linkage disequilibrium ($r^2 > 0.9$; appendix). Gene expression data for rs17238484 were unavailable, but the T allele of rs12916 was associated with lower hepatic *HMGCR* expression (p=1.30×10^{-5}) but not with expression of adjacent genes (appendix).

Data for up to 195 444 individuals (43 studies) for the *HMGCR* rs17238484 SNP and 94 652 individuals (21 studies) for the rs12916 SNP (or suitable proxies in studies in which these were not directly measured) contributed to the analysis of genetic associations with biomarkers and outcomes. The mean age of study participants was 59 years (range 26–75; appendix).

The association of the rs17238484 genotype with circulating concentrations of major lipid fractions followed an additive model in the meta-analysis of available data (figure 1A). Each additional rs17238484-G allele was associated with 0.06 mmol/L (95% CI 0.05–0.07) lower LDL cholesterol (p=1.34×10^{-35}; 101 919 individuals, 26 studies), 0.07 mmol/L (0.06–0.08) lower total cholesterol (p=6.46×10^{-36}; 117 545 individuals, 30 studies), and 0.07 mmol/L (0.06–0.08) lower non-HDL cholesterol (p=3.32×10^{-30}; 103 375 individuals, 27 studies). The association of genotype with LDL cholesterol concentration was consistent between subgroups (data available in up to 29 studies, 116 327 individuals), with all meta-regression p values greater than 0.05 (appendix). Associations of rs12916 with plasma lipids were directionally concordant with rs17238484 and of similar magnitude (appendix).

The rs17238484-G allele was associated with 1.62% (95% CI 0.53–2.72; p=0.004) higher plasma insulin concentration (37 453 individuals, 12 studies) and with higher plasma glucose concentration (0.23%, 0.02–0.44; p=0.03; 73 490 individuals, 23 studies; figure 1B). Each rs17238484-G allele was also associated with 0.30 kg higher bodyweight (95% CI 0.18–0.43; p=3.15×10^{-6}; 143 113 individuals, 30 studies) and 0.11 kg/m² higher BMI (0.07–0.14; p=1.77×10^{-7}; 152 004 individuals, 32 studies; figure 1C), but not with height (p=0.23; 77 291 individuals, 23 studies; appendix). Each additional rs17238484-G allele was associated with greater waist circumference (0.32 cm, 95% CI 0.16–0.47; p=8.32×10^{-5}; 69 163 individuals, 19 studies), hip circumference (0.21 cm, 0.10–0.32; p=1.67×10^{-4}; 69 159 individuals, 19 studies), and waist:hip ratio (0.001, 0.0003–0.002; p=0.01; 95 496 individuals, 23 studies; figure 1D). The rs12916 SNP showed directionally concordant associations with these biomarkers (appendix). Additive association patterns were noted with all these traits, and no differences in the rs17238484 SNP effect occurred between subgroups (all meta-regression p values >0.05; appendix). The appendix shows estimates from random-effects meta-analyses.

Public domain data from a meta-analysis of genome-wide association studies of BMI[29] and an Illumina Metabochip-based[32] analysis of plasma insulin[30] revealed directionally concordant associations of the rs17238484 and rs12916 SNPs or suitable proxies with both these traits: log plasma insulin rs12916 β 0.007 (95% CI 0.002–0.012; p=4.72×10^{-3}) and rs17238484 β 0.01 (0.004–0.016; p=5.92×10^{-4}); and BMI rs17238484 p=9.28×10^{-6} and rs12916 p=1.45×10^{-4}. Associations of both SNPs with fasting insulin were attenuated to the null after adjustment for BMI in the same datasets (rs17238484 p=0.74; rs12916 p=0.63).

