

Exploring repositioning opportunities and side-effects of statins: a Mendelian randomization study of HMG-CoA reductase inhibition with 55 complex traits

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Abstract

Statin is one of the most commonly prescribed medications worldwide. Besides reduction of cardiovascular risks, statins have been proposed for the prevention or treatment of other disorders, but results from clinical studies are mixed. There are also controversies concerning the adverse effects caused by statins.

In this study we employed a Mendelian randomization (MR) approach across a wide range of complex traits to explore repositioning opportunities and side-effects of statins. MR is analogous to a “naturalistic” randomized controlled trial (RCT), which is much less susceptible to confounding and reverse causation as compared to observational studies.

We employed two genetic instruments (rs12916 and rs17238484) in the *HMGCR* gene which have been shown to provide reliable estimates of the risk of statins on type 2 diabetes and weight gain. We observed in the joint-SNP analysis that low density lipoprotein cholesterol (LDL-C) reduction from HMG-CoA reductase inhibition results in increased depressive symptoms ($p = 0.002$, q -value = 0.094). This finding appeared to be supported by nominally significant results of raised major depression risk in single-SNP MR analysis of rs17238484, and analyses using LDL-C as the exposure. Several other outcomes also reached nominal significance ($p < 0.05$) in single- or joint-SNP analyses; for example, we observed causal associations of LDL-C lowering from HMG-CoA reductase inhibition with *reduced* risks of schizophrenia, anorexia nervosa, Alzheimer disease, Parkinson disease, as well as increased forearm bone mineral density and sleep duration (highest q -value = 0.289). These findings were at least partially supported by previous clinical studies. We also identified polygenic associations of low LDL-C (from all or only *HMGCR* lead variants) with extreme parental longevity. We did not observe associations with cognitive test profiles, renal outcomes, autoimmune diseases or cancers. While MR has its limitations and our findings remain to be confirmed in further studies, this work demonstrates the potential of a phenome-wide approach to reveal novel therapeutic indications and unknown drug side-effects.

INTRODUCTION

With the rising cardiovascular disease burden over the world, statins have become one of the most commonly prescribed classes of medications. For example, it was estimated that in the US over 25% (30 millions) of people were taking statins from 2005 to 2008¹. Statins act on the 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase to reduce cholesterol synthesis, and there exist strong evidence that statins reduce cardiovascular risks²⁻⁴. Statins however are associated with side-effects such as myopathy, raised liver enzymes and increased risk of type 2 diabetes and probably hemorrhagic strokes⁵. There are also reports of statins being associated with other adverse effects, such as muscle-related symptoms other than myopathy⁶, cognitive decline⁷⁻⁹, mood changes or aggression^{10,11} and cataracts¹², but there is yet no conclusive evidence. On the other hand, statins have also been proposed as a treatment for other non-cardiovascular traits, for example in cancers¹³, neurological diseases¹⁴, infectious diseases¹⁵ and psychiatric disorders¹⁴. Since statins are very widely prescribed, understanding its side-effects as well as non-cardiovascular benefits and the corresponding mechanisms is of great public health importance. Also given the escalating cost in new drug development, repositioning of a relatively cheap medication like statin represents a cost-effective way of finding novel therapeutics.

Recently a few studies have been using a new approach known as Mendelian randomization (MR)¹⁶ to explore the efficacy or side-effects of medications^{1,17-21}. The principle is that genetic variants in the gene encoding the drug target act as “instruments” to reflect the actual drug action. A person having the lipid-lowering allele (or allelic score) at the relevant locus is analogous to receiving a lipid-lowering drug, and vice versa. The random allocation of alleles at conception is analogous to randomization in clinical trials. MR, when compared to conventional clinical studies, are much less susceptible to confounding bias and problems of reversed causality²². By studying genetic variations at the drug target, we may also infer whether the effects or side-effects are at least partially due to “on-target” mechanisms. MR therefore represents a promising approach to explore new indications and unintended adverse effects of drugs, as reported in a few recent studies. For example, Swerdlow et al. examined common variants in the *HMGCR* gene and found that the low density lipoprotein cholesterol (LDL-C) lowering allele is associated with higher body weight, waist circumference, insulin and glucose levels, as well as heightened type 2 diabetes risk. Remarkably, the results from this MR analysis are highly concordant with a meta-analysis of randomized controlled trial (RCT) of 129710 individuals¹. This study also demonstrated that raised diabetic risk is at last partially attributed to “on-target” effects of statins¹. Adopting a similar approach, Lotta et al. showed that SNPs in the *NPC1L1* and *HMGCR* genes (proxy for actions of ezetimibe and statins respectively) are both associated with elevated diabetic risks²¹. Another two MR studies on PCSK9 inhibition demonstrated similar findings of raised diabetic risks^{18,19}.

The MR approach can be extended to screen for associations of a larger variety of outcomes, also

referred to as a “phenome-wide” scan. For instance, Millard et al. reported a phenome-wide MR study on BMI with 172 phenotypic outcomes, and found associations with cardiometabolic traits as well as novel associations with global self-worth score²³. Another recent study investigated the effect of a loss-of-function variant in *PLA2G7* encoding lipoprotein-associated phospholipase A2 (Lp-PLA2), a drug target for atherosclerosis-related diseases, across 41 different non-vascular outcomes in the China Kadoorie Biobank²⁴. Overall no significant associations were found, implying a lack of major side-effects but also limited potential for repurposing²⁴. A recent commentary nicely summarizes the potential of using MR and a “phenome-wide” approach to facilitate drug discovery and reveal unknown drug side-effects²⁵.

In this study, we employ the principle of Mendelian randomization to explore repositioning opportunities and adverse effects of statins. Using variants of the *HMGCR* gene as instruments, we study the associations with up to 55 somatic and psychiatric traits, mainly on non-cardiovascular outcomes.

METHODS

Genetic instruments for effects of statins

We followed a previous landmark MR study which investigated the effects of HMG-CoA reductase inhibition on body-weight and type 2 diabetes risks¹. We used two SNPs (rs17238484 and rs12916) in the *HMGCR* gene as instruments that have been shown to provide reliable estimates of the risk of statins on type 2 diabetes and weight gain. The variant rs17238484 was used for the main analysis in Swerdlow et al., and the LDL-lowering G allele was associated with higher waist circumference, weight, insulin and glucose concentrations and type 2 diabetes risk¹. The effects were consistent with (and of comparable magnitude to) meta-analysis of RCTs covering 129170 participants. The other SNP allele rs12916-T had similar effects in general. As reported by Swerdlow et al., rs12916-T is also associated with significantly lower expression of *HMGCR* in the liver ($p = 1.3e-5$) but has no associations with expressions of neighboring genes¹. It was shown that this SNP likely drives the shared association between expression QTL and LDL-C levels¹. In addition, the two SNPs achieved genome-wide significance ($p < 5e-8$) in the Global Lipid Genetics Consortium (GLGC) meta-analysis²⁶ (Table 1). The effect sizes and standard errors of rs17238484 and rs12916 were extracted from meta-analysis results of the GLGC MetaboChip studies. Note that the original GLGC study use inverse normal transformed trait values as the outcome variable, hence the coefficient estimate (approximately) corresponds to one SD change (~ 38.7 mg/dl or ~ 1 mmol/L) of LDL-C level per unit change in allelic count.

As the functional significance of *HMGCR* variants has not been fully elucidated (such that we do not know exactly which SNP or SNP combinations may represent the best proxy for statin action), we performed both single-SNP analyses (as in Swerdlow et al.¹) and a combined analysis of both

SNPs. Since linkage disequilibrium (LD) between the two SNPs may lead to over-precise estimates²⁷, we computed LD from the 1000 genome phase 3 data and performed a multivariable regression of the two genetic variants from summary statistics, using the “COJO-joint” approach²⁸ implemented in GCTA²⁹. The adjusted effect size estimates were used for the joint SNP analysis, while the unadjusted estimates were used for individual SNP analyses.

We also checked that neither SNPs have any significant genetic associations in the GWAS catalog (<https://www.ebi.ac.uk/gwas/>), with the exception of LDL-C or total cholesterol. The results are hence unlikely to be affected by association of genetic instruments with potential confounders.

