A. OVERALL COVER PAGE

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Human Subjects: NA	**Vertebrate Animals:** NA
hESC: No	**Inventions/Patents:** No

B. OVERALL ACCOMPLISHMENTS

B.1 WHAT ARE THE MAJOR GOALS OF THE PROJECT?

We are leveraging two unique and contemporaneous cohorts to examine chemical and psychosocial stressors in relationship to proximity to the WTC site and self-reported exposures, and evaluate birth, neurodevelopment and cardiometabolic outcomes. The first is comprised of mothers who delivered in one of three lower Manhattan hospitals in the months after the disaster, and the other is the northern Manhattan-based Columbia Children's Environmental Health Center (NM) cohort. The NM cohort includes children born just before and after September 11, 2001 permitting nested evaluations of stress-related exposures. Except for cardiometabolic outcomes, the data are already available including freshly obtained measurements of POPs, which we will extend to include PFCs with NIOSH support. In both populations, neurodevelopmental outcomes have been assessed through 6-7 years of age.
Aim 1. To evaluate the impact of WTC-related psychosocial stress in the WTC and NM cohorts on birth and neurodevelopmental outcomes.
Aim 2. To evaluate PCBs and PBDEs in relationship to birth and neurodevelopmental outcomes in WTC and NM newborns.
Aim 3. To evaluate PFCs in relation to birth, neurodevelopmental and cardiometabolic outcomes in the WTC cohort.

B.1.a Have the major goals changed since the initial competing award or previous report?

No

B.2 WHAT WAS ACCOMPLISHED UNDER THESE GOALS?

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B.3 COMPETITIVE REVISIONS/ADMINISTRATIVE SUPPLEMENTS

For this reporting period, is there one or more Revision/Supplement associated with this award for which reporting is required?

No

B.4 WHAT OPPORTUNITIES FOR TRAINING AND PROFESSIONAL DEVELOPMENT HAS THE PROJECT PROVIDED?

NOTHING TO REPORT

B.5 HOW HAVE THE RESULTS BEEN DISSEMINATED TO COMMUNITIES OF INTEREST?

NOTHING TO REPORT

B.6 WHAT DO YOU PLAN TO DO DURING THE NEXT REPORTING PERIOD TO ACCOMPLISH THE GOALS?

Not Applicable

Prenatal WTC Chemical Exposures, Birth Outcomes and Cardiometabolic Risks

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Abstract

Perinatal exposure to the World Trade Center (WTC) disaster has been associated with adverse birth outcomes. However, little is known about the long-term consequences of exposures in this population, who are now teenagers. Intrauterine growth restriction has long been known to produce adverse effects on neurodevelopment, and the “thrifty phenotype” hypothesis first described by Barker et al, suggests that early life adaptations to poor in utero exposures can produce a profile of maladaptation ex utero in which the ability to acquire energy results in increased adiposity beginning in childhood and cardiovascular risks later in life. If cardiometabolic consequences are identified in children born to women living or working in lower Manhattan on September 11, 2001, the present represents a relatively narrow opportunity for proactive medication and behavioral modification to prevent serious consequences as these children age into adulthood. The premise that adverse neurodevelopmental and cardiometabolic consequences could arise from prenatal exposure to the disaster, is grounded in studies that have documented highly adverse and synergistic WTC–related chemical and psychosocial exposures. The better studied psychologically stressful exposures were common in pregnant women living/working near the site, and post-traumatic stress symptoms were associated with decrements in head circumference in the offspring. However, the disaster also released large amounts of particulate matter, heavy metals and persistent organic pollutants (POPs), including polychlorinated dibenzo-p dioxins, polychlorinated dibenzofurans and perfluorinated chemicals (PFAS), which have been associated with adverse birth outcomes, neurodevelopmental and cardiometabolic risks later in life. Studies have examined and failed to detect differences in blood mercury and polybrominated diphenyl ethers (PBDEs) among women living/working near the site, though women in their second half of pregnancy on September 11,2001 did have children with higher cord blood PBDEs. Yet, these studies did not include a comparison group, limiting generalizability. A newer concern has arisen from our NIOSH-funded study (U01OH01394 and 01714) which most recently identified increases in levels of multiple PFAS among postnatally-exposed children participating in the WTC Health Registry compared to a socio demographically matched group, and increases in PFAS among those who were exposed sub-chronically to dust in their homes. This was the first study to examine PFAS in postnatally-exposed youth, and raises new concerns about adverse birth, neurodevelopmental and cardiometabolic outcomes among youth exposed in utero. Another research gap is represented by the reality that no study has examined the potential and differential effects of psychological and chemical exposures and their possible interaction in contributing to adverse effects on later child health. Furthermore, adolescence is well-known to be a period when cardiometabolic issues emerge, adding timeliness to the proposed study.

Section 1

Significant or Key Findings.

We identified novel associations between geographical proximity to the WTC site and both prenatal dioxins and PFAS.

Our research was the first to try to disentangle the competing roles of exposure to chemical mixtures and psychological stress in the association between geographical proximity to the WTC and birth outcomes. Our findings suggested dioxins played mediating role in this relationship.

