Reviewer’s report

Title: Associations of Perfluoroalkyl Substances with Blood Lipids and Apolipoproteins in Lipoprotein Subspecies: the POUNDS-Lost Study

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Reviewer: Rikard Landberg

Reviewer's report:

In this study entitled "Associations of Perfluoroalkyl Substances with Blood Lipids and Apolipoproteins in Lipoprotein Subspecies: the POUNDS-Lost Study", Liu et al. investigates the associations between plasma PFAS concentrations and lipoprotein and apolipoprotein subspecies in samples from the POUNDS-LOST study conducted in a subset of 326 American women and men. The study is important since it includes 5 PFAS and investigates different lipoproteins apolipoprotein subfractions separately, which is the first time. The authors find that PFAS are associated with LDL and HDL that carry ApoC-III, which are associated with increased CVD risk in observational studies.

Overall, the study is excellently conducted and reported and I have only minor suggestions for improvements.

- From the current paper it appears the PFAS is associated with lipid metabolism and it is hinted that they may cause altered lipid metabolism (through provision of reference examples in animals where this has been shown). However, could it be that the PFAS are transported in lipoproteins fractions and thus are determined by the concentrations of such fractions? Could the authors elaborate on this please and mention what implication it may have. I know that several authors have looked into this with regards to POPs.
- The authors report significant associations in particular for PFOS and APOC-III in LDL. However, the difference across tertile, how can that be translated into altered CVD risk? Could the authors provide a rough estimate?

Line 109: Were both base line and 2 year samples for the 326 used?
Line 141: "Assessment of other covariates" -> "Assessment of covariates"
Line 181: Since many of the PFAS are highly correlated, why did the authors not consider to derive latent variables reflecting orthogonal variation in PFAS and use such variables in studies in relation to lipids (latent variables derived by PCA for example).

Table 2: As now stated with PFAS in the columns and lipids in the rows, it gives the impression that PFAS is expressed per tertile of lipid and not the other way around. I suggest the authors move PFAS to the rows and lipids to the columns. Moreover, please provide concentrations ranges of PFAS for the tertiles.

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Quality of written English
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