Outcome data

We made use of the MR-base platform and R package which collects GWAS summary statistics from mostly publicly available sources³⁰. A small percentage of the data available at MR-base were not openly available but obtained through communication with individual investigators. We performed analyses on several categories of complex traits or diseases as follows:

- (1) Psychiatric disorders or traits including anorexia nervosa, autism, bipolar disorder, bulimia nervosa, depressive symptoms, major depressive disorder, schizophrenia and sleep duration;
- (2) Neurological disorders including Alzheimer’s disease, amyotrophic lateral sclerosis and Parkinson’s disease;
- (3) Renal traits or disorders including chronic kidney disease, microalbuminuria, IgA nephropathy; eGFR (creatinine) and urinary albumin to creatinine ratio (UACR) within diabetic subjects and within non-diabetic subjects;
- (4) Cancers including melanoma, pancreatic cancer, neuroblastoma, lung adenocarcinoma, squamous cell lung cell and lung cancer (irrespective of subtypes);
- (5) Autoimmune or inflammatory conditions including celiac disease, asthma, eczema, gout, Crohn’s disease, ulcerative colitis, inflammatory bowel disease (combined), multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus;
- (6) Bone mineral density (BMD) measures including femoral neck, forearm and lumbar spine BMDs;
- (7) Hematological traits including haemoglobin (Hb) concentration, mean cell Hb, mean cell Hb concentration, mean cell volume, packed cell volume, red blood cell count, platelet count and mean platelet volume;
- (8) Neurocognitive test profiles including 2-choice, 4-choice and 8-choice reaction times, digit symbol, G speed factor, inspection time, simple reaction time and symbol search. This category is included due to previous reports of possible links between statin use and cognitive deficits (e.g. ref. ^{8,9});
- (9) Aging and longevity related traits including age of parents’ death and top 1% survival in parents, which serve a proxy measure of longevity in the individual. The original study by Pilling et al.³¹

explains the advantages of such an approach instead of recruiting very old cases and younger controls. An exact causal inference was not attempted here but the genetic variants or genetic score of the offspring can be regarded to reflect the genetically determined LDL-C-level (due to HMG-CoA reductase inhibition) of the parents. We aimed to test for a genetic (or polygenic) association with longevity similar to Marioni et al.³². The effect size estimate is likely to be biased downwards as we are over-estimating the correlation between the genetic instruments and the risk factor (the denominator of an MR estimate).

A full list of references is included in supplementary information.

Statistical analysis

Mendelian randomization was performed with the Wald ratio test for individual SNP analyses and the inverse variance weighted (IVW) approach for analyses involving >1 SNP, which are default methods employed in MR-base³⁰. If a SNP was not available in the outcome GWAS, we allowed using a “proxy SNP” provided the r-squared was at least 0.8 with the requested SNP. As different statistical approaches may lead to different results, we also assessed the results of fixed effects meta-analysis (standard error calculated by the delta method) and maximum likelihood estimation for outcomes with at least one nominally significant ($p \leq 0.05$) result in either individual or combined SNP analyses³³.

For a significant association of statins with a measured outcome, the association can be due to a general effect on LDL-C lowering, or more specifically due to HMG-CoA reductase inhibition. We therefore also examined the causal effects of LDL-C levels on outcomes with at least one nominally significant result in our analyses. Genetic instruments for LDL-C were chosen according to the GLGC GWAS meta-analysis results²⁶. The genetic variants were LD-clumped in PLINK 1.9 with r-squared < 0.05 within 10Mb region. The weighted median³⁴ and MR-Egger³⁵ approaches were used to assess and correct for possible (unbalanced) horizontal pleiotropic effects for MR analyses on LDL-C.

Multiple testing was corrected by the false discovery rate (FDR) approach with the Benjamini-Hochberg method³⁶, which controls the expected proportion of false discoveries. The corresponding q -values³⁷ were presented.

RESULTS

The effect size estimates of the SNPs rs17238484 and rs12916 from GLGC and COJO-joint analysis are listed in Table 1. The alleles associated with *lower* LDL-C levels are designated as the effect alleles. Note that the coefficient estimates refer to the effect of LDL-C *lowering* due to HMG-CoA reductase inhibition. The estimated R-squared between the 2 SNPs is 0.452 from 1000 Genome phase 3 data (all Caucasians).

Combined analysis of rs17238484 and rs12916

For the combined analysis of rs17238484 and rs12916, three outcomes showed nominal significance ($p < 0.05$), including depressive symptoms (beta = 0.151, 95% CI = 0.055 to 0.246, $p = 0.0020$, $q = 0.094$), mean platelet count (beta = -14.32, 95% CI = -0.768 to -27.9, $p = 0.0384$, $q = 0.595$) and top 1% survival (beta = 0.031, OR = 1.03, 95% CI = 1.003 to 1.060, $p = 0.03$, $q = 0.595$) (Table 2). In practical terms, the results meant that for one SD (~ 38.7 mg/dl or ~ 1 mmol/L) decrease in LDL-C genetically due to HMG-CoA reductase inhibition, it would lead to 0.151 SD increase in depressive symptoms and decrease of platelet level by $14.32 \times 10^9/L$; it is also associated with top 1% survival (parental survival as proxy) with an odds ratio (OR) of 1.03 (an exact causal inference is not applicable as parental phenotype was used).

Of note, for anorexia nervosa, although the IVW estimate was not significant, the maximum likelihood (ML) approach (beta = -1.251, SE = 0.548, $p = 0.0223$, corresponding $q = 0.447$) and fixed effects meta-analysis (beta = -1.082, SE = 0.535, $p = 0.0432$, corresponding $q = 0.505$) both yielded nominally significant results. For other traits different approaches yield similar results.

Single-SNP analyses

For single-SNP analysis of rs17238484 (Table 3), a number of outcomes showed nominal significance, including anorexia nervosa (beta = -1.46, OR = 0.231, 95% CI = 0.068 to 0.786, $p = 0.019$), major depressive disorder (beta = 0.863, OR = 2.37, 95% CI = 1.06 to 5.34, $p = 0.037$), schizophrenia (beta = -0.496, OR = 0.609, 95% CI = 0.413 to 0.897, $p = 0.012$), sleep duration (beta = 0.186, 95% CI = 0.0378 to 0.334, $p = 0.014$), Alzheimer disease (beta = -0.797, OR = 0.450, 95% CI = 0.253 to 0.801, $p = 6.58e-3$), Parkinson disease (beta = -1.779, OR = 0.169, 95% CI = 0.035 to 0.803, $p = 0.025$), celiac disease (beta = 1.13, OR = 3.10, 95% CI = 1.04 to 9.18, $p = 0.042$) and forearm bone mineral density (beta = 0.719, 95% CI = 0.125 to 1.31, $p = 0.018$). The corresponding q -values ranged from 0.209 to 0.289. The results suggest possible beneficial effects of genetically lower LDL-C from HMG-CoA reductase inhibition on most aforementioned diseases, except for major depression and celiac disease.

Single-SNP analysis of rs12916 yielded three results with unadjusted $p < 0.05$ (Table 4), including depressive symptoms (beta = 0.129, 95% CI = 0.045 to 0.214, $p = 2.70e-3$), platelet count (beta = -12.6, 95% CI = 0.458 to 24.7, $p = 0.042$) and top 1% survival (parental survival as proxy) (beta = 0.025, OR = 1.025, 95% CI = 1.00 to 1.05, $p = 0.048$). Of note, there was a trend towards significance for anorexia nervosa ($p = 0.063$), which was significant in single-SNP analysis of rs17238484 as well.

MR analysis of LDL-C with selected outcomes

We also performed MR analysis with LDL-C as the exposure for selected outcomes with nominal significant results (Table 5). Of note, the directions of associations from IVW analysis are fully

concordant with the joint- and single-SNP analyses, except for celiac disease. The strongest associations were observed for Alzheimer's disease and extreme parental longevity. Lower LDL-C level is casually linked to a lower risk of Alzheimer disease, supported by the IVW and MR-Egger regression results (MR-Egger $p = 1.12e-04$). A polygenic association of lower LDL-C with higher probability of parental extreme longevity was also detected (lowest $p = 8.43e-09$). In addition, we noted a highly significant polygenic association of lower LDL-C with longer sleep duration (IVW $p = 4.47e-6$), but there is evidence of pleiotropy ($p = 0.011$). The casual estimate given by weighted median approach was significant ($p = 0.019$) but not for the MR-Egger method.

We observed a nominally significant causal relationship between lower LDL-C and increased depressive symptoms (IVW $p = 0.042$), although the MR-Egger and weighted median approach did not yield significant results. The test for horizontal pleiotropy from MR-Egger regression was however not significant ($p = 0.103$), implying that approaches that do not adjust for pleiotropy can be taken into consideration. Notably, lower LDL-C may also be causally related to raised major depression risk (IVW $p = 0.014$; weighted median $p = 0.084$), despite modest evidence for horizontal pleiotropy ($p = 0.040$). For other selected traits we did not observe any significant associations, suggesting that for these traits any causal relationships with statins, if present, may be to a greater extent attributed to HMG-CoA reductase inhibition than to a general lowering effect of LDL-C.