In 26 236 cases and 164 842 controls in 35 population studies, the *HMGCR* rs17238484-G allele, which was associated with lower LDL cholesterol and higher
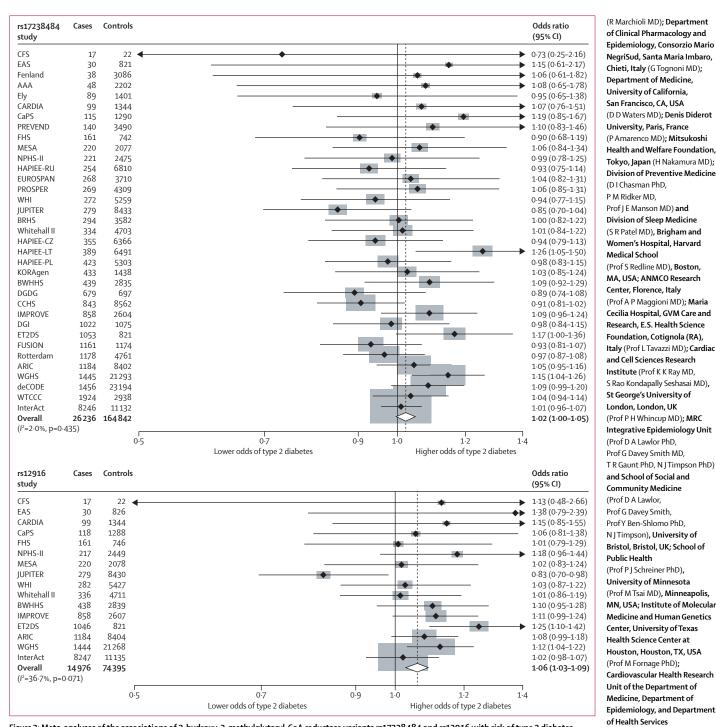
rs17238484 study	Cases	Controls	Odds ratio (95% CI)
CFS	17	22	0·73 (0·25–2·16)
EAS	30	821	1·15 (0·61–2·17)
Fenland	38	3086	1·06 (0·61–1·82)
AAA	48	2202	1·08 (0·65–1·78)
Ely	89	1401	0·95 (0·65–1·38)
CARDIA	99	1344	1·07 (0·76–1·51)
CaPS	115	1290	1·19 (0·85–1·67)
PREVEND	140	3490	1·10 (0·83–1·46)
FHS	161	742	0·90 (0·68–1·19)
MESA	220	2077	1·06 (0·84–1·34)
NPHS-II	221	2475	0·99 (0·78–1·25)
HAPIEE-RU	254	6810	0·93 (0·75–1·14)
EUROSPAN	268	3710	1·04 (0·82–1·31)
PROSPER	269	4309	1·06 (0·85–1·31)
WHI	272	5259	0·94 (0·77–1·15)
JUPITER	279	8433	0·85 (0·70–1·04)
BRHS	294	3582	1·00 (0·82–1·22)
Whitehall II	334	4703	1·01 (0·84–1·22)
HAPIEE-CZ	355	6366	0·94 (0·79–1·13)
HAPIEE-LT	389	6491	1·26 (1·05–1·50)
HAPIEE-PL	423	5303	0·98 (0·83–1·15)
KORAgen	433	1438	1·03 (0·85–1·24)
BWHHS	439	2835	1·09 (0·92–1·29)
DGDG	679	697	0·89 (0·74–1·08)
CCHS	843	8562	0·91 (0·81–1·02)
IMPROVE	858	2604	1·09 (0·96–1·24)
DGI	1022	1075	0·98 (0·84–1·15)
ET2DS	1053	821	1·17 (1·00–1·36)
FUSION	1161	1174	0·93 (0·81–1·07)
Rotterdam	1178	4761	0·97 (0·87–1·08)
ARIC	1184	8402	1·05 (0·95–1·16)
WGHS	1445	21293	1·15 (1·04–1·26)
deCODE	1456	23194	1·09 (0·99–1·20)
WTCCC	1924	2938	1·04 (0·94–1·14)
InterAct	8246	11132	1·01 (0·96–1·07)
Overall	26236	164842	1·02 (1·00–1·05)
(I²=2·0%, p=0·435)			

