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


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 therapy. 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, 95% CI 0·18–0·43), and waist circumference (0·32 cm, 95% CI 0·16–0·47), plasma insulin concentration (1·62%, 95% CI 0·53–2·72), the rs12916 SNP had similar effects on LDL cholesterol, waist circumference (0·32 cm, 95% CI 0·16–0·47), plasma insulin concentration (1·62%, 95% CI 0·53–2·72), and 1·12, 95% CI 1·04–1·22 in intensive-dose 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.14 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 and an estimated 56 million might be eligible for statin treatment under new guidelines.3 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 20127 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 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 statins9–11 (eg, mediated through isoprenoid intermediates and G-protein signalling)3 is uncertain.

To investigate the mechanism underlying the glucose-raising effect of statins, we used the mendelian randomisation paradigm,16–17 with common variants in the gene encoding a drug target as uncon founded, 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 glucose, and plasma insulin. 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).
type 2 diabetes at baseline. Two trials (ALLHAT and A to Z) 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 Trialsists’ Collaboration meta-analysis for 18 trials, whereas data for mean changes in LDL cholesterol during two trials were taken from the primary publications. 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.
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 univariable 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. 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, a Metabochip analysis of plasma insulin, and a genome-wide association study and Metabochip analysis of type 2 diabetes.

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 Cardiочip 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 ($p=1.30 \times 10^{-5}$) 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 ($p=1.34 \times 10^{-35}$; 101 919 individuals, 26 studies), 0.07 mmol/L (0.06–0.08) lower total cholesterol ($p=0.46 \times 10^{-36}$; 117 545 individuals, 30 studies), and 0.07 mmol/L (0.06–0.08) lower non-HDL cholesterol ($p=3.32 \times 10^{-30}$; 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; $p=3.15 \times 10^{-6}$; 143 113 individuals, 30 studies) and 0.11 kg/m² higher BMI (0.07–0.14; $p=1.77 \times 10^{-7}$; 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 $0.16$–$0.47$; $p=8.32 \times 10^{-5}$; 69 163 individuals, 19 studies), hip circumference ($0.21$ cm, 0.10–0.32; $p=1.67 \times 10^{-4}$; 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 and an Illumina Metabochip-based analysis of plasma insulin revealed directionally concordant associations of the rs17238484 and rs12916 SNPs or suitable proxies with both these traits: log plasma insulin $17238484 \beta=0.007$ (95% CI $0.002$–$0.012$; $p=4.72 \times 10^{-3}$) and rs17238484 $\beta=0.01$ (0.004–0.016; $p=5.92 \times 10^{-4}$); and BMI rs17238484 $p=9.28 \times 10^{-6}$ and rs12916 $p=1.45 \times 10^{-4}$. 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
Data were analysed by fixed-effects meta-analysis.

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 HMGCRR 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=9·8×10^{-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 analysis with those from a large genome-wide association study (appendix).
### Table: Baseline data for participants without diabetes in 20 large statin trials

