PCSK9 genetic variants and risk of type 2 diabetes: a mendelian randomisation study


Summary

Background Statin treatment and variants in the gene encoding HMG-CoA reductase are associated with reductions in both the concentration of LDL cholesterol and the risk of coronary heart disease, but also with modest hyperglycaemia, increased bodyweight, and modestly increased risk of type 2 diabetes, which in no way offsets their substantial benefits. We sought to investigate the associations of LDL cholesterol-lowering PCSK9 variants with type 2 diabetes and related biomarkers to gauge the likely effects of PCSK9 inhibitors on diabetes risk.

Methods In this mendelian randomisation study, we used data from cohort studies, randomised controlled trials, case control studies, and genetic consortia to estimate associations of PCSK9 genetic variants with LDL cholesterol, fasting blood glucose, HbA1c, fasting insulin, bodyweight, waist-to-hip ratio, BMI, and risk of type 2 diabetes, using a standardised analysis plan, meta-analyses, and weighted gene-centric scores.

Findings Data were available for more than 550 000 individuals and 51 623 cases of type 2 diabetes. Combined analyses of four independent PCSK9 variants (rs11583680, rs11591147, rs2479409, and rs11206510) scaled to 1 mmol/L lower LDL cholesterol showed associations with increased fasting glucose (0·09 mmol/L, 95% CI 0·02 to 0·15), bodyweight (1·03 kg, 0·24 to 1·82), waist-to-hip ratio (0·006, 0·003 to 0·010), and an odds ratio for type diabetes of 1·29 (1·11 to 1·50). Based on the collected data, we did not identify associations with HbA1c (0·03%, –0·01 to 0·08), fasting insulin (0·00%, –0·06 to 0·07), and BMI (0·11 kg/m², –0·09 to 0·30).

Interpretation PCSK9 variants associated with lower LDL cholesterol were also associated with circulating higher fasting glucose concentration, bodyweight, and waist-to-hip ratio, and an increased risk of type 2 diabetes. In trials of PCSK9 inhibitor drugs, investigators should carefully assess these safety outcomes and quantify the risks and benefits of PCSK9 inhibitor treatment, as was previously done for statins.

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Introduction The benefit of statins in reducing LDL cholesterol and coronary heart disease (CHD) risk is well established. More recently, and only after completion of numerous randomised controlled trials, was it discovered that statins increase risk of type 2 diabetes,1,2 although this effect is modest and greatly outweighed by the benefits of this drug class. Genetic studies based on common variants in the gene encoding the target of statins, HMG-CoA reductase (HMGCR), suggest the effect is mechanism-based (ie, on-target).3 Genetic studies assessing the effects of variants in a broader range of
Research in context

Evidence before this study

We searched PubMed for "pcsk9[All Fields] AND ("antagonists and inhibitors"[Subheading] OR ("antagonists"[All Fields] AND "inhibitors"[All Fields]) OR "antagonists and inhibitors")[All Fields] OR "inhibitors"[All Fields]) AND ("diabetes mellitus"[MeSH Terms] OR ("diabetes"[All Fields] AND "mellitus"[All Fields]) OR "diabetes mellitus"[All Fields])" for articles published up to Oct 8, 2016, to identify studies that assessed treatment with PCSK9 inhibitors or carriage of genetic variants in PCSK9 in relation to diabetes. This search identified 17 studies, two of which presented novel, yet contrasting findings in relation to genetic variants in PCSK9 and glycaemic status.

Randomised trials of treatment with statins and carriage of corresponding genetic variants in HMGRCh that lower LDL cholesterol both show and increase in the risk of type 2 diabetes. More recently, genetic predisposition to lower LDL cholesterol concentrations has been linked to an increased risk of diabetes, suggesting that dysglycaemia might be a consequence of lowering LDL cholesterol in general. Whether lowering of LDL cholesterol by PCSK9 inhibitors results in increased risk of diabetes is currently unknown. Clinical trials of PCSK9 inhibitors to assess their effect on cardiovascular outcomes are ongoing, but reliable evidence for a possible association between PCSK9 inhibition and risk of diabetes could take longer to accru.

