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# Circulating levels of perfluoroalkyl substances and left ventricular geometry of the heart in the elderly

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ABSTRACT

*Aims:* Some persistent organic pollutants (POPs) such as hexachlorobenzene (HCB) and some polychlorinated biphenyls (PCBs) have been shown to interfere with myocardial function and geometry. We therefore investigated if also another group of POPs: per- and polyfluoroalkyl substances (PFASs) were associated with alterations in left ventricular geometry.
*Methods:* 801 subjects aged 70 years were investigated in a cross-sectional study within the scope of the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Eight PFASs were detected in > 75% of participants´ plasma by ultra-performance liquid chromatograph/tandem mass spectrometry. Left ventricular geometry was determined by echocardiography. Multivariable linear regression was used to investigate the associations between PFASs and left ventricular geometry of the heart after exclusion of subjects with previous myocardial infarction ($n = 72$).
*Results:* When adjusting for multiple comparisons, none of the eight PFASs evaluated were significantly related to left ventricular mass. However, perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA) were related to relative wall thickness (RWT) in a negative fashion ($p < 0.0021$). Besides being inversely related to RWT, PFNA was also positively related to left ventricular end-diastolic volume (LVEDD) ($p < 0.0021$). These analyses were adjusted for traditional cardiovascular risk factors.
*Conclusion:* In this cross-sectional study, several of the PFASs evaluated, especially PFNA, were related to myocardial geometry: a reduction in relative wall thickness and an increase in left ventricular diameter following adjustment for traditional cardiovascular risk factors, suggesting a role for PFASs in cardiac remodeling.

## 1. Introduction

It has been known for many years now that per- and polyfluoroalkyl substances (PFASs) can be detected in human and environmental samples all over the world, from the Great Lakes in North America to the Pearl River in China (Lau et al., 2007; Boulanger et al., 2004; So et al., 2007; Stubleski et al., 2016). PFASs have highly desirable properties and are therefore used in a vast number of products such as textiles, paper and food packaging, cosmetics, non-stick products and electric equipment (Buck et al., 2011). However, knowledge about possible adverse health effects from PFASs exposure is scarce, and epidemiological studies on the effects of PFASs on the adult heart are lacking. Although a few animal studies on developmental cardiotoxicity have been performed, studies on humans are needed to confirm the results of animal studies and to help restrict the use of substances hazardous to human health.

In humans, remodeling of the left ventricle of the heart is associated with increased morbidity and mortality in cardiovascular disease (CVD), besides being an independent risk factor for death due to any cause (Ghali et al., 1992; Koren et al., 1991). There are a number of well-known risk factors for left ventricular hypertrophy (LVH) such as hypertension, diabetes, hyperlipidemia and obesity (Levy et al., 1988;

*Abbreviations:* BMI, Body mass index; CVD, Cardiovascular disease; CAR, Constitutive androstane receptor; GFR, Glomerular filtration rate; HCB, Hexachlorobenzene; HDL, High density lipoprotein; IVS, Inter ventricular septum; LDL, Low density lipoprotein; LVEDD, Left ventricular end diastolic diameter; LVM, Left ventricular mass; LVMI, Left ventricular mass index; PFASs, Per- and polyfluoroalkyl substances; PIVUS, The Prospective Investigation Of The Vasculature In Uppsala Seniors; POP, Persistent organic pollutants; PPAR, Peroxisome proliferator-activated receptors; PW, Posterior wall thickness; RWT, Relative wall thickness; PXR, Pregnane X-receptor

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Saunders et al., 2008; Ho et al., 1993). However, LVH is multicausal, and less well-known risk factors can play a significant role in the development of LVH. Recently, some persistent organic pollutants (POPs), such as hexachlorobenzene (HCB) and some polychlorinated biphenyls (PCBs), have been shown to be associated with increased wall thickness of the left ventricle, ventricular remodeling, and impairments in left ventricular systolic and diastolic function (Sjoberg Lind et al., 2013a; Sjoberg Lind et al., 2013b). Previous studies have reported associations between PFASs exposure and developmental cardiotoxicity in chicken (Jiang et al., 2012), as well as atherosclerosis in the elderly (Lind et al., 2017; Jiang et al., 2012). Given these results, and considering that PFASs are also classified as POPs, it is desirable to investigate whether also PFASs affect the geometry of the adult human heart. Therefore, the aim of the present cross-sectional study was to investigate the association between circulating levels of PFASs and alterations in left ventricular geometry in a 70-year-old population in Sweden in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study.

## 2. Method

### 2.1. Participants and sampling - PIVUS study

Data was collected from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Participants were 70 years old, and just over half were female (52%). For details on subjects and basic investigation, see (Lind et al., 2005). In total, 1016 subjects participated in the study. Participants with previous myocardial infarction were excluded from this present study ($n = 72$), since a myocardial infarction can alter left ventricular geometry. Following exclusion (previous heart attack) and deficient quality of ultrasound and information on confounders, the final number of subjects used for statistical calculations was 801. Informed consent was given by all participants, and the study was approved by the Ethics Committee of Uppsala University.