<table>
<thead>
<tr>
<th>Case and Control</th>
<th>Number of patients (statin vs control)</th>
<th>Treatment (active vs control)</th>
<th>Follow-up (years)</th>
<th>Trial population</th>
<th>Age (years)</th>
<th>Diabetes diagnostic criteria</th>
<th>Weight change data available</th>
<th>Absolute LDL cholesterol lowering at 1 year (%)</th>
<th>Number of cases of type 2 diabetes on statin (or intensive statin)</th>
<th>Number of cases of type 2 diabetes on control (or low-dose statin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S (1994)</td>
<td>4242 (216 vs 2126)</td>
<td>S 10–40 mg vs placebo</td>
<td>2</td>
<td>Angina or previous MI</td>
<td>59</td>
<td>I, II, III</td>
<td>Yes</td>
<td>-1·77 (-27%)</td>
<td>198</td>
<td>193</td>
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<tr>
<td>WOSCOPS (1995)</td>
<td>5974 (2999 vs 2975)</td>
<td>P 40 mg vs placebo</td>
<td>4·8</td>
<td>Male, hypercholesterolemia, no history of MI</td>
<td>55</td>
<td>II, III</td>
<td>Yes</td>
<td>-1·07 (-24%)</td>
<td>75</td>
<td>93</td>
</tr>
<tr>
<td>AFCAPS TenCAPS (1998)</td>
<td>6211 (3094 vs 3117)</td>
<td>L 20–40 mg vs placebo</td>
<td>5·2</td>
<td>Average cholesterol concentrations, no CVD</td>
<td>58</td>
<td>I, II, III</td>
<td>Yes</td>
<td>-0·94 (-27%)</td>
<td>72</td>
<td>74</td>
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<tr>
<td>LIPID (1998)</td>
<td>6997 (3496 vs 3501)</td>
<td>P 40 mg vs placebo</td>
<td>5·9†</td>
<td>Hospital admission for unstable angina or previous MI</td>
<td>62†</td>
<td>I, III</td>
<td>Yes</td>
<td>-1·03 (-24%)</td>
<td>126</td>
<td>138</td>
</tr>
<tr>
<td>GISSI-Prevenzione (2000)</td>
<td>3460 (1742 vs 1717)</td>
<td>P 20 mg vs standard care</td>
<td>1·9</td>
<td>Recent MI</td>
<td>59</td>
<td>III</td>
<td>Yes</td>
<td>-0·35 (-12%)</td>
<td>96</td>
<td>105</td>
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<tr>
<td>LIPS (2001)</td>
<td>1475 (724 vs 751)</td>
<td>F 80 mg vs placebo</td>
<td>3·9†</td>
<td>Recent percutaneous coronary intervention</td>
<td>60</td>
<td>I</td>
<td>No</td>
<td>-0·92 (-27%)</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>HPS (2002)</td>
<td>14 573 (7291 vs 7282)</td>
<td>S 40 mg vs placebo</td>
<td>5·0</td>
<td>CVD or diabetes</td>
<td>65</td>
<td>I, II</td>
<td>No</td>
<td>-1·29 (-29%)</td>
<td>335</td>
<td>293</td>
</tr>
<tr>
<td>PROSPER (2002)</td>
<td>5023 (2510 vs 2512)</td>
<td>P 40 mg vs placebo</td>
<td>3·2</td>
<td>Age 70–82 years with CVD or risk factors</td>
<td>75</td>
<td>II, III</td>
<td>Yes</td>
<td>-1·04 (-31%)</td>
<td>165</td>
<td>127</td>
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<tr>
<td>ALLHAT-LLT (2002)</td>
<td>6087 (3057 vs 3070)</td>
<td>P 40 mg vs no treatment</td>
<td>4·8</td>
<td>CHD or CHD risk factors</td>
<td>66</td>
<td>III</td>
<td>No</td>
<td>-0·54 (-18%)</td>
<td>238</td>
<td>212</td>
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<tr>
<td>ASCOT-LA (2003)</td>
<td>7773 (3910 vs 3863)</td>
<td>A 10 mg vs placebo</td>
<td>3·3†</td>
<td>Hypertension, no CHD</td>
<td>63</td>
<td>IV</td>
<td>Yes</td>
<td>-1·07 (-35%)</td>
<td>154</td>
<td>134</td>
</tr>
<tr>
<td>PROVE-IT TIMI 32 (2004)</td>
<td>3195 (1707 vs 1688)</td>
<td>A 80 mg vs placebo</td>
<td>2·0</td>
<td>Recent hospital admission for ACS</td>
<td>58</td>
<td>I, III</td>
<td>Yes</td>
<td>-0·65 (-22%)</td>
<td>101</td>
<td>99</td>
</tr>
<tr>
<td>A to Z (2004)</td>
<td>3504 (1768 vs 1736)</td>
<td>S 40–80 mg vs Placebo – S 20 mg</td>
<td>2·0†</td>
<td>Recent hospital admission for ACS</td>
<td>60</td>
<td>I, II</td>
<td>No</td>
<td>-0·30 (-35%)</td>
<td>65</td>
<td>47</td>
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<tr>
<td>TNT (2005)</td>
<td>7595 (3798 vs 3797)</td>
<td>A 80 mg vs placebo</td>
<td>5·0</td>
<td>Stable CHD</td>
<td>61</td>
<td>I, III</td>
<td>Yes</td>
<td>-0·62 (-22%)</td>
<td>418</td>
<td>358</td>
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<tr>
<td>IDEAL (2005)</td>
<td>7481 (3737 vs 3742)</td>
<td>A 80 mg vs placebo</td>
<td>4·8†</td>
<td>Previous MI</td>
<td>62</td>
<td>I, II, III</td>
<td>Yes</td>
<td>-0·55 (-16%)</td>
<td>240</td>
<td>209</td>
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<tr>
<td>SPARCL (2006)</td>
<td>2803 (1995 vs 1898)</td>
<td>A 80 mg vs placebo</td>
<td>4·4</td>
<td>Recent stroke or transient ischaemic attack</td>
<td>62</td>
<td>I, II, III§</td>
<td>Yes</td>
<td>-1·43 (-42%)</td>
<td>166</td>
<td>115</td>
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<tr>
<td>MEGA (2006)</td>
<td>6086 (3034 vs 3073)</td>
<td>P 10–20 mg vs no treatment</td>
<td>5·3</td>
<td>Hypercholesterolemia, no previous CHD or stroke</td>
<td>58</td>
<td>II, III</td>
<td>Yes</td>
<td>-0·67 (-17%)</td>
<td>172</td>
<td>164</td>
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<tr>
<td>CORONA (2007)</td>
<td>3534 (1717 vs 1763)</td>
<td>R 10 mg vs placebo</td>
<td>2·5</td>
<td>Systolic heart failure</td>
<td>73</td>
<td>I</td>
<td>Yes</td>
<td>-1·63 (-45%)</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>JUPITER (2008)</td>
<td>17 802 (8901 vs 8901)</td>
<td>R 20 mg vs placebo</td>
<td>1·9†</td>
<td>No CVD, no diabetes, hsCRP ≥ 2·0 mg/L</td>
<td>66†</td>
<td>I, II</td>
<td>Yes</td>
<td>-1·09 (-50%)</td>
<td>270</td>
<td>216</td>
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<tr>
<td>GISS-HF (2008)</td>
<td>3378 (1660 vs 1218)</td>
<td>R 10 mg vs placebo</td>
<td>3·6</td>
<td>Chronic heart failure</td>
<td>67</td>
<td>III</td>
<td>Yes</td>
<td>-0·92 (-35%)</td>
<td>225</td>
<td>215</td>
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<tr>
<td>SEARCH (2010)</td>
<td>10 797 (5298 vs 5299)</td>
<td>S 80 mg vs placebo</td>
<td>6·7</td>
<td>Previous MI</td>
<td>64</td>
<td>I</td>
<td>No</td>
<td>-0·39 (-12%)</td>
<td>625</td>
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<td>Total</td>
<td>129 170 (64 558 vs 64 612)</td>
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<td>3858</td>
<td>3481</td>
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</table>