Added value of this study

Mendelian randomisation is an established approach that uses randomly allocated variants in the encoding gene to infer mechanism-based efficacy and safety outcomes from pharmacological perturbation of a drug target. We used four genetic variants in PCSK9 in more than 550 000 individuals (including about 50 000 diabetes cases) and showed that PCSK9 genetic variants associated with lower LDL cholesterol concentrations were associated with increased concentration of fasting glucose, bodyweight, and risk of diabetes. This finding adds robust new evidence to previous research that identified weak associations of PCSK9 with risk of diabetes.

Implications of all the available evidence

Similar to statin therapy, treatment with PCSK9 inhibitors is likely to increase the risk of diabetes. Patients treated with PCSK9 inhibitors should be carefully monitored for dysglycaemia, including within ongoing and future clinical trials.

Methods

Genetic variant selection

We selected four SNPs in or near PCSK9 on the basis of a strong association with LDL cholesterol, as reported by the Global Lipids Genetics Consortium (GLGC); low pairwise linkage disequilibrium (r²<0.30) with SNPs within the same and adjacent genes (1000 Genomes CEU data); high prior probability of being a functional variant based on the combined annotation dependent depletion (CADD) score, or the SNP being non-synonymous, or both; or previous reported associations with CHD. On the basis of these criteria, we selected the SNPs rs11583680 (minor allele frequency 0.14), rs11591147 (0.01), rs2479409 (0.36), and rs11206510 (0.17; appendix).

Individual participant-level and summary-level data

Data were analysed from two sources. Participating studies executed a common analysis script on their own data, submitting summary estimates to a central analysis centre at University College London, London, UK. Main
effect estimates from the participating studies were then meta-analysed with pooled summary estimates from the public domain data repositories of relevant genetic (genome-wide association study [GWAS]) consortia, but only if the study-level estimates had not previously contributed to consortia results, to prevent double counting. All studies contributing data to these analyses were approved by their local ethics committees.

Data were collected for LDL cholesterol, insulin (fasting and non-fasting), glucose (fasting and non-fasting), Hba1c, insulin resistance and secretion via basal homeostatic model assessments (HOMA-IR and HOMA-B), bodyweight, height, BMI, waist-to-hip ratio, and history or incidence of type 2 diabetes.

Publicly available summary-level data were available on blood lipids from the GLGC; type 2 diabetes-related biomarkers (plasma insulin, glucose, Hba1c, HOMA-IR, and HOMA-B) from the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC); bodyweight, height, BMI, and waist-to-hip ratio from the Genetic Investigation of Anthropometric Traits consortium (GIANT); and type 2 diabetes from the Diabetes Genetics Replication and Meta-analysis consortium (DIAGRAM) and Exome chip 80k. Additionally, cross-sectional data were obtained for adiposity traits and the prevalence of type 2 diabetes from UK Biobank.

Statistical analyses

In all analyses we assumed an additive allele effect with genotypes coded as 0, 1, and 2, representing the number of minor alleles. We analysed continuous biomarkers using linear regression models; the composite endpoint of prevalent or incident type 2 diabetes was analysed with logistic regression. Study-specific associations were pooled for each SNP by use of the inverse-variance weighted method for fixed-effect and random-effects meta-analysis. We assessed between-study heterogeneity using the Q-test and I² statistic with a one-sided upper 97·5% CI. Study-specific associations were excluded if the SNP was not in Hardy-Weinberg equilibrium (appendix).

Our approach to SNP selection was designed to prune the number of SNPs at PCSK9 used in the analysis, without loss of information. We decided a priori to combine the four approximately independent SNPs in a weighted gene-centric score (GS) using the inverse-variance weighted method for fixed and random effects. The GS provides a more precise estimate of the downstream effects of variation at PCSK9 by incorporating maximum biological variation. Furthermore, if the four SNP effects are homogenous (assessed by the heterogeneity measures Q-test and I²), the GS estimates will be more powerful and precise compared with individual SNPs in isolation. If, however, the SNP effects are heterogeneous (meaning that the PCSK9 effects are different according to which part of the gene is assessed), the GS method will be less powerful than the individual SNP tests (depending on the degree of heterogeneity). Our aim was to estimate the effect of the PCSK9 locus as a whole, but SNP-specific estimates are also reported. Other important assumptions of the GS approach are (approximate) independence of the included SNPs (assessed by pairwise linkage disequilibrium (r²) and use of multivariable regression models) and the additivity of allele effects. We also investigated whether the association of individual SNPs with diabetes risk was in proportion to the association with LDL cholesterol lowering.