Lower odds of type 2 diabetes — Higher odds of type 2 diabetes
(0·5 0·7 0·9 1·0 1·2 1·4)

rs12916 study	Cases	Controls	Odds ratio (95% CI)
CFS	17	22	1·13 (0·48–2·66)
EAS	30	826	1·38 (0·79–2·39)
CARDIA	99	1344	1·15 (0·85–1·55)
CaPS	118	1288	1·06 (0·81–1·38)
FHS	161	746	1·01 (0·79–1·29)
NPHS-II	217	2449	1·18 (0·96–1·44)
MESA	220	2078	1·02 (0·83–1·24)
JUPITER	279	8430	0·83 (0·70–0·98)
WHI	282	5427	1·03 (0·87–1·22)
Whitehall II	336	4711	1·01 (0·86–1·19)
BWHHS	438	2839	1·10 (0·95–1·28)
IMPROVE	858	2607	1·11 (0·99–1·24)
ET2DS	1046	821	1·25 (1·10–1·42)
ARIC	1184	8404	1·08 (0·99–1·18)
WGHS	1444	21268	1·12 (1·04–1·22)
InterAct	8247	11135	1·02 (0·98–1·07)
Overall	14976	74395	1·06 (1·03–1·09)
(I²=36·7%, p=0·071)			

Lower odds of type 2 diabetes — Higher odds of type 2 diabetes
(0·5 0·7 0·9 1·0 1·2 1·4)

Figure 2: Meta-analyses of the associations of 3-hydroxy-3-methylglutaryl-CoA reductase variants rs17238484 and rs12916 with risk of type 2 diabetes
Data were analysed by fixed-effects meta-analysis.

bodyweight and BMI, seemed to be associated with increased risk of type 2 diabetes (OR per allele 1·02, 95% CI 1·00–1·05; p=0·09; figures 1E and 2). Data on the association between *HMGCR* rs12916 and type 2 diabetes were available for 14976 cases and 74395 controls (16 studies). The OR per rs12916-T allele was 1·06 (95% CI 1·03–1·09; p=9·58×10⁻⁵). The associations of both SNPs were confirmed when our data were combined in a meta-analysis with those from a large genome-wide association and Metabochip study of risk of type 2 diabetes (rs17238484 OR 1·03, 95% CI 1·01–1·06; rs12916 1·02, 1·00–1·04; appendix).[31]

