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Prenatal and childhood air pollution exposure, cellular immune biomarkers, and brain connectivity in early adolescents

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ABSTRACT

Introduction: Ambient air pollution is a neurotoxicant with hypothesized immune-related mechanisms. Adolescent brain structural and functional connectivity may be especially vulnerable to ambient pollution due to the refinement of large-scale brain networks during this period, which vary by sex and have important implications for cognitive, behavioral, and emotional functioning. In the current study we explored associations between air pollutants, immune markers, and structural and functional connectivity in early adolescence by leveraging cross-sectional sex-stratified data from the Adolescent Brain Cognitive Development℠ Study®.

Methods: Pollutant concentrations of fine particulate matter, nitrogen dioxide, and ozone were assigned to each child's primary residential address during the prenatal period and childhood (9-10 years-old) using an ensemble-based modeling approach. Data collected at 11-13 years-old included resting-state functional connectivity of the default mode, frontoparietal, and salience networks and limbic regions of interest, intracellular directional and isotropic diffusion of available white matter tracts, and markers of cellular immune activation. Using partial least squares correlation, a multivariate data-driven method that identifies important variables within latent dimensions, we investigated associations between 1) pollutants and structural and functional connectivity, 2) pollutants and immune markers, and 3) immune markers and structural and functional connectivity, in each sex separately.

Results: Air pollution exposure was related to white matter intracellular directional and isotropic diffusion at ages 11–13 years, but the direction of associations varied by sex. There were no associations between pollutants and resting-state functional connectivity at ages 11–13 years. Childhood exposure to nitrogen dioxide was negatively correlated with white blood cell count in males. Immune biomarkers were positively correlated with white matter intracellular directional diffusion in females and both white matter intracellular directional and isotropic diffusion in males. Lastly, there was a reliable negative correlation between lymphocyte-to-monocyte ratio and default mode network resting-state functional connectivity in females, as well as a compromised immune marker profile associated with lower resting-state functional connectivity between the salience network and the left hippocampus in males. In post-hoc exploratory analyses, we found that the PLSC-identified white matter tracts and resting-state networks related to processing speed and cognitive control performance from the NIH Toolbox.

Conclusions: We identified novel links between childhood nitrogen dioxide and cellular immune activation in males, and brain network connectivity and immune markers in both sexes. Future research should explore the potentially mediating role of immune activity in how pollutants affect neurological outcomes as well as the potential consequences of immune-related patterns of brain connectivity in service of improved brain health for all.

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1. Introduction

Outdoor ambient air pollution is a known risk factor for acute and chronic disease states, such as asthma (Nishimura et al., 2013; Jerrett et al., 2008; Clark et al., 2010), cardiovascular disease (Pope et al., 2004; Peters et al., 2000), and increasingly, neurological health (Costa et al., 2020; Lin et al., 2021; H.-C. Fan et al., 2022; Reuben et al., 2021; Lee et al., 2016). Important criteria pollutants tracked by the World Health Organization (WHO) and the United States Environmental Protection Agency (US EPA) include particulate matter with diameter <2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2), and ground-level ozone (O_3) (US EPA 2015). $PM_{2.5}$ and NO_2 result from combustion of gasoline, oil, diesel fuel, coal, or wood. O_3 results from ultraviolet light-driven photooxidation of volatile organic compounds and precursors such as nitric oxide (NO) and NO_2 (US EPA 2016b; US EPA, OAR, 2016a). These three pollutants have complicated environmental and chemical interactions, such that O_3 is often increased when other criteria pollutants exist in lower levels, and vice versa (Brancher 2021). Inhalation of these ambient pollutants can cause an innate immune response, resulting in increased systemic and neuroinflammation, circulation of immune components, oxidative stress, and compromised tissue barriers throughout the body, including the nasal epithelium, blood-brain barrier (BBB), and in the case of prenatal exposure, the blood-placental barrier (Glencross et al., 2020; Tripathy et al., 2021; Heidari Nejad et al., 2015; Bové et al., 2019). However, it is important to note that mechanisms of air pollution effects for various health outcomes, including the nervous system, may also differ based on both the timing of the exposure as well as an individual's biological sex (Brunst et al., 2015; Costa et al., 2017; Liao et al. 2023).

