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## Serum perfluoroalkyl substances and cardiometabolic consequences in adolescents exposed to the World Trade Center disaster and a matched comparison group

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### ARTICLE INFO

#### Keywords:

Perfluoroalkyl substances  
Adolescents  
World trade center disaster  
Cardiometabolic consequences

### ABSTRACT

**Background:** Large amounts of various chemical contaminants, including perfluoroalkyl substances (PFASs), were released at the time of the World Trade Center (WTC) disaster. Thousands of children who lived and/or attended school near the disaster site were exposed to these substances but few studies have examined the possible consequences related to these exposures.

**Objectives:** To examine the relationship of PFASs serum levels with cardiometabolic profile in children and adolescents enrolled in the World Trade Center Health Registry (WTCHR) and a matched comparison group.

**Methods:** We evaluated WTCHR enrollees who resided in New York City and were born between September 11, 1993 and September 10, 2001, and a matched comparison group consisting of individuals who were ineligible for WTCHR participation upon distance of their home, school or work from the WTC and lack of participation in rescue and recovery activities. Matching was based on date of birth, sex, race, ethnicity, and income. We assessed exposure to PFASs, as measured by serum levels and association with cardiometabolic profile as measured by arterial wall stiffness, body mass index, insulin resistance, fasting total cholesterol, HDL, LDL and triglycerides.

**Results:** A total of 402 participants completed the study and serum samples were analyzed from 308 participants, 123 in the WTCHR group and 185 in the comparison group. In multivariable regression analysis, after adjusting for relevant confounders, we observed a significant, positive association of perfluorooctanoic acid (PFOA) with triglycerides (beta coefficient = 0.14, 95% CI: 0.02, 0.27, 15.1% change), total cholesterol (beta coefficient = 0.09, 95% CI: 0.04, 0.14, 9.2% change), and LDL cholesterol (beta coefficient = 0.11, 95% CI: 0.03, 0.19, 11.5% change). Perfluorohexanesulfonic acid levels were associated with decreased insulin resistance (beta coefficient = -0.09, 95% CI: -0.18, -0.003, -8.6% change); PFOA and perfluorononanoic acid were associated with increased brachial artery distensibility.

**Conclusions:** This research adds to our knowledge of the physical health impacts in a large group of children exposed to the WTC disaster. Abnormal lipid levels in young adults might be an early marker of atherosclerosis

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and cardiovascular diseases and our findings highlight the importance of conducting longitudinal studies in this population.

## 1. Introduction<sup>1</sup>

During the terrorist attack on the World Trade Center (WTC) on September 11, 2001, and in the months that followed, children in lower Manhattan were exposed to large amounts of contaminants such as particulate matter, heavy metals and persistent organic pollutants (POP) (Landrigan et al., 2004). Elevated concentrations of perfluoroalkyl substances (PFASs), a group of chemicals widely used in various building and construction material (Becanova et al., 2016), upholstery, carpet, and nonstick cookware (Kotthoff et al., 2015; Trier et al., 2011), have been found in window films and in samples of dust, water, sediment, and sewage collected in and around the WTC site (Litten et al., 2003; Offenberget al., 2005; Offenberget al., 2004). The US Environmental Protection Agency (EPA) has recently established drinking water health advisories of 0.07 micrograms per liter for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), two of the most environmentally persistent PFASs (EPA, 2016-a; EPA, 2016-b).

We recently documented that the children enrolled in the World Trade Center Health Registry (WTCHR) had higher levels of serum PFASs than matched comparisons years after the WTC disaster (Trasande et al., 2017). This observation is in agreement with data showing that PFASs persist in the environment and in humans, with half-lives ranging from 3 to 5 years to 8 years and longer (Olsen et al., 2007; Zhang et al., 2013). It is also consistent with studies of responders that documented increases in PFASs in relationship to WTC-exposure (Tao et al., 2008).

The consequences of WTC-related PFASs exposure are less clear. Current evidence suggests that PFASs interfere with important biological processes, specifically activation of alpha- and gamma-peroxisome proliferator activated receptors (Zhang et al., 2014), which play key roles in lipid and carbohydrate metabolism and are also involved in lipid transport, cholesterol synthesis, cell communication, inflammation and oxidative stress (Lau et al., 2007; Yao and Zhong, 2005). Human studies have shown a positive association between levels of PFASs and total and non-high-density cholesterol in the NHANES, despite the relatively low level of exposure (Nelson et al., 2010). In addition, among PFASs, concentrations of perfluorooctanesulfonic acid (PFOS) and perfluorononanoic acid (PFNA) have been associated with lower levels of IGF-1 in boys and girls 6–9 years of age (Lopez-Espinosa et al., 2016). In turn, decreased levels of IGF-1 have been associated with metabolic syndrome (Aguirre et al., 2016) and increased risk of cardiovascular events in later life (Carlzon et al., 2014).