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	Number of patients (statin vs control)	Treatment (active vs control)	Follow-up (years)	Trial population	Age (years)	Diabetes diagnostic criteria*	Weight change data available	Absolute LDL cholesterol lowering at 1 year (%)†	Number of cases of type 2 diabetes on statin (or intensive statin)	Number of cases of type 2 diabetes on control (or low-dose statin)
4S (1994)	4242 (2116 vs 2126)	S 10–40 mg vs placebo	5·2	Angina or previous MI	59	I, II, III	Yes	–1·77 (–37%)	198	193
WOSCOPS (1995)	5974 (2999 vs 2975)	P 40 mg vs placebo	4·8	Male, hypercholesterolaemia, no history of MI	55	II, III	Yes	–1·07 (–24%)	75	93
AFCAPS TexCAPS (1998)	6211 (3094 vs 3117)	L 20–40 mg vs placebo	5·2	Average cholesterol concentrations, no CVD	58	I, II, III	Yes	–0·94 (–27%)	72	74
LIPID (1998)	6997 (3496 vs 3501)	P 40 mg vs placebo	5·9‡	Hospital admission for unstable angina or previous MI	62‡	II, III	Yes	–1·03 (–25%)	126	138
GISSI-Prevenzione (2000)	3460 (1743 vs 1717)	P 20 mg vs standard care	1·9	Recent MI	59	III	Yes	–0·35 (–12%)	96	105
LIPS (2001)	1475 (724 vs 751)	F 80 mg vs placebo	3·9‡	Recent percutaneous coronary intervention	60	I	No	–0·92 (–27%)	17	14
HPS (2002)	14573 (7291 vs 7282)	S 40 mg vs placebo	5·0	CVD or diabetes	65	I, II	No	–1·29 (–29%)	335	293
PROSPER (2002)	5023 (2510 vs 2513)	P 40 mg vs placebo	3·2	Age 70–82 years with CVD or risk factors	75	II, III	Yes	–1·04 (–31%)	165	127
ALLHAT-LLT (2002)	6087 (3017 vs 3070)	P 40 mg vs no treatment	4·8	CHD or CHD risk factors	66	III	No	–0·54 (–18%)	238	212
ASCOT-LLA (2003)	7773 (3910 vs 3863)	A 10 mg vs placebo	3·3‡	Hypertension, no CHD	63	IV	Yes	–1·07 (–35%)	154	134
PROVE-IT TIMI 22 (2004)	3395 (1707 vs 1688)	A 80 mg vs P 40 mg	2·0	Recent hospital admission for ACS	58	I, II, III	Yes	–0·65 (–22%)	101	99
A to Z (2004)	3504 (1768 vs 1736)	S 40–80 mg vs Placebo –S 20 mg	2·0‡	Recent hospital admission for ACS	60	I, II	No	–0·30 (–15%)	65	47
TNT (2005)	7595 (3798 vs 3797)	A 80 mg vs A 10 mg	5·0	Stable CHD	61	I, II, III	Yes	–0·62 (–22%)	418	358
IDEAL (2005)	7461 (3737 vs 3724)	A 80 mg vs S 20–40 mg	4·8‡	Previous MI	62	I, II, III	Yes	–0·55 (–16%)	240	209
SPARCL (2006)	3803 (1905 vs 1898)	A 80 mg vs placebo	4·4	Recent stroke or transient ischaemic attack	63	I, II, III§	Yes	–1·43 (–42%)	166	115
MEGA (2006)	6086 (3013 vs 3073)	P 10–20 mg vs no treatment	5·3	Hypercholesterolaemia, no previous CHD or stroke	58	I, II, III	Yes	–0·67 (–17%)	172	164
CORONA (2007)	3534 (1771 vs 1763)	R 10 mg vs placebo	2·5	Systolic heart failure	73	I	Yes	–1·63 (–45%)	100	88
JUPITER (2008)	17802 (8901 vs 8901)	R 20 mg vs placebo	1·9‡	No CVD, no diabetes, hsCRP ≥2·0 mg/L	66‡	I, II	Yes	–1·09 (–50%)	270	216
GISSI-HF (2008)	3378 (1660 vs 1718)	R 10 mg vs placebo	3·6	Chronic heart failure	67	III	Yes	–0·92 (–35%)	225	215
SEARCH (2010)	10797 (5398 vs 5399)	S 80 mg vs S 20 mg	6·7	Previous MI	64	I	No	–0·39 (–12%)	625	587
Total	129170 (64558 vs 64612)	..	4·2 (1·6)	..	..	..	..	..	3858	3481

A=atorvastatin. CHD=coronary heart disease. CVD=cardiovascular disease. F=fluvastatin. L=lovastatin. P=pravastatin. MI=myocardial infarction. R=rosuvastatin. S=simvastatin. *Diagnostic criteria: I=adverse event report or physician report; II=glucose lowering therapy; III=raised fasting plasma glucose (≥7·0 mmol/L) on at least one occasion. †Change in lipid values at 1 year except for SPARCL (average difference during trial) and CORONA (difference at 3 months). ‡Median values. §Included criterion that diagnostic raised fasting plasma glucose must be at least 2·0 mmol/L higher than baseline glucose.

Table: Baseline data for participants without diabetes in 20 large statin trials

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Data from 129 170 participants free from type 2 diabetes at baseline were available from 20 statin trials (table). At 1-year of follow-up, mean LDL cholesterol reduction was 0·92 mmol/L (95% CI 0·18–1·67) across all 20 trials, 1·07 mmol/L (0·44–1·70) in the 15 placebo-controlled and standard care-controlled trials (96 418 individuals), and 0·50 mmol/L (0·25–0·76) in the intensive-dose versus moderate-dose trials (32 752 individuals).

