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Circulating levels of perfluoroalkyl substances (PFASs) and carotid artery atherosclerosis

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ABSTRACT

Background and objective: During recent years, some persistent organic pollutants (POPs) have been linked to atherosclerosis. One group of POPs, the poly- and perfluoroalkyl substances (PFASs) have not been investigated with regard to atherosclerotic plaques.

Methods: Carotid artery atherosclerosis was assessed by ultrasound in 1016 subjects aged 70 years in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Eight PFASs were detected in > 75% of participants' plasma by ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS).

Results: No significant linear associations were observed between the PFASs and intima-media thickness (IMT), or the echogenicity in the intima-media complex (IM-GSM, a marker of lipid infiltration in the artery) when men and women were analyzed together. Neither was occurrence of carotid plaques related to PFASs levels. However, highly significant interactions were observed between some PFASs and sex regarding both IM-GSM and plaque prevalence. Perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), and perfluoroundecanoic acid (PFUnDA), were all related to IM-GSM in a positive fashion in women (p=0.002–0.003), while these relationships were negative in men. The levels of PFUnDA were significantly related to carotid plaque in women (OR 1.59, 95%CI 1.03–2.43, p=0.03), but not in men (OR 0.93, 95%CI 0.62–1.42, p=0.75).

Conclusions: In this cross-sectional study, a pronounced gender difference was observed regarding associations between some PFASs, especially the long-chain PFUnDA, and markers of atherosclerosis, with more pronounced relationships found in women. These findings suggest a sex-specific role for PFASs in atherosclerosis.

1. Introduction

Per- and polyfluoroalkyl substances (PFASs) are a huge class of compounds used to manufacture a wide variety of industrial and household applications due to their unique properties of being both water and oil repellent. The production of PFASs was initiated in the late 1940s and ubiquitous amounts of PFASs have since then been released to the environment (Lindstrom et al., 2011). The most widely used among the large group of PFASs are the perfluoroalkyl sulfonic acids (PFSAs) and perfluoroalkyl carboxylic acids (PFCAs), including perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). PFOS and PFOA share the feature of being fully fluorinated, eight-carbon chain organic acids (C_8). However, numerous perfluoroalkyls with varying carbon chain length, from four carbons to fourteen carbons (C_4-C_{14}), can be detected in various compartments in the environment (Lau et al., 2007).

Global regulatory actions to control the emissions and production of PFASs have only recently been implemented for perfluorooctane sulfonate (PFOS) and its precursors which were included in the Annex B of the 2009 Stockholm Convention (UNEP, 2015). Furthermore,

Abbreviations: AMS, Artery Measurement Software; CV, cardiovascular; HRGC/ HRMS, high-resolution mass spectrometry; IM-GSM, grey scale median of the carotid artery intima-media complex; IMT, intima media thickness; L-PFOS, linear isomer of perfluorooctane sulfonic acid; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; PCBs, polychlorinated biphenyls; PFASs, per- and polyfluoroalkyl substances; PFCAs, perfluoroalkyl carboxylic acids; PFDA, perfluorodecanoic acid; PFDS, perfluorodecane sulfonic acid; PFHpA, perfluoroheptanoic acid; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOSA, perfluorooctane sulfonamide; PFUnDA, perfluoroundecanoic acid; POPs, persistent organic pollutants; UPLC-MS/MS, ultra-performance liquid chromatography coupled to tandem mass spectrometry

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voluntary discontinuation agreements from major manufacturers of PFOS and PFOA have been implemented in the United States and Western Europe (US EPA, 2006, 2014) . Although recent temporal studies suggest that these phase-out policies have resulted in reduced emissions and decreasing concentrations of PFOS and PFOA in humans and wildlife (Bjerregaard-Olesen et al., 2016; Johansson et al., 2014; Nost et al., 2014; Okada et al., 2013; Rigét et al., 2013; Wang et al., 2011; Yeung et al., 2013), it is yet unclear whether the effect is due to a change in the global production as there is a dynamic shift in the industrial production of PFASs.

The presence of PFASs in men, women, and children has been extensively reported (Bjerregaard-Olesen et al., 2016; Frisbee et al., 2009; Wang et al., 2011) and an integral part of the exposure in the general population arises through the dietary exposure including drinking water (Fromme et al., 2009). The bioaccumulation and toxic potential of perfluoroalkyls has been suggested to increase with increased carbon-chain lengths (Liao et al., 2009; Martin et al., 2003) and the most frequently detected compounds in the general population are PFOS and PFOA followed by perfluorononanoic acid (PFNA), and perfluorohexane sulfonic acid (PFHxS) (Glynn et al., 2012; Karrman et al., 2010; Kato et al., 2011; Sundström et al., 2011; Wang et al., 2011).

A number of adverse health effects have been linked to elevated levels of PFASs (Steenland et al., 2010a). However, there is no uniform picture on the cardiovascular effects in response to PFASs exposure, and most studies up to date have been based on occupational or accidental settings (Borg et al., 2013; Sakr et al., 2007; Simpson et al., 2013; Steenland et al., 2010b; Winquist and Steenland, 2014) with a gender bias in favor of men. However, many studies show uniformly that certain PFASs are related to high serum cholesterol levels (Nelson et al., 2010; Skuladottir et al., 2015; Winquist and Steenland, 2014). Since high serum cholesterol levels are linked to atherosclerosis, it is of importance to evaluate if cholesterol mediates possible relationships between PFASs and cardiovascular diseases.

