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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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## 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[1]

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; Offenberg et al., 2005; Offenberg et 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 ($< \$25{,}000$, $\geq \$25{,}000$). 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 ($\geq$ 6 h); anthropometric measurements; and brachial artery

[1] 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).

distensibility/pulse wave velocity measurements.

#### 2.2.1. Measurement of PFASs

Eleven PFASs were measured in serum using a solid phase extraction (SPE) procedure and high-performance liquid chromatograph interfaced with an electrospray tandem mass spectrometer, using the methods similar to those described elsewhere (Taniyasu et al., 2005; Kannan et al., 2004), and documented in our previous manuscript (Trasande et al., 2017). For further details related to the methodology, please see Supplemental Material. The following PFASs were measured: perfluorohexanesulfonic acid (PFHxS); *n*-methyl perfluorooctanesulfonamido acetic acid (N-meFOSAA); perfluorooctane sulfonamide (PFOSA); perfluorooctanesulfonate (PFOS); perfluorodecanesulfonate (PFDS); perfluoroheptanoic acid (PFHpA); perfluorooctanoic acid (PFOA); perfluorononanoic acid (PFNA); perfluorodecanoic acid (PFDA); perfluoroundecanoic (PFUnDA); and perfluorododecanoic acid (PFDoDA).

### 2.3. Assessment of cardiometabolic profile

#### 2.3.1. Anthropometric measures

Weight and height were measured using calibrated stadiometers (Shorr Productions, Olney, MD) and scales (Seca model 881; Seca Corp., Hanover, MD). Body mass index *Z*-scores were derived from 2000 Centers for Disease Control and Prevention (CDC) norms, incorporating height, weight and sex; overweight and obese were categorized as BMI Z-score ≥ 1.036 and ≥ 1.64, (Ogden et al., 2002) which correspond to the 85th and 95th age- and sex-adjusted percentiles.

#### 2.3.2. Dietary data and physical activity

To obtain dietary data, participants completed a web-based version of the Diet History Questionnaire II (DHQ II), a publicly available food frequency questionnaire (FFQ) developed by the National Cancer Institute, which has been previously validated. (Rockett et al., 1997) Participants also completed a three-day physical activity diary, based on the International Physical Activity Questionnaire-Short Last Seven Days, which is well validated (Craig et al., 2003). Physical activity data from the diary were converted into energy expenditure estimates as MET using published values (Ainsworth et al., 2000).

#### 2.3.3. Blood pressure (BP) and brachial artery distensibility (BrachD)

Brachial artery distensibility (BrachD) measurement is a rapid method of accurately assessing the relative stiffness of a peripheral artery. A lower value indicates a stiffer vessel. The DynaPulse Pathway instrument derives BrachD and BP using the technique of pulse waveform analysis of arterial pressure signals obtained from a standard cuff sphygmomanometer (Urbina et al., 2002). Following a 5 min rest period, a BP cuff appropriate for the subject's upper arm size was applied, and three automatic recordings of systolic, diastolic, mean arterial BP and heart rate were obtained. Off-line analyses of brachial artery pressure curve data were then performed by Pulse Metric, Inc. using an automated system to derive parameters from the pulse curves to calculate BrachD (Urbina et al., 2011). Because BP varies widely by age, sex and height, we calculated systolic/diastolic BP *Z*-scores from mixed-effects linear regression models derived using data from 1999 to 2000 National Health and Nutrition Examination Survey (National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents, 2004).

