

TITLE: Per- and poly-fluoroalkyl substances, apolipoproteins, and risk of coronary heart disease

A. SCIENTIFIC ABSTRACT U.S. populations are ubiquitously exposed to per- and poly-fluoroalkyl substances (PFASs) that are widely used in numerous consumer products. Recently-revealed widespread contamination of drinking water by PFASs further underscores the importance of understanding detrimental health effects of these pollutants. PFASs are known to disturb cholesterol metabolism in animal models, although evidence regarding PFASs and blood lipids in humans was not consistent. Our recent analysis in the POUNDS-Lost Trial showed that PFASs were not associated with total, low-density lipoprotein (LDL), or high-density lipoprotein (HDL) cholesterol. However, PFASs were associated with higher levels of LDL and HDL subspecies that carry proatherogenic apolipoprotein CIII (apoC-III). This novel discovery may partially explain the inconsistent evidence regarding PFASs-lipids relationships as previous studies only examined the broad lipid categories. To generate more evidence that will lead to strong applications of NIH awards, we aim to achieve **three goals**: 1) to examine cross-sectional associations of plasma PFAS levels with HDL and LDL subspecies with/without apoC-III and other apolipoproteins; 2) to examine prospective associations between plasma PFAS levels and risk of CHD; and 3) to examine whether the HDL and LDL subspecies mediate the association between PFASs and CHD risk. The well-established Nurses' Health Study (NHS) and Health Professionals Follow-Up Study (HPFS), with prospectively-collected blood samples, existing data of lipoprotein subspecies, and long-term CHD follow-up in these two cohorts, enable us to accomplish these aims in a highly cost-effective fashion. Data to be generated will facilitate further research that substantiates these important relationships in large-scale epidemiological investigations.

B. OVERVIEW AND BACKGROUND

B.1. Overview. The PI's recent research in the POUNDS-Lost Trial showed that plasma levels of PFASs were significantly associated with increased levels of HDL and LDL subspecies that carry atherogenic apoC-III and/or apoE, but not the levels of total HDL, LDL, or triglycerides (TG).¹ This novel observation may help explain the inconsistent findings regarding PFASs in relation to blood lipids,² although it is unknown whether this finding may be extrapolated to an elevated risk of developing CHD in humans. The proposed research, therefore, aims to address **three aims**: 1) to examine cross-sectional associations of plasma PFAS levels with HDL and LDL subspecies with/without apoC-III and other apolipoproteins in 100 healthy CHD controls in the NHS and HPFS, 2) to examine prospective associations between plasma PFAS levels and risk of developing CHD in 100 incident CHD case-control pairs in the NHS and HPFS, and 3) to examine whether the HDL and LDL subspecies mediate the association between PFASs and CHD risk (**Figure 1**).

Existing data, including HDL/LDL subspecies, diet, lifestyle, cardiovascular disease (CVD) risk markers, and

prospectively ascertained CHD outcomes, make this proposed research highly cost-effective. Findings from this pilot project will pave the way for substantiating research that elucidates the important inter-relationships between PFASs, lipid subspecies, apolipoproteins, and CHD risk in large-scale epidemiological investigations.

B.2. PFAS Exposures and Blood Lipids in Humans. Many epidemiological studies have examined relationships between PFAS exposures and dyslipidemia, although findings are not consistent. In the C8 Health Project among individuals who were exposed to high levels of PFASs, levels of both perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) were significantly associated with higher levels of total and LDL cholesterol,² although lack of associations was observed in other highly-exposed populations.² In the National Health and Nutrition Examination Survey, PFOS levels were associated with lower HDL, but not other blood lipids.² In contrast, in the Canadian Health Measures Survey, perfluorohexanesulfonic acid (PFHxS), but not other PFASs, was associated with higher total and LDL cholesterol.² Inconsistent findings were also observed in other study populations.^{2, 3} Potential reasons underlying these inconsistent findings are unclear, although background PFAS exposure levels and residual or unmeasured confounding by diet and lifestyle might play a role in this regard. More importantly, these previous studies focused on total, HDL, and LDL cholesterol which consist of subspecies that have heterogeneous biological functions and effects.

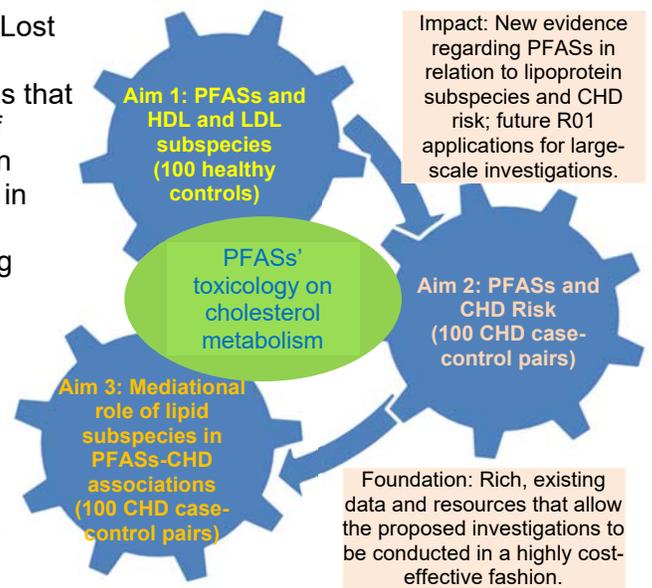


Figure 1. Conceptual framework of the proposal.