Mean follow-up across all 20 trials was 4·2 years (range 1·9–6·7). Over this time, 3858 individuals allocated to statin

	Statin treatment		Control			OR (95% CI)	Weight (%)
	Case	Non-case	Case	Non-case			
Placebo-controlled or standard care-controlled							
SSSS	198	1918	193	1933		1·03 (0·84–1·27)	5·51
WOSCOPS	75	2924	93	2882		0·79 (0·58–1·08)	2·77
AFCAPS TexCAPS	72	3022	74	3043		0·98 (0·71–1·36)	2·47
LIPID	126	3370	138	3363		0·91 (0·71–1·17)	4·14
GISSI Prevenzione	96	1647	105	1612		0·89 (0·67–1·19)	3·19
LIPS	17	707	14	737		1·27 (0·62–2·59)	0·55
HPS	335	6956	293	6989		1·15 (0·98–1·35)	8·32
ALLHAT-LLT	238	2779	212	2858		1·15 (0·95–1·40)	6·27
PROSPER	165	2345	127	2386		1·32 (1·04–1·68)	4·38
ASCOT-LLA	154	3756	134	3729		1·14 (0·90–1·44)	4·46
SPARCL	166	1739	115	1783		1·48 (1·16–1·89)	4·12
MEGA	172	2841	164	2909		1·07 (0·86–1·34)	5·02
CORONA	100	1671	88	1675		1·14 (0·85–1·53)	3·01
JUPITER	270	8631	216	8685		1·26 (1·05–1·51)	6·88
GISSI-HF	225	1435	215	1503		1·10 (0·90–1·34)	5·86
Subtotal	2409	45741	2181	46087		1·11 (1·03–1·20)	66·98
(I^2=29·6%, p=0·134)							
Intensive vs moderate dose							
PROVE-IT TIMI22	101	1606	99	1589		1·01 (0·76–1·34)	3·18
A to Z	65	1703	47	1689		1·37 (0·94–2·01)	1·87
TNT	418	3380	358	3439		1·19 (1·02–1·38)	9·25
IDEAL	240	3497	209	3515		1·15 (0·95–1·40)	6·33
SEARCH	625	4773	587	4812		1·07 (0·95–1·21)	12·39
Subtotal	1449	14959	1300	15044		1·12 (1·04–1·22)	33·02
(I^2=0·0%, p=0·598)							
Overall	3858	60700	3481	61131		1·12 (1·06–1·18)	100·00
(I^2=16·2%, p=0·253)							

Lower odds of type 2 diabetes in the treatment arm — Higher odds of type 2 diabetes in the treatment arm

Figure 3: Effect of statin treatment on new-onset type 2 diabetes
Data were analysed by random-effects meta-analysis. OR=odds ratio. Case=developed type 2 diabetes. Non-case=did not develop type 2 diabetes.

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See Online for appendix

or intensive-dose statin and 3481 allocated to placebo, standard care, or moderate-dose statin were diagnosed with new-onset type 2 diabetes. The OR for new-onset type 2 diabetes with statin treatment was 1·12 (95% CI 1·06–1·18; figure 3), with little heterogeneity between trial-specific ORs (I^2 16·2%, 95% CI 0·0–50·7). The appendix provides fixed-effects meta-analysis estimates. There was no association between LDL cholesterol lowering at 1 year and within-trial ORs for new-onset type 2 diabetes (log-odds per 1% reduction in LDL cholesterol 0·004, 95% CI –0·001 to 0·009; p=0·10; appendix), or between duration of follow-up and risk of type 2 diabetes in either univariate meta-regression (log odds per year increase in trial duration –0·021, 95% CI –0·058 to 0·017; p=0·26), or after adjustment for trial type (ie, placebo-controlled and standard care-controlled or intensive vs moderate statin dose) and percent LDL cholesterol change (log odds –0·006, –0·051 to 0·039; p=0·77).

Data on the effect of statin treatment on bodyweight were available from 15 trials, including 91393 participants free from type 2 diabetes at baseline. Mean follow-up was 3·9 years (range 1·9–5·9). Recipients of statin treatment or intensive-dose statin treatment were 0·24 kg (95% CI 0·10–0·38) heavier by the end of follow-up than were control recipients in a random-effects meta-analysis (figure 4), although there was substantial heterogeneity between trials (I^2 78·6%, 95% CI 65·3–86·8). The

