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HDL Cholesterol and Risk of Type 2 Diabetes: A Mendelian Randomization Study

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Observationally, low levels of HDL cholesterol are consistently associated with increased risk of type 2 diabetes. Therefore, plasma HDL cholesterol increasing has been suggested as a novel therapeutic option to reduce the risk of type 2 diabetes. Whether levels of HDL cholesterol are causally associated with type 2 diabetes is unknown. In a prospective study of the general population (*n* = 47,627), we tested whether HDL cholesterol–related genetic variants were associated with low HDL cholesterol levels and, in turn, with an increased risk of type 2 diabetes. HDL cholesterol–decreasing gene scores and allele numbers associated with up to −13 and −20% reductions in HDL cholesterol levels. The corresponding theoretically predicted hazard ratios for type 2 diabetes were 1.44 (95% CI 1.38–1.52) and 1.77 (1.61–1.95), whereas the genetic estimates were nonsignificant. Genetic risk ratios for type 2 diabetes for a 0.2 mmol/L reduction in HDL cholesterol were 0.91 (0.75–1.09) and 0.93 (0.78–1.11) for HDL cholesterol–decreasing gene scores and allele numbers, respectively, compared with the corresponding observational hazard ratio of 1.37 (1.32–1.42). In conclusion, genetically reduced HDL cholesterol does not associate with increased risk of type 2 diabetes, suggesting that the corresponding observational association is due to confounding and/or reverse causation.

Low levels of HDL cholesterol are consistently associated with increased risk of type 2 diabetes in epidemiological studies (1,2). Therefore plasma HDL cholesterol increasing has been suggested as a novel therapeutic option to reduce risk of type 2 diabetes (3–5). Low levels of HDL cholesterol and high levels of triglycerides are part of the diabetic dyslipidemia (6–8), and high levels of triglycerides have recently been shown to be a marker of type 2 diabetes rather than playing a causal role (9). Whether low levels of HDL cholesterol causally influence the risk of type 2 diabetes remains to be determined.

Experimental evidence suggests that levels of HDL cholesterol may contribute to the pathophysiology of type 2 diabetes through direct effects on plasma glucose levels (5). Indeed, HDL cholesterol stimulates pancreatic β-cell insulin secretion and modulates glucose uptake in skeletal muscle in different experimental and human settings (10–13). However, genetic data from humans and mice relating genes influencing HDL cholesterol levels with glycemic control and risk of type 2 diabetes are conflicting (11,12,14–17). Furthermore, genome-wide association studies have not identified associations between such HDL cholesterol–related genes and risk of type 2 diabetes (18,19).

Despite consistent observational evidence to support an association between low HDL cholesterol and type 2 diabetes, such data cannot overcome the problems of confounding and reverse causation, and therefore do not have the ability to establish causality (20). One useful method to help untangle causality is Mendelian randomization, where HDL cholesterol–related genetic variants are used as unconfounded proxies for lifelong low HDL cholesterol levels to test a potential causal association with type 2 diabetes risk (21).

We tested the following hypotheses in 47,627 individuals from the general population: *1*) low HDL cholesterol

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levels are associated with the increased risk of type 2 diabetes in epidemiological studies; *2*) HDL cholesterol–related genetic variants affect the levels of HDL cholesterol; *3*) HDL cholesterol–related genetic variants, causing lifelong low levels of HDL cholesterol, were associated with the risk of type 2 diabetes to the extent predicted by the observational data; and *4*) HDL cholesterol levels are causally associated with the risk of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Studies were approved by institutional review boards and Danish ethical committees and were conducted according to the Declaration of Helsinki. Written informed consent was obtained from participants. All participants were white and of Danish descent. There was no overlap between studies.

Participants

We included participants from the Copenhagen City Heart Study (CCHS) and the Copenhagen General Population Study (CGPS), totaling 47,627 participants, of whom 2,587 developed type 2 diabetes during 36 years of survey. Details of these studies have previously been described (17,22,23).

