Vitamin D concentration, obesity, and risk of diabetes: a mendelian randomisation study

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Summary

Background Low plasma 25-hydroxyvitamin D (25[OH]D) concentration and high BMI have been associated with increased risk of diabetes. We tested the hypotheses that genetic variants associated with low concentrations of 25(OH)D are associated with diabetes, and that the effect on diabetes of genetic variants associated with high BMI is partly mediated through reduced plasma 25(OH)D concentration.

Methods In this mendelian randomisation study, we genotyped 96 423 white Danes aged 20–100 years from three studies. 5037 of these participants had type 2 diabetes. All individuals were surveyed for diabetes from 1977 to 2011. 31 040 participants had their plasma 25(OH)D concentration measured and 90 169 had their BMI measured. We assessed the effects of genetic variation in *DHCR7* (related to endogenous production) and *CYP2R1* (related to liver conversion) on plasma 25(OH)D concentration, and the effects of variation in *FTO*, *MCR4*, and *TMEM18* on BMI. We then assessed the effect of genetic variation in these genes on risk of type 2 diabetes, and the association of measured plasma 25(OH)D concentration and BMI with risk of type 2 diabetes. We did a mediation analysis to assess how much of the effect of BMI genotype on risk of diabetes was mediated through plasma 25(OH)D concentration.

Findings The odds ratios for type 2 diabetes for participants who had a 20 nmol/L reduction in plasma 25(OH)D concentration as determined by genetics were 1·51 (95% CI 0·98–2·33) for *DHCR7* and 1·02 (0·75–1·37) for *CYP2R1*. The *DHCR7* allele score was significantly associated with increased risk of type 2 diabetes (p for trend=0·04), whereas the allele score for *CYP2R1* was not. For participants who had a measured 20 nmol/L reduction in plasma 25(OH)D concentration, the adjusted odds ratio for type 2 diabetes was 1·16 (1·08–1·25). For participants who had a 10 kg/m² increase in BMI as determined by genetics, the odds ratio for type 2 diabetes was 19·4 (6·4–59·1); this was associated with an 11·1 nmol/L (2·6–19·6) lower plasma 25(OH)D concentration. For a 10 kg/m² increase in measured BMI, the adjusted odds ratio for type 2 diabetes was 4·33 (3·70–5·07); this was associated with a 9·1 nmol/L (8·4–9·7) lower plasma 25(OH)D concentration. Mediation analysis showed that 3% (1–5) of the effect of BMI on risk of type 2 diabetes was mediated through lowered plasma 25(OH)D concentrations.

Interpretation Genetic variants associated with low plasma 25(OH)D concentrations are associated with type 2 diabetes and low plasma 25(OH)D concentrations might be a modest mediator between obesity and increased risk of diabetes. Genetic variants associated with endogenous production of 25(OH)D might partially explain this increased risk; however, as findings for *DHCR7* were not statistically significant, our results require independent confirmation.

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Introduction

Vitamin D deficiency, which has been associated with obesity, might lead to diabetes. Observational evidence supports this assertion: vitamin D deficiency is associated with increased risk of type 1 and type 2 diabetes[1,2] and obesity is associated with low plasma 25-hydroxyvitamin D (25[OH]D) concentrations in observational studies and in a mendelian randomisation study.[3] Furthermore, results of randomised intervention studies indicate that obesity causes diabetes.[4–7] However, observational associations are susceptible to confounding and reverse causation.[8]

An alternative to classical observational studies are mendelian randomisation studies, which are largely free of confounding and reverse causation.[8,9] In such studies, genetic variants associated with lifelong low plasma concentration of 25(OH)D could be used to test the unconfounded association between low vitamin D concentrations and risk of diabetes. Likewise, genetic variants associated with lifelong increased BMI could be used to assess whether an unconfounded association exists between BMI and both low 25(OH)D concentration and risk of diabetes.

We tested the hypotheses that low plasma 25(OH)D concentrations caused by genetic variants are associated with increased risk of type 2 or any diabetes, and that the effect of genetic variants associated with high BMI on diabetes is partly mediated through reduction of plasma 25(OH)D concentration. The latter hypothesis requires that genetically increased BMI is associated with low plasma 25(OH)D concentration and with increased risk of diabetes.

Methods

Study design and participants

Figure 1 shows the study design. We did several observational analyses of relations between measured

variables (susceptible to confounding and reverse causation) and several genetic analyses of relations between genotypes and measured variables (not susceptible to confounding or reverse causation). First, we assessed the relation between genetic variants associated with vitamin D and plasma 25(OH)D concentration (figure 1A), and the relation between genetic variants thought to have a role in BMI and measured BMI (figure 1A). Second, we assessed the association between measured plasma 25(OH)D concentration and BMI (figure 1B). Third, we assessed the effect of genetic variants thought to have a role in BMI on plasma 25(OH)D concentration (figure 1C). Fourth, we did observational assessments of the relation between plasma 25(OH)D concentration and diabetes, and BMI and diabetes (figure 1D). Finally, we assessed the effects of genetic variants associated with vitamin D and BMI on the risk of diabetes (figure 1E).