Our work added evidence to the previously reported relationship between PFAS and cardiometabolic outcomes and was the first to evaluate the association between PFAS and cord lipids.

We identified sex- and compound-specific associations between PFAS and child cognitive outcomes.

Translation of Findings. Our findings suggest additional need for long-term medical monitoring of children exposed to the World Trade Center disaster in utero, and potential addition of conditions to the covered list under the Zadroga act.

Research Outcomes/Impact. Identification of subpopulations vulnerable to WTC-associated exposures and health effects could facilitate targeted and proactive interventions such as treatment with antihypertensive medications which have been documented to prolong survival among adults with suboptimal cardiovascular profile.

Section 2 – Scientific Report

Study Participants

Aims 1-3a were conducted in the Columbia University World Trade Center birth cohort. For this cohort, 329 women with singleton pregnancies were enrolled between December 13, 2001 and June 26, 2002 at one of three hospitals located near the WTC site: Beth Israel, St. Vincent's, and New York University Downtown. Participants provided at least one blood sample (maternal blood at the time of delivery and/or cord blood), access to their medical record and their newborn's medical record, and completion of a 30- to 45-minute interview after delivery. The postpartum interview was administered at the hospital in the woman's preferred or native language (English, Spanish, or Chinese). For aim 3b, children, aged 18-20, that had blood samples from the original cohort were contacted via phone or email. Unfortunately despite multiple years of effort, only subsequently consented <50 and performed visits in <20.

Exclusion criteria: Eligibility requirements for aims 1-3a included: ages between 18 and 39 years, had not smoked (>1 cigarette/at any time) during pregnancy, and self-report of no diabetes, hypertension, HIV infection or AIDS, and no use of illegal drugs in the last year. Eligibility requirements for aim 3b included children from the original cohort who had a blood sample (n=249).

Sociodemographic and Risk Factor Variables

For the original cohort (aims 1-3a), the postpartum interview was administered at the hospital, post-delivery and prior to discharge, in the woman's preferred or native language (English, Spanish, or Chinese). Information on maternal education, date of birth, race, parity, material hardship during pregnancy, marital status and family smoking exposure was collected through a structured questionnaire during the interview. Two study-specific variables relating to exposure to the 9/11 WTC event were also drawn from the structured questionnaire; these variables were trimester on 9/11 and residential and occupational (if applicable) distance to the 9/11 site. Gestational age on 9/11 was used to determine trimester on that day. Mothers were classified as being in their first trimester on 9/11 if their child had a gestational age of ≤91 days on 9/11, and in their second or third trimester if their child had a gestational age >91 days. Eighteen participants were not pregnant yet on 9/11 but were still included in the study in the first trimester group, because exposures to the disaster persisted for months following the initial collapse. Distance to the 9/11 site was categorized into two groups: those who either lived or worked within 2 miles of the 9/11 site versus those who did not, using geocoded residential and work addresses (for the 4 weeks starting on and following 9/11). Maternal pre-pregnancy BMI was calculated using weight in kilograms divided by height in meters squared, both abstracted from the participants' medical chart. In the case of missing height or from the medical record, self-reported information on these variables from the hospital interview was used. Among participants with both self-reported and medical record weight and height, correlations were very high (r=0.99 and r=0.91, respectively). Child sex and date of birth were abstracted from the child's medical record. Gestational age in days was also abstracted from the medical record (if missing), date of last menstrual period from the interview minus the child's date of birth was used). Maternal age at delivery was determined by subtracting the child's date of birth from the mother's date of birth. Maternal demoralization was measured during the post-partum interview using the Psychiatric Epidemiology Research Instrument Demoralization scale (PERI-D), which provides a measure of nonspecific psychological distress, with demonstrated reliability across

different ethnic groups.30-32 Maternal intelligence was evaluated during the first study visit, which took place at approximately 12 months post-partum, using the Test of Non-Verbal Intelligence, Second Edition (TONI-2), a validated instrument for measuring general cognitive ability, considered to be free of cultural bias.33 Institutional Review Board approval was obtained before enrollment began and all women gave written informed consent before delivery.

For aim 3b, the follow-up visit was performed at a dedicated research site in close proximity to the 33rd Street 6 subway station (at 403 E 34th St). Visits occured on evenings, weekends and during school holidays to maximize convenience, and were structured so that they were no longer than ~90 minutes each (learning from U01OH010394). Participants arrived having fasted for >6 hours. After informed consent, initial follow-up visits included ~31 mL fasting blood collection as: one aliquot of ~4 ml blood in a lavender top vacutainer for CBC; one aliquot of ~4 ml blood in a green top vacutainer for whole blood; one 3 ml of blood in a PAX Gene (PreAnalitycX–Hombrechtikon, Switzerland) tube for RNA isolation; 1 aliquot of 4 mL of blood will be collected in a red top for insulin, glucose and lipid measurements; and another 2 aliquots of 8 ml of blood in a red top vacutainers for serum retrieval. We also collected urine in Kendall Precision 4.5 oz graduated wide mouth specimen container, as well as a saliva sample for future cotinine analysis. All samples not being analyzed immediately were stored at -80$_{o}$C for future analyses. Visits were structured identically to the cardiometabolic component of U01OH01394, and evaluated anthropometrics; blood pressure/brachial artery distensibility; arterial wall stiffness, diet and physical activity.

