Optimal blood lipid levels counterbalance high polygenic risk of coronary artery disease in 130,000 individuals

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Topic(s):
Risk Factors and Prevention – Epidemiology

Background
Coronary artery disease (CAD) is a complex multifactorial disease leading cause of morbidity and mortality worldwide. Identifying individuals at high risk is crucial to guide lifestyle and therapeutics interventions. Polygenic Risk Score (PRS) is a weighted sum of common genetic variants that showed to be able to identify a population at greater than threefold risk of CAD compared to the average. Notably, individuals at high genetic risk who adhere to a healthy lifestyle displayed between two and three-fold relative risk reduction, compared to individuals with a poor lifestyle. Despite such evidences, a systematic assessment of the interplay between PRS and CAD risk factors such as blood lipid levels in contributing to the overall CAD risk is still lacking.

Methods
We analysed in more than 130,000 individuals of the UK Biobank the association of incident CAD with PRS and blood lipids (LDL, TC, HDL, TC:HDL, LDL:HDL) using a Cox Proportional Hazard Model. We defined three populations: i) Carriers: PRS >95%, Reminders: PRS <=95% and Reference: PRS <=95% with optimal blood lipid levels. Carriers and Reminders were stratified by blood lipid levels according to international guidelines. We investigated a potential interaction between blood lipids and PRS and assessed the relative increased risk magnitude in Carriers and Reminders for different blood lipid levels.

Results
Carriers showed between two and three fold increased risk of incident CAD compared to Reminders at each non-optimal blood lipid level and their ratios. Carriers with LDL between 130 and 160 mg/dL showed higher CAD risk (HR 3.65, 95% CI 2.85-4.63) than Reminders with LDL above 190 mg/dL (HR 2.73, 95% CI 2.18-3.40). Despite that, Carriers displayed non significant increased risk respect to the Reference population for the following blood lipid thresholds: LDL <115 mg/dL, TC <200 mg/dL, HDL >70 mg/dL, LDL:HDL <2.0 and TC:HDL <3.5. The association between LDL cholesterol and CAD was modified by the PRS due to significant interaction (P-value <0.005). The magnitude of increased CAD risk by LDL was higher in Carriers (HR 1.64 95% CI 1.45-1.86 per LDL level) compared to Reminders (HR 1.40, 95% CI 1.34-1.46 per LDL level).

Conclusion
Using the largest prospective genotyped cohort available to date, we identified for the first time a significant interaction between LDL and genetics in determining CAD incidence. This result have deep implications in a CAD primary prevention perspective. For example individuals with high PRS and borderline-high LDL levels (130-159 mg/dL) are not currently considered to be at elevated risk, despite having higher CAD risk than Reminders with statin-recommended LDL level (>190 mg/dL). Finally, the evidence that optimal lipid levels counterbalance high genetic risk opens new scenarios in the research of targeted risk reduction in the era of precision medicine.
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