Estimates are presented as mean differences or odds ratios (ORs) with 95% CIs, presented either per LDL cholesterol-decreasing allele or, in the case of GS, per 1 mmol/L (38.67 mg/dL) lower LDL cholesterol. The per 1 mmol/L GS effect estimates were derived by multiplying point estimates and their variances by the multiplicative inverse of the estimated SNP-LDL cholesterol effects. Similar to most genetic studies, missing data were excluded in an available case manner, assuming a missing-completely-at-random mechanism. To avoid potential bias due to population stratification and non-modelled ancestry interactions, analyses excluded individuals of non-European ancestry. Differences in ancestry can be a potential source of confounding bias (ie, population stratification bias) when environment is related to both the genes and the outcome of interest. Analyses were done with the statistical programme R (version 3.3.0).

Sensitivity analyses

We assumed that the allele effects were additive, which we assessed in available individual participant data by comparing an additive model to a non-additive model (allowing for dominance or recessiveness) using a likelihood ratio test (meta-analysed by Fisher’s method). Because measurement error might be larger in prevalent cases (ascertained, for example, from hospital records) we did a further sensitivity analysis in which we separately analysed incident and prevalent type 2 diabetes. This sensitivity analysis was done not because we expect the true associations of PCSK9 to be different with respect to prevalent and incident case status, but merely reflected a quality-control check. Although SNPs were selected to be independent, there was some degree of residual dependency (appendix; maximum r² 0.26). To explore the effect of this residual correlation between the four study SNPs (appendix), we compared results from a multivariable analysis (including the four SNPs in the same model) in studies with individual participant data (correcting for this correlation) to pairwise results (ignoring any between-SNP correlation) based on the same data.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (AFS) had full access
Results

50 studies shared participant-level data from up to 245 942 individuals, which was supplemented by summary effect estimates from data repositories, resulting in a maximum available sample size of 568 448 individuals, including 51 623 cases of incident or prevalent type 2 diabetes. Individual studies were similar with respect to the distribution of biochemical measures (assessed by the median of study-specific means): LDL cholesterol 3.41 mmol/L (IQR 0.39), fasting glucose 5.38 mmol/L (0.58), and HbA\textsubscript{1c} 5.50% (appendix). Pooled pairwise linkage disequilibrium estimates for the four PCSK9 SNPs all had \( r^2 \) values less than 0.30 (appendix), confirming that the selected SNPs were in low correlation in the collected data.

The four PCSK9 SNPs were associated with reductions in LDL cholesterol ranging from –0.02 mmol/L (95% CI –0.03 to –0.02) for rs11583680 to –0.34 mmol/L (–0.36 to –0.32) for rs11591147 per LDL cholesterol-decreasing allele (figure 1).

Figure 2 depicts the associations of the four PCSK9 SNPs after scaling the SNP effect to 1 mmol/L lower LDL cholesterol. Results of the PCSK9 GS analysis show that a 1 mmol/L lower LDL cholesterol was associated with an increase in bodyweight of 1.03 kg (95% CI 0.24 to 1.82; and for fasting glucose, bodyweight, and waist-to-hip ratio, and with a 1 mmol/L lower LDL cholesterol was associated with an increased risk of type 2 diabetes (OR 1.26, 95% CI 1.14 to 1.41). The corresponding scaled estimate for this association was 1.39 (95% CI 1.12 to 1.73), similar to an estimate based on SNPs encoding the target of statin drugs, with statins modestly increasing bodyweight and the risk of type 2 diabetes. When scaled to 1 mmol/L lower LDL cholesterol, the risk for type 2 diabetes based on \textit{HMGR} variants was an OR of 1.39 (95% CI 1.12 to 1.73), similar to the corresponding scaled estimate for this PCSK9 GS (1.29, 1.11 to 1.50), and similar to an estimate based on SNPs affecting LDL cholesterol selected from throughout the genome (1.27, 1.14 to 1.41). Effect estimates obtained from mendelian randomisation studies proxy lifetime exposure to natural genetic variation, and might therefore not directly translate to the size of effect of any corresponding pharmacological treatment introduced much later in life and thus for a shorter duration of time. In the case of statins, the treatment benefit in terms of CHD risk reduction greatly outweighs any potential adverse effect on risk of type 2 diabetes, partly because the size of the risk reduction in CHD is greater than the risk increase in type 2 diabetes, and partly because the absolute risk of CHD in primary prevention populations eligible for statin treatment is greater than the absolute risk of type 2 diabetes. A similarly precise risk assessment for PCSK9 inhibitors awaits results from larger and longer-term randomised trials. In a recent pooled analysis, researchers reported that treatment with alirocumab was associated with an OR for type 2 diabetes of 0.89 (95% CI 0.62 to 1.28) compared with placebo, based on 133 type 2 diabetes events. Variants that affect circulating LDL cholesterol have been reported previously to affect the probability of being