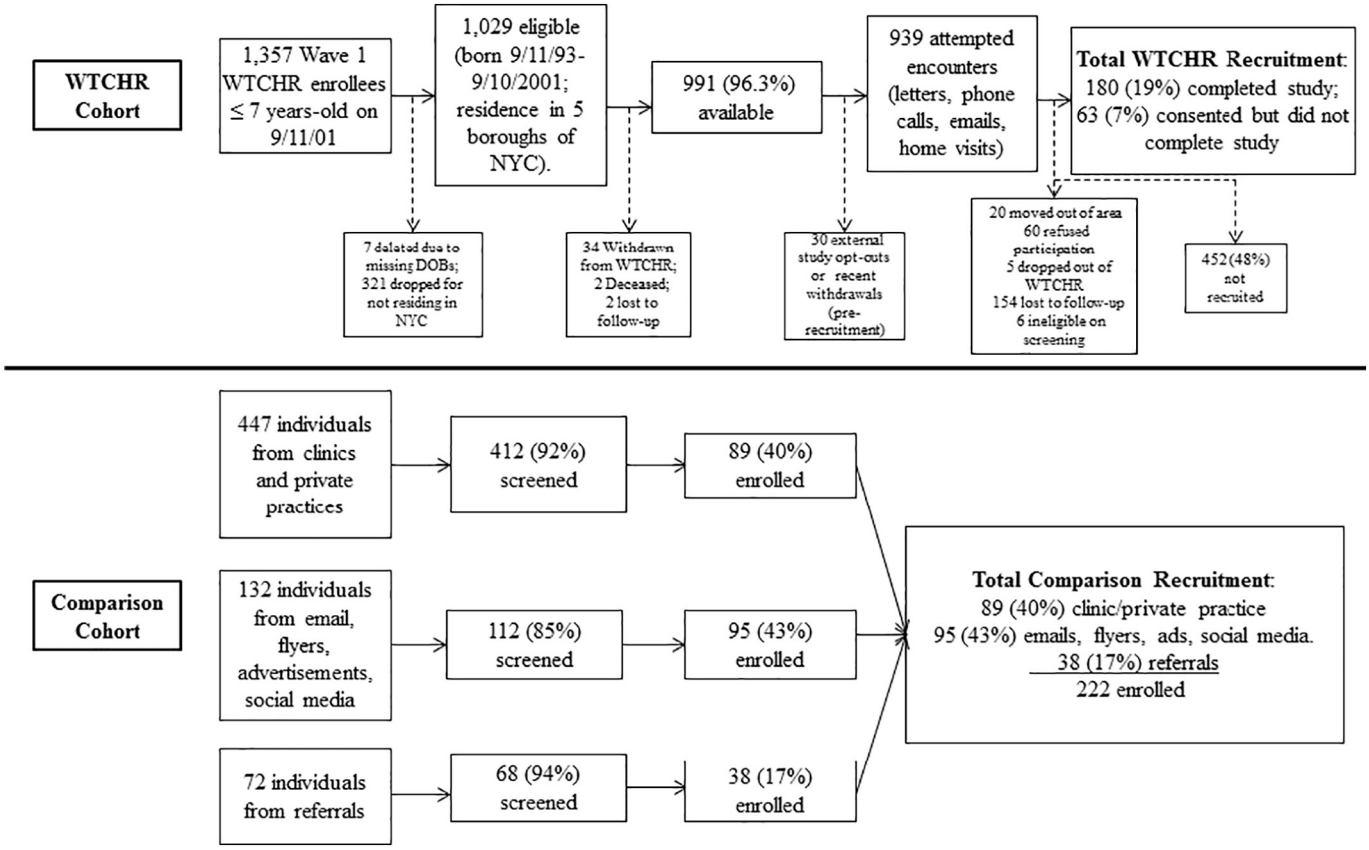


**Fig. 1.** Recruitment flowchart for WTCHR and comparison cohort.

WTCHR individuals enrolled in this study were more likely to be older and to be from low income families ($p < 0.001$) than those excluded. There were no differences in sex, race or ethnicity between WTCHR individuals who participated in this study and nonparticipants (Table S1, Supplemental material). In total, 180 children from the WTCHR and 222 socio-demographically matched controls were included in the analysis; among them, information on PFAS was available in 185 and 123 individuals, respectively (participants with consent to venous blood sampling). Characteristics of the two study populations are presented in Table 1.

**Table 1**
Characteristics of the two study populations. [a]n = 43 missing for comparison group; n = 27 missing for WTCHR group; [b]n = 1 missing for race/ethnicity; [c]n = 2 missing for caloric intake; [d]evaluated by saliva cotinine concentration and questionnaire. For subjects without saliva cotinine concentration, we categorized no smoker and no secondhand smoke exposure into "low", no smoker but secondhand smoke exposure into "medium", and smoker into "high" category.