appendix provides fixed-effects meta-analysis estimates. When limited to individuals not experiencing a cardiovascular event, estimates were similar (0·21 kg, 95% CI 0·08–0·35; 83959 individuals). The effect on bodyweight change was noted only in trials comparing statin treatment with placebo or standard care (0·33 kg, 95% CI 0·25 to 0·42; I^2 18·6%), but not in trials comparing moderate-dose with intensive-dose statin treatment (–0·15 kg, 95% CI –0·39 to 0·08; I^2 63·2%). No association was noted between relative LDL cholesterol reduction and within-trial bodyweight change (meta-regression β 0·004, 95% CI –0·012 to 0·021; p=0·58; appendix). There was no relation between duration of follow-up and bodyweight change in either univariate meta-regression (β –0·028 kg/year, 95% CI –0·147 to 0·092; p=0·63) or multivariate meta-regression analysis (β –0·009, 95% CI –0·091 to 0·073; p=0·81) after adjustment for relative LDL cholesterol change and trial type. No relation was noted between bodyweight change and risk of new-onset type 2 diabetes across the trials (log-odds per 1 kg bodyweight increase –0·14, 95% CI –0·41 to 0·13; p=0·29).

Discussion
HMGCR genetic variants in population studies and statin treatment in trials were associated with higher bodyweight and higher risk of type 2 diabetes, suggesting that these effects are a consequence of HMGCR

	Statin treatment	Control		Change in bodyweight (kg 95% CI)	Weight (%)
Placebo-controlled or standard care-controlled					
4S	2029	2026		0·42 (0·07 to 0·77)	5·94
WOSCOPS	2999	2975		0·31 (0·06 to 0·56)	7·34
AFCAPS TextCAPS	3220	3230		0·41 (0·19 to 0·63)	7·71
LIPID	4116	4116		0·60 (0·08 to 1·12)	4·16
GISSI-Prevenzione	1743	1717		0·31 (0·04 to 0·58)	7·06
PROSPER	2459	2475		0·44 (0·17 to 0·71)	7·08
ASCOT-LLA	3752	3660		0·29 (0·05 to 0·53)	7·43
SPARCL	1970	1967		−0·10 (−0·49 to 0·29)	5·43
MEGA	2867	2974		0·18 (0·00 to 0·36)	8·27
CORONA	1771	1763		0·30 (−0·07 to 0·67)	5·68
JUPITER	7437	7331		0·40 (0·23 to 0·57)	8·35
GISSI-HF	1660	1718		0·72 (0·28 to 1·16)	4·88
Subtotal (I^2=18·6%, p=0·261)	36023	35952		0·33 (0·25 to 0·42)	79·32
Intensive vs moderate dose					
PROVE-IT TIMI 22	1649	1626		−0·13 (−0·64 to 0·38)	4·18
TNT	4209	4225		−0·03 (−0·13 to 0·07)	9·13
IDEAL	3843	3866		−0·35 (−0·59 to −0·10)	7·37
Subtotal (I^2=63·2%, p=0·066)	9701	9717		−0·15 (−0·39 to 0·08)	20·68
Overall (I^2=78·6%, p<0·0001)	45724	45669		0·24 (0·10 to 0·38)	100·00
Note: weights are from random-effects analysis					

Lower bodyweight (kg) in the treatment arm · Higher bodyweight (kg) in the treatment arm · −0·5 · 0 · 0·5 · 1

Figure 4: Effect of statin treatment on bodyweight
Data were analysed by random-effects meta-analysis. In most trials, the total number of participants without type 2 diabetes at baseline for whom bodyweight data were available was smaller than the total number for whom data were available for the analysis of new-onset type 2 diabetes.

inhibition. The association of *HMGCR* SNPs with risk of type 2 diabetes is new, as is the association of statin treatment and *HMGCR* SNPs with increased bodyweight.