DISCUSSION

In this study we have employed a Mendelian randomization approach to study the casual effects of genetically lowered LDL-C due to HMG-CoA reductase inhibition (analogous to the action of statins) on a large variety of traits. The analyses revealed several potential repositioning opportunities as well as adverse effects of statins. We shall discuss below associations showing at least nominal significance ($p < 0.05$) in our analyses.

Depressive symptoms and statins

The strongest association observed from this study is a potential causal link between genetically lower LDL-C from HMG-CoA reductase inhibition and increased depressive symptoms ($p = 0.002$, $q = 0.094$). Consistent with this observation, we also detected a possible causal link between low LDL-C levels and elevated major depression risk and depressive symptoms, although the association was less conclusive. A number of studies have been performed to elucidate the relationships between cholesterol levels (including LDL-C), statins and depression, although the results were mixed. You et al.¹⁰ provided a detailed review of the evidence linking depression with low cholesterol levels and statin use. For example, low serum cholesterol has been reported to increased rates of suicide and increased depressive symptoms in a number of reports (*e.g.* ref.³⁸⁻⁴²). Similarly, statin use has been suggested to be associated with elevated rates of depression (*e.g.* ref.⁴³⁻⁴⁶). The underlying mechanism remains to be elucidated, but some studies suggested that reduction of

cholesterol may result in disruption of serotonin receptor functions¹⁰. For instance, Shrivastava et al. showed that chronic cholesterol depletion resulted in impaired ligand binding and G-protein coupling to serotonin 1A receptors⁴⁷. Another possible mechanism is through reduced synthesis of neurosteroids⁴⁸, which are important for normal brain functioning such as synaptogenesis⁴⁹.

On the other hand, it has been postulated that the reduction of inflammatory responses by statins may contribute to antidepressant effects and some studies also found reduced depression risks among statin users⁵⁰. For example, a recent meta-analysis of 3 randomized controlled trials (RCTs) (total $N = 165$) revealed efficacy of statins in treating depression, although one should caution against the small sample size and number of studies⁵¹. An earlier meta-analysis showed no significant differences in mental well-being between patients on statins or placebo, however there was high heterogeneity between the studies and psychological well-being were mainly assessed by self-report questionnaires⁵². There were also concerns of publications bias.

In the present study, we employed genetic instruments to model LDL-C levels, which reflect a life-long exposure to reduced LDL-C and it may not fully mimic the case of statin users. Therefore, it remains to be elucidated whether the observed effects on depressive symptoms from MR analyses can be directly translated to clinical practice. However, our results suggest that clinicians could be alerted to the possibility that development or exacerbation of depressive symptoms can be casually related to prescription of statins. For patients with risk factors for depression (*e.g.* family history or past history of depression) who intend to receive or are receiving statins for prolonged periods, a greater awareness on mood changes and other psychiatric symptoms might be particularly warranted.

Our results do not invalidate the possibility that statins may exert antidepressant properties under certain clinical scenarios. For example, significant results in RCTs⁵¹ imply that a relatively short-term course of statin to ameliorate inflammatory responses may be beneficial for certain depressive patients. Further studies are required to clarify how the duration of statin treatment and patient characteristics (*e.g.* age, sex, presence of pre-existing depressive risk factors, cardiometabolic profiles, concomitant use of other medications like antidepressants etc.) may be associated with worsening or improvement of depressive symptoms.

Other psychiatric disorders and statins

For anorexia nervosa (AN), we observed relatively consistent results from single-SNP analysis of rs17238484 and rs12916, as well as from joint SNP analysis, that reduction of LDL-C from HMG-CoA reductase inhibition decreases AN risk, although the statistical significance was not too strong. Hypercholesterolemia, including raised LDL-C, is a well-known phenomenon in AN patients, although this association may appear paradoxical as these patients are generally malnourished and consume less fat than healthy individuals⁵³. The underlying mechanism remains unclear. Although

hypercholesterolemia is generally considered a consequence of AN, our results suggest that raised LDL (especially related to increased HMG-CoA reductase activity) may also be a casual risk factor for the disorder. Raised cholesterol synthesis has been suggested as a possible reason for hypocholesterolemia in these patients⁵⁴. Nevertheless, we are not aware of any studies on the effects of statins in AN patients. Clearly, clinical observational studies and preferably RCTs are required before one can conclude the role of LDL-C and benefits of statins in these patients.

We also observed some evidence that statins may reduce schizophrenia risk from individual SNP analysis of rs17238484. Statin has been proposed as a novel treatment for the disorder, presumably based on its potential to ameliorate neuroinflammation⁵⁵, and was tested in small number of clinical trials. For instance, Vincenzi et al. reported improvement in the Positive and Negative Syndrome Scale (PANSS) from baseline to 6 weeks with pravastatin although the effect failed to maintain at 12 weeks⁵⁶. In another study, there was preliminary evidence that simvastatin improved PANSS scores, although the results were not statistically significant⁵⁷.

We found a slightly unexpected association of statin action with increased sleep duration in single-SNP MR analyses of rs17238484; interestingly, a polygenic and probably casual association of reduced LDL-C with longer sleep duration was also detected. A limited number of observational studies suggested both short and long sleep durations are associated with lipid abnormalities^{58,59}, although the current analyses could not detect non-linear relationships. With regards to effects of statins on sleep, observational studies have found statins may be associated with sleep disturbances⁶⁰. However a recent meta-analysis of 5 RCTs ($N = 231$) showed that statins do not have adverse effects on sleep duration or efficiency⁶¹. A more recent study reported significantly lower rate of sleep disturbance in patients assigned atorvastatin than those assigned placebo in a double-blind RCT setting⁶². The potential link with lengthened sleep duration is not necessarily contradictory to the putative association with increased depressive symptoms, as reduced sleep duration may not be experienced by every depressive patient, and some may have hypersomnia especially in atypical depression⁶³.

Neurological disorders and statins

Alzheimer disease (AD) is a common neurodegenerative disease for which few effective treatments are available. We found some evidence ($p = 6.58e-3$, $q = 0.256$) for statins to reduce AD risk from single-SNP MR analysis. The results from MR using LDL-C as exposure were concordant, showing a causal relationship between lower LDL and reduced AD risk. The relationship between cholesterol lowering and statins with AD has been quite extensively studied. There is evidence from pre-clinical and clinical observational studies that statins may be able to prevent AD or mitigate the course of the disease^{14,64,65}. The results from RCTs were more mixed, and no conclusive benefits of statins can be ascertained yet^{66,67}. As with the study with other neuropsychiatric disorders, AD itself is a

heterogeneous condition, and different patient characteristics (e.g. severity of illness, age, sex, comorbid illnesses etc.) in different studies may lead to mixed results. For Parkinson's disease (PD), there was only one matching SNP but the MR result was nominally significant ($p = 0.025$, $q = 0.274$). There is some evidence from animal⁶⁸ and observational studies (e.g. meta-analysis in ref.⁶⁹⁻⁷¹) that statins may reduce PD risk.

We noted a very recent study¹⁷ which employed MR to study the effects of statins, PCSK9 inhibitors and LDL-C on AD and PD risks. The study revealed lower LDL is causally associated with reduced AD risk, using summary statistics from GLGC and International Genomics of Alzheimer's Project (IGAP). The current analysis is very similar but we imposed a more stringent threshold (the consensus genome-wide significance threshold of $5e-8$) instead of the p threshold $1e-7$ by Benn et al.; we also included APOE variants that were excluded in Benn et al. due to possible pleiotropy, as the MR-Egger analysis can provide a correct casual estimate even when all instruments are invalid and it is difficult to ascertain whether all APOE variants would have pleiotropic effects. Benn et al.¹⁷ also studied the *HMGCR* variant rs17238484 as a proxy for statin action in a Danish cohort. No associations were found with AD or PD, however the number of incident AD and PD cases was relatively small (1001 and 460 respectively), which may have limited the power to detect significant associations. We have found some evidence for beneficial effects of statins in this study, but further studies are required to confirm the findings.

It is also worth mentioning that there are concerns about cognitive impairment as a side-effect of statins⁷². Besides studying AD, we also included a panel of cognitive test profiles as outcomes but did not find any significant associations. Although there is a chance of false negatives, this study and the previous work by Benn et al.¹⁷ appeared to show no causal relationship between statins and cognitive impairment.