We included participants from three studies. The Copenhagen General Population Study was initiated in 2003 with ongoing enrolment.[10] Individuals aged 20–100 years were invited from the national Danish Central Person Register to represent the general Danish population. We included 25 580 participants with data for plasma 25(OH)D concentration for the observational analyses and 80 404 participants with all genotypes for the genetic analyses. The Copenhagen City Heart Study was initiated in 1976–78, with follow-up in 1981–83, 1991–94, and 2001–03,[11] and was recruited as was the Copenhagen General Population Study. We included 5460 participants with data for plasma 25(OH)D concentration for observational analyses and 9765 participants for genetic analyses. The Copenhagen Ischemic Heart Disease Study includes patients from the Copenhagen region referred for coronary angiography in 1991–2011.[10,12] For genetic analyses we included 6254 participants with a diagnosis of ischaemic heart disease and with all genotypes. The studies were approved by institutional review boards and Danish ethics committees, and participants provided written informed consent. No participants appeared in more than one study, all were white—of Danish descent—and none were lost to follow-up.

Procedures

25(OH)D concentration was measured with the LIAISON 25 OH Vitamin D TOTAL Assay (DiaSorin, Stillwater, MN, USA) by investigators who were masked to phenotypic and genotypic data. For the Copenhagen General Population Study, plasma samples were collected in 2004–05 (n=12 489; stored at –80°C for roughly 5 years) and 2009–11 (n=13 091; tested immediately). For the Copenhagen City Heart Study, plasma samples were collected in 1981–83 (n=5460; stored at –20°C for roughly 26 years). Samples from the Copenhagen Ischemic Heart Disease Study were not analysed for plasma 25(OH)D. Assay precision was tested daily, whereas assay accuracy was tested monthly with an external quality control programme. The interassay coefficient of variance was 10% for low-level controls (around 40 nmol/L) and 8% for high-level controls (about 135 nmol/L).

Genotyping was done with TaqMan assays by researchers masked to data for 25(OH)D concentrations and phenotypes. We used genotypes with the strongest and largest association with 25(OH)D concentration in genome-wide association studies.[13,14] We chose genetic variants around *DHCR7* (rs7944926 and rs11234027; indicating endogenous vitamin D production) and *CYP2R1* (rs10741657 and rs12794714; indicating vitamin D liver conversion). We did not include polymorphisms in the gene encoding the vitamin D binding protein, since we wanted to study polymorphisms affecting bioavailability of vitamin D, not just total plasma concentrations.

For BMI, we a priori selected genotypes with the largest reported effect sizes[10,15]—*FTO* (rs9939609), *MC4R* (rs17782313), and *TMEM18* (rs6548238). We verified genotypes by sequencing 48 selected samples in total. Call rates for the genotypes were >99% after two reruns.

For *DHCR7* and *CYP2R1*, we constructed an aggregate allele score of 0–4, on the basis of the sum of the number of 25(OH)D-lowering alleles across the two genotypes in each gene. Likewise, we constructed an aggregate allele score of 0–6 based on the number of alleles associated with high BMI across the three genes.[10] We used the data for the Caucasian population from the HapMap project[16] to check whether the genotypes we selected for 25(OH)D were in linkage disequilibrium with genotypes associated with obesity or diabetes on chromosome 11. Because of the role of *DCHR7* in endogenous cholesterol synthesis and the role *CYP2R1* might have in metabolism of steroid hormones, we tested the association of *DHCR7* and *CYP2R1* allele scores with plasma cholesterol, cortisol, estradiol, and testosterone.

Participants reported their smoking habits, income, and intensity of leisure-time physical activities in self-reported questionnaires, reviewed together with an examiner on the day of attendance. To assess diabetes,

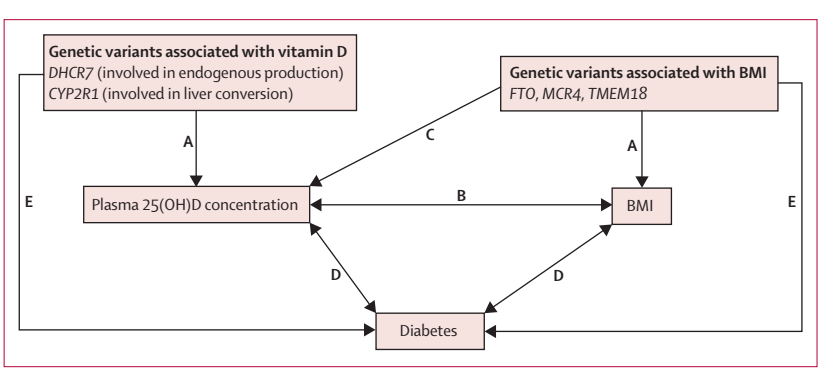

Figure 1: **Study design and associations tested**
We investigated five possible associations. Two-sided arrows represent observational associations (B and D), one-sided arrows represent genetic associations indicating the direction of the associations (A, C, and E).

participants were surveyed in national registries from 1977 until death, emigration, or May 2011, whichever came first. Patients were classed as having either type 1 diabetes (ICD-8 code 249; ICD-10 code E10) or type 2 or unspecified diabetes (ICD-8 code 250; ICD-10 code E11, E13, or E14), on the basis of data in the national Danish Patient Registry or the national Danish Causes of Death Registry, self-reported diabetes, use of antidiabetic drugs, or a non-fasting plasma glucose concentration of greater than 11 mmol/L.[2] The appendix shows details for participants who developed diabetes in each cohort. We used both prevalent and incident cases for genetic analyses.