Events and Covariates

Information on diagnoses of type 2 diabetes and ischemic heart disease were collected as previously described (17, 22,23). Follow-up time began at the time of blood sampling (observational risk by levels of HDL cholesterol), or at the establishment of the National Danish Patient Registry (1 January 1977), or on the birthday of the participant, whichever came later (risk by genotypes). Follow-up ended at occurrence of event, death (n = 7,135), emigration (n = 278), or on 23 April 2013 (last update of registry), whichever came first. Median follow-up was 7 years (range 0–22 years) and 36 years (range 0–36 years) in epidemiological and genetic analyses, respectively, and was 100% complete. Definitions of covariates are detailed in the legends to Supplementary Tables 2–4.

Genotyping

We carefully selected nine variants in five genes encoding proteins known to have a major influence on biogenesis and levels of HDL cholesterol (Supplementary Fig. 1). ATP-binding cassette transporter A1 (*ABCA1*) N1800H (rs146292819), cholesteryl-ester transfer protein (*CETP*) −629C>A (rs1800775) and *Taq*1bG>A (rs708272), lecithin-cholesterol acyltransferase (*LCAT*) S208T (rs4986970), hepatic lipase (*LIPC*) −480C>T (rs1800588), apolipoprotein A1 (*APOA1*) S36A (rs199759119), F71Y (rs138407155), K107del (rs number not available), and L144R (rs number not available) were genotyped using an ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Life Technologies, Paisley, U.K.) and TaqMan-based assays. Combining all genotypes, we generated two different genetic instruments for HDL cholesterol based on *1*) an HDL cholesterol gene score in quartiles and *2*) number of HDL cholesterol–decreasing alleles carried by each participant. The first genetic instrument was calculated for each participant using a weighted sum of HDL cholesterol–decreasing alleles, as previously performed by Talmud et al. (24), and subsequently categorized into four groups of approximate equal size, named "gene score quartiles" for simplicity. The weights correspond to the per–HDL-decreasing allele β-coefficients adjusted for age, sex, and study cohort (Supplementary Table 1 and Supplementary Fig. 2). The second genetic instrument was a simple, unweighted counting of the number of HDL cholesterol–decreasing alleles in each individual. Biochemical analyses were performed as previously described (17,22,23).

Statistical Analysis

Data were analyzed using STATA/SE version 12.0 (Stata Corp., College Station, TX). The statistical strategy used for the Mendelian randomization analysis was performed as previously described (25). In brief, Cox proportional hazards regression models with age as time scale and delayed entry (left truncation) were used in observational and genetic analyses. A potential causal relationship was assessed using instrumental variable analysis, and the risks associated with 0.2 mmol/L reductions in HDL cholesterol were calculated.

RESULTS

Baseline characteristics of the 47,627 study participants by type 2 diabetes status are shown in Supplementary Table 2 for the CCHS and CGPS combined, and in Supplementary Table 3 for the CCHS and CGPS separately. The risk factors for type 2 diabetes were equally distributed among gene score quartiles (Supplementary Table 4). All genotypes were in Hardy-Weinberg equilibrium (all P values >0.21) (Supplementary Table 1).

HDL Cholesterol and Risk of Type 2 Diabetes: Observational Estimates

The risk of type 2 diabetes increased stepwise as a function of high to low HDL cholesterol quartiles (P for trend = 3×10^{-58}) (Fig. 1). For individuals in the fourth quartile versus the first quartile, the hazard ratio was 5.74 (95% CI 4.43–7.43) for type 2 diabetes. Results were similar in the CCHS and the CGPS separately (Supplementary Fig. 3). The hazard ratio was 4.82 (4.00–5.82) per 1 mmol/L decrease in HDL cholesterol, corresponding to previous estimates (2).