Cognitive Outcomes

Child neurodevelopment was measured using the Bayley Scales of Infant Development (BSID-II) at approximately 1, 2 and 3 years of age. The BSID-II is a tool to evaluate neurodevelopment in infants and toddlers aged 1-42 months through two indices, the Mental Development Index (MDI), which measures memory, problem solving, sensory perception, hand–eye coordination, imitation and early language, and the Psychomotor Development Index (PDI), which measures fine and gross motor development.[1] The assessment provides a developmental quotient (raw score/chronological age), generating continuous MDI and PDI scores, which are normed and have a mean of 100 and a standard deviation of 15, with higher scores indicating better development. The BSID-II has demonstrated reliability and validity.[1] Child neurodevelopment at 4 and 6 years of age was measured using The Wechsler Preschool and Primary Scale of Intelligence (WPPSI). WPPSI-R, the first revision to the scale and the version used in this study, is a standardized assessment designed to measure the cognitive development of children ages 3 years to 7 years and 3 months.[2] The scale is composed of 12 core subtests which are used to develop three main index scores: verbal, performance and full scale IQ. Not all children were available for all developmental assessments, resulting in different numbers of children tested at each age. Assessments were conducted in the first language of the child (English or Chinese) by trained research technicians. In some cases, when the primary language of the child was not English or Chinese (e.g., Yiddish), we relied on maternal translation. The majority of follow-up assessments were conducted at the Columbia Center for Children's Environmental Health, however a small number of assessments were conducted in the child's home if the parents were unable or unwilling to travel to the Center.

Birth Outcomes

Child birth weight and length were abstracted from the medical record or obtained from the maternal interview if the medical record was incomplete.

Lipid Measurements

Plasma triglycerides and total cholesterol were measured on a Hitachi 704 Analyzer at the CDC's Persistent Organic Pollutants Biomonitoring Laboratory at the National Center for Environmental Health using commercially available test kits from Roche Diagnostics Corp (Indianapolis, IN). Cholesterol was measured enzymatically using the Cholesterol High Performance reagent (cat.no. 704036), Roche Diagnostics). Triglycerides were analyzed enzymatically simultaneously with cholesterol, using reagents from the same manufacturer (Triglycerides/GPO, cat. no. 1488872). Triglyceride blanks were measured in CDC surveillance materials using the same reagent, but without lipase. Total lipids were determined from total triglycerides and total cholesterol, as described in statistical methods.

Chemical Exposure Variables

Blood samples from the umbilical cord were collected at the time of delivery; maternal samples were typically collected on the day after delivery. On average, 30.7 mL blood was collected from the umbilical cord, and 30–35 mL blood was collected from the mothers. Blood samples were transported to Columbia University laboratory facilities in Northern Manhattan and processed within hours of collection. The buffy coat, packed red blood cells and plasma were separated and stored at −70 °C.

Perfluoroalkyl substances (PFAS): Twelve PFAS [PFOS, PFOA, PFHxS, PFDS, PFNA, perfluorobutanesulfonic acid (PFBS), perfluorooctane sulfonamide (PFOSA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorodecanoic acid (PFDA), perfluoroundecanoic (PFUnDA) and perfluorododecanoate (PFDoDA)] were measured in maternal plasma (n=48) and cord blood (n=231) using a solid phase extraction procedure and high-performance liquid chromatograph interfaced with an electrospray tandem mass spectrometer, at the New York State Department of Health Wadsworth Center Laboratory, using methods similar to those used in prior studies.[3,4] Internal standards for C-labeled PFAS were added into plasma samples prior to the addition of reagents for extraction.[5] Solvents and method blanks (blinded to the laboratory) were tested for the presence of the PFAS. Target chemicals were not found in procedural blanks at concentrations above the limits of quantification (LOQs). The LOQs of target chemicals ranged from 0.08 to 0.20 ng/mL. A standard reference material from the National Institute of Standards and Technology was analyzed with every batch of 50 samples, and recoveries of target chemicals were between 90% and 115% of the certified values. Recoveries of target chemicals passed through the entire analytical procedure ranged between 100% and 124%. Quantification was by isotope dilution and target chemicals were monitored by multiple reaction monitoring mode under negative ionization.