| | Control group $n$ = 222 | WTCHR group $n$ = 180 | $p$ value |
|---|---|---|---|
| Sex | | | |
| Male | 89 (40.1%) | 97 (53.9%) | **0.008** |
| Female | 133 (59.9%) | 83 (46.1%) | |
| Date of birth | | | |
| 9/11/93–9/10/95 | 45 (20.3%) | 47 (26.1%) | 0.159 |
| 9/11/95–9/10/98 | 89 (40.1%) | 77 (42.8%) | |
| 9/11/98–9/10/01 | 88 (39.6%) | 56 (31.1%) | |
| Income < $25,000[a] | 49 (27.4%) | 28 (19.4%) | 0.126 |
| Race/ethnicity[b] | | | |
| Non-Hispanic White (%) | 89 (40.1%) | 66 (36.9%) | 0.053 |
| Non-Hispanic Black (%) | 19 (8.6%) | 16 (8.9%) | |
| Non-Hispanic Asian (%) | 44 (19.8%) | 49 (27.4%) | |
| Non-Hispanic other (%) | 10 (4.5%) | 16 (8.9%) | |
| Hispanic (%) | 60 (27.0%) | 32 (17.9%) | |
| Caloric intake[c], median (IQR) | 1535 (1061, 2087) | 1621 (1141, 2331) | **0.028** |
| Physical activity, MET hours per week (IQR) | 150 (90, 240) | 180 (120, 285) | **0.087** |
| Body mass index category | | | |
| Normal weight/underweight | 162 (73.0%) | 150 (83.3%) | **0.045** |
| Overweight | 36 (16.2%) | 19 (10.6%) | **0.028** |
| Obese | 24 (10.8%) | 11 (6.1%) | **0.087** |
| Smoking status | | | |
| Smokers | 23 (10.4%) | 24 (13.3%) | 0.443 |
| Median cotinine concentration | 0.324 (0.106, 0.690) | 0.412 (0.106, 0.984) | 0.294 |
| Tobacco smoke exposure[d] | | | |
| Low (< 0.15 ng/mL) | 102 (45.9) | 73 (40.6) | 0.353 |
| Medium (≥ 0.15 to < 2.32 ng/mL) | 95 (42.8) | 79 (43.9) | 0.443 |
| High (≥ 2.32 ng/mL) | 25 (11.3) | 28 (15.6) | 0.294 |
| Cardiometabolic markers, median (IQR) | | | |
| Triglycerides (mg/dL) | 66.5 (48, 95.3) | 63.5 (49.8, 88.5) | 0.891 |
| High-density lipoprotein (mg/dL) | 53 (44, 66) | 52 (43.75, 60.25) | 0.294 |
| Low-density lipoprotein (mg/dL) | 77 (66, 94) | 80 (69, 96) | 0.131 |
| Insulin resistance (HOMA-IR) | 1.54 (1.14, 2.23) | 1.37 (1.05, 2.04) | 0.087 |
| Total cholesterol (mg/dL) | 148.5 (133, 166.3) | 148.5 (133, 170) | 0.827 |

Bold data indicates significant at $p > 0.1$.

#### 2.3.4. Arterial wall stiffness assessment

Pulse wave velocity (PWV) reflects the speed for the pressure wave generated by cardiac ejection to reach the periphery. A higher value indicates a stiffer vessel. PWV was measured by obtaining the arterial pulse waveform at the common carotid and femoral arteries using the SphygmoCor CPV System (AtCor Medical, Sydney, Australia) (Laurent et al., 2006). Arterial waveforms gated to the R-wave on the ECG tracing are recorded from the carotid then distal artery of interest, and PWV is then calculated as the difference in the carotid-to-distal path length divided by the difference in R-wave-to-waveform foot times. The SphygmoCor CPV System was also used to measure central aortic pressure and the Augmentation Index (AIx), a vascular parameter incorporating both central stiffness and wave reflections (a higher value indicates arterial dysfunction) (Chen et al., 1997).

#### 2.3.5. Blood lipid profile, glucose and insulin

We measured fasting total cholesterol, triglycerides, HDL, LDL, insulin, and glucose. We examined continuous as well as categorical abnormal values for lipid levels, applying cut-off points for HDL of < 40 mg/dL and ≥ 100 mg/dL for triglycerides, as recently done to assess components of the metabolic syndrome in analyses of adolescents in 2001–2006 NHANES (Johnson et al., 2009). For insulin resistance we used the validated homeostatic model assessment of insulin resistance (HOMA-IR), calculated by dividing the product of insulin (μU/mL) and glucose (mMol/L) by 22.5 (Bergman et al., 1987; Conwell et al., 2004; Keskin et al., 2005).