Genotype and Levels of HDL Cholesterol

The association between genetic variants, combined as an HDL cholesterol gene score in quartiles and as number of HDL cholesterol–decreasing alleles, with levels of HDL cholesterol and triglycerides are shown in Fig. 2. HDL cholesterol gene score quartiles and number of HDL cholesterol–decreasing alleles were associated with differences in HDL cholesterol levels of up to −13% (P for trend = 4×10^{-287}) for individuals in the fourth versus the first quartile, and up to −20% (P for trend = 2×10^{-299}) for individuals with seven to eight decreasing alleles versus zero to one. The corresponding influence on triglycerides (Fig. 2 and Supplementary Fig. 4) and on measures of glucose metabolism and inflammation was minimal (Supplementary Fig. 5).

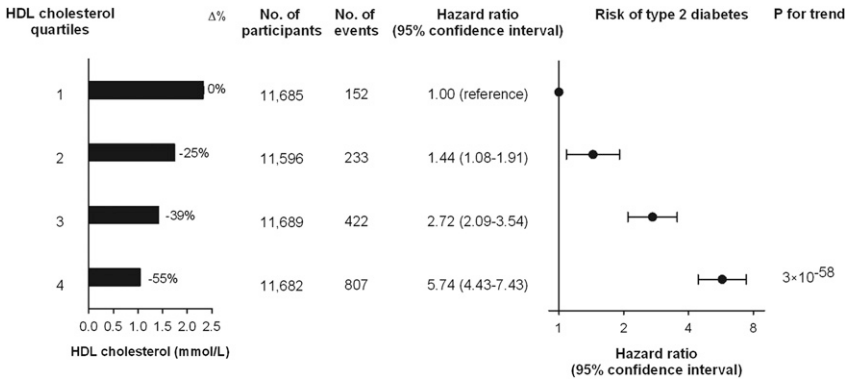

Figure 1—Risk of type 2 diabetes as a function of plasma HDL cholesterol level in quartiles in the CCHS and the CGPS combined. Individuals with type 2 diabetes before blood sampling were excluded, leaving 46,652 individuals for this analysis. Multifactorial adjustment was for age (as time scale), sex, study, BMI, hypertension, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy, and educational level. Hazard ratios including CIs were corrected for regression dilution bias. *P* for trend from Cox regression trend test. To convert HDL cholesterol to mg/dL, divide by 0.0259.

Genotype and Risk of Type 2 Diabetes

The theoretically predicted and observed risks of type 2 diabetes as a function of HDL cholesterol gene score quartiles and number of HDL cholesterol–decreasing alleles are shown in Fig. 3, middle and right panels, respectively. The 13 and 20% reductions in HDL cholesterol observed, respectively, in the fourth versus the first HDL cholesterol gene score quartile and in individuals with seven to eight HDL cholesterol–decreasing alleles versus zero to one, theoretically predicted increased hazard ratios of 1.44 and 1.77, respectively, for type 2 diabetes (Fig. 3, middle panel). However, neither the HDL cholesterol gene score quartiles nor the number of HDL cholesterol–decreasing alleles were associated with the risk of type 2 diabetes (*P* for trend = 0.41 and 0.55, respectively) (Fig. 3, right panel).

In sensitivity analyses, the lack of association with type 2 diabetes remained across individual genetic variants and strata of type 2 diabetes risk factors (Supplementary Figs. 6–8).

HDL Cholesterol and Risk of Type 2 Diabetes: Causal Estimates

We examined a potential causal association of HDL cholesterol with the risk of type 2 diabetes in a Mendelian randomization approach using the HDL cholesterol gene score in quartiles and number of HDL cholesterol–decreasing alleles as genetic instruments in instrumental variable analysis. This analysis incorporates both the