Polybrominated Diphenyl Ethers (PBDEs): Detailed methods regarding the analysis of the plasma samples for PBDEs at the Centers for Disease Control and Prevention have been previously described[39, 40]. Briefly, the samples were automatically fortified with 13C-labeled internal standards. The samples were subjected to an initial liquid/liquid extraction with hexane:methyl-tert-butyl ether after denaturation with 1 M HCl and isopropanol.[39] Coextracted lipids were then removed on a silica:silica/sulfuric acid column using the Rapid Trace equipment

(Zymark, Hopkinton, MA) for automation. Final determination of the target analytes was performed by gas chromatography-isotope dilution high-resolution mass spectrometry employing an MAT95XP (ThermoFinnigan MAT, Bremen, Germany) instrument.[40] Concentrations of target analytes are reported as nanograms per gram lipid weight (weight of plasma lipids) (ng/g). The plasma lipid concentrations were determined using commercially available test kits from Roche Diagnostics Corp. (Indianapolis, IN) for the quantitative determination of total triglycerides (product no. 011002803-0600) and total cholesterol (product no. 011573303-0600). Final determinations were made on a Hitachi 912 Chemistry Analyzer (Hitachi, Tokyo, Japan). 210 cord blood and 163 maternal plasma samples were analyzed for the following PBDE congeners (by International Union of Pure and Applied Chemistry numbers): 2,2′,4,4′-tetraBDE (PBDE-47); 2,2′,3,4,4′-pentaBDE (PBDE-85); 2,2′,4,4′,5-pentaBDE (PBDE-99); 2,2′,4,4′,6-pentaBDE (PBDE-100); 2,2′,4,4′,5,5′-hexaBDE (PBDE-153); 2,2′,4,4′,5,6′-hexaBDE (PBDE-154); 2,2′,3,4,4′,5′,6-heptaBDE (PBDE-183); and 2,2′,4,4′,5,5′-hexaBB (BB-153).

Polychlorinated Biphenyls (PCBs), Polychlorinated Dibenzo-p-Dioxins (PCDDs) and Polychlorinated Dibenzofurans (PCDFs): PCBs and PCDD/Fs were analyzed at the Centers for Disease Control and Prevention. Detailed methods regarding the analysis of PCBs and PCDD/Fs in blood have been previously described.[41, 42] Briefly, the samples were spiked with 13C-labeled internal standards, then extracted with organic solvents that were processed through a five-column cleanup procedure. Final determination of the target analytes was performed by gas chromatography-isotope dilution high-resolution mass spectrometry for PCDD/Fs and by gas chromatography-isotope dilution high-and-low-resolution mass spectrometry for PCBs. Concentrations of target analytes are reported as nanograms per gram lipid weight (weight of plasma lipids) (ng/g) for PCBs and picograms per gram lipid weight (pg/g) for PCDD/Fs. Final determinations were made on a Hitachi 912 Chemistry Analyzer (Hitachi, Tokyo, Japan). 210 cord blood and 173 maternal plasma samples were analyzed for 35 PCB congeners and 17 PCDD/F congeners. PCB congeners included: PCB18, PCB28, PCB 44, PCB 49, PCB 52, PCB 66, PCB 74, PCB 87, PCB 99, PCB 101, PCB 105, PCB 110, PCB 118, PCB 128, PCB 138.158, PCB 146, PCB 149, PCB 151, PCB 153, PCB 156, PCB 157, PCB 167, PCB 170, PCB 172, PCB 177, PCB 178, PCB 180, PCB 183, PCB 187, PCB 189, PCB 194, PCB 195, PCB 196.203, PCB 201, PCB 206, PCB 209. PCDD congeners included: 2,3,7,8-tetrachlorodibenzo-p-dioxin (2378D); 1,2,3,7,8-pentachlorodibenzo-p-dioxin (12378D); 1,2,3,4,7,8-hexachlorodibenzo-p-dioxin (123478D); 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin (123678D); 1,2,3,7,8,9-hexachlorodibenzo-p-dioxin (123789D); 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin (1234678D); and octachlorodibenzodioxin (OCDD). PCDF congeners included: 2,3,7,8-tetrachlorodibenzo-furan (2378F); 1,2,3,7,8-pentachlorodibenzo-furan (12378F); 2,3,4,7,8-pentachlorodibenzo-furan (23478F); 1,2,3,4,7,8-hexachlorodibenzo-furan (123478F); 1,2,3,6,7,8-hexachlorodibenzo-furan (123678F); 2,3,4,6,7,8-hexachlorodibenzo-furan (234678F); 1,2,3,7,8,9-hexaachlorodibenzo-furan (123789F); 1,2,3,4,6,7,8-heptachlorodibenzo-furan (1234678F); 1,2,3,4,7,8,9-heptachlorodibenzo-furan (1234789F); and octachlorodibenzofuran (OCDF)

Adolescent Measurements (Aim 3b)

Cardiovascular Assessments. We began by assessing systolic (first Korotkoff phase) and diastolic (fifth Korotkoff phase) BP three consecutive times in participants after they sat quietly for 5 minutes. A fourth attempt was made if ≥1 of the initial measurements is incomplete or

interrupted. We followed common practice of averaging BP measurements to generate continuous and categorical BP variables.

