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


Summary

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 a 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 (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-T allele association was consistent with bodyweight, and waist circumference. The rs17238484-G allele seemed to be associated with higher risk of prevalent and incident 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). The increased risk of type 2 diabetes noted with statins is at least partially explained by HMGCR inhibition.

Interpretation

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

Funding

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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 20088 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 20129 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.10,11 Although type 2 diabetes is a cardiovascular risk factor, there remains a net benefit of statin treatment for prevention of CVD1 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 statins13,14 (eg, mediated through isoprenoid intermediates and G-protein signalling) is uncertain.

To investigate the mechanism underlying the glucose-raising effect of statins, we used the mendelian randomisation principle,15,16 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 on the basis of genetic association with bodyweight, body-mass index (BMI), waist circumference, HOMA-R (homeostasis model assessment of insulin resistance), 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)8 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=1·00×10–39).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.13

Introduction

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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 statins13,14 (eg, mediated through isoprenoid intermediates and G-protein signalling) is uncertain.

To investigate the mechanism underlying the glucose-raising effect of statins, we used the mendelian randomisation principle,15,16 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 on the basis of genetic association with bodyweight, body-mass index (BMI), waist circumference, 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-analyses23 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...
type 2 diabetes at baseline. Two trials (ALLHAT\(^{24}\) and A to Z\(^{26}\)) 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

Triallists’ Collaboration meta-analysis for 18 trials,\(^{26-28}\) 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.
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 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 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, rs1723848 and rs12916, were in strong linkage disequilibrium ($r^2$<0.9; appendix). Genotype expression data for rs1723848 and rs12916 SNPs or suitable proxies 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. 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 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 heterogeneity using the $I^2$ statistic and used Stata version 10.1 for trial-related 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 rs1723848 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 rs1723848 $β$ 0.01 (0.004–0.016; p=5.92 × 10–³); and BMI rs1723848 $β$ 0.23% (0.02–0.44; p=0.004) and rs12916 $β$ 0.11 kg/m² higher (95% CI 0.08–0.14; p=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 rs1723848 SNP effect occurred between subgroups (all meta-regression p values >0.05; appendix). The appendix shows estimates from random-effects meta-analyses.
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 14 976 cases and 74 395 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 study and a Metabochip study of risk of type 2 diabetes (results not shown) (95% CI). The associations of both SNPs were confirmed when our data were combined in a meta-analysis with those from a large genome-wide association study and a Metabochip study of risk of type 2 diabetes (results not shown) (95% CI). The associations of both SNPs were confirmed when our data were combined in a meta-analysis with those from a large genome-wide association study and a Metabochip study of risk of type 2 diabetes (results not shown) (95% CI). The associations of both SNPs were confirmed when our data were combined in a meta-analysis with those from a large genome-wide association study and a Metabochip study of risk of type 2 diabetes (results not shown) (95% CI).
Baseline data for participants without diabetes in 20 large statin trials