See **Online** for appendix

Statistical analysis

We used Stata/SE (version 12.0) for all analyses. We assessed Hardy-Weinberg equilibrium with χ^2 tests and linkage disequilibrium with Haploview.

For **Haploview** see http://www.broadinstitute.org/scientific-community/science/programs/medical-and-population-genetics/haploview/haploview

The three studies were pooled to maximise statistical power, and all analyses were adjusted for study. All analyses including measurements of plasma 25(OH)D concentration (figure 1A–D) were adjusted for month of blood sample to account for seasonal variation. We also did statistical tests with adjusted BMI or standardised 25(OH)D values. We log transformed the data to obtain percentage differences. We compared the results from the observational analyses (figure 1B, 1D) and genetic analyses (figure 1C, 1E) with a generalised Hausman test. Observational analyses were adjusted for age, sex, smoking, leisure-time physical activity, income, and month of blood sampling; the estimates for 25(OH)D and BMI were adjusted for each other because both were included in the regressions.

For our analysis of the association between genotypes associated with vitamin D and plasma 25(OH)D concentration, and between genotypes associated with BMI and measured BMI (figure 1A), we used Cuzick's non-parametric trend test. We assessed the reliability of genotypes and allele scores as genetic instruments (ie, a genetic variant that affects the outcome only through its effect on the specific investigated phenotype) with the *F*-statistic—*F* greater than 10 indicates that the instrument is sufficiently strong for instrumental variable analyses (referred to in our study as genetic analyses)—and by R^2 as a measure of variation explained by genotype.[9]

To assess the relation between BMI and plasma 25(OH)D concentration (figure 1B), we used adjusted linear regression models. Because the 31040 participants with plasma 25(OH)D measurements all had BMI genotype and BMI measurement data, we used a generalised method of moments estimator for instrumental variable analysis to assess the relation between genetic variants associated with BMI and plasma 25(OH)D concentration (figure 1C). For subsequent analyses in which measurements were only available for a subset of participants, we used the Wald estimator.

We used adjusted Cox regression—corrected for regression dilution bias[17,18]—to calculate hazard ratios (HRs) for the association of measured 25(OH)D concentration and BMI with risk of diabetes (figure 1D). We investigated the association between genotypes associated with low 25(OH)D and high BMI and the risk of diabetes (figure 1E) by Cox regression adjusted for sex, study, and year of birth, with age as the timescale. The increases in the HRs for diabetes for a 1 nmol/L decrease in 25(OH)D concentration and a 1 kg/m² increase in BMI in the Copenhagen City Heart Study were used to predict theoretical HRs for diabetes associated with the changes in 25(OH)D concentration and BMI caused by the genotypes, as done previously.[12] The assumption that a genotype associated with low 25(OH)D should confer the same increase in diabetes risk as that of low plasma 25(OH)D concentration rests on the assumption that the observational association between plasma 25(OH)D concentration and diabetes is unconfounded, which is unlikely. However, we believe that a theoretical HR is informative.

We calculated instrumental variable estimates of genetically determined odds ratios (figure 1E) with the Wald-type estimator, which is the exponentiated ratio of the log-transformed odds ratio of the allele score with outcome (diabetes) to the coefficient of the relationship between allele score with exposure (25[OH]D or BMI).[9,10,19,20] The effect of genotypes on BMI was extrapolated to correspond to a 10 kg/m² increase in BMI for genetic analyses to increase the parity between observational and genetic estimates. The genetic estimate was an estimate of the association free of confounding and reverse causation. We used a 10 kg/m² increment because it roughly corresponds to a shift from normal weight to obesity. We derived SEs for the Wald-type instrumental variable log odds ratios by the delta method.[20] The adjusted 25(OH)D allele score and adjusted BMI allele score coefficient come from 31040 and 84526 participants, respectively, who had both valid genotype and phenotype data. Observational odds ratios were derived with adjusted logistic regression models.

Finally, we did mediation analysis with genetic instruments using the product of coefficients method (taking the product of coefficients derived from steps C and D in figure 1), and calculating the indirect effect of BMI genotype on risk of diabetes mediated through 25(OH)D concentration compared with the total effect of BMI allele score on risk of diabetes.[21] The observational mediation analysis was done the same way except using measured BMI instead of the BMI allele score. SEs were calculated using the delta method.[21] In both genetic and observational mediation analyses, plasma 25(OH)D concentrations (not 25[OH]D allele score) were used, since the mediation analysis assumes an association between the causal predictor and the mediator. Furthermore, any mediation analysis assumes causality between the predictors, mediators, and outcome.