Discussion

In this mendelian randomisation study, genetic variants in PCSK9, used as a proxy for pharmacological inhibition of PCSK9, were associated with lower LDL cholesterol concentration and increased risk of type 2 diabetes. The same variants were also associated with higher fasting glucose, bodyweight, and waist-to-hip ratio, and with directionally consistent but non-significant associations for BMI and HbA\textsubscript{1c} and a seemingly neutral association for fasting insulin. These results are in agreement with previous findings for variants in the \textit{HMGR} gene encoding the target of statin drugs, with statins modestly increasing bodyweight and the risk of type 2 diabetes.
prescribed a lipid-lowering drug.14 We were unable to account for this effect in the analysis because prescription data for these treatments were often not available, and when they were recorded they were only available for a single follow-up point. For lipid-lowering treatments, one record of treatment does not properly reflect the single follow-up point. For lipid-lowering treatments, when they were recorded they were only available for a single record when in fact treatment varies over follow-up time-varying therapy received, and adjusting for only a single record of treatment does not properly account for this effect in the analysis because prescription analyses cannot predict off-target effects of treatments. We refer to on-target effects as those that are due to a drug effect on the intended target (in this case PCSK9) and off-target effects as those that might occur because of the drug also binding to an unintended target (in this case, any target other than PCSK9). Although monoclonal antibody therapeutics are often highly specific, perhaps more so than small molecule therapeutics, they retain the potential for off-target effects. Hence, in the presence of off-target effects, results from ongoing randomised controlled trials could differ from the genetic associations reported here. Our main findings are based on four PCSK9 SNPs in combination and scaled to 1 mmol/L lower LDL-cholesterol. This approach assumes additive effects across the SNPs, an assumption that held well in sensitivity analyses. A potentially unobserved non-additive effect might explain why we identified a genetic association with fasting glucose and a concordant (although non-significant) association with HbA1c, whereas fasting

Figure 2: Association of genetic variants in PCSK9 with glycaemic and anthropometric biomarkers

Effect estimates are presented as mean difference with 95% CIs. Associations were scaled to a 1 mmol/L reduction in LDL cholesterol. SNP-specific results are pooled by use of a fixed-effect model; weighted gene-centric score (GS) models combining all four SNP-specific estimates are presented as fixed-effect and random-effects estimates. The size of the black dots representing the point estimates is proportional to the inverse of the variance. Between-SNP heterogeneity was measured as a two-sided Q-test (χ²) and an I² with one-sided 97.5% CI. Note that results from individual participant data are supplemented by repository data from the Global Lipids Genetics Consortium, the Meta-Analyses of Glucose and Insulin-related traits Consortium, and the Genetic Investigation of Anthropometric Traits consortium.
Effect estimates are presented as odds ratios (ORs) for the incidence or prevalence of type 2 diabetes, with 95% CIs. Associations were scaled to a 1 mmol/L reduction in LDL cholesterol. SNP-specific results are pooled by use of a fixed-effect model; weighted gene-centric score (GS) models combining all four SNP-specific estimates are presented as fixed-effect and random-effects estimates. The size of the black dots representing the point estimates is proportional to the inverse of the variance. Between-SNP heterogeneity was measured as a two-sided Q-test ($\chi^2$) and an $I^2$ = 0 (97.5% CI 0–81.16)
insulin seemed unaffected. Conflicting evidence exists about a possible role of PCSK9 and PCSK9 monoclonal antibodies in disruption of pancreatic islet function.\textsuperscript{8,9}\n
Although concordant with fasting glucose, the HbA\textsubscript{1c} association was non-significant in the collected data, which might be related to the large amount of heterogeneity between the four SNPs (upper-bound R 72%). Interestingly, the association of the PCSK9 GS with BMI was smaller than that with bodyweight, which (partially) explained by a slightly greater average height among individuals with PCSK9 variants associated with lower LDL cholesterol concentrations. A further potential reason for the slight discrepancy between the BMI and bodyweight associations could be the greater heterogeneity in the associations of PCSK9 SNPs with BMI than with weight. Notably, the GS effect estimates were often driven by a large effect of SNP rs11591147; as our dose-response analysis shows (figure 4), the larger influence of this SNP appropriately reflects the proportionally larger LDL cholesterol effect of this SNP. Finally, we did not have access to measures of PCSK9 concentration in this analysis, but others\textsuperscript{10} have shown associations between common and rare PCSK9 alleles (including some of the same SNPs used here) and circulating PCSK9 concentrations.