### 2.4. Covariates

Information on other covariates including race/ethnicity (White, African American, Asian, Other and Hispanic) and sex (male or female) was obtained through questionnaire. Exposure to tobacco smoke was evaluated by saliva cotinine concentration and questionnaire. Salivary cotinine was analyzed using a highly reliable ($r$ = 0.99 compared with serum) and sensitive (limit of detection 0.05 ng/mL) test from Salimetrics, Inc. (State College, PA). Cotinine was measured as a continuous variable, and categorized into low (< 0.15 ng/mL), medium (≥ 0.15 to < 2.32 ng/mL) and high (≥ 2.32 ng/mL) categories, using established conventions (Strauss, 2001; Wilson et al., 2011). For subjects without saliva cotinine concentration, we categorized using questionnaires (low: no smoker and no secondhand smoke exposure; medium: no smoker but secondhand smoke exposure; high: smoker).

### 2.5. Statistical analysis

We conducted descriptive, univariate, and multivariate analyses with R Statistical Software (version 3.3.1). Chi-square test or Fisher exact test was used to compare the sociodemographic variables of two study populations. Wilcoxon Rank Sum test was used to compare caloric intake, physical activity levels, cardiometabolic markers, and serum PFASs between the two groups. PFAS concentrations were log-transformed to account for skewed distribution; following published practices, levels less than the LOD were imputed to be LOD/√2, and we limited our statistical analyses to PFASs detected in ≥ 50% of the samples (Helsel, 2012). Simple linear and logistic regression was used to compare cardiometabolic profiles (blood lipids, BMI, PWV, AIx, and insulin resistance) by serum PFASs. Multiple linear regression or multiple logistic regression was used for continuous or discrete outcomes, controlling for sex, race, caloric intake, physical activity, smoke exposure, BMI category (but not for BMI related outcomes). All statistical tests were two-sided, and $p$ values were considered significant if < 0.05.

## 3. Results

Fig. 1 provides an overview of the enrollment process for the WTCHR study population and matched comparison group.

Compared to the WTCHR cohort, participants in the comparison group were more likely to be female (59.9% vs. 46.1%). Caloric intake was higher in the WTCHR population (1621 cal) than the comparison group (1535 cal) but overweight and obesity status were more likely in the comparison than the WTCHR group ($p$ = 0.045). Table 2 shows the characteristics of the participants who agreed to venous sampling.

Several significant associations were detected between single chemicals and cardiometabolic outcomes in univariable analysis (Table S2, Supplemental material), and most remained significant after adjusting for confounders in the multivariable model (Table 3).

Adjusted analyses showed consistent associations between higher serum PFASs and higher lipid levels. PFOS was associated with higher total and LDL cholesterol (beta coefficient for total cholesterol in natural log scale = 0.082, 95% CI: 0.047, 0.117, corresponding to 8.5% change; beta coefficient for LDL = 0.102, 95% CI: 0.046, 0.159, 10.7% change, respectively) as well as higher HDL cholesterol (beta coefficient = 0.064, 95% CI: 0.003, 0.125, 6.6% change). PFOA was associated with higher triglycerides (beta coefficient = 0.141, 95% CI:

**Table 2**
Serum PFASs Population Characteristics (with exclusion of those who opted out of venous blood sampling). [a]n = 38 missing for comparison; n = 27 missing for WTCHR; [b]n = 1 missing for race/ethnicity; [c]n = 2 missing for caloric intake.