Basic characteristics were collected, presented in Table 1. To evaluate alcohol and energy consumption, a seven-day recording of all food and drinking items consumed by the participants was performed. All of the above baseline information was collected using standardized methods (self-reported questionnaires filled in at home right before the examination, fasting plasma samples for determinations of glucose and lipids, and clinical examination). Glomerular filtration rate (GFR) was estimated by measurements of serum creatinine using the MDRD (Modification of Diet in Renal Disease) formula (Levey et al., 1999).

### 2.2. Analysis of PFASs

Details on the analysis of PFASs have previously been described (Salihovic et al., 2013). A total of eight PFASs for which > 75% of the study population showed measurable levels above the lower level of detection were evaluated in the present study: perfluoroheptanoic acid (PFHpA), perfluorohexane sulfonic acid (PFHxS), linear isomer of perfluorooctane sulfonic acid (L-PFOS), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluorooctane sulfonamide (PFOSA), perfluoroundecanoic acid (PFUnDA). These PFASs were measured in serum using ultra-performance liquid chromatography coupled to tandem mass-spectrometry (UPLC-MS/MS).

### 2.3. Echocardiography

For details on performance of the echocardiography see Sjoberg Lind et al. (2013a). The M-mode measurements performed were: interventricular septum (IVS), posterior wall thickness (PW), and left ventricular end diastolic diameter (LVEDD). From these values, the relative wall thickness (RWT) was calculated (RWT = (IVS + PW)/LVEDD). To determine the left ventricular mass (LVM), the Penn convention was applied, and thereafter indexed for height$^{2.7}$ to retrieve left ventricular mass index (LVMI). A technician unaware of other collected data performed the evaluation of the left ventricular data.

**Table 1**
Basic characteristics and major cardiovascular risk factors of the subjects ($n = 801$).

| Women/men (%) | 417/384 (52) |
|---|---|
| High degree of education, *n* (%) | 200 (25) |
| Current smoking, *n* (%) | 80 (10) |
| Regular physical activity, *n* (%) | 216 (27) |
| Waist circumference (cm) | 90.91 ± 11.6 |
| Fasting blood glucose (mmol/l) | 5.29 ± 1.5 |
| Systolic blood pressure, (mm Hg) | 149.74 ± 22.53 |
| HDL-cholesterol (mmol/l) | 1.53 ± 0.43 |
| LDL-cholesterol (mmol/l) | 3.42 ± 0.86 |
| Serum triglycerides (mmol/l) | 1.27 ± 0.59 |
| BMI (kg/m$^2$) | 26.96 ± 4.31 |
| Energy consumption per day (kcal) | 1883.4 ± 464.9 |
| Alcohol consumption, g/day | 2.55 ± 2.81 |
| Antihypertensive treatment, *n* (%) | 240 (30) |
| PFHpA ng/ml (SD) | 0.7 ± 0.7 |
| PFHxS | 3.41 ± 3.64 |
| L-PFOS | 14.9 ± 8.88 |
| PFOA | 3.59 ± 1.69 |
| PFNA | 0.8 ± 0.43 |
| PFDA | 0.34 ± 0.15 |
| PFOSA | 0.14 ± 0.14 |
| PFUnDA | 0.31 ± 0.14 |
| LVMI (g/m$^{2.7}$) | 42.48 ± 12.79 |
| LVEDD (mm) | 46.79 ± 5.35 |
| RWT | 0.44 ± 0.09 |

Values expressed as *n*, means ± SD or medians (25th to 75th percentile). The mean concentration of PFASs is given as SD, ng mL$^{-1}$. High degree of education is defined as > 9 years of education. Regular physical activity is defined as moderate or hard physical activity > 1 time per week. HDL, High density lipo-protein; LDL, Low density lipo-protein. PFASs, Per- and polyfluoroalkyl substances; Perfluoroheptanoic acid (PFHpA), Perfluorohexane sulfonic acid (PFHxS), Linear isomer of perfluorooctane sulfonic acid (L-PFOS), Perfluorooctanoic acid (PFOA), Perfluorononanoic acid (PFNA), Perfluorodecanoic acid (PFDA), Perfluorooctane sulfonamide (PFOSA), Perfluoroundecanoic acid (PFUnDA). Heart geometry: LVMI, Left ventricular mass indexed for height$^{2.7}$; LVEDD, Left ventricular end diastolic diameter, RWT, Relative wall thickness of the left ventricle.

### 2.4. Statistics

To obtain normal distributions of the skewed PFASs, the data was log transformed. To evaluate the relationships between the different PFASs and left ventricular geometry, linear regression analysis was used with LVMI, RWT and LVEDD as dependent variables in different models and the PFASs as independent variables in separate analyses for each PFASs. As a first step the regression model was adjusted for sex only (same age for all subjects). Thereafter multiple adjustments were made for classical risk factors for LVH and life-style factors (sex, blood pressure, antihypertensive medication, high density lipoprotein (HDL) and low density lipoprotein (LDL), cholesterol, blood glucose, waist circumference, triglycerides, body mass index (BMI), education levels, exercise habits, smoking, energy consumption and alcohol intake). As an additional step, the squared form of the PFAS data was included to analyze potential non-linear relationships. Furthermore, an interaction term between the PFASs and sex was included to investigate possible differences between the sexes. Stata 14 (Stata, College Station, TX, USA) was the statistical software used for the calculations. The critical *p*-value for significance was set to 0.0021 according to the Bonferroni correction (0.05/8 PFASs/3 outcomes).