A-atorvastatin. CHD—coronary heart disease. CVD—cardiovascular disease. F—fluvastatin. L—lovastatin. P—pravastatin. M—myocardial infarction. R—rosuvastatin. S—simvastatin. *Diagnostic criteria 1—adverse event report or physician report. 2—glucose lowering therapy. 3—raised fasting plasma glucose (≥7·0 mmol/L) on at least one occasion. 4—change in lipid values at 1 year except for SPARCL (average difference during trial) and CORONA (difference at 3 months). ¤Median values. †Excluded criterion that diagnostic raised fasting plasma glucose must be at least 2·0 mmol/L higher than baseline glucose.
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 0·95–1·22; appendix). There was no association between LDL cholesterol lowering 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 change was noted only in trials comparing moderate-dose with intensive-dose statin treatment (β –0·091 to 0·073; p=0·81) after adjustment for relative LDL cholesterol (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...
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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 trial34 that was ineligible for the present study reported 2 months of atorvastatin treatment led to higher glycated haemoglobin (HbA1c) and insulin concentrations and lower insulin sensitivity than with placebo, and findings from a previous meta-analysis35 of statin trials suggested differential sensitivities on insulin sensitivity between statins. In JUPITER7 and PROVE-IT TIMI 22,9 small increases in HbA1c were noted in individuals randomly assigned to statin treatment compared with control individuals, and in AFORRD,16 HbA1c 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.19

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 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 HMGR at a genome-wide level of significance \((p=2.17 \times 10^{11})\), although with no other variants within the HMGR gene. In publicly available data from two genome-wide association studies, 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 HMGR mRNA expression for one of the SNPs (rs12916; appendix) supports their validity as genetic instruments in this analysis.