Role of the funding source

The sponsors had no role in the design and conduct of the study, collection, management, analyses, and interpretation of data, or preparation or approval of the article. SA and BGN had complete access to the data, and BGN had final responsibility for the decision to submit for publication.

Results

Plasma 25(OH)D concentration and measured BMI were associated with several potential confounders, whereas allele scores used as instruments for 25(OH)D or BMI were not (appendix). *DHCR7* and *CYP2R1* were in linkage equilibrium (R^2=0%), implying that variants of the two genes were unrelated (appendix). For genetic variants within *DHCR7* the R^2 was 49% and for genetic variants within *CYP2R1* the R^2 was also 49%. We detected no association of *DHCR7* and *CYP2R1* allele scores with plasma cholesterol, cortisol, estradiol, and testosterone (appendix). Genetic variants on chromosome 11 shown by genome-wide association studies to be associated with diabetes or obesity showed no sign of linkage disequilibrium with *DHCR7* and *CYP2R1* variants in the HapMap population (appendix). All genotypes were in Hardy-Weinberg equilibrium.

Plasma 25(OH)D concentrations were 4·1 nmol/L (95% CI 2·8–5·4) lower for participants with an allele

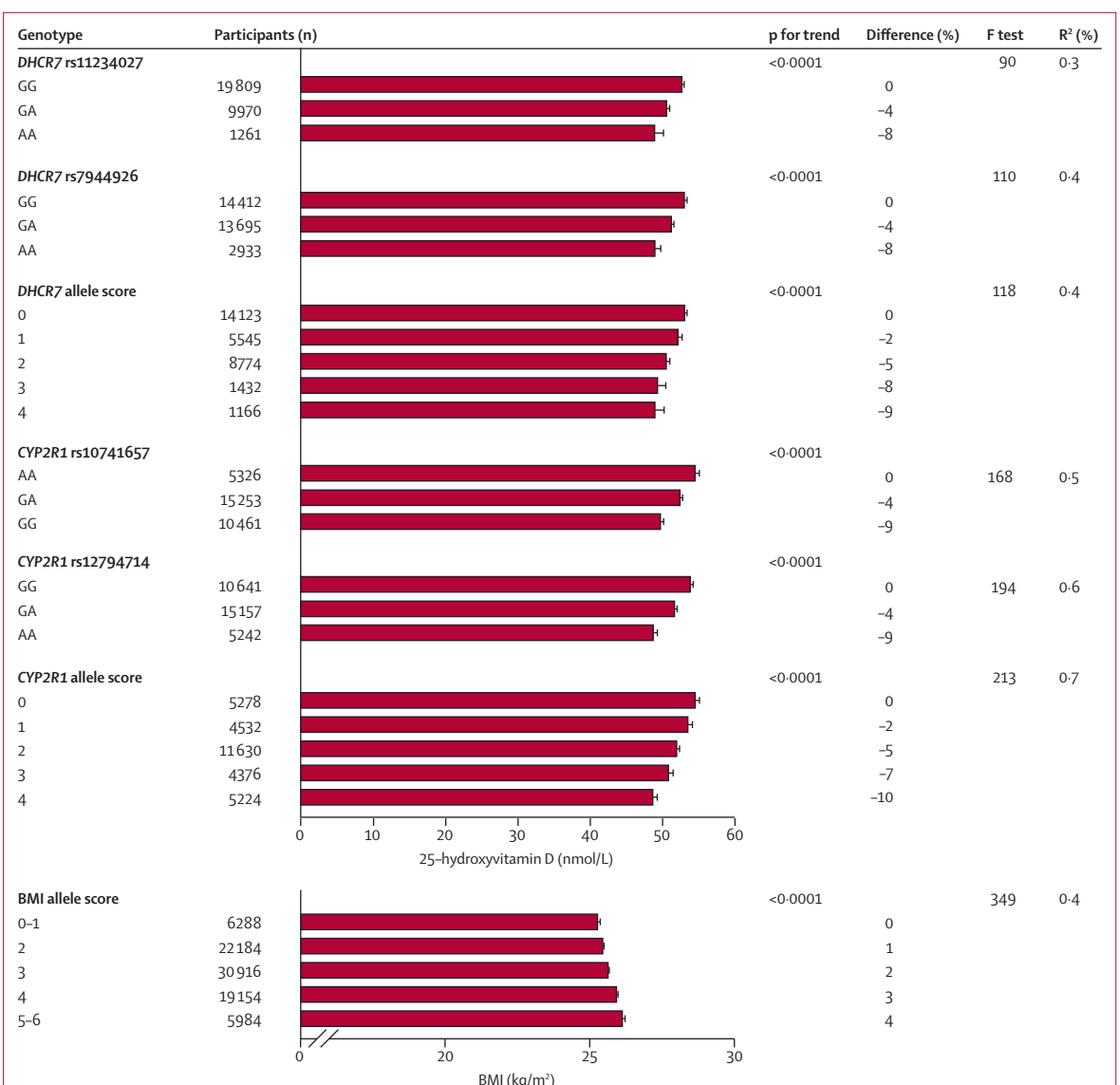

Figure 2: **Effects of genotypes and allele scores on plasma 25-hydroxyvitamin D concentration and BMI**

Corresponds to Figure 1A. Shows means and 95% CIs. p values are for trend across genotypes and allele scores, *F*-test is for statistical strength of the genotype or allele score as an instrument, and R^2 is a measure of explained variation. 25-hydroxyvitamin D analyses are based on 31040 participants, and the BMI analyses are based on 84526 participants where both genotype and phenotype were measured.