| | Comparison ($n$ = 185) | WTCHR ($n$ = 123) | $p$ value |
|---|---|---|---|
| Sex, *n* (%) | | | |
| Male | 74 (40%) | 69 (56.1%) | **0.010** |
| Female | 111 (60%) | 54 (44.9%) | |
| Date of birth, *n* (%) | | | |
| 9/11/93–9/10/95 | 35 (18.9%) | 34 (27.6%) | **0.070** |
| 9/11/95–9/10/98 | 73 (39.5%) | 52 (42.3%) | |
| 9/11/98–9/10/01 | 77 (41.6%) | 37 (30.1%) | |
| Income < $25,000[a] | 42 (22.7%) | 19 (15.4%) | 0.170 |
| Race/Ethnicity,[b] *n* (%) | | | |
| Non-Hispanic White | 72 (38.9%) | 42 (34.4%) | **0.040** |
| Non-Hispanic Black | 17 (9.2%) | 13 (10.7%) | |
| Non-Hispanic Asian | 37 (20%) | 30 (24.6%) | |
| Non-Hispanic other | 6 (3.2%) | 13 (10.7%) | |
| Hispanic | 53 (28.6%) | 24 (19.7%) | |
| Serum PFASs, median (IQR), ng/mL | | | |
| PFHxS (n < LOD = 0%) | 0.53 (0.47) | 0.67 (0.69) | < **0.0001** |
| PFOS (n < LOD = 0%) | 2.78 (2.18) | 3.72 (2.82) | < **0.0001** |
| PFOA (n < LOD = 0%) | 1.39 (0.75) | 1.81 (0.90) | < **0.0001** |
| PFNA (n < LOD = 0.3%) | 0.49 (0.33) | 0.61 (0.36) | < **0.0001** |
| PFDA (n < LOD = 25%) | 0.11 (0.15) | 0.14 (0.12) | < **0.0001** |
| PFUnDA (n < LOD = 47%) | 0.04 (0.16) | 0.12 (0.21) | **0.007** |
| Calories[c], median (IQR) | 1537 (1014) | 1709 (1317) | **0.008** |
| Tobacco smoke exposure | | | |
| Low | 102 (45.9) | 73 (40.6) | 0.353 |
| Medium | 95 (42.8) | 79 (43.9) | |
| High | 25 (11.3) | 28 (15.6) | |
| Body mass index category | | | |
| Normal weight/underweight | 137 (74.1) | 98 (79.7) | 0.387 |
| Obese | 20 (16.3) | 8 (4.3) | |
| Overweight | 28 (15.1) | 17 (13.8) | |

0.017, 0.265, 15.1% change), total cholesterol (beta coefficient = 0.088, 95% CI: 0.039, 0.137, 9.2% change), and LDL cholesterol (beta coefficient = 0.109, 95% CI: 0.031, 0.187, 11.5% change). Similar associations were observed with PFNA, PFDA, and PFUnDA. Higher levels of PFHxS were significantly associated with decreased insulin resistance (beta coefficient = − 0.090, 95% CI: − 0.176, − 0.003, − 8.6% change), and higher LDL cholesterol (beta coefficient = 0.049, 95% CI: 0.007, 0.091, 5.0% change). We also detected an association between higher levels of PFOA and PFNA and increased brachial artery distensibility (beta coefficient for % change/mm Hg = 0.453, 95% CI 0.038, 0.868; beta coefficient = 0.343, 95% CI: 0.016, 0.670, respectively). No association was detected between serum levels of PFASs and PWV and AIx. PFUnDA was associated with lower odds of being overweight (odds ratio per unit increase in natural log PFUnDA = 0.951, 95% CI: 0.911, 0.993), but other PFASs examined in this study were not associated with BMI status. Table 4 shows the results of multivariate analyses presented as percent change in the outcome of interest for each log unit increase of the chemicals examined.

## 4. Discussion

This research study examined the cardiometabolic profiles of adolescents participating in the WTCHR compared to a socio-demographically-matched control group of NYC residents, to examine the potentially contributing role of PFASs exposures to cardiometabolic risks in exposed children. We have previously documented that children with subchronic dust exposure and dust cloud exposure related to the WTC disaster have higher levels of PFASs, and here we report that higher serum levels of PFASs are associated with increased blood lipid levels (triglycerides and cholesterol) (Trasande et al., 2017). Since abnormal lipid levels in young adults might be an early marker of atherosclerosis and cardiovascular diseases (Pletcher et al., 2016), this population may benefit from continuous monitoring and early interventions to prevent adverse cardiometabolic outcomes as a result of PFASs exposure.

