Genetically-influenced lower TG levels on top of genetically-influenced lower LDL-C levels are associated with an improved lipoprotein profile

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Abstract

Aim and objectives: Lipoprotein lipase (*LPL*) is a key player in lipoprotein remnant clearance, and therefore a druggable target. Recent Mendelian randomization studies have provided evidence that TG-lowering alleles in the *LPL* pathway are associated with lower risk of coronary disease independently of LDL-C–lowering genetic mechanisms (Lotta et al. JAMA Cardiology. 2018). Here, we aimed to provide insight into the casual mechanisms behind these effects by assessing through Mendelian randomization the effect of genetically-influenced lower TG levels via *LPL* alleles on the nuclear magnetic resonance (NMR) determined metabolomic profile on top of genetically-influenced lower LDL-C levels.

Methods: We quantified over 100 lipoprotein (sub)components in 4,838 participants of the NEO study. The TG genetic score was based on five TG-lowering *LPL* alleles and the LDL-C score on 19 LDL-C–lowering alleles. These genetic scores were dichotomized at their corresponding median value to “naturally randomize” the participants into 4 groups comprising high/low TG levels and high/low LDL-C levels and were analysed in a 2 × 2 factorial design. Replication of these analyses was performed in an independent cohort of Oxford Biobank (OBB) (N=6999).

Results: In the discovery cohort, 44 % were male, and the mean (SD) age was 55.9 (6.01) years. Naturally randomizing people to both lower TG and lower LDL-C levels resulted in the highest number (102) of significant NMR-metabolite associations and the largest effect sizes of these associations. The effects of the *LPL* and LDL-C genetic scores were additive, but independent from each other (p-interaction<0.05). Our findings were confirmed in the replication cohort.

Conclusion: Our study provides evidence of an additional beneficial effect of pharmacologically enhanced *LPL* activity on top of cholesterol lowering, which may consequently further improve cardiovascular outcomes.