Mendelian randomisation, lipids, and cardiovascular disease

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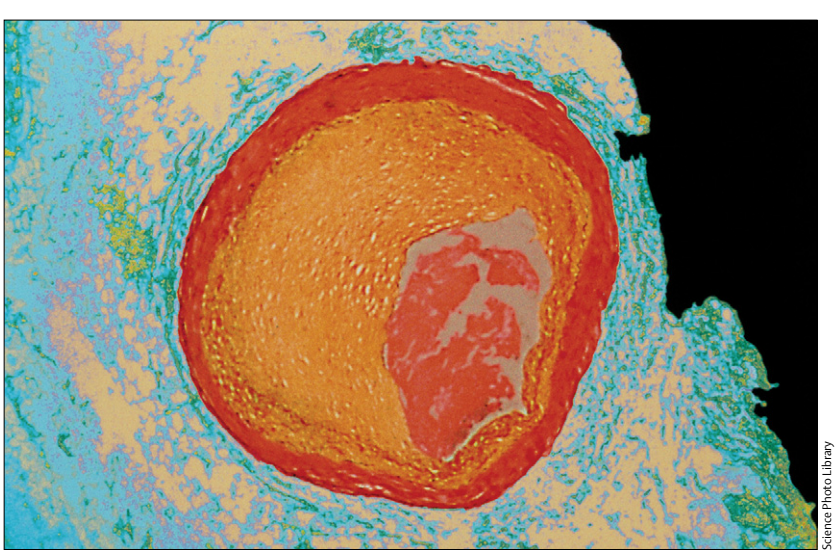
In *The Lancet,* Benjamin Voight and colleagues[1] use mendelian randomisation analysis to investigate the relation between HDL cholesterol and coronary heart disease. High HDL cholesterol concentration is associated with reduced risk of coronary heart disease in observational studies,[2] but whether the association is causal cannot be unequivocally ascertained from these studies alone, and whether raising of HDL cholesterol would be an effective means to reduce risk of coronary heart disease remains uncertain. The ILLUMINATE trial of torcetrapib, a cholesteryl ester transport protein (CETP) inhibitor that raises HDL cholesterol, was stopped early because of an increase in the number of cardiovascular events.[3] This outcome might have been due to an off-target action of torcetrapib on blood pressure that appears not to be shared by newer drugs from the same class, and the effect of these drugs on risk of coronary heart disease is now being evaluated in phase 3 trials.

Mendelian randomisation exploits genetic information to investigate associations between exogenous or endogenous exposures (or both) and disease outcomes.[4] The random allocation of genotype at gametogenesis (like the randomised allocation to a drug in a clinical trial) minimises confounding. If HDL-cholesterol-mediated pathways were causal for coronary heart disease, carriers of genetic variants associated with high concentrations of HDL cholesterol (representing lifelong exposure to high HDL cholesterol) would be expected to have a reduced risk of coronary heart disease.

Voight and colleagues used a rare non-synonymous variant in the endothelial lipase gene (*LIPG* Asn396Ser, minor allele frequency about 2·6%) that showed a consistent association with high HDL cholesterol concentrations, but no association with LDL cholesterol or triglycerides. In view of the observed effect of the *LIPG* variant on HDL cholesterol, this allele was expected to result in roughly a 13% reduced risk of coronary heart disease. However, in pooled data from 20 913 cases and 95 407 controls, the observed odds ratio for coronary heart disease was 0·99 (95% CI 0·88–1·11), suggesting that *LIPG*-mediated increases in HDL cholesterol do not reduce risk of the disease. In Voight and colleagues' analysis, a panel of 14 common variants, each with a small effect on HDL cholesterol,[5] was combined into a genetic risk score. The risk score was also not associated with coronary heart disease in pooled data from 12 482 cases and 41 331 controls (odds ratio per SD increase in weighted genetic risk 0·93, 95% CI 0·68–1·26). On the basis of these results, genetically raised HDL cholesterol concentrations do not seem to reduce risk of coronary heart disease—an observation that calls into question whether raising of HDL cholesterol therapeutically would translate into the expected clinical benefit.

The validity of a mendelian randomisation analysis is determined by various factors. First, the intermediate phenotype (HDL cholesterol) must associate with the outcome (coronary heart disease). Second, the genetic instrument must associate with the outcome only through effects on the intermediate phenotype. Third, the genetic instrument should be sufficiently strongly associated with the intermediate phenotype to avoid weak instrument bias.[6] The *LIPG* variant used here had a fairly large effect on HDL cholesterol, but is rare in the population and so might not represent a strong instrument. We should note, however, that the case-control analysis of this variant was adequately powered to detect even a small effect, and the negative association of this variant can be regarded as definitive. For the genetic risk score, variants with the largest effects were excluded because of associations with other lipid fractions, and although each of the



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Coloured light micrograph of an occluded coronary artery

risk score variants showed association with HDL cholesterol, individual effect sizes were small, which might not translate into a powerful instrument even when combined.

These findings are consistent with previous mendelian randomisation analyses that also refute a causal role of HDL cholesterol in coronary heart disease.[7,8] Furthermore, they are supported by rare mendelian disorders such as Tangier disease, caused by mutations in *ABCA1*, resulting in very low HDL cholesterol concentrations, which do not show convincing associations with premature coronary disease.[9] One notable exception is that variants in *CETP* that raise HDL cholesterol have been reported to be associated with lowered risk of coronary heart disease,[10] a finding replicated by Voight and colleagues. The *CETP* variant, however, has effects on both HDL and LDL cholesterol and therefore attribution of its protective effect solely to HDL cholesterol might not be valid. For the same reason, ongoing randomised trials of CETP inhibitors might not provide definitive evidence about a causal role for HDL cholesterol in coronary heart disease. However, even if HDL cholesterol concentration is not validated as a causal factor, further investigation into the mechanisms of HDL cholesterol dysfunction[11] and its role in coronary heart disease is warranted.

This report adds to a growing number of mendelian randomisation analyses investigating biomarkers of coronary heart disease. Previous reports suggest that genetic variants underlying lipoprotein (a)[12] and triglycerides are likely to be causal,[13] whereas those in C-reactive protein are not.[14] These studies have focused on single variants as instruments, but combination of variants into a score represents a potential improvement of the technique. As the research area matures, a consensus for methodology and reporting will be important, particularly when the potentially powerful, but also complex, genetic risk score approach is used. Taken together with adequately powered studies, mendelian randomisation is likely to yield insights that can both guide public health policy and prioritise potential therapeutic targets.

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SEH is medical director and minority shareholder of the UCL start-up coronary heart disease risk genetic testing company Storegene, and has received honoraria for speaking at educational meetings with a pharmaceutical sponsor, donating all sums to medical charities. MVH and SCH declare that they have no conflicts of interest.

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