Brachial Artery Distensibility (BAD) Assessment. BAD measurement is a rapid method of accurately assessing relative stiffness of a peripheral artery, and may detect earlier arterial narrowing produced by oxidative stress which we posit to occur from WTC exposure. The DynaPulse Pathway instrument derives BAD using the technique of pulse waveform analysis of arterial pressure signals obtained from a standard cuff sphygmomanometer.[86] The pressure waveform is calibrated and incorporated into a physical model of the cardiovascular system, assuming a straight tube brachial artery and T-tube aortic system. The DynaPulse has been previously validated with high correlation between compliance measurements obtained during cardiac catheterization and the noninvasive brachial method (r = 0.83).[86,87] Reproducibility studies using blind duplicate recordings demonstrated good intraclass correlation coefficient for arterial compliance, from which distensibility is calculated (0.72).[88] Off-line analyses of BAD curve data are performed by PulseMetric, Inc. using an automated system to derive parameters from pulse curves to calculate BAD.[88]

Approach to Femoral Arterial Wall Stiffness Assessment. Pulse wave velocity (PWV) measures the speed for the pressure wave generated by cardiac ejection to reach the periphery. In children, PWV was found to be influenced by both genetic and hormonal influences[89] and was associated with snoring, which is important since sleep apnea has recently become recognized as a cardiovascular risk factor.[90] Increased PWV has also been identified in obese and type 2 diabetic children.[91] PWV will be measured using the SphygmoCor CPV System (AtCor Medical, Sydney, Australia).[92] Arterial waveforms gated to the R-wave on the ECG tracing are recorded from the carotid then distal artery of interest. PWV is the difference in the carotid-to-distal path length divided by the difference in R-wave-to-waveform foot times. Bland-Altman analyses for reproducibility of PWV yielded repeatabililty coefficient of 2.34m/sec (for mean value of 8.15±3.01 m/sec) with between-observer values of 2.50 m/sec.[93] This demonstrates excellent agreement as compared to an average PWV of near 5 m/sec measured in a healthy population of children.[89] Recent data from our investigators have shown excellent reproducibility with coefficients of variability less than 7% even in obese adolescents.[94] Reproducibility studies by consultant Urbina, an internationally renowned pediatric expert in arterial wall stiffness dating to its use in Bogalusa,[94-99] demonstrated intraclass correlation coefficients between 0.7-0.9.[98]

Assessment of Adiposity, Obesity and Sleep Disordered Breathing. We measured weight and height and using calibrated stadiometers (Shorr Productions, Olney, MD) and scales (Seca model 881; Seca Corp., Hanover, MD). We derived Body Mass Index Z-scores from 2000 Centers for Disease Control and Prevention (CDC) norms, incorporating height, weight and gender; overweight and obese were categorized as BMI Z-score ≥1.036 and ≥1.64.[100] We also measured waist circumference, waist circumference/height ratio, and presence of sleep disordered breathing. All may impact cardiometabolic function.[101,102]

Control for Dietary and Physical Activity. In recognition of diet and physical activity as independent cardiovascular risk factors in children,[103-105] we measured these factors contemporaneously in adolescents, recognizing that we cannot reliably measure diet and physical activity in earlier life using retrospective recall. Adolescents 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. We selected the DHQ version

that asks about diet in the past month, with portion size, so that we can quantify caloric intake. The DHQ II benefits from validation, confirming that it provides as good as or superior to the Willett and Block FFQs instruments for most nutrients.[106] Participants also completed a three-day physical activity diary based on the International Physical Activity Questionnaire-Short Last Seven Days, which is well validated.[107] Measures used included: (1) Metabolic Equivalent Task (MET) hours/wk and (2) hours reported in moderate- and vigorous intensity activity/week. Questionnaire data were transformed into energy expenditure estimates as MET using published values.[108,109]

Insulin Resistance, Uric Acid, Glomerular Filtration Rate and Hyperlipidemia. We measured fasting cholesterol, triglycerides, HDL, LDL (calculated), VLDL (calculated), insulin, liver function and glucose. We examined continuous as well as categorical abnormal values for lipid levels, applying cutpoints of HDL <40 mg/dL and triglycerides ≥100 mg/dL, as they were recently applied to assess components of the metabolic syndrome in analyses of adolescents in 2001-2006 NHANES.[110] We used the highly validated homeostasis model assessment (HOMA-IR) to quantify insulin resistance. Validation of HOMA-IR as a measure of insulin resistance in nondiabetic children has demonstrated correlations as high as 0.91 with a gold standard test of insulin resistance, the intravenous glucose tolerance test.[111-113] HOMA-IR was calculated by dividing the product of insulin (μU/mL) and glucose (mMol/L) by 22.5. We quantitated uric acid in mg/dL with spectrophotometry in the NYUSOM Core Laboratory using a validated and published method, and performed a comprehensive evaluation of glomerular function using serum creatinine (Cr), cystatin C and beta trace protein (BTP). Serum BTP was measured in the NYUSOM Immune Monitoring Core using commercially available kits (Biovender). Cr and Cystatin C were measured at ARUP (Salt Lake City, UT), a reference laboratory. We also measured the albumin-to-creatinine ratio (ACR). We used multiple formulas, evaluating sensitivity of associations of POP exposures to use of formula as an indicator of robustness of effects on glomerular function. These included the revised Schwartz formula to calculate eGFR from serum Cr biannually.[114] We also calculated eGFR using the Cr-Cystatin C formula, and we used formulas for calculating eGFR in children using BTP which have recently been described.[115]

Cotinine. In light of literature documenting primary/second-hand tobacco smoke exposure as an independent risk for cardiovascular disease,[116-118] we measured salivary cotinine using a highly reliable (r=.99 compared with serum) and sensitive (limit of detection 0.05 ng/mL) test from Salimetrics, Inc. (State College, PA). Cotinine was measured continuously, and categorized into low (<0.015 ng/mL), medium (<2 and ≥0.015 ng/mL) and high (≥2 ng/mL), following previous practices.[119,120]

Institutional Review Board (IRB) Approval

The study was reviewed and approved by the Columbia University Institutional Review Board. Consent was obtained before enrollment began and all women gave written informed consent before delivery.