The aim of the current study was therefore to examine the relationship of serum PFASs levels with cardiometabolic profile, as measured by blood lipids, insulin resistance, arterial stiffness, and body mass index (BMI) in children and adolescents enrolled in the WTCHR and a matched comparison group, while controlling for an array of possible confounding factors. Cardiovascular risk factors such as insulin resistance and hypertension do not typically emerge until adolescence, and identifying the adolescents who are at risk and intervening to

modify diet, treat with medications and/or increase physical activity may help reduce the burden of subsequent adult chronic disease in this vulnerable group.

For the purpose of this analysis we combined the two study populations (WTCHR and comparison group), which allowed us to increase the range of exposures studied, but no comparisons were made between these two populations with regard to the outcomes of interest.

## 2. Methods

### 2.1. Study population

#### 2.1.1. WTCHR population

This group consisted of WTCHR enrollees who resided in New York City and were born between September 11, 1993 and September 10, 2001. Participants were enrolled with the assistance of the New York City Department of Health (NYCDOHMH) using mail, email, phone, and in-person communication methods. Details of recruitment process are described elsewhere (Trasande et al., 2017).

#### 2.1.2. Comparison group

This group consisted of individuals who were not eligible for WTCHR participation due to their specific location on the morning of 9/11 (Friedman et al., 2011). We aimed to recruit a matched comparison group and utilized the WTCHR's 2011–12 survey cycle as a matching tool. We created a table of desired frequency distribution of the matching variables for comparisons using age (0–2, 3–5 or 6–8 years-old on 9/11/2001, with age 8 years being the upper bound for age restriction), sex, race (White, African-American, Asian, other), ethnicity (Hispanic, non-Hispanic) and income (< \$25,000, ≥ \$25,000). Multiple recruitment strategies were used (Trasande et al., 2017), and a screening questionnaire was used to determine individuals' eligibility based on the frequency-matching table. Individuals were excluded as matched comparisons if they otherwise could qualify for enrollment in the WTCHR due to location on 9/11.

#### 2.1.3. Exclusion criteria

Participants were not considered eligible for either the WTCHR or the control group if any of the following was present: i) inability to follow study procedures for measurement of arterial stiffness; ii) serious lung or heart condition; iii) heart or lung surgery; and iv) pregnancy.

#### 2.1.4. Institutional review board approval

The study was reviewed and approved by the NYU School of Medicine Institutional Review Board, as well as research committees at Bellevue and Gouverneur Hospital Centers. Adolescents under 18 years of age provided informed assent forms along with parental informed consent forms before undergoing study procedures. A Certificate of Confidentiality was obtained to protect participant privacy. The study was approved by New York State Department of Health (NYSDOH) for the analysis of serum samples.

### 2.2. Study visits

Visits took place on evenings, weekends and during school holidays to maximize convenience, either in 1 or 2 visits at the study site. Participants were instructed to fast for 6 h before study visits, and to avoid food, caffeine-containing products, and sugary drinks. After providing informed consent, the following were performed: a fasting blood draw (≥ 6 h); anthropometric measurements; and brachial artery

<sup>1</sup> Body mass index (BMI); HDL (high-density lipoprotein); Limits of Detection (LODs); N-methylperfluoro-1-octanesulfonamidoacetic acid (N-MeFOSAA); N-methyl perfluorooctanesulfonamido acetic acid (N-meFOSAA); New York State Department of Health (NYSDOH); NYC Department of Health & Mental Hygiene (NYC DOHMH); perfluoroalkyl substances (PFASs); perfluorodecane sulfonate (PFDS); perfluorodecanoic acid (PFDA); perfluorododecanoic acid (PFDoDA); perfluoroheptanoic acid (PFHpA); perfluorohexanesulfonic acid (PFHxS); perfluorononanoic acid (PFNA); perfluorooctane sulfonamide (PFOSA); perfluorooctanesulfonic acid (PFOS); perfluorooctanoic acid (PFOA); perfluoroundecanoic acid (PFUnDA); World Trade Center (WTC); WTC Health Registry (WTCHR).

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