Cardiovascular events in people with discordantly high levels of small/medium LDL particles

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Is small/medium LDL-P discordance associated with elevated risk of MACE?

Background

Low-density lipoprotein cholesterol (LDL-C) is the canonical risk factor, and interventional target, for major adverse cardiovascular events (3-point **MACE**).

LDL particles (LDL-P), carrying a single Apo-B, range from small to large and vary in cholesterol content and atherogenicity. **Small to medium (S/M)** particles are often considered more atherogenic.

S/M LDL-P concentration may be higher than predicted by LDL-C levels (**discordance**) in **metabolically perturbed** states (e.g. T2DM, obesity) or with modified protein activity such as by CETP (e.g. in people with genetic variants for ***CETP* Loss or Gain of function**) which alter LDL-P subclass combinations.

We sought to evaluate the contribution of **S/M LDL-P discordance** on MACE risk that was **independent of LDL-C** by comparing predicted and observed S/M LDL-P in the UK Biobank.

Methods

QC'ed Nightingale NMR were available for **470K participants**.

Participants were **defined as having high metabolic burden** if they met any of the following criteria: history of ASCVD, T2DM, pre-diabetes, obesity, total cholesterol > 200 mg/dL, total triglycerides > 150 mg/dL, and low burden in the absence of any of the above.

S/M LDL-P was regressed on LDL-C using linear regression, with **S/M LDL-P discordance defined** as the difference between observed and predicted S/M LDL-P.

Whole genome sequencing was used to determine *CETP* Loss of Function (**LoF**) Protein Truncating Variant (**PTV**) or Gain of Function (**GoF**) carriership.

Cox's proportional hazards models were used to estimate the association with incident MACE.

Results & Discussion

S/M LDL-P discordance (**observed vs predicted**) was independent of LDL-C concentration (correlation 0.01).

Individuals with high cardiometabolic burden had higher concentrations of **Apo-B containing particles** including S/M LDL-P concentration, LDL-C, and non-HDL-C as well as **expected elevated metabolic** characteristics; Figure 1.

People carrying a **LoF PTV genetic variants for *CETP*** had lower/less S/M LDL-P concentrations/discordance. **GoF variants for *CETP*** showed a cardiometabolic dependent association with higher S/M LDL-P discordance; Figure 2.

The MACE hazard ratio (HR) for **LDL-C independent S/M LDL-P** discordance was most pronounced in people with a high cardiometabolic burden (1.24, 95%CI 1.21; 1.27), compared to people with a low burden (1.12, 95%CI 1.07; 1.16); Figure 3.

Baseline results

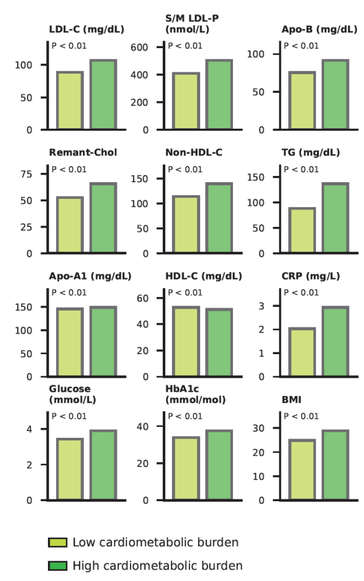

Figure 1 Baseline difference between UKB participants with low/high cardiometabolic burden (n: 178,166/309,355). P-values derived from a Mann-Witney U test.

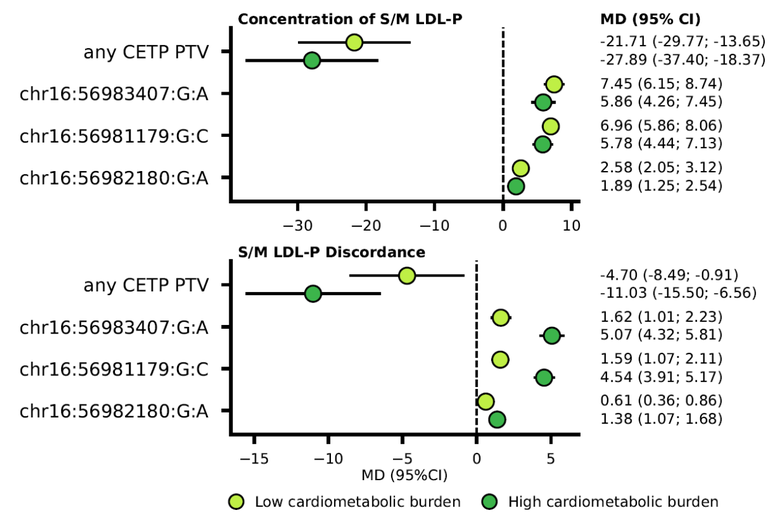

Figure 2 Associations of LoF PTV and three GoF *CETP* variants with S/M LDL-P concentration and S/M LDL-P discordance stratified by baseline cardiometabolic burden. Mean difference (MD) estimates, in nmol/L, are corrected for genetic principal components.