Results

Cardiovascular Outcomes

We found significant associations between greater PFOS, PFOA and PFHxS and higher total cord lipids; greater PFDS and higher total cholesterol but lower triglycerides; and greater PFOA and PFHxS and higher triglycerides. Quartile and cubic spline analyses were generally consistent and suggested strong linear trends for PFOA and PFHxS with triglycerides. As part of Aim 3b, we obtained cardiometabolic measurements on XX children (now aged 18-20) from the original cohort, including: fasting cholesterol, triglycerides, HDL, LDL (calculated), VLDL (calculated), insulin, liver function, glucose, PWV, waist circumference, waist circumference/height ratio, presence of sleep disordered breathing, BP and BAD, as well as related measures of physical activity and diet. Unfortunately, due to COVID delays, relocation of adolescents to college and length of time since last contact (~11+ years), recruitment was limited and we were not able to reach the anticipated number of participants.

Cognitive Outcomes

Several PFAS were associated with increases in cognitive outcomes in females and overall (males and females combined). Child sex modified the association between PFOS and the mental development index measured using BSID-II, with the observed relationship being positive for females and negative for males. Through principal component analyses, we observed a negative relationship between PFNA and the psychomotor development index measured using BSID-II and the verbal IQ measured using WPPSI. Our results suggest a sex- and compound-specific relationship between prenatal PFAS exposures and childhood neurodevelopment.

Birth Outcomes

Geographical exposure to WTC was associated with a principal component (PC3) reflecting higher PCDD exposure (β= 0.60, 95% CI: 0.03, 1.18 for living/working within 2 miles of WTC; and β=0.73, 95% CI=0.08, 1.38 for living within 2 miles of WTC). Previously reported reductions in birth weight and length associated with WTC proximity (β=-215.2, 95% CI: -416.2, -14.3; and -1.47, 95% CI: -2.6, -0.34, respectively) were attenuated and no longer significant for birth weight (β=-156.4, 95% CI: -358.2, 45.4) after adjusting for PC3, suggesting PCDDs may act as partial mediators in this previously observed association.

WTC-related Exposure

We evaluated the association between WTC exposure and PFAS concentrations using three exposure variables: 1) living/working within two miles of WTC; 2) living within two miles of WTC regardless of work location; and 3) working but not living within two miles of WTC. Exposure was compared with those not living/working within two miles of WTC (reference group). Living/working within two miles of WTC was associated with 13% higher PFOA concentrations compared with the reference group [GMR (95% CI): 1.13 (1.01, 1.27)]. The association was stronger when comparing only those who lived within two miles of WTC to the reference group [GMR (95% CI): 1.17 (1.03, 1.33)], regardless of work location. Our results provide evidence that exposure to the WTC disaster during pregnancy resulted in increases in PFAS concentrations, specifically PFOA.

Discussion

Cardiovascular Outcomes

In our study, we observed several significant associations between cord PFAS and cord lipids, including evidence of a dose-response relationship for both PFOA and PFHxS with triglycerides. Of note, the association between PFOA and triglycerides is consistent with findings from a cross-sectional analysis of serum PFAS and lipids measured in adolescents enrolled in the World Trade Center Health Registry (children exposed to the WTC disaster either prenatally or during childhood) and a matched comparison group.[6] We also identified a novel association between PFDS, a PFAS compound with limited toxicological information available, and total cholesterol. This observed relationship, despite low cord levels of PFDS in comparison to the other PFAS measured, highlights the need for more research on this compound as well as other understudied PFAS that may be present at lower quantities than the more well-known PFAS. Interestingly, we also observed a negative association between PFDS and triglycerides in quartile analyses, again, emphasizing the need for more research to understand the mechanisms behind this PFAS and its association with lipids. Our associations between cord PFAS and altered cord lipid profiles in this study, including with PFOA and both triglycerides and total lipids, provides one potential pathway between prenatal WTC exposure and adverse health outcomes. Continued monitoring of this population and additional studies are needed to evaluate whether these exposures are associated with health effects as the population ages into adulthood.