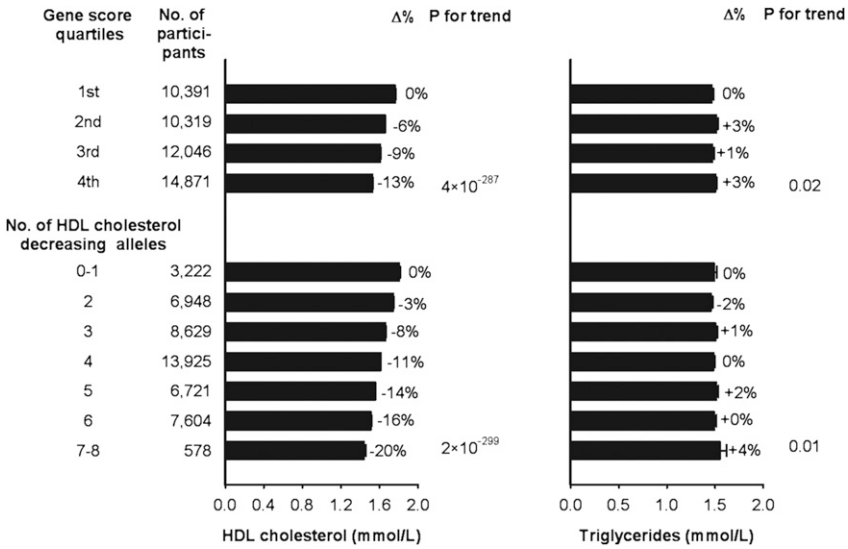

Figure 2—Plasma levels of HDL cholesterol and triglycerides as a function of HDL cholesterol gene score quartiles and number of HDL cholesterol–decreasing alleles in the CCHS and the CGPS combined (n = 47,627). Values are mean or geometric mean (triglycerides) and SEM. Percentages are changes in mean level from first quartile and zero to one decreasing allele, respectively. *P* values are tests for trend by linear regression. To convert HDL cholesterol to mg/dL, divide by 0.0259. To convert triglycerides to mg/dL, divide by 0.0113.

