Reply: Not all HDL particles are equal in idiopathic pulmonary fibrosis

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Reply to T. Yasuma and co-workers:

We thank T. Yasuma and co-workers for their interest in our study about the association between small high-density lipoprotein particles measured by nuclear magnetic resonance spectroscopy (S-HDLP$_{NMR}$) and clinical outcomes, including mortality, in idiopathic pulmonary fibrosis (IPF) [1]. We found that there was no significant difference in mean total HDLP$_{NMR}$ levels between the healthy volunteers and the validation cohort, or between the IPF patients (discovery and validation cohorts combined) and the healthy volunteers. We specifically did state that our study was not designed to identify biomarkers for IPF. Rather, we sought to explore the nature of any associations between serum lipids or lipoproteins and IPF severity or outcomes. To that end, we utilised correlations between these two groups of variables at the individual level rather than comparing group averages. Thus, even if there were significant differences in mean concentrations of serum high-density lipoprotein (HDL) particles between the IPF groups and healthy volunteers, individual values of serum HDL particles could not be employed to differentiate between IPF and non-IPF subjects based on our study.

We did not previously assess whether total HDLP$_{NMR}$ had a significant association with a lower risk of lung transplantation or death at 1, 2 or 3 years, since our study design called for further analyses of individual lipids/lipoproteins only if the correlations between lipids and clinical outcomes that were observed in the discovery cohort were confirmed in the validation cohort. Serum total HDLP$_{NMR}$ did not correlate significantly with forced vital capacity (FVC), Gender Age Physiology (GAP) index or 6-min walk distance in the discovery cohort, although it did correlate with FVC and GAP in the validation cohort. In response to T. Yasuma and co-workers, we carried out further analyses and found that total HDLP$_{NMR}$ did not have a significant association with the combined outcome of death or lung transplantation at 1, 2 or 3 years in the adjusted models.

As described in the Methods section of our paper [1], the multivariable models all started by including five additional variables (age, sex, race, body mass index and C-reactive protein levels), chosen *a priori* for their potential effect on serum lipid levels, and kept in the model only those that remained significant ($p<0.2$) using a backwards selection approach. We followed this pre-specified approach for all the linear regression models in order to maintain consistency in our analytic approach. We acknowledge that the GAP index incorporates age and sex. However, we included age and sex in the models assessing the association between GAP index and S-HDLP$_{NMR}$ to address the possibility that age and sex could influence S-HDLP$_{NMR}$ levels. We treated S-HDLP$_{NMR}$ and not the GAP score as the dependent variable in these models, the object of which was to determine any association between GAP and S-HDLP$_{NMR}$ while accounting for any effect of the additional variables. Furthermore, the significant association between levels of S-HDLP$_{NMR}$ and actual mortality or lung transplantation in IPF subjects confirms that the association we found between GAP index and S-HDLP$_{NMR}$ in our multivariable model was likely not erroneous, since the GAP index does predict mortality in IPF patients.

Shareable abstract (@ERSpublications)
Small HDL particles are associated with both GAP as well as observed mortality/lung transplantation in IPF https://bit.ly/3oVWSHJ

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Conflict of interest: S.J. Levine, N. Weir, S.D. Barnett and A.V. Barochia have nothing to disclose. S.D. Nathan is a consultant and is on the speakers' bureau for Roche-Genentech and Boehringer Ingelheim, and has received research funding from both companies.

Reference

1 Barochia AV, Kaler M, Weir N, *et al.* Serum levels of small HDL particles are negatively correlated with death or lung transplantation in an observational study of idiopathic pulmonary fibrosis. *Eur Respir J* 2021; 58: 2004053.