Cognitive Outcomes

Our findings are reflective of the apparent complicated nature of the relationship between PFAS and neurodevelopment. The significant associations we observed between PFOA, PFHxS and PC1 (i.e., higher PFAS exposure overall) and better MDI scores at 3 years, are inconsistent with the results of studies from Taiwan and Japan, but consistent with the studies outlined above that have reported surprising protective associations between various PFAS and cognitive outcomes. The mechanism by which PFAS could exert neuroprotective effects is not clear, however, their activation of human peroxisome proliferator-activated receptor (PPAR) alpha and PPARγ in several experimental studies[7-9] has been identified as one potential pathway, since other PPARγ agonists have been shown to be neuroprotective.[10-12] Still, *in vivo* and *in vitro* models have also suggested PFAS have neurotoxic potential through effects on the cholinergic system[13-15], neuronal differentiation[16], protein levels necessary for proper brain development[17,18] and thyroid homeostasis[19]. Our results highlight the complex and inconsistent relationships between prenatal PFAS exposures and childhood neurodevelopment. Given the large amount of missing data, as well as the number of statistical tests, these findings should be interpreted with caution. However, they emphasize the need for both experimental studies, to better elucidate the biological mechanisms behind these relationships, and large-scale epidemiologic studies with high retention to reduce any effects of missing data. Further, additional research should be dedicated to evaluating possible sex-specific associations between PFAS and neurodevelopment.

Birth Outcomes

In this cohort of mother-child dyads who delivered in New York City, NY, in the months following the WTC disaster, we evaluated the mediating role of both chemical exposures and maternal stress in previously observed associations between proximity to the WTC site and lower birth weight and birth length. We used PCA to summarize prenatal exposure to PCBs, PBDEs, and PCDDs and the PERI-D scale (demoralization) to summarize maternal prenatal stress. Four

PCs captured most (85%) of the variance in chemical exposures. We found that both of our geographic WTC proximity exposure variables, mothers who lived or worked within 2 miles of the WTC site and mothers who just lived within 2 miles of the WTC site, were associated with the PC reflective of higher exposure to PCDDs. Demoralization was not associated with either geographic WTC proximity exposure variable. We also found that both our geographic WTC proximity exposure variables were associated with lower birth weight and birth length, however, this relationship was only significant for those who lived within 2 miles of the WTC site. After adjustment for each PC as well as demoralization, in separate models, the relationship between proximity to the WTC and birth outcomes remained consistent except when adjusting for the PC reflecting higher PCDD exposure. In this case, the associations were attenuated, and no longer significant between living within 2 miles of the WTC site and birth weight, suggesting dioxins may act as partial mediators in these associations. There were no significant additive interactions between demoralization and PCs with birth outcomes. In contrast to our findings, studies suggest a consistent trend with WTC-related stress: among pregnant women residing in close proximity to the WTC disaster, post-traumatic stress symptomatology[28] and probable WTC-related posttraumatic stress disorder[29] have been associated with decrements in fetal growth. Some studies even suggest that the magnitude of the disaster resulted in stress-related adverse birth outcomes even outside of New York City.[31, 33] Therefore, the lack of association we observed between proximity to the WTC and maternal stress may be a result of the PERI-D scale being designed as a measure of general psychological distress and may not accurately capture disaster-related stress or trauma. Another limitation of this study that should be considered when interpreting findings is that our unexposed comparison group resided in New York City and may have been exposed to WTC-related chemicals and stress. This could have attenuated differences in chemical concentrations and stress between comparison groups and may have contributed to the null findings we observed between proximity to the WTC and demoralization, PBDEs and PCBs.

WTC-related Exposure

Sociodemographic trends in PFAS vary by compound, with certain similarities in trends for PFOA and PFHxS and for PFOS and PFNA, potentially suggesting shared exposure sources that should be researched further. In addition, living or working within 2 miles of the WTC site was associated with increases in PFOA cord blood among women who were pregnant at the time of, or within the weeks following, the WTC disaster. These results identify a vulnerable population that should be monitored for the development of later-life health effects arising from these early life exposures; highlighting the importance of longitudinal analyses in this cohort. Home dust exposures, specifically, appear to be a driving factor in elevating blood levels of PFAS, and potentially other chemicals, and should be an important focus of cleanup in the event of other environmental disasters.

Cumulative Inclusion Enrollment Table: See Attachment.

Inclusion of gender and minority study subjects: See Attachment.

Inclusion of Children. Children were the focus of the study and the study will inform our ability to assess whether pulmonary and cardiovascular conditions should be covered as WTC-related conditions.

Materials available for other investigators: None.

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C. OVERALL PRODUCTS

C.1 PUBLICATIONS

Are there publications or manuscripts accepted for publication in a journal or other publication (e.g., book, one-time publication, monograph) during the reporting period resulting directly from this award?

No

C.2 WEBSITE(S) OR OTHER INTERNET SITE(S)

NOTHING TO REPORT

C.3 TECHNOLOGIES OR TECHNIQUES

NOTHING TO REPORT

C.4 INVENTIONS, PATENT APPLICATIONS, AND/OR LICENSES

Have inventions, patent applications and/or licenses resulted from the award during the reporting period? No

If yes, has this information been previously provided to the PHS or to the official responsible for patent matters at the grantee organization? No

C.5 OTHER PRODUCTS AND RESOURCE SHARING

NOTHING TO REPORT

D. OVERALL PARTICIPANTS

D.1 WHAT INDIVIDUALS HAVE WORKED ON THE PROJECT?