Previous reports from cross-sectional data support the association between concentrations of PFASs and altered lipid profiles, specifically elevated plasma cholesterol and triglycerides, (Nelson et al., 2010; Fisher et al., 2013; Starling et al., 2014) although the evidence is not uniform and shows some inconsistencies in the results, also depending on the specific chemical examined. PFOS and PFOA are the two chemicals for which the evidence is the strongest, while other compounds like PFHxS and PFNA have not been studied as extensively, mainly because they are normally present in lower concentrations compared with the two PFOS and PFOA (Nelson et al., 2010). Positive associations between PFOS and both HDL and LDL cholesterol have been reported among adults (Starling et al., 2014), children and adolescents (Frisbee et al., 2010; Geiger et al., 2014). Similarly, positive associations between PFOA and PFOS and triglycerides have been reported in adults (Steenland et al., 2009), as well as in children (Zeng et al., 2015). Instead, for compounds like PFHxS the evidence is not consistent: Nelson and colleagues reported an inverse association between PFHxS and total cholesterol (Nelson et al., 2010) whereas others have found a significant positive association with total and LDL cholesterol (Fisher et al., 2013). In the present study we report that, in addition to PFOS and PFOA, PFHxS, PFNA and PFDA were also positively associated with increased lipid concentrations (total and LDL cholesterol). PFDA and PFUnDA, which were the two compounds with the lowest median serum concentrations among all PFASs in the WTCHR group, were both positively associated with HDL cholesterol.

With respect to insulin resistance, we detected an inverse relationship with PFHxS. Recently published data from a prospective cohort study, reporting that children with higher levels of PFASs had significantly lower insulin resistance (Fleisch et al., 2017), are consistent with our findings, and so are previous analysis from NHANES data (Nelson et al., 2010). However, other studies have reported a positive association between PFOS and insulin resistance, although this was only present in overweight children (Timmermann et al., 2014). In addition, some available data suggest that the association of PFOS with insulin resistance differs between adults and adolescents, with the former showing increased insulin resistance with higher PFOS concentrations, whereas the opposite was noted for adolescents (Lin et al., 2009). This sample was not large enough for stratified analysis.

The biological mechanisms underlying the associations between PFAS and lipid levels and insulin resistance is less understood. Most of our information comes from animal studies showing that PFAS have affinity for PPARα and acts as agonists to these receptors. Nonetheless, these studies also indicate that the degree of agonist effect is variable and depends on the specific compound examined (Wolf et al., 2012). Affinity to PPARγ has also been demonstrated (Takacs and Abbott, 2007) and PPARγ activation could potentially lead to increased insulin sensitivity (Jiang et al., 2015), a mechanism similar to that of thiazolidinediones, which are used to in the treatment of type 2 diabetes. Despite providing valuable insight, findings of toxicological research are not directly applicable to humans and further studies are therefore warranted to elucidate the underlying mechanisms. The long-term health consequences of an increase in serum lipid levels in the ranges observed in this study are unclear. However, if confirmed in further longitudinal studies, such increments may become significant when considered at the population level, in which even small increments can result in large increases in the prevalence of hyperlipidemia, shifting the distribution of blood lipids and increasing the number of individuals who are above the cut off points to identify hyperlipidemic individuals.

In this study we also detected an inverse association between PFOA and PFNA and increased brachial artery distensibility. To our knowledge, this is the first time that such an association is reported, since not many studies have examined the association between PFASs and

**Table 3**
Multivariable linear and logistic regression analysis of cardiometabolic outcomes associated with serum PFASs. Each column represents an examination of a single exposure variable or study arm controlled for sex, race, caloric intake, physical activity, cotinine concentration and BMI category (except when the outcome examined was BMI); Beta coefficients represent the change associated with each natural log-unit increase in the PFASs examined. *$p < 0.05$; **$p < 0.01$. BMI: Body mass index; BMIz: BMI Z-score; logTrig: log-transformed triglycerides; log homair: log-transformed homeostatic model of insulin resistance; logChol: log-transformed total cholesterol; logLDL: log-transformed LDL cholesterol; logHDL: log-transformed HDL cholesterol; BrachD: brachial artery distensibility; AIx: Augmentation Index; PWV: pulse wave velocity.