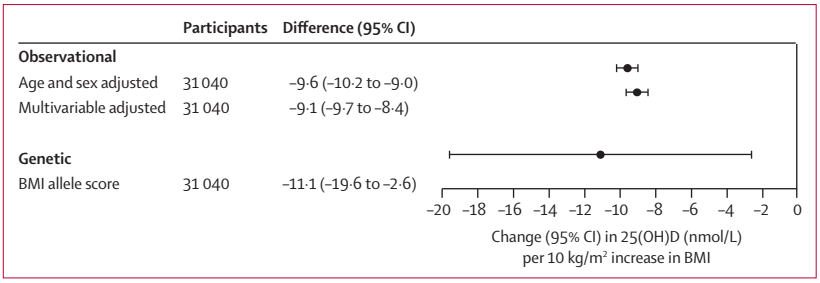

Figure 3: **Observational and genetic associations between BMI and 25(OH)D concentration**
Corresponds to Figure 1B, C. For the observational versus genetic association p=0·73. P value was evaluated by a Hausman test. 25(OH)D=25-hydroxyvitamin D.

score of 4 versus those with a score of 0 for *DHCR7*, and 5·9 nmol/L (5·0–6·7) lower for participants with an allele score of 4 compared with those with a score of 0 for *CYP2R1* (figures 1A, 2). Likewise, BMI was 0·86 kg/m² (0·72–0·99) higher for participants with a BMI allele score of 5–6 compared with those with a score of 0–1.

Obese participants had 9·5 nmol/L (95% CI 8·7–10·2) lower plasma 25(OH)D concentration than normal weight participants (figure 1B, appendix). In genetic analyses, a 10 kg/m² increase in BMI was associated with a 11· 1 nmol/L (2·6–19·6) reduction in plasma 25(OH)D (figure 1C), with a corresponding observational reduction of plasma 25(OH)D of 9·1 nmol/L (8·4–9·7; figure 3). Low allele scores for 25(OH)D were not associated with change in measured BMI (appendix). When we repeated the tests with adjusted BMI or standardised 25(OH)D values the results were much the same (data not shown).

The multivariable adjusted HR for type 2 diabetes was 1·96 (95% 1·26–3·03) for plasma 25(OH)D concentration of 25 nmol/L or less versus 50 nmol/L or greater. The HR was 6·44 (5·30–7·83) for BMI of 30 kg/m² or greater versus less than 25 kg/m² (figure 1D, appendix).

Increasing allele score for *DHCR7* was associated with a higher risk of diabetes (p for trend=0.04; figures 1E, 4). Increasing BMI allele score was also associated with increased risk of diabetes (p for trend <0.0001; figures 1E, 4). For tests of trend with p values close to 0·05, however, one should also judge consistency of dose-response relationships avoiding uncritical interpretation of p values only. We report no significant associations between *CYP2R1* genotypes or allele scores and risk of diabetes (figure 4). For illustrative purposes, we estimated that a 10% reduction of plasma 25(OH)D concentration caused by 25(OH)D-lowering genotypes should theoretically predict increased risk of type 2 diabetes up to an HR of 1·09 (1·07–1·10; figure 4). We obtained similar results for any diabetes as the outcome and adjusting the *DHCR7* analyses for BMI (appendix).

For type 2 diabetes, the odds ratio for a genetically determined 20 nmol/L lower plasma 25(OH)D concentration via endogenous production (*DHCR7*) was 1·51 (95% CI 0·98–2·33) and via liver conversion (*CYP2R1*) it was 1·02 (0·75–1·37; figures 1E, 5A), with a corresponding observational multivariable adjusted odds ratio of 1·16 (1·08–1·25; figures 1D, 5A). The odds ratio for type 2 diabetes was 19·4 (6·4–59·1) for a genetically determined 10 kg/m² higher BMI (figures 1E, 5A), with a corresponding observational multivariable adjusted odds ratio of 4·33 (3·70–5·07; figures 1D, 5A). Use of any diabetes as the outcome produced similar results (figure 5B).

Mediation analyses showed that 3% (95% CI 1–5; p=0·01) of the observational association of BMI with risk of type 2 diabetes was mediated through low plasma 25(OH)D concentration. Corresponding genetic mediation analysis using a BMI allele score instead of measured BMI, showed similar results with an estimate of 4% (0–7; p=0·02). For any diabetes, the results were much the same (data not shown).

Discussion

To our knowledge, this is the first study to report a relation between *DHCR7* genotypes associated with low 25(OH)D concentration via endogenous production and increased risk of type 2 diabetes; this result was not statistically significant, although the relation was significant when assessing any diabetes. Thus, these results should be viewed as hypothesis-generating and should be confirmed in independent studies. We also show that genotypes associated with high BMI are associated with low plasma 25(OH)D concentration and with increased risk of type 2 diabetes. Last, we show that the effect of BMI on risk of type 2 diabetes might be partly mediated through low plasma 25(OH)D concentration.

