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# Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population

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ABSTRACT

*Background:* Perfluoroalkyl chemicals (PFCs) as possible cardiovascular disrupters are universally detected in humans. However, evidence from epidemiological studies appears insufficient and ambiguous.
*Objectives:* We aim to examine the serum PFCs levels and their associations with the prevalence of cardiovascular diseases (CVD) and related outcomes in general US population.
*Methods:* We investigated the serum levels of 12 major PFCs, including perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), perfluorohexane sulfonic acid (PFHxS), 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate (EPAH), 2-(*N*-methyl-perfluorooctane sulfonamido) acetate (MPAH), perfluorodecanoic acid (PFDE), perfluorobutane sulfonate (PFBS), perfluoroheptanoic acid (PFHP), perfluorononanoic acid (PFNA), perfluorooctane sulfonamide (PFSA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic acid (PFDO), in 10,859 participants from the National Health and Nutritional Examination Survey (NHANES) 1999–2014. Logistic regression models were used to estimate the associations between serum PFCs and 5 self-reported CVD outcomes, including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. Linear regression analyses were used to estimate the PFCs and their associations with 8 traditional CVD risk factors like serum triglyceride and total cholesterol.
*Results:* In multivariable-adjusted models, total PFCs were positively associated with total CVD ($p$ for trend = 0.0166), independent of traditional CVD risk factors, such as smoking status, diabetes, hypertension and serum cholesterol level. Compared with reference quartile of total PFCs levels, the multivariable adjusted odds ratios in increasing quartiles were 1.23 [95% confidence interval (CI): 0.91–1.66], 1.47 (95% CI: 1.14–1.89) and 1.45 (95% CI: 1.06–1.98) for total CVD. Similar positive associations were found if considering individual PFCs including PFOS, PFUA, MPAH, EPAH, PFDO, PFSA and PFBS. In addition, serum levels of MPAH and PFDO were positively associated with congestive heart failure; PFNA, PFDE, and PFUA were positively associated with coronary heart disease; PFUA and PFDO were positively associated with angina pectoris; and PFNA was positively associated with heart attack.
*Conclusions:* Our findings suggested that exposure to PFCs was positively associated with risk of CVD. Further longitudinal studies are needed to increase our understanding about the role of PFCs exposure in the prevalence of CVD.

## 1. Introduction

Perfluoroalkyl chemicals (PFCs) as a group of synthetic organic compounds have widely been used in various manufacturing industries and related commercial applications since 1950s (Prevedouros et al., 2006), including surfactants, lubricants, paper and textile coatings, and water and oil repellents in cosmetics, food packaging, clothing and furnishings (Lindstrom et al., 2011). As emerging anthropogenic pollutants, reports from national biomonitoring surveys suggested that PFCs, such as perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS), have been universally detected not only from environmental sources such as surface water, wastewater, soil and indoor dust but also in human blood *in vivo* (CDC, 2017; De Silva et al., 2012; Jin et al., 2015; Llorca et al., 2012).

The primary routes of exposure to PFCs in general population mainly include dietary intake, migration from food packaging and cookware, and drinking water, indoor air and house dust ingestion (Haug et al., 2010; Miralles-Marco and Harrad, 2015). Human exposure

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to PFCs is of rising concern because these chemicals are not susceptible to degradation in addition to their slow elimination by human bodies (Butenhoff et al., 2004). Some long-chain PFCs such as PFOA, PFOS, perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) could bioaccumulate through food chain in biosphere, and thereafter the exposure persists in the environment and human bodies for several months and even years, depending on different types of PFCs (Wang et al., 2014). Potential adverse health concerns about long-term exposure to PFOA and PFOS include developmental disorders in fetuses during pregnancy or in breastfed infants, carcinogenesis, organ damage, immune injury, thyroid disease and endocrine disruption (Chang et al., 2016; Cui et al., 2009; Klaunig et al., 2012; Olsen et al., 2009; White et al., 2011; Yu et al., 2009). In 2015, PFOA has been classified as possible carcinogens (2B group) in humans by International Agency for Research on Cancer (IARC) (IARC, 2015).

Cardiovascular diseases (CVD) are the major cause of death globally (Roth et al., 2015). Accumulating evidence indicated that exposure to environmental pollutants may increase the risk of CVD (Bhatnagar, 2006; Mastin, 2005). A considerable number of population studies reported the potential role of PFCs exposure in the risk factors of CVD, such as glucose homeostasis, metabolic syndrome, body weight, and insulin resistance (Geiger et al., 2013; Lin et al., 2009; Nelson et al., 2010). In addition, two studies also have shown the positive associations of serum PFOA and PFOS with lipid profiles, including the total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride, in a nationally representative sample of US adolescents and adults (Geiger et al., 2014; Liu et al., 2018). Evidence indicated the causal relationships between these chemicals and dyslipidemia, an acknowledged risk factor of CVD. However, few studies have identified the associations between common PFCs and CVD prevalence so far, except one study which only focused on the associations between one PFC (PFOA) and two CVD outcomes (coronary heart disease and stroke) based on the population of 1216 subjects (Shankar et al., 2012). In this study, we aim to comprehensively evaluate serum levels of 12 major PFCs including PFOA and PFOS, the emerging compounds PFHxS and PFNA, etc., and directly link them to several CVD outcomes including congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke as well as CVD-related risk factors. We expect to explore the potential understanding of the relationships based on the large and representative US population from National Health and Nutrition Examination Survey (NHANES) 1999–2014.