| | PFHxS | | PFOS | | PFOA | | PFNA | | PFDA | | PFUnDA | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiometabolic outcomes (continuous) | Unit change (95% CI) | *p* | Unit change (95% CI) | *p* | Unit change (95% CI) | *p* | Unit change (95% CI) | *p* | Unit change (95% CI) | *p* | Unit change (95% CI) | *p* |
| BMI | 0.43 (−0.38, 1.23) | 0.30 | −0.35 (−1.432, 0.743) | 0.53 | 0.65 (−0.841, 2.143) | 0.39 | −0.48 (−1.72, 0.77) | 0.45 | −0.42 (−1.030, 0.19) | 0.18 | −0.48 (−1.01, 0.06) | 0.08 |
| BMIz | 0.05 (−0.15, 0.25) | 0.62 | −0.22 (−0.49, 0.06) | 0.12 | −0.02 (−0.38, 0.33) | 0.90 | −0.18 (−0.47, 0.10) | 0.21 | −0.08 (−0.23, 0.06) | 0.27 | −0.13 (−0.26, −0.01) | **0.03*** |
| log_trig | 0.04 (−0.02, 0.11) | 0.20 | 0.04 (−0.05, 0.13) | 0.36 | 0.14 (0.02, 0.27) | **0.03*** | −0.007 (−0.11, 0.01) | 0.89 | 0.01 (−0.047, 0.057) | 0.85 | −0.04 (−0.09, 0.003) | 0.07 |
| log_homair | −0.09 (−0.18, −0.003) | **0.04*** | −0.06 (−0.18, 0.06) | 0.31 | −0.05 (−0.21, 0.12) | 0.58 | 0.01 (−0.13, 0.14) | 0.89 | −0.04 (−0.11, 0.03) | 0.26 | −0.04 (−0.10, 0.02) | 0.21 |
| logChol | 0.04 (0.01, 0.06) | **0.01*** | 0.08 (0.05, 0.12) | **< 0.001** | 0.09 (0.04, 0.14) | **< 0.001** | 0.05 (0.01, 0.09) | **0.01*** | 0.04 (0.02, 0.06) | **< 0.001** | 0.02 (0, 0.04) | 0.06 |
| logLDL | 0.05 (0.01, 0.09) | **0.02*** | 0.10 (0.05, 0.16) | **< 0.001** | 0.11 (0.03, 0.19) | **0.006**** | 0.07 (0.01, 0.14) | **0.03*** | 0.04 (0.00, 0.07) | **0.03*** | 0.01 (−0.02, 0.04) | 0.49 |
| logHDL | 0.03 (−0.02, 0.07) | 0.26 | 0.06 (0.003, 0.13) | **0.04*** | 0.04 (−0.04, 0.12) | 0.34 | 0.05 (−0.02, 0.12) | 0.13 | 0.05 (0.02, 0.09) | **0.003**** | 0.04 (0.01, 0.07) | **0.01*** |
| BrachD | 0.15 (−0.07, 0.38) | 0.69 | 0.30 (−0.01, 0.62) | 0.06 | 0.45 (0.04, 0.87) | **0.03*** | 0.34 (0.02, 0.67) | **0.04*** | 0.11 (−0.06, 0.28) | 0.10 | 0.11 (−0.04, 0.26) | 0.97 |
| AIx | −0.48 (−2.20, 1.25) | 0.89 | −0.24 (−2.02, 2.41) | 0.85 | −1.41 (−4.59, 1.78) | 0.39 | −0.51 (−2.51, 2.53) | 0.70 | 0.08 (−1.23, 1.39) | 0.14 | 0.37 (−0.79, 1.52) | 0.35 |
| PWV | −0.05 (−0.16, 0.07) | 0.43 | −0.06 (−0.23, 0.11) | 0.51 | 0.05 (−0.17, 0.28) | 0.64 | −0.13 (−0.30, 0.04) | 0.14 | −0.04 (−0.13, 0.05) | 0.39 | −0.03 (−0.11, 0.05) | 0.41 |
| Cardiometabolic outcomes (dichotomous) | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* | OR (95% CI) | *p* |
| Overweight | 1.04 (0.97, 1.11) | 0.30 | 0.98 (0.90, 1.07) | 0.66 | 1.00 (0.90, 1.13) | 0.97 | 1.01 (0.92, 1.13) | 0.72 | 0.98 (0.93, 1.03) | 0.49 | 0.95 (0.91, 0.99) | **0.02*** |