Several lines of evidence should be considered for assessment of the role of vitamin D in the development of diabetes (panel). First, observational studies indicate a dose-dependent increase in risk of type 2 diabetes with low plasma 25(OH)D concentration.[2] Second, in-vitro and animal studies suggest that vitamin D deficiency or vitamin D receptor knockout impairs glucose-induced insulin secretion, insulin receptor expression, insulin-induced glucose transport, and β-cell function.[22–24] Third, animal and human studies suggest that the insulin secretory response and insulin sensitivity improve after vitamin D supplementation in patients with vitamin D deficiency, and with high plasma 25(OH)D concentrations.[22,23,25–27] Fourth, genetic variants in *DHCR7* and *CYP2R1* are associated with increased risk of type 1 diabetes.[28] Finally, we show that genetically determined lifelong low plasma 25(OH)D concentrations (via reduced endogenous production) might be associated with increased risk of type 2 diabetes, although the result was only statistically significant when using the combined endpoint of any diabetes. However, randomised intervention trials have shown contradictory results for vitamin D supplementation on risk of diabetes,[29,30] and no recent studies of glucose metabolism disorders have found that vitamin D supplementation improves glycaemic control in diabetes.[31]

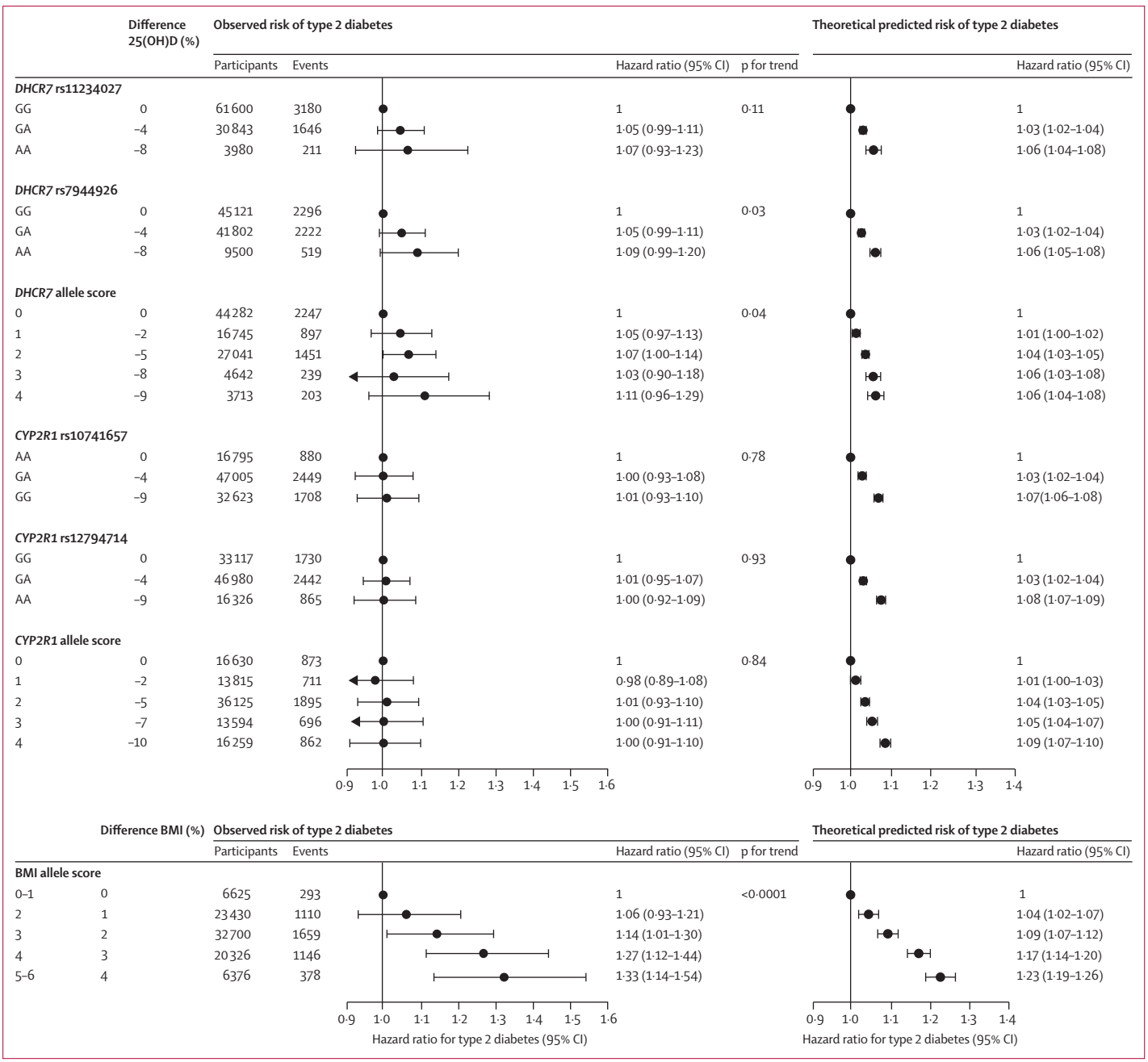

Figure 4: **Risk of type 2 diabetes according to genotypes and allele scores associated with reduced 25(OH)D concentration and increased BMI**
Corresponds to Figure 1E. Based on 96 423 (for 25-hydroxyvitamin D) and 89 457 (for BMI) genotyped participants. 25(OH)D=25-hydroxyvitamin D.