## 2. Material and methods

### 2.1. Study population

NHANES is a nationally representative survey of the US non-institutionalized population continuously conducted every other year by the Centers for Disease Control and Prevention (CDC). Study protocol was approved by the Institutional Review Board of National Center for Health Statistics (NCHS), and the consent in written form was obtained from all participants. More detailed description about NHANES has been available elsewhere (CDC, 2018a).

In this study, we constructed weights for combined survey cycles of NHANES 1999–2000, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012 and 2013–2014 according to the NHANES analytical guidelines (CDC, 2013). A total of 38,382 participants aged ≥20 years were surveyed. Among them, 10,912 participants were available for the measurement of serum levels of PFCs. Then, people who did not complete medical examination of CVD were excluded ($n$ = 53). Eventually, 10,859 participants were included in the final analysis.

### 2.2. Assessment of polyfluoroalkyl chemicals levels

A total of 12 kinds of PFCs were measured in serum samples of one-third of the participants who were randomly selected from NHANES, including PFOA, PFOS, PFHxS, PFNA, 2-(*N*-ethyl-perfluorooctane sulfonamido) acetate (EPAH), 2-(*N*-methyl-perfluorooctane sulfonamido) acetate (MPAH), perfluorodecanoic acid (PFDE), perfluorobutane sulfonate (PFBS), perfluoroheptanoic acid (PFHP), perfluorooctane sulfonamide (PFSA), perfluoroundecanoic acid (PFUA), and perfluorododecanoic acid (PFDO). Specially, the isomers of PFOA [linear perfluorooctanoate (n-PFOA) and branched isomer of perfluorooctanoate (Sb-PFOA)] and isomers of PFOS [linear perfluorooctane sulfonate (n-PFOS), and monomethyl branched isomer of PFOS (Sm-PFOS)] were detected instead of the PFOA and PFOS in the 2013–2014 cycle, and the calculated sum of isomers in the PFOA and PFOS dataset for the 2013–2014 cycle is comparable to the total levels reported in previous cycles of NHANES. In addition, data for serum levels of PFBS in the 1999–2000 cycle and EPAH and PFSA in the 2013–2014 cycle were missing. Online solid phase extraction coupled to high performance liquid chromatography-turbo ionspray ionization-tandem mass spectrometry (online SPE-HPLC-TIS-MS/MS) was used to quantitatively measure serum PFCs. This method allowed for the rapid determination of PFCs in serum with limits of detection (LOD) around 0.1 ng/mL and linear range from 0.01 to 20–50 ng/mL. Detailed laboratory protocols for the measurement of serum PFCs have been described elsewhere (CDC, 2016).

### 2.3. Assessment of CVD outcomes

We defined total CVD outcomes as any positive self-reported physician diagnosis of congestive heart failure, coronary heart disease, angina pectoris, heart attack, and stroke. Briefly, a standardized medical condition questionnaire was conducted during the personal interview. All participants were asked: “Has a doctor or other health professional ever told you that you have congestive heart failure/coronary heart disease/angina pectoris/heart attack/stroke?” These were 5 separate questions with the same wording style. Answering yes to either of questions was coded as positive for CVD.

### 2.4. Covariates and CVD risk factors

We obtained the information on age (years), gender (male/female), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American and other), family poverty income ratio (PIR, a ratio of family income to the poverty threshold), and education levels (lower than high school, high school, and higher than high school) from the demographic questionnaire. Information on physical activity levels (never, moderate, and vigorous), alcohol drinking status (never, former, and current), smoking status (never, former, and current), and family history of CVD (yes/no) was obtained from the physical activity, alcohol use, smoking-cigarette use and medical conditions questionnaires, respectively (CDC, 2018b). Body mass index (BMI, kg/m$^2$, < 25, 25 to < 30, and ≥30) was obtained and calculated using measurement data of weight and height from the physical examination (Yanovski and Yanovski, 2011). Serum cotinine (ng/mL), total cholesterol (mg/dL) and total protein (g/dL) were used in log-transformation as covariates (CDC, 2018b). The estimated glomerular filtration rate (eGFR, mL/min/1.73 m$^2$) was calculated based on previous studies (Levey et al., 2009; Selvin et al., 2007). The other CVD risk factors, including total triglyceride (mg/L), total cholesterol (mg/dL), HDL-cholesterol (mg/dL), LDL-cholesterol (mg/dL), fasting plasma glucose (mg/dL), glycosylated hemoglobin (HbA1c, %), C-reactive protein (CRP, mg/L), and insulin (μU/mL), were all measured in serum using laboratory methods (CDC, 2018b). The composite covariates were comprehensively evaluated. Hypertension (yes/no) was defined as a positive history of physician diagnosis, elevated blood pressure (BP, systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg), or the use of antihypertensive medications (Chobanian et al., 2003). Diabetes (yes/no) was defined as a positive history of physician diagnosis, elevated fasting plasma glucose