Increased bodyweight plays a causal part in the development of type 2 diabetes,[33] suggesting a possible mechanism for the dysglycaemic effect of statin treatment. However, whether the relation between HMGCR inhibition and type 2 diabetes is mediated exclusively by changes in body composition remains unknown. Statin treatment led to higher bodyweight and increased risk of type 2 diabetes, and both *HMGCR* SNPs studied were associated with higher bodyweight and waist circumference, and one with higher plasma insulin and glucose concentrations. Insulin resistance might accompany bodyweight gain and a central distribution of adipose tissue. However, we were unable to identify a specific association of statin treatment with insulin resistance in these analyses because the relevant measures were unavailable from trials. One small trial[34] that was ineligible for the present study reported 2 months of atorvastatin treatment led to higher glycated haemoglobin (HbA_{1c}) and insulin concentrations and lower insulin sensitivity than with placebo, and findings from a previous meta-analysis[35] of statin trials suggested differential effects on insulin sensitivity between statins. In JUPITER[36] and PROVE-IT TIMI 22,[37] small increases in HbA$_{1c}$ were noted in individuals randomly assigned to statin treatment compared with control individuals, and in AFORRD,[38] HbA$_{1c}$ also increased slightly in patients on atorvastatin compared with placebo after 4 months. Nevertheless, the association of one *HMGCR* SNP with fasting insulin and glucose concentrations, and its attenuation to the null

after adjustment for BMI, support a bodyweight-mediated association between *HMGCR* inhibition and insulin resistance as a possible mechanistic explanation. Conversely, the magnitude of bodyweight gain we noted in both statin trials and genetic studies seems insufficient to account for the corresponding risk of type 2 diabetes. Intensive statin treatment also showed no greater effect on bodyweight than low-dose or moderate-dose treatment, although type 2 diabetes risk was greater with intensive statin treatment.

The anatomical site of the genetic and drug effects on energy metabolism that we report is not completely certain. The liver is a likely location, in view of its important involvement in lipid metabolism; however, the dysglycaemic phenotypes reported here might be caused by modulation of HMGCR function in skeletal muscle. Additional, off-target effects of statins might also make a further contribution to bodyweight gain.[39]

Inhibition of HMGCR by statins impairs hepatocyte cholesterol synthesis, upregulates hepatic LDL receptor expression, and reduces circulating LDL cholesterol concentrations. Although the genetic findings provide evidence that the effect of statins on bodyweight and type 2 diabetes risk is caused by HMGCR inhibition, whether this effect requires or is independent of reductions in circulating LDL cholesterol remains unclear. A meta-regression analysis of trial data did not provide evidence for an association between LDL cholesterol reduction and bodyweight or type 2 diabetes risk, but these analyses were done with summary-level data, which might have limited our ability to detect any such relation. Studies of genetic variants from other loci

affecting LDL cholesterol[22] or drugs lowering LDL cholesterol by other mechanisms would probably help to resolve this uncertainty.

An association with BMI has been identified for a SNP 350 kb from *HMGCR* at a genome-wide level of significance (p=2·17×10^{-13}),[29] although with no other variants within the *HMGCR* gene. In publicly available data from two genome-wide association studies,[29–30] associations of the rs17238484 and rs12916 with BMI and plasma insulin concentration were noted at strong but sub-genome-wide levels of significance. This evidence, the consistent effect of both SNPs on LDL cholesterol, and a specific association with hepatocyte HMGCR mRNA expression for one of the SNPs (rs12916; appendix) supports their validity as genetic instruments in this analysis.

We used two *HMGCR* SNPs in the genetic analysis, one for the main (rs17238484) and another (rs12916) for a subsidiary analysis. Although the findings were broadly consistent, the small differences in effect estimates between the two variants could be caused by the different allele frequencies, available sample size for each, and the association of each with a functional variant or variants that were not identified.

This study has some limitations. Not all phenotypes measured in genetic studies were available in the statin trials—notably plasma glucose and insulin, waist and hip circumference, and waist:hip ratio. Moreover, not all studies in the genetic analysis measured glucose in fasting samples. In view of the wide age range of participants included in these analyses, survival bias might have affected our findings; however, this is unlikely and any such effect, if present, would probably have been limited. The *HMGCR* variants might affect the odds of being prescribed lipid-lowering drugs and thus introduce bias to the association between *HMGCR* and risk of type 2 diabetes. However, we found no evidence of an interaction between genotype, lipid-lowering drug use at study baseline, and risk of type 2 diabetes (appendix). The source of the heterogeneity between the statin trials that provided bodyweight data, particularly for dose-comparison trials, remains uncertain. Reductions in LDL cholesterol between arms in the dose comparison trials was smaller than that achieved in the placebo-controlled trials. Our analysis was restricted to participants without type 2 diabetes at baseline. However, we did not have access to data on within-trial death, withdrawal, or loss to follow-up. Although observational pharmacoepidemiological studies have also examined the association of statin prescription with the development of type 2 diabetes, studies of this type can be prone to confounding and bias. For this reason, and to permit more direct comparison with the genetic analysis, we focused on data from randomised trials. Finally, trial analyses were done with summary-level data, which limited power for meta-regression.