That low 25(OH)D concentration via *DHCR7*, but not via *CYP2R1*, is associated with increased risk of diabetes was a surprising finding and should be interpreted carefully. One possible explanation is that low vitamin D concentration via reduced endogenous production (from sunlight exposure) is associated with increased diabetes risk, whereas low vitamin D concentration via liver conversion from all sources (sunlight, food, and supplementation) is not. Alternatively, *CYP2R1* genetic variants might be poorly predictive of plasma 25(OH)D concentration because these variants were preferentially associated with plasma 25(OH)D concentration at only high concentrations (appendix), contrary to genetic variants of *DHCR7*.[14,28,32] A third explanation is that another factor associated with endogenous production of vitamin D, but not with vitamin D derived from diet or supplementation, is responsible for the apparent association between 25(OH)D and diabetes. Last, because

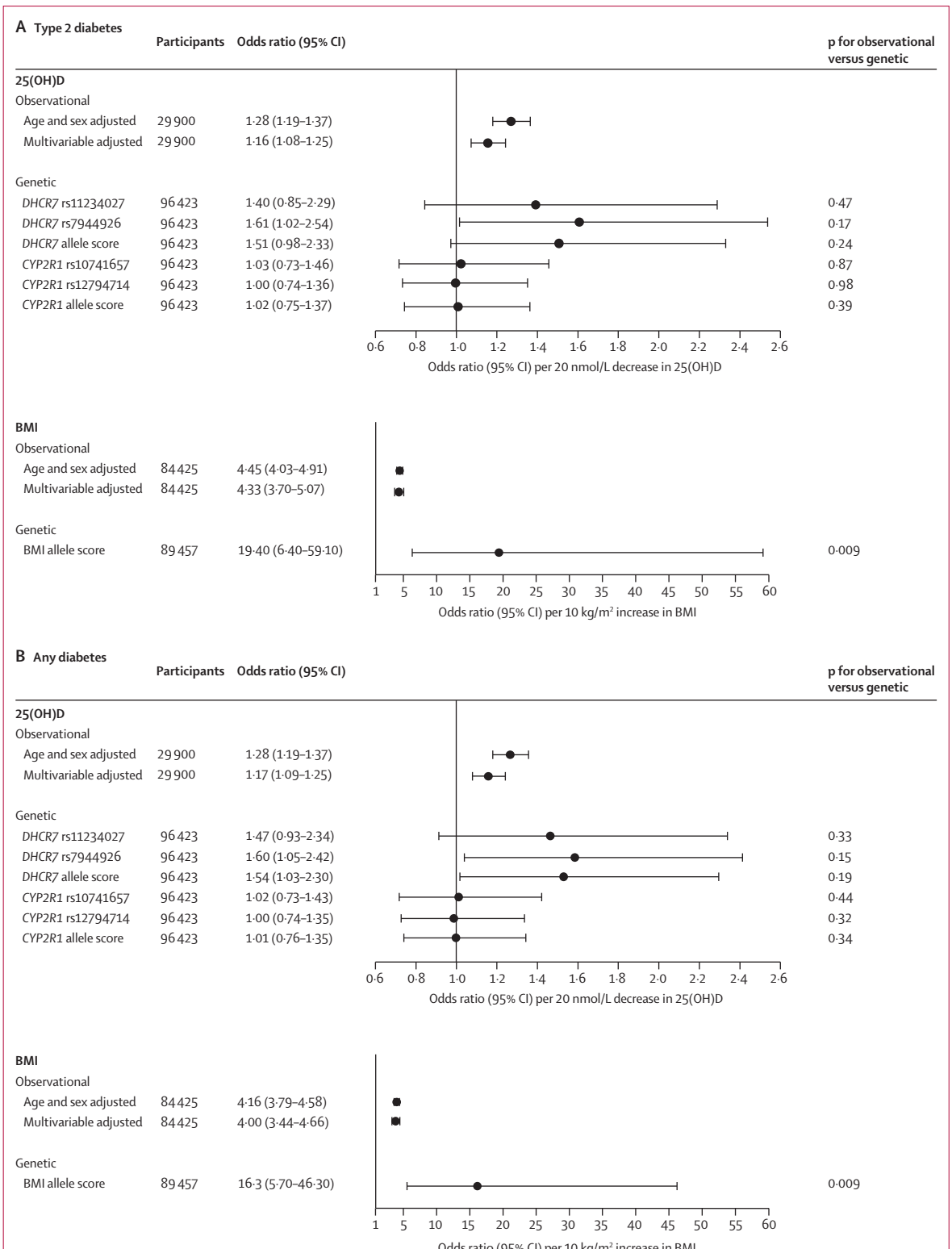

Figure 5: **Estimates of risk of type 2 diabetes (A) and any diabetes (B) for a 20 nmol/L decrease in 25-hydroxyvitamin D concentration and a 10 kg/m² increase in BMI, for observational and genetic measures**

Corresponds to Figure 1D, E. Observational estimates were done by logistic regression including incident cases only; genetic estimates were by instrumental variable analyses. P value was evaluated by a Hausman test. 25(OH)D=25-hydroxyvitamin D.

no convincing a priori reason exists for why *DHCR7* should have an effect and not *CYP2R1*, we cannot exclude that the findings could have arisen by chance.