Commons ID	S/K	Name	Degree(s)	Role	Cal	Aca	Sum	Foreign Org	Country	SS
LTRASANDE	Y	Trasande, Leonardo	AB,MOTH,MD	PD/PI	2.8	0.0	0.0			NA
HERBSTMANJ	Y	Herbstman, Julie Beth	MS,PHD	PD/PI	1.8	0.0	0.0			NA
LIUM05	Y	Liu, Mengling	PHD,MS	Co-Investigator	1.4	0.0	0.0			NA
	N	Jenkins, Matthew T		Research Data Associate	6.5	0.0	0.0			NA

Glossary of acronyms:
S/K - Senior/Key
Cal - Person Months (Calendar)
Aca - Person Months (Academic)
Sum - Person Months (Summer)
Foreign Org - Foreign Organization Affiliation
SS - Supplement Support
RS - Reentry Supplement
DS - Diversity Supplement
OT - Other
NA - Not Applicable

D.2 PERSONNEL UPDATES

D.2.a Level of Effort

Not Applicable

D.2.b New Senior/Key Personnel

Not Applicable

D.2.c Changes in Other Support

Not Applicable

D.2.d New Other Significant Contributors

Not Applicable

D.2.e Multi-PI (MPI) Leadership Plan

Not Applicable

E. OVERALL IMPACT

E.1 WHAT IS THE IMPACT ON THE DEVELOPMENT OF HUMAN RESOURCES?

Not Applicable

E.2 WHAT IS THE IMPACT ON PHYSICAL, INSTITUTIONAL, OR INFORMATION RESOURCES THAT FORM INFRASTRUCTURE?

NOTHING TO REPORT

E.3 WHAT IS THE IMPACT ON TECHNOLOGY TRANSFER?

Not Applicable

E.4 WHAT DOLLAR AMOUNT OF THE AWARD'S BUDGET IS BEING SPENT IN FOREIGN COUNTRY(IES)?

NOTHING TO REPORT

G. OVERALL SPECIAL REPORTING REQUIREMENTS SPECIAL REPORTING REQUIREMENTS

G.1 SPECIAL NOTICE OF AWARD TERMS AND FUNDING OPPORTUNITIES ANNOUNCEMENT REPORTING REQUIREMENTS

NOTHING TO REPORT

G.2 RESPONSIBLE CONDUCT OF RESEARCH

Not Applicable

G.3 MENTOR'S REPORT OR SPONSOR COMMENTS

Not Applicable

G.4 HUMAN SUBJECTS

G.4.a Does the project involve human subjects?

Not Applicable

G.4.b Inclusion Enrollment Data

File(s) uploaded:
combined IER.pdf

G.4.c ClinicalTrials.gov

Does this project include one or more applicable clinical trials that must be registered in ClinicalTrials.gov under FDAAA?

G.5 HUMAN SUBJECTS EDUCATION REQUIREMENT

NOT APPLICABLE

G.6 HUMAN EMBRYONIC STEM CELLS (HESCS)

Does this project involve human embryonic stem cells (only hESC lines listed as approved in the NIH Registry may be used in NIH funded research)?

No

G.7 VERTEBRATE ANIMALS

Not Applicable

G.8 PROJECT/PERFORMANCE SITES

Not Applicable

G.9 FOREIGN COMPONENT No foreign component
G.10 ESTIMATED UNOBLIGATED BALANCE Not Applicable
G.11 PROGRAM INCOME Not Applicable
G.12 F&A COSTS Not Applicable

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Prenatal WTC Chemical Exposures, Birth Outcomes and Cardiometabolic Risks

Comments: CCCEH Northern Manhattan cohort

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0		0	0					**0**
Asian	0	0		2	1					**3**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	127	127		6	8					**268**
White	0	0		7	5					**12**
More Than One Race	0	0		234	210					**444**
Unknown or Not Reported										**0**
Total	**127**	**127**	**0**	**249**	**224**	**0**	**0**	**0**	**0**	**727**

Cumulative Inclusion Enrollment Report

This report format should NOT be used for collecting data from study participants.

Study Title: Prenatal WTC Chemical Exposures, Birth Outcomes and Cardiometabolic Risks

Comments: CCCEH Northern Manhattan cohort

Racial Categories	Ethnic Categories									Total
	Not Hispanic or Latino			Hispanic or Latino			Unknown/Not Reported Ethnicity			
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	
American Indian/ Alaska Native	0	0		0	0					**0**
Asian	0	0		2	1					**3**
Native Hawaiian or Other Pacific Islander	0	0		0	0					**0**
Black or African American	127	127		6	8					**268**
White	0	0		7	5					**12**
More Than One Race	0	0		234	210					**444**
Unknown or Not Reported										**0**
Total	**127**	**127**	**0**	**249**	**224**	**0**	**0**	**0**	**0**	**727**

I. OVERALL OUTCOMES

I.1 What were the outcomes of the award?

Identification of subpopulations vulnerable to WTC-associated exposures and health effects could facilitate targeted and proactive interventions such as treatment with antihypertensive medications which have been documented to prolong survival among adults with suboptimal cardiovascular profile.