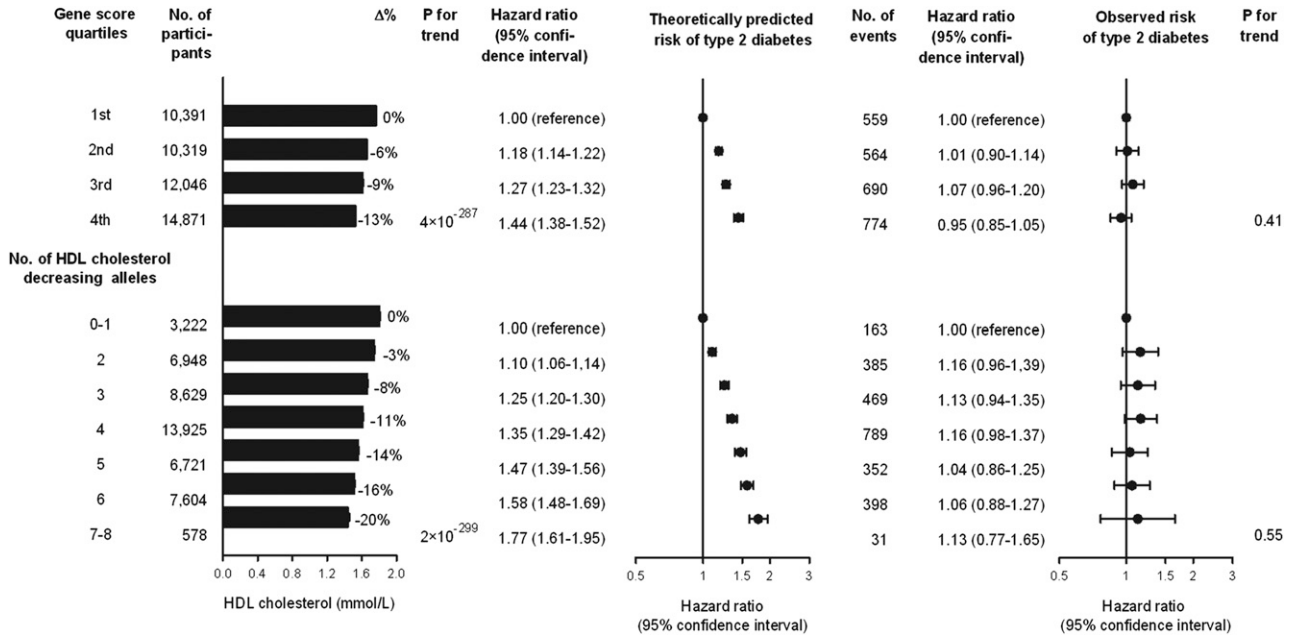

Figure 3—Mean plasma HDL cholesterol levels (left) and corresponding theoretically predicted (middle) and observed (right) hazard ratios for type 2 diabetes as a function of HDL cholesterol gene score quartiles (top) and number of HDL cholesterol–decreasing alleles (bottom) in the CCHS and the CGPS combined (n = 47,627). Theoretically predicted hazard ratios were calculated from delta HDL cholesterol levels and the known association of HDL cholesterol levels with risk of type 2 diabetes in the observational study (see Fig. 1). The corresponding theoretically predicted 95% CIs were based on the distribution of changes in HDL cholesterol levels generated from simulated HDL cholesterol data sets (normal distributed with one million entries), corresponding to the HDL cholesterol distributions observed in each category of gene score quartiles and number of HDL cholesterol–decreasing alleles. Observed hazard ratios were multifactorially adjusted for age (as time scale), sex, study, BMI, hypertension, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy, and educational level. HDL cholesterol values are mean (±SEM). P values are test for trend. To convert HDL cholesterol to mg/dL, divide by 0.0259.

genotype effect on HDL cholesterol levels and the effect of genotype on the risk of type 2 diabetes. The causal risk ratio for type 2 diabetes for a 0.2 mmol/L reduction in genetically determined HDL cholesterol was 0.91 (95% CI 0.75–1.09) and 0.93 (0.78–1.11), respectively, using the HDL cholesterol gene score quartiles and number of HDL cholesterol–decreasing alleles as genetic instruments (Fig. 4). In contrast, the observational, multifactorially adjusted hazard ratio for type 2 diabetes for a 0.2 mmol/L reduction in HDL cholesterol was 1.37 (95% CI 1.32–1.42) (P for comparison = 2×10^{-5} and 3×10^{-5} with HDL score quartiles and number of HDL cholesterol–decreasing alleles, respectively). The F statistics for the genetic instruments were 447 and 231, respectively, indicating substantial strength to ensure statistical validity of the genetic instruments (21).

DISCUSSION

The principal novel finding of this study is that lifelong low levels of HDL cholesterol due to genetic variation in HDL cholesterol–related genes are not associated with the increased risk of type 2 diabetes in the general population. These findings suggest that low levels of HDL cholesterol per se do not cause type 2 diabetes and thus that the corresponding observational association may be due to reverse causation. Consequently, this questions plasma HDL cholesterol increasing as a novel therapeutic option for treatment or prevention of type 2 diabetes, as recently suggested (3–5).

The present negative findings are in line with a previous study of 40,000 individuals in which we found no association between loss-of-function mutations in *ABCA1* and *ABCG1* and the risk of type 2 diabetes (17), and in line with recent genome-wide association studies and meta-analyses, which did not detect any associations between HDL cholesterol–related genes and type 2 diabetes (18,19). In contrast, in smaller studies, genetic variation in *ABCA1* has been associated with the increased risk of type 2 diabetes (14), and one study suggested that loss-of-function mutations in *ABCA1* were associated with impaired β-cell function, but not with the development of type 2 diabetes (15).