<table>
<thead>
<tr>
<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>
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</thead>
<tbody>
<tr>
<td>4S (1994)</td>
<td>5.2</td>
<td>4S 10–40 mg vs placebo</td>
<td>59</td>
<td>I, II, III</td>
<td>Yes</td>
<td>-1.77 (-37%)</td>
<td>198</td>
<td>193</td>
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<tr>
<td>WOSCOPS (1995)</td>
<td>4.8</td>
<td>P 40 mg vs placebo</td>
<td>55</td>
<td>II, III</td>
<td>Yes</td>
<td>-1.07 (-24%)</td>
<td>75</td>
<td>93</td>
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<tr>
<td>AFCAPS TenCAPS (1998)</td>
<td>5.2</td>
<td>L 20–40 mg vs placebo</td>
<td>58</td>
<td>I, II, III</td>
<td>Yes</td>
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<td>72</td>
<td>74</td>
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<td>LIPID (1998)</td>
<td>5.9</td>
<td>P 40 mg vs placebo</td>
<td>62‡</td>
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<td>Yes</td>
<td>-0.03 (-45%)</td>
<td>126</td>
<td>138</td>
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<td>GISSI-Prevenzione (2000)</td>
<td>1.9</td>
<td>P 20 mg vs standard care</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>3.9</td>
<td>F 80 mg vs placebo</td>
<td>60</td>
<td>I</td>
<td>No</td>
<td>-0.92 (-27%)</td>
<td>17</td>
<td>14</td>
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<tr>
<td>HPS (2002)</td>
<td>5.0</td>
<td>S 40 mg vs placebo</td>
<td>65</td>
<td>I, II</td>
<td>No</td>
<td>-1.29 (-29%)</td>
<td>335</td>
<td>293</td>
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<tr>
<td>PROSPER (2002)</td>
<td>3.2</td>
<td>P 40 mg vs placebo</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-LTT (2002)</td>
<td>4.8</td>
<td>P 40 mg vs no treatment</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>3.3</td>
<td>A 10 mg vs placebo</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 22 (2004)</td>
<td>2.0</td>
<td>A 80 mg vs placebo</td>
<td>58</td>
<td>I, II, III</td>
<td>Yes</td>
<td>-0.65 (-22%)</td>
<td>101</td>
<td>99</td>
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<tr>
<td>A to Z (2004)</td>
<td>2.0</td>
<td>S 40–80 mg vs Placebo-S 20 mg &amp; Placebo</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>5.0</td>
<td>A 80 mg vs placebo</td>
<td>61</td>
<td>I, II, 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>4.8</td>
<td>A 80 mg vs placebo</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>4.4</td>
<td>A 80 mg vs Placebo-S 20 mg &amp; Placebo</td>
<td>63</td>
<td>I, II, III§</td>
<td>Yes</td>
<td>-1.04 (-42%)</td>
<td>166</td>
<td>115</td>
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<tr>
<td>MEGA (2006)</td>
<td>5.3</td>
<td>P 10–20 mg vs no treatment</td>
<td>58</td>
<td>I, II, III§</td>
<td>Yes</td>
<td>-0.67 (-17%)</td>
<td>172</td>
<td>164</td>
</tr>
<tr>
<td>CORONA (2007)</td>
<td>2.5</td>
<td>R 10 mg vs placebo</td>
<td>73</td>
<td>I</td>
<td>Yes</td>
<td>-1.63 (-45%)</td>
<td>100</td>
<td>88</td>
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<tr>
<td>JUPITER (2008)</td>
<td>2.0</td>
<td>R 20 mg vs placebo</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>3.6</td>
<td>R 10 mg vs placebo</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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<td>SEARCH (2010)</td>
<td>6.7</td>
<td>S 80 mg vs Placebo-S 20 mg &amp; Placebo</td>
<td>64</td>
<td>I</td>
<td>No</td>
<td>-0.39 (-12%)</td>
<td>625</td>
<td>587</td>
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<tr>
<td>Total</td>
<td>4.2</td>
<td>129 170</td>
<td>3858</td>
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</tbody>
</table>

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

Cardiology Division, Massachusetts General Hospital, Boston, MA, USA (S Kathiresan MD); Program in Medical and Population Genetics, Broad Institute, 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...
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 0.95–1.34; 83 959 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; I² 18.6%), but not in trials comparing moderate-dose with intensive-dose statin treatment (0.32 kg, 95% CI 0.17 to 0.47; I² 63.2%). No association was noted between relative 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 91 393 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 (I² 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; 83 959 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; I² 63.2%), but not in trials comparing moderate-dose with intensive-dose statin treatment (0.32 kg, 95% CI 0.17 to 0.47; I² 63.2%). No association was noted between relative LDL cholesterol reduction and within-trial bodyweight change (meta-regression β 0.004, 95% CI 0.002 to 0.007; p=0.001; appendix). There was no relation between relative LDL cholesterol change and risk of new-onset type 2 diabetes after adjustment for relative LDL cholesterol change and trial type (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
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, 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 that was ineligible for the present study reported 2 months of atorvastatin treatment led to higher glycated haemoglobin (HbA1c) and lower insulin sensitivity than placebo, and findings from a previous meta-analysis of statin trials suggested differential effects on insulin sensitivity between statins. In JUPITER and PROVE-IT TIMI 22, small increases in HbA1c were noted in individuals randomly assigned to statin treatment compared with control individuals, and in AFORRDMa 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.

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

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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.

