Abstract

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Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study.


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BACKGROUND: High plasma HDL cholesterol is associated with reduced risk of myocardial infarction, but whether this association is causal is unclear. Exploiting the fact that genotypes are randomly assigned at meiosis, are independent of non-genetic confounding, and are unmodified by disease processes, mendelian randomisation can be used to test the hypothesis that the association of a plasma biomarker with disease is causal.

METHODS: We performed two mendelian randomisation analyses. First, we used as an instrument a single nucleotide polymorphism (SNP) in the endothelial lipase gene (LIPG Asn396Ser) and tested this SNP in 20 studies (20,913 myocardial infarction cases, 95,407 controls). Second, we used as an instrument a genetic score consisting of 14 common SNPs that exclusively associate with HDL cholesterol and tested this score in up to 12,482 cases of myocardial infarction and 41,331 controls. As a positive control, we also tested a genetic score of 13 common SNPs exclusively associated with LDL cholesterol.

FINDINGS: Carriers of the LIPG 396Ser allele (2.6% frequency) had higher HDL cholesterol (0.14 mmol/L higher, p=8×10(-13)) but similar levels of other lipid and non-lipid risk factors for myocardial infarction compared with non-carriers. This difference in HDL cholesterol is expected to decrease risk of myocardial infarction by 13% (odds ratio [OR] 0.87, 95% CI 0.84-0.91). However, we noted that the 396Ser allele was not associated with risk of myocardial infarction (OR 0.99, 95% CI 0.88-1.11, p=0.85). From observational epidemiology, an increase of 1 SD in HDL cholesterol was associated with reduced risk of myocardial infarction (OR 0.62, 95% CI 0.58-0.66). However, a 1 SD increase in HDL cholesterol due to genetic score was not associated with risk of myocardial infarction (OR 0.93, 95% CI 0.68-1.26, p=0.63). For LDL cholesterol, the estimate from observational epidemiology (a 1 SD increase in LDL cholesterol associated with OR 1.54, 95% CI 1.45-1.63) was concordant with that from genetic score (OR 2.13, 95% CI 1.69-2.69, p=2×10(-10)).

INTERPRETATION: Some genetic mechanisms that raise plasma HDL cholesterol do not seem to lower risk of myocardial infarction. These data challenge the concept that raising of plasma HDL cholesterol will uniformly translate into reductions in risk of myocardial infarction.


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