Our findings pertain to the mechanism by which statins slightly increase the risk of type 2 diabetes—an association that has already been established. Findings from recent analyses of trials have shown that, although this association is robust, the absolute risk of developing type 2 diabetes is greatly offset by the benefits of statin treatment for CVD risk.[3,40] Indeed, the efficacy of statin treatment to reduce the risk of CVD has been shown conclusively in several large primary and secondary prevention randomised controlled trials, including in individuals with type 2 diabetes, with a favourable risk:benefit profile.[1,3,4] For this reason, our findings provide mechanistic insight, but should not alter present guidance on prescription of statins for prevention of CVD. Nevertheless, our results, including the new finding of increased bodyweight with statin treatment, suggest lifestyle interventions such as bodyweight optimisation, healthy diet, and adequate physical activity should be emphasised as important adjuncts to prevention of CVD with statin treatment to attenuate risks of type 2 diabetes. The reason why bodyweight change does not seem to be greater with intensive statin treatment compared with moderate-dose treatment needs further investigation.

In conclusion, both statin treatment in randomised trials and carriage of common SNPs in the *HMGCR* gene in population studies were associated with bodyweight gain and higher risk of type 2 diabetes. Bodyweight gain is physiologically linked to insulin resistance and is one of the strongest risk factors for type 2 diabetes, which might partly explain the higher risk of type 2 diabetes in statin-treated patients.

Contributors
DIS, DP, ADH, and NS conceived the project, established and coordinated the consortium of studies, designed and executed the analysis, interpreted the findings, and wrote and revised the first and subsequent drafts of the manuscript. KBK contributed to analysis design and execution. MVH and FDr contributed to data analysis, interpretation of findings, and manuscript preparation. JELE, YG, AAm, YRL, MCWS, SGB, RT-M, US, PJS, MF, AW, LAL, and HH contributed to data collection and preparation. TS and RS contributed to analysis design. SS and AT-H contributed to data collection, data analysis, interpretation of findings, and manuscript preparation. PCDJ and SJS contributed to data preparation and analysis. RAS, ML, and NV contributed to data analysis and manuscript preparation. CG contributed to data analysis, interpretation of findings, and manuscript preparation. CC and JAC contributed to data collection, preparation, and analysis. APe, NGF, NCO-M, RBS, BS, IF, and OHK contributed to data collection and preparation, and manuscript preparation. KWL, JP, and PH contributed to genotyping, data collection, and preparation. GL contributed to data collection and interpretation of findings. JG, YTvdS, APa, SM, UdF, AAl, PAD, JK, JRD, ACK, GT, DDW, PA, WMMV, SRP, TRG, and JC contributed to data collection and manuscript preparation. IT contributed to data collection and analysis, and interpretation of findings. DLvdA, RK, MBa, AT, WS, DD, PSS, NRP, HN, CD, DK, RH, BAC, MGM, and MT contributed to data collection. JAH, JWJ, GJdB, PAdJ, PHW, RWM, DAL, GDS, YB-S, DSS, MC, and MV contributed to data collection and preparation, interpretation of findings, and manuscript preparation. DB and ET contributed to data collection, preparation, and analysis, and manuscript preparation. FV, RMK, and FDu contributed to interpretation of findings. RGJW, AHM-vdZ, CBE, JGR, AMG, RM, TRP, JJVM, JDL, PMR, APM, LT, KKR, JEM, JFP, JCW, JAD, SK, and PvdH contributed to data collection, interpretation of findings, and manuscript preparation. AdB contributed to manuscript preparation. DIC contributed to data collection and preparation, data analysis, interpretation of findings, and manuscript preparation. SRKS and RCH contributed to interpretation of findings and manuscript preparation.

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