Longevity and statins

We also revealed a potential polygenic association of *HMGCR* variants with extreme longevity (top 1% survival) and a highly significant association of LDL-C polygenic score with this trait (lowest $p = 8.43e-9$), which to our knowledge is the first report of such associations. The association is probably at least partially attributed to reduction in cardiovascular events. It remains unclear whether and by how much statins or reduction in LDL-C will benefit survival. A microsimulation study predicted that statin therapy is associated with an increased life expectancy of 0.3 years⁷³. Our point OR estimate for extreme longevity was also relatively small for joint SNP analysis in *HMGCR* (OR = 1.031, 95% CI 1.003-1.060) and for LDL-C (OR = 1.012, 95% CI 1.008-1.016), although as explained above the estimate might be biased downwards. It is interesting to note that the effect size of statins appears to be higher than LDL-C lowering (although the CIs overlap); whether statins confers survival benefits beyond cholesterol-lowering effects and reduction of cardiovascular deaths

is worthy of further investigation.

Other possible associations

We observed a nominally significant association of increased forearm bone mineral density (BMD) with *HMGCR* variant. Statins are postulated to stimulate bone formation and hence improve BMD^{74,75}. A recent meta-analysis of RCTs reported a small but significant benefit on BMD but no effects on fracture risk⁷⁶. As we only detected a positive association for forearm BMD but not at two other sites (femoral neck and lumbar spine), the findings should be viewed with caution. Another nominal association was a potential decrease in platelet count with statins. We did not find evidence from the literature that statins reduce platelet levels, although there might be an effect on reducing platelet aggregation⁷⁷ and mean platelet volume⁷⁸, which in turn might confer cardiovascular benefits. Limited evidence suggests a relationship between lower platelet counts and reduced cardiovascular risks⁷⁹. Another nominal association was with celiac disease; again we did not find support from previous studies of any relationship between statins and celiac disease, except one study which showed that atorvastatin had no effect on gluten-induced production of inflammatory cytokines in intestinal biopsies⁸⁰.

Negative findings

While a number of findings are negative, given the very widespread use of statins, these negative results are probably also of important public health significance. We did not find evidence that statins improve renal outcomes from MR analysis. A Cochrane review showed consistently lower mortality and cardiovascular events in chronic kidney disease (CKD) patients not requiring dialysis, but the effect on kidney function was inconclusive⁸¹. A more recent meta-analysis however showed beneficial effects of high-intensity statin therapy on estimated glomerular filtration rate (eGFR), while moderate- or low-intensity treatment did not show benefits⁸². Our negative findings may be due to statins only having an effect in a subgroup of patients with high-intensity therapy (which may be beyond the lipid-lowering effect of the studied genetic instruments). Alternatively, such beneficial effects may be due to off-target mechanisms. Similarly, no associations with cancers were found. There is currently no strong evidence to support chemopreventive potential of statins against most cancers^{83,84}. Our results suggest that statins did not reduce or increase cancer risks. The current analysis, however, is limited by a relative lack of GWAS summary statistics available for cancers and relatively moderate sample sizes for some datasets. Finally, there were no associations found with autoimmune diseases. Parallel to this finding, there is lack of high-quality observational studies or RCTs demonstrating clear benefits of statins on the treatment of autoimmune disorders, although pre-clinical studies suggested statins may be useful for certain autoimmune diseases⁸⁵. On the other hand, our results do not support the claim that statins may be a risk factor for autoimmune disorders in previous reports⁸⁶.

We provided a discussion regarding our significant results with unadjusted $p < 0.05$ above, and noted many associations were supported by previous pre-clinical or clinical studies. Nevertheless, some of the findings could represent false positives (we also provided estimates of FDR in this report), and care must be taken before application of any results to clinical settings. Due to various limitations of an MR approach, we believe that the results did not yet provide confirmatory evidence for the repositioning potential or adverse effects of statins in actual practice, and further large-scale studies especially RCTs are still needed to confirm the findings.

Strengths and Limitations

This is the first study to employ a “phenome-wide” MR approach to explore drug repositioning opportunities and adverse side effects of statins and of a commonly used medication. The MR approach is analogous to a “naturalistic” RCT which is much less susceptible to confounding and reverse causation compared to clinical observational studies. This phenome-wide analysis provides an unbiased and comprehensive assessment of the therapeutic potential and side-effects of statins.

This study has several limitations. Firstly, as discussed previously, we employed genetic instruments to model the risk factor, reflecting a life-long exposure to altered LDL-C levels. Statin users typically receive the drug for a shorter period of time, and whether the effects of statins will be similar to those observed in the MR analyses requires further investigation via clinical studies. In addition, we focused on *HMGCR* variants which modelled the “on-target” effects of statins on HMG-CoA reductase (and its downstream pathways⁸⁷). Off-targets effects might be missed. In a similar vein, we focused on a common mechanism of action by all statins, but it is possible that individual statins may exert more specific effects that are currently unknown. Pharmacokinetic properties of different statins, including ability to cross the blood-brain barrier, will need to be considered before applying specific statins for drug repositioning. Another potential limitation is that current GWAS mainly focus on identifying susceptibility variants for the development of disease, but few investigated the genetic basis underlying disease progression. As a result, MR analyses with drug target genes may be able to detect drugs potentially useful for disease prevention, but their effects on altering disease progression is less certain⁸⁸. Nonetheless, a drug can be useful both in prevention and altering the disease course or preventing relapses, as is the case for statins for coronary heart disease⁸⁹. A recent commentary⁸⁸ provided a discussion on this issue. Also, the power of the MR analysis depends on the sample size of the GWAS studies, for several traits in our analysis (e.g. neurocognitive profiles and several cancers) the sample sizes are relatively modest and false negative results are possible.

In summary, we showcased a phenome-wide MR approach to uncover repositioning opportunities and side-effects for statins. Many findings, such as potential adverse effects on depressive symptoms and repositioning potential for several neuropsychiatric disorders, are worthy of further investigation.

On the other hand, negative findings might also be of value due to the very widespread use of the drug. We hope that further preclinical experiments, clinical studies and RCTs will help to verify our findings.

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Conflicts of interest

The author declares no conflict of interest.

Table 1 SNPs used as genetic instruments in Mendelian randomization analysis

chr	SNP	effect_allele (lipid-lowering)	other_allele	beta	se	<i>p</i>	eaf	beta_joint	se_joint
5	rs12916	T	C	0.0695	0.0053	1.79E-34	0.5686	0.0602	0.0070
5	rs17238484	G	T	0.0627	0.0062	1.47E-21	0.7467	0.0166	0.0082

Effect sizes are extracted from meta-analysis performed by the Global Lipid Genetics Consortium. Beta: regression coefficient; se, standard error; eaf, effect allele frequency; beta_joint and se_joint, coefficient and standard error estimate from COJO-joint analysis.

Table 2 Mendelian randomization results from joint analysis of rs17238484 and rs12916

Outcome	<i>N</i>	<i>b</i> (lower LDL)	<i>se</i>	<i>p</i>	<i>qval</i>
Psychiatric disorders/traits					
Anorexia nervosa GCAN 2014	17767	-1.201	0.971	*0.216	*0.879
Autism PGC 2015	10263	-0.520	0.453	0.251	0.879
Bipolar disorder PGC 2011	16731	-0.410	0.396	0.300	0.879
Bulimia nervosa 2013	2442	0.029	0.114	0.798	0.913
Depressive symptoms SSGAC 2016	161460	0.151	0.049	2.00E-03	0.094
Major depressive disorder PGC 2013	18759	0.632	0.607	0.298	0.879
Schizophrenia PGC 2014	82315	-0.185	0.402	0.644	0.912
Sleep duration UK Biobank 2016	128266	0.068	0.149	0.645	0.912
Neurological disorders					
Alzheimer's disease IGAP 2013	54162	-0.245	0.680	0.718	0.912
Amyotrophic lateral sclerosis Project MinE 2016	36052	-0.146	0.291	0.616	0.912
Parkinson's disease 2009	5691	NA	NA	NA	NA
Renal disorders					
Chronic kidney disease CKDGen 2015	118142	-0.060	0.258	0.816	0.913
IgA nephropathy 2010	5983	NA	NA	NA	NA
Microalbuminuria CKDGen 2015	54116	0.346	0.343	0.313	0.879
<i>Within DM subjects</i>					
Serum creatinine (eGFR _{crea}) CKDGen 2015	11522	-0.016	0.060	0.788	0.913
Urinary albumin-to-creatinine ratio CKDGen 2015	5825	-0.290	0.469	0.536	0.912
<i>Within non-DM subjects</i>					
Serum creatinine (eGFR _{crea}) CKDGen 2015	118354	0.007	0.015	0.642	0.912
Urinary albumin-to-creatinine ratio CKDGen 2015	46061	-0.008	0.102	0.936	0.956
Cancer					
Lung adenocarcinoma ILCCO 2014	18336	0.293	0.445	0.510	0.912
Lung cancer ILCCO 2014	27209	0.326	0.288	0.258	0.879
Melanoma MDACC 2011	2824	NA	NA	NA	NA
Neuroblastoma 2013	4881	NA	NA	NA	NA
Pancreatic cancer PanScan1 2009	3835	NA	NA	NA	NA
Squamous cell lung cancer ILCCO 2014	18313	0.313	0.442	0.478	0.912
Autoimmune/inflammatory					
Asthma GABRIEL 2007	26475	NA	NA	NA	NA
Celiac disease 2010	15283	NA	NA	NA	NA
Crohn's disease IIBDGC 2015	20883	-0.060	0.376	0.874	0.934
Eczema EAGLE 2014	40530	-0.218	0.276	0.429	0.912
Gout GUGC 2013	69374	0.628	0.534	0.239	0.879