The typical dyslipidemia of type 2 diabetes is characterized by high triglyceride levels, low HDL cholesterol levels, and normal LDL cholesterol levels (6–8). When triglyceride-rich lipoproteins are high, as in type 2 diabetes, exchange of cholesteryl esters in HDL particles for triglycerides in triglyceride-rich lipoproteins is increased, an exchange mediated by CETP, resulting in reduced levels of HDL cholesterol in plasma (7). Hence the inverse relationship between high triglycerides and low levels of HDL cholesterol reflects a physiological process, mediated by plasma CETP, and most likely explains why levels of HDL cholesterol are low in patients with type 2 diabetes,

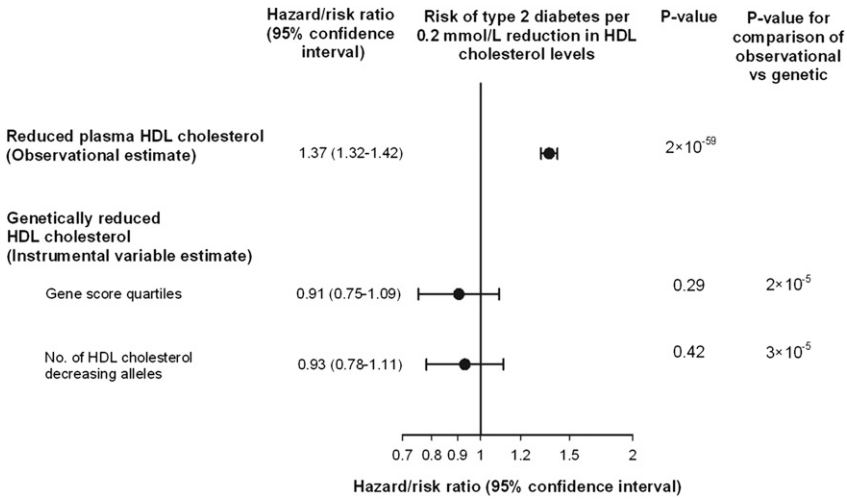

Figure 4—Observational and causal genetic risk estimates for type 2 diabetes for a 0.2 mmol/L reduction in HDL cholesterol. The observational risk estimate for a 0.2 mmol/L reduction in HDL cholesterol is from the CCHS and the CGPS combined as a hazard ratio multifactorially adjusted for age (as time scale), sex, study, BMI, hypertension, smoking, alcohol intake, physical inactivity, postmenopausal status and hormonal replacement therapy in women, lipid-lowering therapy, and educational level. The causal risk estimates for a 0.2 mmol/L reduction in HDL cholesterol are for HDL cholesterol gene score quartiles and number of HDL cholesterol–decreasing alleles in the CCHS and the CGPS combined as risk ratios. *P* values are for significance of risk estimates, and *P* values for comparison are for differences between observational and causal genetic risk estimates using the Altman and Bland method.

although other mechanisms have been proposed as well (7). In contrast to the causal association between triglycerides, marking atherogenic remnant cholesterol, and ischemic heart disease (23), a recent Mendelian randomization study showed that raised triglyceride levels were not causally associated with the risk of type 2 diabetes (9). Collectively, these data together with the present findings constitute the most convincing human genetic evidence to date that changes in HDL cholesterol and triglyceride levels are secondary to the diabetes disease process, as would be expected from the well-known diabetic dyslipidemia (6–8). A prediabetes state with increased glucose levels and BMI and dyslipidemia was observed when only those individuals with type 2 diabetes after blood sampling were considered. Thus, the observational association between low HDL cholesterol and the increased risk of type 2 diabetes is most likely explained by reverse causation, due to a state of prediabetes prior to the diabetes diagnosis.

In conclusion, combining rare and common genetic variation in five key HDL cholesterol–related genes into a strong genetic instrument, we found that genetic and hence lifelong reductions in HDL cholesterol levels are not associated with the increased risk of type 2 diabetes in the general population. These data suggest that reduced levels of HDL cholesterol are not a causal risk factor for type 2 diabetes, and that the corresponding observational association is most likely explained by reverse causation. This questions plasma HDL cholesterol increasing as a novel therapeutic option for reducing the risk of type 2 diabetes.

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Author Contributions. C.L.H. and R.F.-S. designed, analyzed, and interpreted the data and wrote the manuscript. A.T.-H. and B.G.N. contributed substantially to conception and design of the study and revised the manuscript for important intellectual content. R.F.-S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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