Setting aside associations with glycaemia and weight, risk of type 2 diabetes could also be increased because lifelong exposure to genetic variation in PCSK9 could reduce mortality, making it conceivable that individuals with these variants survive longer and hence have more time to develop type 2 diabetes. However, whether PCSK9 genotype reduces mortality has not been conclusively shown.\textsuperscript{11,12} Irrespective of the nature of the PCSK9 association with type 2 diabetes, large randomised trials should determine whether this relation also holds for PCSK9 monoclonal antibodies.

In a recent study,\textsuperscript{13} investigators used a single SNP in PCSK9 and also reported evidence of an association with type 2 diabetes (OR 1·19, 95% CI 1·02 to 1·38; per 1 mmol/L reduction in LDL cholesterol). In the present study, we incorporated data from four SNPs, instead of a single SNP, in a PCSK9 gene score with participant data from 50 studies supplemented by large genetic consortia and are able to confirm their results, and also show this increase in type 2 diabetes risk is likely to be related to PCSK9-related increases in bodyweight and glucose. Previous studies of LDL cholesterol lowering HMGCR\textsuperscript{14} and NPC1L\textsuperscript{15} variants (encoding pharmacological targets of statins and ezetimibe, respectively) and more widely on LDL cholesterol-lowering variants from multiple GWAS-associated loci,\textsuperscript{16} as well as analyses of patients with monogenic hypercholesterolaemia,\textsuperscript{17} have provided evidence of a link between LDL cholesterol and type 2 diabetes, compatible with the findings from the present study. However, it is far from certain that all LDL cholesterol-lowering interventions will increase risk of type 2 diabetes, as not all share the same mechanism of action. The major site of both statins and PCSK9 inhibitors is thought to be the liver, through increased cellular membrane expression of the LDL receptor. The liver is also the site of action of the investigational apolipoprotein B antisense oligonucleotide mipomersen, whereas ezetimibe, the other licensed LDL cholesterol lowering drug, acts in the intestine to limit LDL cholesterol absorption. A potential unifying mechanism might be pancreatic β cell LDL receptor upregulation, increased lipid accumulation, and β cell dysfunction,\textsuperscript{18} but this suggestion will need to be tested experimentally.

In conclusion, genetic variants in PCSK9 that associate with lower concentrations of LDL cholesterol are also associated with a modestly higher risk of type 2 diabetes and with associated differences in measures of glycaemia and bodyweight. Investigators of ongoing and future randomised controlled trials of PCSK9 inhibitors should carefully monitor changes in metabolic markers, including bodyweight and glycaemia, and the incidence of type 2 diabetes in study participants. Genetic studies of the type used here could be more widely used to interrogate the safety and efficacy of novel drug targets.