Inflammatory bowel disease IIBDGC 2015	34652	0.105	0.278	0.706	0.912
Multiple sclerosis IMSGC 2013	38589	0.506	0.272	0.063	0.696
Rheumatoid arthritis 2014	58284	0.127	0.204	0.532	0.912
Systemic lupus erythematosus 2008	3094	NA	NA	NA	NA
Ulcerative colitis IIBDGC 2015	27432	0.157	0.352	0.656	0.912

Bone

Femoral neck bone mineral density GEFOS 2015	49988	0.015	0.129	0.910	0.950
Forearm bone mineral density GEFOS 2015	10805	0.430	0.534	0.421	0.912
Lumbar spine bone mineral density GEFOS 2015	44731	0.081	0.145	0.576	0.912

Haematological

Haemoglobin concentration HaemGen 2012	54908	-0.097	0.097	0.318	0.879
Mean cell haemoglobin HaemGen 2012	47229	0.207	0.171	0.225	0.879
Mean cell haemoglobin concentration HaemGen 2012	50336	-0.045	0.058	0.442	0.912
Mean cell volume HaemGen 2012	51903	0.782	0.439	0.074	0.696
Mean platelet volume HaemGen 2011	19261	0.007	0.018	0.683	0.912
Packed cell volume HaemGen 2012	52758	0.003	0.384	0.994	0.994
Platelet count HaemGen 2011	66867	-14.322	6.915	0.038	0.595
Red blood cell count HaemGen 2012	49103	-0.049	0.037	0.186	0.879

Cognitive tests

2-choice reaction time 2011	2602	0.751	0.449	0.095	0.744
4-choice reaction time 2011	2829	0.123	0.528	0.816	0.913
8-choice reaction time 2011	1382	-0.109	0.662	0.869	0.934
Digit symbol 2011	2956	-0.261	0.434	0.548	0.912
G speed factor 2011	2430	0.574	0.491	0.243	0.879
Inspection time 2011	2645	-0.135	0.462	0.770	0.913
Simple reaction time 2011	2378	0.326	0.449	0.468	0.912
Symbol search 2011	991	0.308	0.737	0.676	0.912

Aging and longevity

Parents' age at death UK Biobank 2016	75244	-0.117	0.124	0.345	0.901
Top 1 % survival UK Biobank 2016	75244	0.031	0.014	0.030	0.595

*For anorexia nervosa, although the IVW estimate was not significant, the maximum likelihood approach (beta = -1.251, SE = 0.548, p = 0.0223, corresponding $q = 0.442$) and fixed effects meta-analysis by delta method (beta = -1.082, SE = 0.535, p = 0.0432, corresponding $q = 0.495$) both yielded nominally significant results.

N , sample size; b (lower LDL), effect size (coefficient) estimate of having lower LDL cholesterol; q val, q -value. Nominally significant results (unadjusted $p < 0.05$) are in bold. NA, not available.

Table 3 Mendelian randomization analysis of rs17238484

Outcome	<i>N</i>	b (lower LDL)	se	p	qval
Psychiatric disorders/traits					
Anorexia nervosa GCAN 2014	17767	-1.462	0.623	0.019	0.209
Autism PGC 2015	10263	-0.341	0.522	0.513	0.825
Bipolar disorder PGC 2011	16731	-0.214	0.450	0.634	0.850
Bulimia nervosa 2013	2442	0.080	0.144	0.579	0.850
Depressive symptoms SSGAC 2016	161460	0.048	0.064	0.453	0.825
Major depressive disorder PGC 2013	18759	0.863	0.413	0.037	0.289
Schizophrenia PGC 2014	82315	-0.496	0.198	0.012	0.209
Sleep duration UK Biobank 2016	128266	0.186	0.075	0.014	0.209
Neurological disorders					
Alzheimer's disease IGAP 2013	54162	-0.797	0.293	6.58E-03	0.209
Amyotrophic lateral sclerosis Project MinE 2016	36052	-0.212	0.333	0.525	0.825
Parkinson's disease 2009	5691	-1.779	0.796	0.025	0.229
Renal disorders					
Chronic kidney disease CKDGen 2015	118142	-0.207	0.287	0.470	0.825
IgA nephropathy 2010	5983	2.437	1.638	0.137	0.825
Microalbuminuria CKDGen 2015	54116	0.323	0.498	0.517	0.825
<i>Within DM subjects</i>					
Urinary albumin-to-creatinine ratio CKDGen 2015	5825	-0.351	0.542	0.518	0.825
Serum creatinine (eGFR _{crea}) CKDGen 2015	11522	-0.067	0.070	0.340	0.825
<i>Within non-DM subjects</i>					
Urinary albumin-to-creatinine ratio CKDGen 2015	46061	-0.120	0.121	0.324	0.825
Serum creatinine (eGFR _{crea}) CKDGen 2015	118354	0.003	0.018	0.856	0.923
Cancer					
Lung adenocarcinoma ILCCO 2014	18336	0.513	0.502	0.307	0.825
Lung cancer ILCCO 2014	27209	0.271	0.333	0.415	0.825
Melanoma MDACC 2011	2824	-0.929	1.092	0.395	0.825
Neuroblastoma 2013	4881	-0.502	0.870	0.563	0.850
Pancreatic cancer PanScan1 2009	3835	-0.406	1.033	0.694	0.850
Squamous cell lung cancer ILCCO 2014	18313	0.238	0.509	0.640	0.850

Autoimmune/inflammatory

Asthma GABRIEL 2007	26475	0.316	0.374	0.399	0.825
Celiac disease 2010	15283	1.130	0.555	0.042	0.289
Crohn's disease IIBDGC 2015	20883	0.383	0.427	0.371	0.825
Eczema EAGLE 2014	40530	-0.152	0.318	0.632	0.850
Gout GUGC 2013	69374	0.718	0.622	0.249	0.825
Inflammatory bowel disease IIBDGC 2015	34652	0.285	0.314	0.364	0.825
Multiple sclerosis IMSGC 2013	38589	0.206	0.313	0.511	0.825
Rheumatoid arthritis 2014	58284	-0.159	0.242	0.512	0.825
Systemic lupus erythematosus 2008	3094	1.057	0.898	0.239	0.825
Ulcerative colitis IIBDGC 2015	27432	0.128	0.399	0.749	0.858

Bone

Femoral neck bone mineral density GEFOS 2015	49988	-0.022	0.143	0.879	0.930
Forearm bone mineral density GEFOS 2015	10805	0.719	0.303	0.018	0.209
Lumbar spine bone mineral density GEFOS 2015	44731	-0.060	0.166	0.718	0.850

Haematological

Haemoglobin concentration HaemGen 2012	54908	0.040	0.108	0.713	0.850
Mean cell haemoglobin HaemGen 2012	47229	-0.011	0.188	0.953	0.953
Mean cell haemoglobin concentration HaemGen 2012	50336	-0.056	0.065	0.393	0.825
Mean cell volume HaemGen 2012	51903	0.128	0.482	0.791	0.888
Mean platelet volume HaemGen 2011	19261	-0.011	0.021	0.590	0.850
Packed cell volume HaemGen 2012	52758	0.440	0.338	0.193	0.825
Platelet count HaemGen 2011	66867	-3.045	7.579	0.688	0.850
Red blood cell count HaemGen 2012	49103	0.027	0.041	0.513	0.825

Cognitive tests

2-choice reaction time 2011	2602	0.506	0.512	0.323	0.825
4-choice reaction time 2011	2829	0.611	0.518	0.239	0.825
8-choice reaction time 2011	1382	-0.526	0.750	0.483	0.825
Digit symbol 2011	2956	-0.388	0.491	0.430	0.825
G speed factor 2011	2430	0.056	0.558	0.920	0.937
Inspection time 2011	2645	-0.123	0.523	0.814	0.895
Simple reaction time 2011	2378	0.179	0.510	0.726	0.850
Symbol search 2011	991	0.303	0.839	0.718	0.850

Aging and Longevity

Parents' age at death UK Biobank 2016	75244	-0.015	0.143	0.916	0.937
Top 1 % survival UK Biobank 2016	75244	0.017	0.016	0.288	0.825

Nominally significant results (unadjusted $p < 0.05$) are in bold. Please refer to legends of Table 2.

