

# Abstract

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## Triglyceride-mediated pathways and coronary disease: collaborative analysis of 101 studies.

Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration, Sarwar N, Sandhu MS, Ricketts SL, Butterworth AS, Di Angelantonio E, Boekholdt SM, Ouwehand W, Watkins H, Samani NJ, Saleheen D, Lawlor D, Reilly MP, Hingorani AD, Talmud PJ, Danesh J.

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**BACKGROUND:** Whether triglyceride-mediated pathways are causally relevant to coronary heart disease is uncertain. We studied a genetic variant that regulates triglyceride concentration to help judge likelihood of causality.

**METHODS:** We assessed the -1131T>C (rs662799) promoter polymorphism of the apolipoprotein A5 (APOA5) gene in relation to triglyceride concentration, several other risk factors, and risk of coronary heart disease. We compared disease risk for genetically-raised triglyceride concentration (20,842 patients with coronary heart disease, 35,206 controls) with that recorded for equivalent differences in circulating triglyceride concentration in prospective studies (302 430 participants with no history of cardiovascular disease; 12,785 incident cases of coronary heart disease during 2.79 million person-years at risk). We analysed -1131T>C in 1795 people without a history of cardiovascular disease who had information about lipoprotein concentration and diameter obtained by nuclear magnetic resonance spectroscopy.

**FINDINGS:** The minor allele frequency of -1131T>C was 8% (95% CI 7-9). -1131T>C was not significantly associated with several non-lipid risk factors or LDL cholesterol, and it was modestly associated with lower HDL cholesterol (mean difference per C allele 3.5% [95% CI 2.6-4.6]; 0.053 mmol/L [0.039-0.068]), lower apolipoprotein AI (1.3% [0.3-2.3]; 0.023 g/L [0.005-0.041]), and higher apolipoprotein B (3.2% [1.3-5.1]; 0.027 g/L [0.011-0.043]). By contrast, for every C allele inherited, mean triglyceride concentration was 16.0% (95% CI 12.9-18.7), or 0.25 mmol/L (0.20-0.29), higher ( $p=4.4 \times 10^{-24}$ ). The odds ratio for coronary heart disease was 1.18 (95% CI 1.11-1.26;  $p=2.6 \times 10^{-7}$ ) per C allele, which was concordant with the hazard ratio of 1.10 (95% CI 1.08-1.12) per 16% higher triglyceride concentration recorded in prospective studies. -1131T>C was significantly associated with higher VLDL particle concentration (mean difference per C allele 12.2 nmol/L [95% CI 7.7-16.7];  $p=9.3 \times 10^{-8}$ ) and smaller HDL particle size (0.14 nm [0.08-0.20];  $p=7.0 \times 10^{-5}$ ), factors that could mediate the effects of triglyceride.

**INTERPRETATION:** These data are consistent with a causal association between triglyceride-mediated pathways and coronary heart disease.

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