Contributors

AFS, DIS, MVH, RSP, FWA, J-PC, BJK, ADH, DP, and NS contributed to the conception and design of the study. AFS, DIS, and MVH designed the analysis scripts shared with individual centres. AFS did the meta-analysis and had access to all the data. AFS, DIS, and MVH drafted the report. RSP, ZF-H, DML, FP1, BLH, EHY, CP, MM, Evl, GHK, ID, KN, ES-T, JD, LB, TL, SC, JW1, SK, KW, DM, JW2, RM, GW, PW, YB-S, SMc, JFP, MKI, CW, AS-G, PM-V, AN, AGP, NCO-M, YWdS, GM, GF, SGuA, CS, NJW, CL, RS, JL, MBo, SMa, AP, RK, ATA, HP, LLNH, NG, OP, TH, AL, KSS, JC, SEH, MBr, TK, HH, DSC, CAM, Medicine, University of Regensburg, Regensburg, Germany (S Baumstein); Department of Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK (1 Meadle FRS); Division of Pharmacoeconomics and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Faculty of Science, Utrecht University, Utrecht, Netherlands (A H Maitland-van der Zee, E V Baranova MSc); CNRS UMR Bl19, European Genomic Institute for Diabetes (EGGD), Institut Pasteur de Lille, University of Lille, Lille, France (P Frouge, D Thuillier MSc, A Bonnerot); Renal and Cardiovascular Epidemiology, Centre de Recherche en Épidémiologie et Santé des Populations (CEESP), INSERM U1018, Villejuif, France (B Balkau PhD, Institut du Thorax, INSERM, CNRS, University of Nantes, CHU de Nantes, Nantes, France (Prof B Carou MD); Institute for Social and Economic Research, University of Essex, Colchester, Essex, UK (M Smart PhD, Y Bau PhD, Prof M Kumari PhD); Harvard Medical School Center for Cardiovascular Disease Prevention, Brigham and Women’s Hospital, Boston, MA, USA (Prof M F Ridker MD, D I Sherman PhD); Department of Epidemiology, Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA, USA (A P Reiner MD); Anschutz Medical Campus, University of Colorado Denver, Denver, CO, USA (Prof A Lange PhD); Biomedical and Translational Informatics, Geisinger Health System, Danville, PA, USA (M D Ritchie PhD); Department of Biochemistry and Molecular Biology, Huck Institutes of the Life Sciences, Pennsylvania State University, University Park, PA, USA (M D Ritchie); and Department of Surgery, University of Pennsylvania, Philadelphia, PA, USA (B Keaning PhD).

Correspondence to: Dr Amand F Schmidt, Institute of Cardiovascular Science, University College London, London NW1 2DA, UK amand.schmidt@ucl.ac.uk

Figure 4: Correlation between PCSK9 associations with LDL cholesterol concentration and type 2 diabetes

Effect estimates are presented as mean difference in LDL cholesterol concentration (mmol/L) and odds ratios (ORs) for the incidence or prevalence of type 2 diabetes, with 95% CIs. Associations are presented per LDL cholesterol-decreasing allele. The Pearson correlation coefficient, regression line (grey), and its 95% CI (red) were calculated by weighting the SNPs for the inverse of the variance in the type 2 diabetes association. Excluding the SNP with the largest effect on LDL cholesterol (rs11591147) resulted in a correlation coefficient of 0.993 and a p value of 0.437.
Declaration of interests
KH or his institution have received honoraria for consultancy, Aegerion, Pfizer, AstraZeneca, Sanofi, Regeneron, KOWA, Ionis Pharmaceuticals, and Cerenis. GKH has received research support from Aegerion, AMGEN, Sanofi, AstraZeneca, and Synagoga. BC has received research funding from Pfizer and Sanofi, and has received personal fees for lectures from AstraZeneca, Pierre Fabre, Janssen, Eli Lilly, MSD Merck & Co, Novo Nordisk, Sanofi, and Takeda, and has acted as a consultant or advisory panel member for Amgen, Eli Lilly, Novo Nordisk, Sanofi, and Regeneron. DP has consulted for Sanofi on two occasions in previous employment (related to PCSK9 inhibitors) and was an investigator on clinical trials of PCSK9 inhibition funded by Amgen. NS has consulted for Amgen and Sanofi (related to PCSK9 inhibitors) and was an investigator on clinical trials of PCSK9 inhibition funded by Amgen. He has also consulted for MSD, Boehringer Ingeheim, Janssen, and Novo Nordisk. DJS has consulted for Pfizer for work unrelated to this report. AP has been a consultant and a member of an advisory panel for Amgen. EI is a scientific advisor and consultant for Precision Wellness Inc and a scientific advisor for Cellink, for work unrelated to this paper. All other authors declare no competing interests.

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