Table 4 Mendelian randomization analysis of rs12916

Outcome	<i>N</i>	b (lower LDL)	se	<i>p</i>	qval
Psychiatric disorders/traits					
Anorexia nervosa GCAN 2014	17767	-0.851	0.458	0.063	0.632
Autism PGC 2015	10263	-0.413	0.403	0.305	0.925
Bipolar disorder PGC 2011	16731	-0.336	0.353	0.341	0.925
Bulimia nervosa 2013	2442	0.014	0.101	0.886	0.967
Depressive symptoms SSGAC 2016	161460	0.129	0.043	2.70E-03	0.130
Major depressive disorder PGC 2013	18759	0.425	0.312	0.173	0.923
Schizophrenia PGC 2014	82315	-0.078	0.154	0.613	0.941
Sleep duration UK Biobank 2016	128266	0.029	0.058	0.617	0.941
Neurological disorders					
Alzheimer's disease IGAP 2013	54162	-0.068	0.236	0.774	0.953
Amyotrophic lateral sclerosis Project MinE 2016	36052	0.173	0.259	0.505	0.941
Parkinson's disease 2009	5691	NA	NA	NA	NA
Renal disorders					
Chronic kidney disease CKDGen 2015	118142	-0.014	0.230	0.950	0.999
IgA nephropathy 2010	NA	NA	NA	NA	NA
Microalbuminuria CKDGen 2015	54116	0.273	0.302	0.366	0.925
<i>Within DM subjects</i>					
Urinary albumin-to-creatinine ratio CKDGen 2015	5825	-0.201	0.417	0.629	0.941
Serum creatinine (eGFR _{crea}) CKDGen 2015	11522	-0.003	0.053	0.957	0.999
<i>Within non-DM subjects</i>					
Urinary albumin-to-creatinine ratio CKDGen 2015	46061	0.013	0.091	0.886	0.967
Serum creatinine (eGFR _{crea}) CKDGen 2015	118354	0.006	0.013	0.664	0.941
Cancer					
Lung adenocarcinoma ILCCO 2014	18336	0.171	0.397	0.666	0.941
Lung cancer ILCCO 2014	27209	0.249	0.256	0.331	0.925
Melanoma MDACC 2011	NA	NA	NA	NA	NA
Neuroblastoma 2013	NA	NA	NA	NA	NA
Pancreatic cancer PanScan1 2009	NA	NA	NA	NA	NA
Squamous cell lung cancer ILCCO 2014	18313	0.243	0.393	0.537	0.941

Autoimmune/inflammatory

Celiac disease 2011	24268	-0.115	0.282	0.684	0.941
Crohn's disease IIBDGC 2015	20883	-0.127	0.335	0.706	0.941
Eczema EAGLE 2014	40530	-0.172	0.245	0.484	0.941
Gout GUGC 2013	69374	0.446	0.475	0.348	0.925
Inflammatory bowel disease IIBDGC 2015	34652	0.042	0.247	0.866	0.967
Multiple sclerosis MSGC 2013	38589	0.425	0.242	0.079	0.632
Rheumatoid arthritis 2014	58284	0.143	0.181	0.429	0.941
Ulcerative colitis IIBDGC 2015	27432	0.119	0.314	0.704	0.941

Bone

Femoral neck bone mineral density GEFOS 2015	49988	0.018	0.115	0.878	0.967
Forearm bone mineral density GEFOS 2015	10805	0.264	0.232	0.255	0.925
Lumbar spine bone mineral density GEFOS 2015	44731	0.085	0.129	0.509	0.941

Haematological

Haemoglobin concentration HaemGen 2012	54908	-0.096	0.086	0.264	0.925
Mean cell haemoglobin HaemGen 2012	47229	0.193	0.153	0.206	0.925
Mean cell haemoglobin concentration HaemGen 2012	50336	-0.030	0.052	0.560	0.941
Mean cell volume HaemGen 2012	51903	0.694	0.391	0.076	0.632
Mean platelet volume HaemGen 2011	19261	0.009	0.016	0.585	0.941
Packed cell volume HaemGen 2012	52758	-0.075	0.256	0.770	0.953
Platelet count HaemGen 2011	66867	-12.557	6.173	0.042	0.632
Red blood cell count HaemGen 2012	49103	-0.050	0.033	0.128	0.828

Cognitive tests

2-choice reaction time 2011	2602	0.593	0.400	0.138	0.828
4-choice reaction time 2011	2829	-0.004	0.410	0.992	1.000
8-choice reaction time 2011	1382	0.000	0.590	1.000	1.000
Digit symbol 2011	2956	-0.165	0.387	0.669	0.941
G speed factor 2011	2430	0.515	0.437	0.239	0.925
Inspection time 2011	2645	-0.101	0.412	0.807	0.967
Simple reaction time 2011	2378	0.265	0.400	0.508	0.941
Symbol search 2011	991	0.225	0.656	0.732	0.950

Aging and Longevity

Parents' age at death UK Biobank 2016	75244	-0.104	0.110	0.344	0.925
Top 1 % survival UK Biobank 2016	75244	0.025	0.013	0.048	0.632

Nominally significant results (unadjusted $p < 0.05$) are in bold. Please refer to legends of Table 2.

Table 5 Mendelian randomization analysis using LDL-C as exposure

Outcome	b_IVW (lower LDL)	se_IVW	p_IVW	q_IVW	b_Egger (lowerLDL)	se_Egger	p_Egger	q_Egger	b_median (lowerLDL)	se_median	p_median	q_median	Horizontal pleiotropy <i>p</i>
Anorexia nervosa GCAN 2014	-0.111	0.089	0.213	0.391	-0.177	0.183	0.339	0.880	-0.154	0.133	0.247	0.469	0.681
Depressive symptoms SSGAC 2016	0.014	0.007	0.042	0.092	0.000	0.011	0.967	0.967	0.000	0.011	0.993	0.993	0.103
Major depressive disorder PGC 2013	0.137	0.056	0.014	0.039	-0.076	0.115	0.511	0.891	0.140	0.081	<i>0.084</i>	0.308	0.040
Schizophrenia PGC 2014	-0.002	0.025	0.927	0.958	-0.016	0.037	0.671	0.891	-0.015	0.032	0.649	0.892	0.625
Sleep duration UK Biobank 2016	0.038	0.008	4.47E-06	2.46E-05	0.005	0.015	0.729	0.891	0.028	0.012	0.019	0.105	0.011
Alzheimer's disease IGAP 2013	-0.715	0.195	2.39E-04	8.76E-04	-1.265	0.310	1.12E-04	1.23E-03	-0.043	0.067	0.522	0.820	0.028
Parkinson's disease 2009	0.143	0.155	0.359	0.564	0.396	0.309	0.209	0.766	0.033	0.178	0.855	0.941	0.350
Platelet count HaemGen 2011	-1.341	1.984	0.499	0.686	-0.885	4.129	0.831	0.914	-2.473	1.797	0.169	0.465	0.900
Forearm bone mineral density GEFOS 2015	0.015	0.030	0.617	0.754	0.017	0.044	0.703	0.891	-0.009	0.043	0.835	0.941	0.949
Celiac disease 2010	-0.005	0.092	0.958	0.958	-0.163	0.192	0.400	0.880	-0.145	0.128	0.256	0.469	0.352
Top 1 % survival UK Biobank 2016	0.012	0.002	8.43E-09	9.27E-08	0.011	0.004	0.005	0.028	0.013	0.003	1.50E-06	1.65E-05	0.854

All effect sizes refer to the effect of having lower LDL-C. IVW: inverse variance weighted method; Egger, MR-Egger method; median, weighted median method; horizontal pleiotropy *p*, p-value from test of unbalanced horizontal pleiotropy by the MR-Egger method; q, q-values. P-values < 0.05 are in bold.