In agreement with randomised intervention trials[4–7] and previous similar genetic studies,[33,34] our study also shows that genetic variants associated with high BMI increase the risk of type 2 diabetes irrespective of other risk and lifestyle factors. Furthermore, genetic variants associated with high BMI were associated with low plasma 25(OH)D concentrations, in accordance with another mendelian randomisation study[3] and with observational epidemiological studies.[35] This finding suggests that low plasma 25(OH)D concentrations might be a mediator between high BMI and increased risk of diabetes, as also supported by our mediation analyses. However, a valid mediation analysis requires that the predictor (BMI) and the mediator (25[OH]D) are causally associated with the outcome (diabetes). In our study, only 3–4% of the effect of BMI on diabetes was mediated through reduced 25(OH)D concentration. Thus, high BMI could be associated with other pathways—eg, greater production of adipokine hormones—and genetic variants associated with high BMI could act on diabetes via such alternative pathways.

The contrast between the observational HRs for the association between 25(OH)D or BMI and diabetes, and the HRs from prediction of 25(OH) concentrations according to genetic variants, suggest that our study only addressed a fraction of the complex interactions between BMI, 25(OH)D, and diabetes. Thus, we cannot make firm conclusions about cause–effect relationships. Potential limitations of the mendelian randomisation approach include presence of genetic pleiotropy and linkage disequilibrium between the genetic variants used as instruments and other genetic variants associated with outcome. However, genetic variants in *DHCR7* and *CYP2R1* were not associated with changes of concentrations of cholesterol or steroid hormones processed through these gene products, and *DHCR7* and *CYP2R1* genetic variants were not in linkage disequilibrium with each other or with other variants associated with BMI or any diabetes in genome-wide association studies. Another potential limitation is that we studied white Danes only, and 25(OH)D concentrations vary with sunlight exposure and skin colour. Furthermore, an association with intermediate parameters such as fasting glucose and HbA_{1c} could have strengthened our findings; however, we did not have such data. Last, the best method for measurement of 25(OH)D concentration is mass spectrometry, which we did not use. However, any imprecision introduced by our method would diminish associations—not inflate them—and therefore cannot account for our results.

Strengths of our study include the large sample size and the use of multidirectional mendelian randomisation to delineate genetically determined relations between vitamin D, BMI, and diabetes. Additionally, the instruments we used for genetic analyses were strong (F>10). Last, our participants were all white and of Danish descent, eliminating population admixture as a potential drawback.

Our findings do not accord with findings from randomised intervention trials,[29,30] the gold standard for establishing causality. However, the setting of our study was different: we assessed lifelong exposure to low 25(OH)D concentration and we studied a population with low mean plasma 25(OH)D concentrations. The results of randomised intervention trials stem mostly from post-hoc analyses with different supplementation strategies. Ongoing trials of vitamin D supplementation and diabetes will assess whether a causal relation exists.[36]

Panel: Research in context

Systematic review

We searched Medline and PubMed with the terms "obesity", "body mass index", "vitamin D", "25-hydroxyvitamin", "diabetes", "type 2 diabetes", and "type 1 diabetes" for reports published up to June 30, 2013 in English. We also searched the reference lists of review articles that our search returned for randomised intervention trials showing a causal effect of BMI on type 2 diabetes,[4–8] genetic analyses showing an effect of BMI on vitamin D,[3] and studies showing an association between genotypes linked to low 25-hydroxyvitamin D concentration and type 1 diabetes.[32]

Interpretation

Our study suggests that people who have genetic variants associated with low endogenous production of 25-hydroxyvitamin D could have increased risk of type 2 diabetes. Similar associations exist for type 1 diabetes.[32] Furthermore, in keeping with previous studies we show an association of genotypes linked to high BMI with high risk of type 2 diabetes[33,34] and low 25-hydroxyvitamin D concentrations.[32] 3–4% of the effect of BMI on risk of type 2 diabetes seems to be mediated through reduced 25-hydroxyvitamin D concentrations. These findings will only have implications for public health policies if they are confirmed in other similar studies or—even better—in randomised intervention trials.

Contributors

SA and PB-J searched the published work. SA, SEB, and BGN designed the study. SA, PB-J, SEB, and BGN gathered data and generated laboratory data. SA, PB-J, SEB, and BGN analysed and interpreted data. SA drafted the Article and designed the figures. All authors revised the Article.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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