<table>
<thead>
<tr>
<th>Statin treatment</th>
<th>Control</th>
<th>Change in bodyweight (kg 95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo-controlled or standard care-controlled</td>
<td>2029</td>
<td>2026</td>
<td>0·42 (0·07 to 0·77)</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>2999</td>
<td>2975</td>
<td>0·31 (0·05 to 0·56)</td>
</tr>
<tr>
<td>AFCAPS TextCAPS</td>
<td>3220</td>
<td>3230</td>
<td>0·41 (0·19 to 0·63)</td>
</tr>
<tr>
<td>LIPID</td>
<td>4116</td>
<td>4116</td>
<td>0·60 (0·08 to 1·12)</td>
</tr>
<tr>
<td>GISSI-Prevenzione</td>
<td>1743</td>
<td>1717</td>
<td>0·31 (0·04 to 0·58)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>2459</td>
<td>2475</td>
<td>0·44 (0·17 to 0·71)</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>3752</td>
<td>3660</td>
<td>0·29 (0·05 to 0·53)</td>
</tr>
<tr>
<td>SPARCL</td>
<td>1970</td>
<td>1967</td>
<td>0·10 (0·04 to 0·23)</td>
</tr>
<tr>
<td>MEGA</td>
<td>2867</td>
<td>2914</td>
<td>-0·13 (0·64 to 0·38)</td>
</tr>
<tr>
<td>CORONA</td>
<td>3771</td>
<td>3763</td>
<td>-0·03 (0·13 to 0·07)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>7427</td>
<td>7331</td>
<td>0·35 (0·59 to 0·10)</td>
</tr>
<tr>
<td>GISSI-HF</td>
<td>1660</td>
<td>1718</td>
<td>-0·15 (0·39 to 0·08)</td>
</tr>
<tr>
<td>Subtotal (P=0·18 6%, p=0·261)</td>
<td>36023</td>
<td>35952</td>
<td>-0·33 (0·25 to 0·42)</td>
</tr>
</tbody>
</table>

Intensive vs moderate dose

<table>
<thead>
<tr>
<th>Trial</th>
<th>Change in bodyweight (kg 95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>-0·13 (0·64 to 0·38)</td>
<td>4·18</td>
</tr>
<tr>
<td>TNT</td>
<td>-0·03 (0·13 to 0·07)</td>
<td>9·13</td>
</tr>
<tr>
<td>IDEAL</td>
<td>-0·35 (0·59 to 0·10)</td>
<td>7·37</td>
</tr>
<tr>
<td>Subtotal (P=0·06 2%, p=0·0001)</td>
<td>-0·15 (0·39 to 0·08)</td>
<td>20·68</td>
</tr>
</tbody>
</table>

Overall (P=0·78 6%, p=0·0001) 45724 | 45669 | 0·24 (0·10 to 0·38) | 100·00 |

Note: weights are from random-effects analysis.
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.\(^\text{1,4}\) 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.\(^\text{1,4}\) 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 \textit{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 FD contributed to data analysis, interpretation of findings, and manuscript preparation. PCDJ and SJS contributed to data analysis 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. DLvdA, RK, MBa, AT, WS, DD, PSS, NRP, HN, and MV contributed to data analysis and manuscript preparation. KWL, JP, and PH contributed to genotyping, data collection, and preparation. GL contributed to data collection and interpretation of findings. DD, RAS, AMG, RM, TRP, JJVM, DL, PMR, AP, ICW, JCW, JAD, SK, and PvdH contributed to data collection and analysis, interpretation of findings, and manuscript preparation. KBK contributed to analysis design and execution. MVH and FD 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. 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 FD contributed to data analysis, interpretation of findings, and manuscript preparation. PCDJ and SJS contributed to data analysis 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. DLvdA, RK, MBa, AT, WS, DD, PSS, NRP, HN, and MV contributed to data analysis and manuscript preparation. KWL, JP, and PH contributed to genotyping, data collection, and preparation. GL contributed to data collection and interpretation of findings. DD, RAS, AMG, RM, TRP, JJVM, DL, PMR, AP, ICW, JCW, JAD, SK, and PvdH contributed to data collection and analysis, interpretation of findings, and manuscript preparation. KBK contributed to analysis design and execution. MVH and FD 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.
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. EBP contributed to data collection, study design, and manuscript preparation. SEH, PJT, and MK contributed to data collection and preparation, study design, interpretation of findings, and manuscript preparation. NJT, CL, FWA, MB, and HP contributed to data collection and preparation, data analysis, study design, interpretation of findings, and manuscript preparation. JGW, APR, and BJ 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, Orbus Neich, Novartis, Roche, Servier, Sanofi; Aventis, the Netherlands Heart Foundation, the Interuniversity Cardiology Institute of the Netherlands, and the European Community Framework FP7 Programme. JGR’s institution has received grants for her work from Amgen, Daiichi Sankyo, Esperion, GlaxoSmithKline, Merck, Genentech/Hoffmann-La Roche, and Zinfadel/Takeda. AMG has received funds for board membership of Aegerion, Ariasph, DuPont, VascoVis, and Vatera; consultation for Janssen, 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 Società Prodotti Antibiotici; his institution has received funds from Sigma-Tau, Società Prodotti Antibiotici, 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. JIVM 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 Aegeron, 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 HMGCR spliced isoform. RCH has received funds for board membership of Liposcience, for speaking engagements for Denka Seien, and in the form of grants to his institution from Merck/Schering-Plough, Diadexus, and Denka Seien. All other authors declare no competing interests.

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References


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