References

1. Swerdlow, D.I. *et al.* HMG-coenzyme A reductase inhibition, type 2 diabetes, and bodyweight: evidence from genetic analysis and randomised trials. *Lancet* **385**, 351-361 (2015).
2. Kearney, P.M. *et al.* Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* **371**, 117-125 (2008).
3. Baigent, C. *et al.* Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* **376**, 1670-1681 (2010).
4. Mihaylova, B. *et al.* The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet* **380**, 581-590 (2012).
5. Collins, R. *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet* **388**, 2532-2561 (2016).
6. Buettner, C. *et al.* Statin Use and Musculoskeletal Pain Among Adults With and Without Arthritis. *American Journal of Medicine* **125**, 176-182 (2012).
7. US Food and Drug Administration. FDA Drug Safety Communication 2012: Important safety label changes to cholesterol-lowering statin drugs. (accessed 29th July, 2017).
8. Muldoon, M.F., Ryan, C.A., Sereika, S.A., Flory, J.D. & Manuck, S.B. Randomized trial of the effects of simvastatin on cognitive functioning in hypercholesterolemic adults. *American Journal of Medicine* **117**, 823-829 (2004).
9. Evans, M.A. & Golomb, B.A. Statin-Associated Adverse Cognitive Effects: Survey Results from 171 Patients. *Pharmacotherapy* **29**, 800-811 (2009).
10. You, H., Lu, W., Zhao, S.P., Hu, Z.P. & Zhang, J.N. The relationship between statins and depression: a review of the literature. *Expert Opinion on Pharmacotherapy* **14**, 1467-1476 (2013).
11. Golomb, B.A., Kane, T. & Dimsdale, J.E. Severe irritability associated with statin cholesterol-lowering drugs. *Qjm-an International Journal of Medicine* **97**, 229-235 (2004).
12. Leuschen, J. *et al.* Association of Statin Use With Cataracts A Propensity Score-Matched Analysis. *Jama Ophthalmology* **131**, 1427-1434 (2013).
13. Ishida, J., Konishi, M., Ebner, N. & Springer, J. Repurposing of approved cardiovascular drugs. *Journal of Translational Medicine* **14**(2016).
14. Malfitano, A.M. *et al.* Statins in neurological disorders: An overview and update. *Pharmacological Research* **88**, 74-83 (2014).
15. Hennessy, E., Adams, C., Reen, F.J. & O'Gara, F. Is There Potential for Repurposing

- Statins as Novel Antimicrobials? *Antimicrobial Agents and Chemotherapy* **60**, 5111-5121 (2016).
16. Didelez, V. & Sheehan, N. Mendelian randomization as an instrumental variable approach to causal inference. *Statistical Methods in Medical Research* **16**, 309-330 (2007).
 17. Benn, M. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study (vol 357, j1648, 2017). *Bmj-British Medical Journal* **357**(2017).
 18. Schmidt, A.F. *et al.* PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study. *Lancet Diabetes & Endocrinology* **5**, 97-105 (2017).
 19. Ference, B.A. *et al.* Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. *New England Journal of Medicine* **375**, 2144-2153 (2016).
 20. Ference, B.A., Majeed, F., Penumetcha, R., Flack, J.M. & Brook, R.D. Effect of Naturally Random Allocation to Lower Low-Density Lipoprotein Cholesterol on the Risk of Coronary Heart Disease Mediated by Polymorphisms in NPC1L1, HMGCR, or Both. *Journal of the American College of Cardiology* **65**, 1552-1561 (2015).
 21. Lotta, L.A. *et al.* Association Between Low-Density Lipoprotein Cholesterol-Lowering Genetic Variants and Risk of Type 2 Diabetes A Meta-analysis. *Jama-Journal of the American Medical Association* **316**, 1383-1391 (2016).
 22. Bennett, D.A. & Holmes, M.V. Mendelian randomisation in cardiovascular research: an introduction for clinicians. *Heart* (2017).
 23. Millard, L.A.C. *et al.* MR-PheWAS: hypothesis prioritization among potential causal effects of body mass index on many outcomes, using Mendelian randomization. *Scientific Reports* **5**(2015).
 24. Millwood, I.Y. *et al.* A phenome-wide association study of a lipoprotein-associated phospholipase A(2) loss-of-function variant in 90 000 Chinese adults. *International Journal of Epidemiology* **45**, 1588-1599 (2016).
 25. Walker, V.M., Smith, G.D., Davies, N.M. & Martin, R.M. Mendelian randomization: a novel approach for the prediction of adverse drug events and drug repurposing opportunities. *bioRxiv*, 105338 (2017).
 26. Willer, C.J. *et al.* Discovery and refinement of loci associated with lipid levels. *Nature Genetics* **45**, 1274-+ (2013).
 27. Burgess, S., Dudbridge, F. & Thompson, S.G. Combining information on multiple instrumental variables in Mendelian randomization: comparison of allele score and summarized data methods. *Statistics in Medicine* **35**, 1880-1906 (2016).
 28. Yang, J. *et al.* Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nature Genetics* **44**, 369-U170 (2012).

29. Yang, J.A., Lee, S.H., Goddard, M.E. & Visscher, P.M. GCTA: A Tool for Genome-wide Complex Trait Analysis. *American Journal of Human Genetics* **88**, 76-82 (2011).
30. Hemani, G. *et al.* MR-Base: a platform for systematic causal inference across the phenome using billions of genetic associations. *bioRxiv*, 078972 (2016).
31. Pilling, L.C. *et al.* Human longevity is influenced by many genetic variants: evidence from 75,000 UK Biobank participants. *Aging-Us* **8**, 547-563 (2016).
32. Marioni, R.E. *et al.* Genetic variants linked to education predict longevity. *Proceedings of the National Academy of Sciences of the United States of America* **113**, 13366-13371 (2016).
33. Burgess, S. & Bowden, J. Integrating summarized data from multiple genetic variants in Mendelian randomization: bias and coverage properties of inverse-variance weighted methods. *arXiv preprint arXiv:1512.04486* (2015).
34. Bowden, J., Smith, G.D., Haycock, P.C. & Burgess, S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genetic Epidemiology* **40**, 304-314 (2016).
35. Bowden, J., Smith, G.D. & Burgess, S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *International Journal of Epidemiology* **44**, 512-525 (2015).
36. Benjamini, Y. & Hochberg, Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society Series B-Methodological* **57**, 289-300 (1995).
37. Storey, J.D. The positive false discovery rate: A Bayesian interpretation and the q-value. *Annals of Statistics* **31**, 2013-2035 (2003).
38. Muldoon, M.F., Manuck, S.B. & Matthews, K.A. Lowering Cholesterol Concentrations and Mortality - a Quantitative Review of Primary Prevention Trials. *British Medical Journal* **301**, 309-314 (1990).
39. Engelberg, H. Low Serum-Cholesterol and Suicide. *Lancet* **339**, 727-729 (1992).
40. Morgan, R.E., Palinkas, L.A., Barrettconnor, E.L. & Wingard, D.L. Plasma-Cholesterol and Depressive Symptoms in Older Men. *Lancet* **341**, 75-79 (1993).
41. Aijanseppa, S. *et al.* Serum cholesterol and depressive symptoms in elderly Finnish men. *International Journal of Geriatric Psychiatry* **17**, 629-634 (2002).
42. Vevera, J. *et al.* Cholesterol-lowering therapy evokes time-limited changes in serotonergic transmission. *Psychiatry Research* **133**, 197-203 (2005).
43. Duits, N. & Bos, F.M. Depressive Symptoms and Cholesterol-Lowering Drugs. *Lancet* **341**, 114-114 (1993).
44. Kasslertaub, K.B., Woodward, T. & Markowitz, J.S. Depressive Symptoms and Pravastatin. *Lancet* **341**, 371-372 (1993).
45. Hyyppa, M.T., Kronholm, E., Virtanen, A., Leino, A. & Jula, A. Does simvastatin affect

- mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. *Psychoneuroendocrinology* **28**, 181-194 (2003).
46. Morales, K. *et al.* Simvastatin causes changes in affective processes in elderly volunteers. *Journal of the American Geriatrics Society* **54**, 70-76 (2006).
 47. Shrivastava, S., Pucadyil, T.J., Paila, Y.D., Ganguly, S. & Chattopadhyay, A. Chronic Cholesterol Depletion Using Statin Impairs the Function and Dynamics of Human Serotonin(1A) Receptors. *Biochemistry* **49**, 5426-5435 (2010).
 48. Majewska, M.D. Neurosteroids: endogenous bimodal modulators of the GABAA receptor. Mechanism of action and physiological significance. *Prog Neurobiol* **38**, 379-95 (1992).
 49. Tanaka, M. & Sokabe, M. Continuous de novo synthesis of neurosteroids is required for normal synaptic transmission and plasticity in the dentate gyrus of the rat hippocampus. *Neuropharmacology* **62**, 2373-2387 (2012).
 50. Kohler-Forsberg, O., Gasse, C., Berk, M. & Ostergaard, S.D. Do Statins Have Antidepressant Effects? *Cns Drugs* **31**, 335-343 (2017).
 51. Salagre, E., Fernandes, B.S., Dodd, S., Brownstein, D.J. & Berk, M. Statins for the treatment of depression: A meta-analysis of randomized, double-blind, placebo-controlled trials. *J Affect Disord* **200**, 235-42 (2016).
 52. O'Neil, A. *et al.* The impact of statins on psychological wellbeing: a systematic review and meta-analysis. *BMC Med* **10**, 154 (2012).
 53. Weinbrenner, T. *et al.* Lipoprotein metabolism in patients with anorexia nervosa: a case-control study investigating the mechanisms leading to hypercholesterolaemia. *British Journal of Nutrition* **91**, 959-969 (2004).
 54. Rigaud, D., Tallonneau, I. & Verges, B. Hypercholesterolaemia in anorexia nervosa: Frequency and changes during refeeding. *Diabetes & Metabolism* **35**, 57-63 (2009).
 55. Keller, W.R. *et al.* A review of anti-inflammatory agents for symptoms of schizophrenia. *Journal of Psychopharmacology* **27**, 337-342 (2013).
 56. Vincenzi, B. *et al.* A randomized placebo-controlled pilot study of pravastatin as an adjunctive therapy in schizophrenia patients: Effect on inflammation, psychopathology, cognition and lipid metabolism. *Schizophrenia Research* **159**, 395-403 (2014).
 57. Chaudhry, I.B. *et al.* Add-on Clinical Effects of Simvastatin and Ondansetron in Patients with Schizophrenia Stabilized on Antipsychotic Treatment: Pilot Study. *European Psychiatry* **29**(2014).
 58. Kaneita, Y., Uchiyama, M., Yoshiike, N. & Ohida, T. Associations of usual sleep duration with serum lipid and lipoprotein levels. *Sleep* **31**, 645-652 (2008).
 59. Zhan, Y.Q., Chen, R.Q. & Yu, J.M. Sleep duration and abnormal serum lipids: the China Health and Nutrition Survey. *Sleep Medicine* **15**, 833-839 (2014).

60. Takada, M., Fujimoto, M., Yamazaki, K., Takamoto, M. & Hosomi, K. Association of Statin Use with Sleep Disturbances: Data Mining of a Spontaneous Reporting Database and a Prescription Database (vol 37, pg 421, 2014). *Drug Safety* **37**, 653-653 (2014).
61. Broncel, M. *et al.* Sleep changes following statin therapy: a systematic review and meta-analysis of randomized placebo-controlled polysomnographic trials. *Arch Med Sci* **11**, 915-26 (2015).
62. Gupta, A. *et al.* Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. *Lancet* **389**, 2473-2481 (2017).
63. Posternak, M.A. & Zimmerman, M. Symptoms of atypical depression. *Psychiatry Res* **104**, 175-81 (2001).
64. Shepardson, N.E., Shankar, G.M. & Selkoe, D.J. Cholesterol level and statin use in Alzheimer disease: I. Review of epidemiological and preclinical studies. *Archives of neurology* **68**, 1239-1244 (2011).
65. Shepardson, N.E., Shankar, G.M. & Selkoe, D.J. Cholesterol level and statin use in Alzheimer disease: II. Review of human trials and recommendations. *Archives of neurology* **68**, 1385-1392 (2011).
66. Power, M.C., Weuve, J., Sharrett, A.R., Blacker, D. & Gottesman, R.F. Statins, cognition, and dementia-systematic review and methodological commentary. *Nature Reviews Neurology* **11**, 220-229 (2015).
67. McGuinness, B., Craig, D., Bullock, R. & Passmore, P. Statins for the prevention of dementia. *Cochrane Database of Systematic Reviews* (2016).
68. Selley, M.L. Simvastatin prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. *Brain Research* **1037**, 1-6 (2005).
69. Undela, K., Gudala, K., Malla, S. & Bansal, D. Statin use and risk of Parkinson's disease: a meta-analysis of observational studies. *Journal of Neurology* **260**, 158-165 (2013).
70. Bai, S. *et al.* Statin Use and the Risk of Parkinson's Disease: An Updated Meta-Analysis. *Plos One* **11**(2016).
71. Sheng, Z.G., Jia, X.B. & Kang, M.N. Statin use and risk of Parkinson's disease: A meta-analysis. *Behavioural Brain Research* **309**, 29-34 (2016).
72. Richardson, K. *et al.* Statins and Cognitive Function. *Annals of Internal Medicine* **159**, 688-+ (2013).
73. Ferket, B.S. *et al.* Personalized Prediction of Lifetime Benefits with Statin Therapy for Asymptomatic Individuals: A Modeling Study. *Plos Medicine* **9**(2012).

74. Mundy, G. *et al.* Stimulation of bone formation in vitro and in rodents by statins. *Science* **286**, 1946-1949 (1999).
75. Jadhav, S.B. & Jain, G.K. Statins and osteoporosis: new role for old drugs. *Journal of Pharmacy and Pharmacology* **58**, 3-18 (2006).
76. Wang, Z.Z., Li, Y., Zhou, F.X., Piao, Z. & Hao, J. Effects of Statins on Bone Mineral Density and Fracture Risk A PRISMA-compliant Systematic Review and Meta-Analysis. *Medicine* **95**(2016).
77. Sikora, J. *et al.* Effect of statins on platelet function in patients with hyperlipidemia. *Archives of Medical Science* **9**, 622-628 (2013).
78. Sivri, N. *et al.* Statins decrease mean platelet volume irrespective of cholesterol lowering effect. *Kardiol Pol* **71**, 1042-7 (2013).
79. Thaulow, E., Erikssen, J., Sandvik, L., Stormorken, H. & Cohn, P.F. Blood platelet count and function are related to total and cardiovascular death in apparently healthy men. *Circulation* **84**, 613-7 (1991).
80. Raki, M., Molberg, O., Tollefsen, S., Lundin, K.E. & Sollid, L.M. The effects of atorvastatin on gluten-induced intestinal T cell responses in coeliac disease. *Clin Exp Immunol* **142**, 333-40 (2005).
81. Palmer, S.C. *et al.* HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Sao Paulo Medical Journal* **133**, 541-542 (2015).
82. Sanguaneko, A., Upala, S., Cheungpasitporn, W., Ungprasert, P. & Knight, E.L. Effects of Statins on Renal Outcome in Chronic Kidney Disease Patients: A Systematic Review and Meta-Analysis. *PLoS One* **10**, e0132970 (2015).
83. Boudreau, D.M., Yu, O. & Johnson, J. Statin use and cancer risk: a comprehensive review. *Expert Opinion on Drug Safety* **9**, 603-621 (2010).
84. Bonovas, S. Statins: Do They Have a Potential Role in Cancer Prevention and Modifying Cancer-Related Outcomes? *Drugs* **74**, 1841-1848 (2014).
85. Ulivieri, C. & Baldari, C.T. Statins: From cholesterol-lowering drugs to novel immunomodulators for the treatment of Th17-mediated autoimmune diseases. *Pharmacological Research* **88**, 41-52 (2014).
86. John, S.G., Thorn, J. & Sobonya, R. Statins as a Potential Risk Factor for Autoimmune Diseases: A Case Report and Review. *American Journal of Therapeutics* **21**, E94-E96 (2014).
87. Stancu, C. & Sima, A. Statins: mechanism of action and effects. *Journal of Cellular and Molecular Medicine* **5**, 378-387 (2001).
88. Paternoster, L., Tilling, K.M. & Smith, G.D. Genetic Epidemiology And Mendelian Randomization For Informing Disease Therapeutics: Conceptual And Methodological Challenges. *bioRxiv*, 126599 (2017).
89. Naci, H. *et al.* Comparative benefits of statins in the primary and secondary

prevention of major coronary events and all-cause mortality: a network meta-analysis of placebo-controlled and active-comparator trials. *European Journal of Preventive Cardiology* **20**, 641-657 (2013).