

Association of Cardiovascular Events and Lipoprotein Particle Size: Development of a Risk Score Based on Functional Data Analysis

Background

- Cardiovascular disease (CVD) is associated with many traditional risk factors, but these factors do not account for all CVD risk.¹
- Analysis of nontraditional factors could improve risk assessment. One such factor is lipoprotein particle size, which is usually assessed by grouping particles into regions based on size: very low-density lipoprotein (VLDL) to high-density lipoprotein (HDL).²
- One challenge of this approach is that boundaries between regions are somewhat arbitrary. Thus, risk information can be lost if, for example, 1 region contains particle sizes that increase risk and those that decrease it.
- **Objective:** The investigators developed a model that incorporates the entire spectrum of lipoprotein particle sizes; they also evaluated the ability of this model to assess the association of CVD risk with lipoprotein particle size, after adjusting for traditional risk factors.

Methods

- The investigators developed a Cox regression model to predict CVD risk; the model incorporated information from traditional risk factors as well as lipoprotein particle mass measured at each of 311 particle diameters.
- Including a large number of variables in a model can lead to overfitting, which occurs when the model corresponds so closely to the observed data that it fails to effectively predict future events. To avoid overfitting, CVD risk corresponding to lipoprotein particle mass was represented by a function that was constrained to vary smoothly across the diameter range.
- The model was developed on a training set of 2,888 participants in the Malmö Prevention Project (MPP), a prospective case-cohort study of CVD events.
 - Ion mobility analysis was used to measure particle mass across the lipoprotein size spectrum, from VLDL to HDL, in serum specimens.
 - Traditional risk factors included in the Cox model were age; sex; smoking status; hypertension status; diabetes status; baseline levels of HDL-C, LDL-C, and triglycerides; body mass index; physical activity; and alcohol consumption.
- Functional risk scores, based on the coefficient function estimated in the training set, were then calculated for each of 2,888 MPP participants of a test set. The association of the functional risk score with CVD events was assessed in a Cox regression model adjusting for traditional risk factors.

Results

- When the model was applied to the test set of MPP participants, those grouped in the highest quartile of a functional risk score had an increased risk of CVD events compared to those in the lowest quartile.
 - Hazard ratio: 1.34; 95% confidence interval: 1.05-1.70.

Conclusions

- After adjusting for traditional risk factors, including standard lipids, a functional risk score based on the entire spectrum of lipoprotein particle size was associated with increased risk for CVD events.
- This approach, if validated in other cohorts, could improve risk assessment of CVD.

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Webpage

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