At present, there is limited information on the relationship between PFASs exposure and atherosclerosis in a gender-balanced sample of the general population. One study found a relationship between PFOS levels and the carotid artery intima-media thickness (IMT), especially in women (Lin et al., 2013). We have recently shown that polychlorinated biphenyls (PCBs) are related to atherosclerosis in humans (Lind et al., 2012b). Animal experiments support that this finding is causal (Dalton et al., 2001; Wu et al., 2011). Correspondingly, we hypothesized that also PFASs might have cardiovascular effects in the general population. We measured several PFASs in plasma from a population-based sample of almost 1000 elderly men and women (50% women) in the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS-study) (Lind et al., 2005), with the hypothesis that elevated levels of PFASs are related to atherosclerosis measured by ultrasound in the carotid arteries in this cross-sectional study. Since previous studies have pointed towards a gender difference in the elimination of PFASs (Kudo et al., 2002), and that PFASs might effect sex hormones (Joensen et al., 2013), we paid special attention to the possibility that effects of PFASs on atherosclerosis are sex-specific.

We used three different indices of atherosclerosis in the present study. First, a local thickening of the intima-media complex, which is considered an established atherosclerotic plaque. Second, the intima-media thickness (IMT) in the common carotid artery, which is a common measure of early atherosclerosis, but that could also be increased by media hypertrophy. Third, the echogenicity of the intima-media complex (denoted the intima-media grey scale median, IM-GSM), a measure of the structural composition of the arterial wall. The latter two indices are used as indicators of early changes in the carotid artery.

Table 1
Basic characteristics and major cardiovascular risk factors in the sample (n=1016). Means with SD or proportions are given in parenthesis.

	Total sample	Women	Men
n	1016	509	507
Variable	Mean (SD)	Mean (SD)	Mean (SD)
Height (cm)	168.96 (9.12)	162.14 (5.63)	175.79 (6.45)
Weight (kg)	77.32 (14.42)	71.17 (13.12)	83.49 (12.97)
Waist circumference (cm)	91.16 (11.58)	87.6 (11.56)	94.74 (10.45)
BMI (kg/m2)	27.03 (4.33)	27.08 (4.88)	26.99 (3.71)
SBP (mmHg)	149.63 (22.68)	153.3 (22.6)	145.95 (22.18)
DBP (mmHg)	78.68 (10.18)	78.03 (10.08)	79.33 (10.25)
Serum cholesterol (mmol/l)	5.43 (1.02)	5.72 (0.97)	5.14 (0.98)
LDL-cholesterol (mmol/l)	3.38 (0.88)	3.52 (0.86)	3.24 (0.87)
HDL-cholesterol (mmol/l)	1.51 (0.43)	1.66 (0.43)	1.36 (0.37)
Serum triglycerides (mmol/l)	1.28 (0.6)	1.27 (0.58)	1.29 (0.62)
Fasting blood glucose (mmol/l)	5.3 (1.6)	5.2 (1.5)	5.4 (1.6)
Current smoking (%)	0.11 (0.31)	0.11 (0.32)	0.1 (0.3)
Statin treatment (%)	15	13	16
Antihypertensive treatment (%)	31	31	31
Diabetes mellitus (%)	12	10	14
Myocardial infarction (%)	7	3	11
Stroke (%)	4	2	5
Heart failure (%)	4	3	5

2. Material and methods

2.1. Subjects

Eligible were all subjects aged 70 living in the community of Uppsala, Sweden. The subjects were chosen from the register of community living and were invited in a randomized order. The subjects received an invitation by letter within 2 months of their 70th birthday. Of the 2025 subjects invited, 1016 subjects participated giving a participation rate of 50.1%. The investigation was conducted between 2001 and 2004.

The study was approved by the Ethics Committee of the University of Uppsala and the participants gave informed consent prior to the study.

Basic characteristics of the sample is given in Table 1.

2.2. Basic characteristics and cardiovascular risk factors

The participants were asked to answer a questionnaire about their medical history, smoking habits and regular medication. Regarding medical history, the participants were asked if they have been given a diagnosis by a physician regarding a list of diagnoses. The smoking question was coded as current or no current smoking. All subjects were investigated in the morning after an over-night fast. No medication or smoking was allowed after midnight. After recordings of height, weight, abdominal and hip circumference, an arterial cannula was inserted in the brachial artery for blood sampling and later regional infusions of vasodilators (not dealt with in the present study). Blood pressure was measured by a calibrated mercury sphygmomanometer in the non-cannulated arm to nearest mmHg after at least 30 min of rest and the average of three recordings was used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques.

As the participation rate in baseline investigation of this cohort was only 50%, we carried out an evaluation of cardiovascular disorders and medications in 100 consecutive non-participants. The prevalence of cardiovascular drug intake, history of myocardial infarction, coronary revascularization, antihypertensive medication, statin use and insulin treatment were similar to those in the investigated sample, while the prevalence of diabetes, congestive heart failure and stroke tended to be