**Table 4**
Percent changes of blood lipids and insulin resistance outcomes associated with serum PFASs.[a]

| PFASs | Triglycerides | Insulin resistance (HOMAIR) | Total cholesterol | LDL cholesterol | HDL cholesterol |
|---|---|---|---|---|---|
| | Percent change (95% CI) | Percent change (95% CI) | Percent change (95% CI) | Percent change (95% CI) | Percent change (95% CI) |
| PFHxS | 4.5 (−2.4, 11.7) | −8.6 (−16.1, −0.3) | 3.9 (1.1, 6.6) | 5.0 (0.7, 9.5) | 2.6 (−1.9, 7.4) |
| PFOS | 4.3 (−4.8, 14.3) | −5.8 (−16.3, 5.9) | 8.5 (4.8, 12.4) | 10.7 (4.7, 17.2) | 6.6 (0.3, 13.3) |
| PFOA | 15.1 (−1.7, 30.3) | −4.5 (−18.8, 12.3) | 9.2 (4, 14.7) | 11.5 (3.1, 20.6) | 4.2 (−4.2, 13.2) |
| PFNA | −0.7 (−10.5, 10.2) | 0.9 (−11.8, 15.4) | 5.4 (1.2, 9.9) | 7.4 (0.6, 14.6) | 5.4 (−1.6, 13.1) |
| PFDA | 0.5 (−4.6, 5.9) | −3.7 (−10, 2.8) | 3.9 (1.8, 6.0) | 3.7 (0.4, 7.1) | 5.3 (1.8, 9.0) |
| PFUnDA | −4.1 (−8.2, 0.3) | −3.6 (−9.1, 2.1) | 1.7 (0, 3.6) | 1.0 (−1.8, 3.9) | 4.0 (0.9, 7) |

[a] Percent change in the original unit of measurement for one log unit increase of the chemicals examined; HOMAIR: homeostatic model of insulin resistance.

vascular function. Arterial stiffness is influenced by both genetic and hormonal factors (Rossi et al., 2011), and current evidence suggests an effect of PFASs on sex hormones. Increases in estradiol and decreases in testosterone with PFOA exposure have been observed in rodents (Lau et al., 2007) but the results of the few human studies conducted so far are less clear. Recently, Zhou and colleagues have reported that higher levels of PFASs are associated with lower testosterone and higher estradiol levels, and these associations seem to be more relevant in males than females (Zhou et al., 2016). We could speculate that the associations of PFOA and PFNA with increased arterial distensibility could be partly interpreted in light of concomitant alterations in sex hormone levels which, in turn, may influence vascular stiffness.

### 4.1. Limitations

We cannot rule out the possibility that some of the associations could be chance findings, including the association of PFUnDA with lower odds of being overweight, since none of the other chemicals examined was associated with BMI. In addition, this study collected data at a single time point, and longitudinal studies may be more informative in assessing the extent of cardiometabolic effects related to exposure to the WTC disaster. Another limitation to interpretation is that participants in both groups experienced environmental changes in the fifteen year period following the disaster, and we cannot rule out additional factors or exposures that could contribute to explaining the associations observed here. Furthermore, PFASs increases observed in this study could be correlated with all the other chemical contaminant exposures that were associated with the WTC. We acknowledge that this is a potential confounding factor but one difficult to control in a disaster epidemiology study.

## 5. Conclusion

This research adds to our knowledge of the physical health impacts in a large group of children who were exposed to the WTC disaster, and pinpoints the potential high risk of atherosclerosis and cardiovascular diseases in these children as a result of PFASs exposure.

## Authors' contributions

*Study concept and design*: Leonardo Trasande, Michael Marmor

*Acquisition of data*: Tony Koshy, Joseph Gilbert, Lauren Burdine

*Main analysis and interpretation of data*: Leonardo Trasande, Xiaoxia Han

*Substantial contributions to the design of the work, the analysis and/or the interpretation of data*:

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*Drafting of the manuscript*: Leonardo Trasande, Teresa Attina

*Critical revision of the manuscript for intellectual content*: Leonardo Trasande, Elaine Urbina, Michael Marmor, Teresa Attina

## Data access, responsibility, and analysis

Dr. Trasande had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Conflicts of interest

No competing interests to report.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.envint.2017.08.003.

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