MACE results

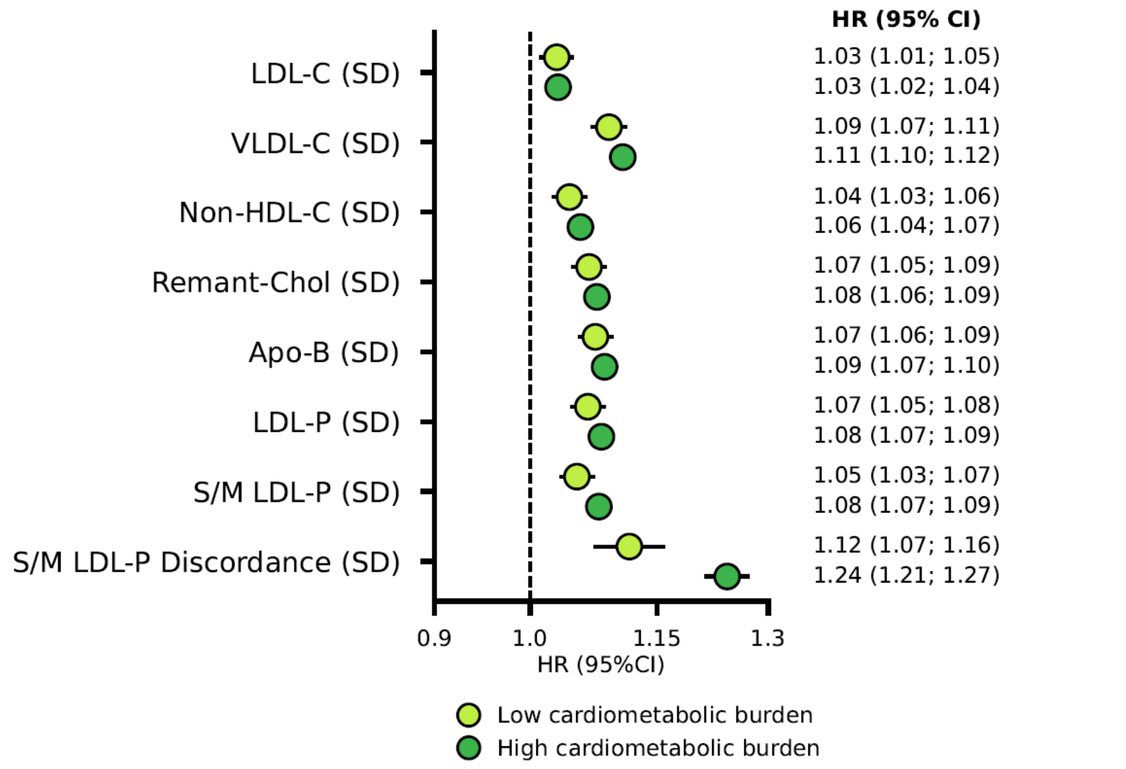

Figure 3 The MACE hazard ratio (HR) per standard deviation (SD) higher concentration of lipid exposures stratified by cardiometabolic burden. Estimates based on 51,221 MACE events, and adjusted for age, sex, BMI, HbA1c, and lipid lowering treatment(s).

Conclusions

Higher S/M LDL-P discordance showed **an LDL-C independent association** with incident MACE, most pronounced with higher **cardiometabolic burden**.

The discordance effect size exceeded that of S/M LDL-P, total LDL-P, Apo-B, and VLDL-C, suggesting **qualitative changes in particle composition** beyond what might be predicted from absolute counts.

S/M LDL-P discordance (potential qualitative changes) was modified by *CETP* genetic variation, **suggesting a role for CETP-mediated lipid remodelling** beyond what might be expected from LDL-C changes alone.

Whether **pharmacological CETP inhibition** modifies outcomes beyond what is expected from LDL-C alone is being evaluated in the ongoing PREVAIL trial.

TAKE HOME MESSAGE

★***S/M LDL-P discordance is strongly associated with MACE independent of LDL-C concentration***

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