We used two HMGR 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 HMGR variants might affect the odds of being prescribed lipid-lowering drugs and thus introduce bias to the association between HMGR 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. 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. 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 HMGR 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.
MKs, NJW, and SR contributed to data collection and preparation, and interpretation of findings. AH and EJB contributed to data collection and interpretation of findings. EMPF contributed to data collection, study design, and manuscript preparation. SEH, PTF, and MK contributed to data collection and preparation, study design, interpretation of findings, and manuscript preparation. NJT, CL, FWA, MBo, and HP contributed to data collection and preparation, data analysis, study design, interpretation of findings, and manuscript preparation. JGW, APR, and BJK contributed to data collection and preparation, coordination of consortium, study design, interpretation of findings, and manuscript preparation.

Declaration of interests

JW has received research grants from and was speaker at CME-accredited meetings sponsored by Astellas, Anthera, AstraZeneca, Bayer, Biotronik, Boston Scientific, Correvio, Daiichi Sankyo, Lilly, Genzyme, Medtronic, Merck-Schering-Plough, Pfizer, Orbis Neich, Novartis, Roche, Servier, Sanofi, Aventis, the Netherlands Heart Foundation, the Intermountain Cardiology Institute of the Netherlands, and the European Community Framework KP7 Programme. JGR’s institution has received grants for her work from Amgen, Daiichi Sankyo, Esperion, GlaxoSmithKline, Merck, Genentech/Hoffmann-La Roche, and Zinfindel/Takeda. AMG has received funds for board membership of Aegerion, Arisaph, DuPont, VascoVis, and Vatera; consultancy for Janssens, Kowa, Merck, and Roche; and manuscript preparation for AstraZeneca. ACK has received funds in the form of grants to his institution, consultancy fees, and travel support from Bristol-Myers Squibb; consultancy fees from AstraZeneca, Merck, Novartis, and Pfizer; grants paid to his institution from AstraZeneca, Merck, Novartis, and Pfizer; and fees for speaking engagements from AstraZeneca, Merck, Novartis, and Pfizer. RM has received funds for speaking engagements from Ferrer, Pronova BioPharma, Sigma-Tau, and Societa Prodotti Antibiotica; his institution has received funds from Sigma-Tau, Societa Prodotti Antibiotica, GlaxoSmithKline, Novartis, Amgen, Pronova BioPharma, and General Electric. PAS has received consultancy fees from Pfizer and Servier, fees for speaking engagements from Pfizer and Servier, and fees for development of educational presentations from Pfizer; his institution has received funds for his work from Pfizer and Servier.

NRP has received fees for speaking engagements from Pfizer and fees for production of books from Servier; his institution has received grants from Pfizer and the Hypertension Trust. DDW has received consultancy fees from Merck-Schering Plough and Pfizer, and fees for speaking engagements from Pfizer. TRP has received consultancy fees, grants, and fees for speaking engagements from Merck; and fees for speaking engagements from AstraZeneca, Roche, and Amgen. PA has received funds for board membership, consultancy, grants, speaking engagements, and the development of educational presentations from Pfizer. JVJM has received reimbursement for travel from AstraZeneca, and his institution has received funds from AstraZeneca. LT’s institution has received funds for his work from the ANMCO Foundation. KKR has received fees for advisory board membership from Pfizer; for involvement in trial management and advisory boards from Roche; for speaking engagements and advisory board membership from MSD; for speaking engagements, advisory board membership, and trial involvement from Sanofi; for advisory board membership from Aegerion, Regeneron, and Abbott; for speaking engagements from Menarini, Novo Nordisk, and theHeart.org; for trial involvement and steering committee membership from GlaxoSmithKline; and for advisory board membership from Novartis. JEM is a co-inventor on a patent held by the Brigham and Women’s Hospital that relates to inflammatory biomarkers in diabetes prediction. JCW is an employee of and holds stock in GlaxoSmithKline. RMK has received funds for advisory board membership from Merck, consultancy fees from Celera and Genentech, and grants from Quest Diagnostics, and his institution receives funds resulting from a patent related to diagnostic use of a HMGCGR spliced isoform. RCH has received funds for board membership of Liposcience, for speaking engagements for Denka Seiken, and in the form of grants to his institution from Merck/Schering-Plough, Diadeexus, and Denka Seiken. All other authors declare no competing interests.

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References