In this regard, the developing brain may be especially sensitive to the neurotoxicant effects of ambient air pollution. Air pollution during the prenatal and childhood periods has been shown to impact the brain connectome (Herting et al., 2019; Burnor et al., 2021; Sukumaran et al., 2023; Cotter et al., 2023b; Pérez-Crespo et al., 2022; Binter et al., 2022; Lubczyńska et al., 2021, 2020; Cotter et al., 2023a; Peterson et al., 2022; Guxens et al., 2022). Defined as the spatial map of neural connections that give rise to function (Shi and Toga 2017), the brain connectome can be characterized both structurally and functionally using multimodal neuroimaging methods, such as diffusion-weighted imaging (DWI) and resting-state functional magnetic resonance imaging (rs-fMRI) (Power et al., 2011; Smith et al., 2009; Yeo et al., 2011; Laumann et al., 2017). To date, our team and others have found ambient air pollutants to relate to both cross-sectional and longitudinal differences in resting-state functional connectivity (rsFC) among large-scaled networks in children between the ages of 8–13 years (Pérez-Crespo et al., 2022; Pujol et al., 2016a; Pujol et al., 2016b; Cotter et al., 2023b). However, while the broader neurodevelopmental literature suggests brain network maturation varies based on sex (Satterthwaite et al., 2015; Schulz and Sisk 2016; Grayson and Fair 2017; Sanders et al., 2023), these studies did not find sex to moderate pollutant effects on rsFC development (Pérez-Crespo et al., 2022; Cotter et al., 2023b). Beyond rsFC, both prenatal and early childhood exposure to outdoor air pollution has been linked to differences in structural connectivity as measured by white matter microstructural integrity estimated using diffusion tensor imaging (Binter et al., 2022; Lubczyńska et al., 2020; Peterson et al., 2022). Building upon this research, our team implemented an advanced multi-compartment DWI modeling technique, known as restriction spectrum imaging (RSI), to cross-sectionally and longitudinally assess how air pollution exposure during childhood influences intracellular compartments of white matter tissue (Burnor et al., 2021; Cotter et al., 2023a). Our findings suggested unique sex- and pollutant-specific associations between air pollution exposure and white matter microstructural integrity. Specifically, we found that exposure to higher levels of $PM_{2.5}$ was associated with higher intracellular isotropic diffusion (RNI; hypothesized to reflect more and/or swollen glial cells) (White et al., 2013; Palmer et al., 2021) in female youth and higher intracellular directional diffusion (RND; increased axon caliber or density) (White et al., 2013; Palmer et al., 2021; C. C. Fan et al., 2022) in both sexes at age 9 years. Alternatively, NO_2 affected maturation patterns of white matter RNI in female youth over time, whereas O_3 exposure influenced white matter RNI and RND development in both sexes, but more prominently in male youth. Taken together, these initial air pollution and MRI studies suggest a link between outdoor air pollution exposure and the brain connectome during development. Yet, despite a growing literature, questions remain about the mechanisms by which air pollution may impart these effects and to what degree these may vary by sex.

A primary candidate for air pollution's neurotoxic effects is activation of the immune system and associated systemic and neuroinflammation (Glencross et al., 2020; Kang et al., 2021), which have well-documented differences depending on an individual's sex chromosomes (Klein and Flanagan 2016; Wilkinson et al., 2022). Our highly dynamic immune system is characterized by its innate (rapid and nonspecific; platelets, monocytes, neutrophils) and adaptive (slow and targeted; T and B lymphocytes) responses to pathogens, with notable sex differences in these processes across the lifespan, particularly during development (Klein and Flanagan 2016). Air pollution, particularly PM and NO_2, has been linked to alterations in white blood cell counts (WBC), lymphocytes, and eosinophils, as well as interruptions in antiviral immune functions (Steenhof et al., 2014a; Glencross et al., 2020; Hung et al., 2021). Additionally, air pollution has been shown to have a direct and cumulative detrimental effect on lung-associated innate and adaptive immunity, potentially increasing the risk for poor health outcomes in older adults ("Effect of Air Pollution on the Human Immune System" 2022). However, few studies to date have examined the link between air pollution and immune response during childhood, let alone how they relate to neurodevelopment. Air pollution studies in pediatric samples have primarily examined blood-based pro- or anti-inflammatory cytokines, albeit with mixed results and without examining potential sex differences (Hahn et al., 2021; García-Serna et al., 2022; Latzin et al., 2011; Barraza-Villarreal et al., 2008; Calderón-Garcidueñas et al., 2013; Klümper et al., 2015; Armijos et al., 2015; Brown et al., 2012). More recently, however, Li et al. (2019) found altered monocyte, lymphocyte, and immunoglobulin levels in school-aged children exposed to air pollution with sex-specific patterns of alteration. Thus, in addition to studies on cytokines, it is likely imperative to consider how air pollution may influence the balance of innate and adaptive immune responses. In this regard, recent studies have begun using blood-based immune cell composites and ratios, such as the systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and lymphocyte-to-monocyte ratio (LMR), to quantify immune reactivity (H. Zhang et al., 2022; Hu et al., 2014; Dadouli et al., 2022; Y. Wei et al., 2022; Mazza et al., 2020; Benedetti et al., 2021; Kurtul et al., 2014; Zahorec 2021). Importantly, these immune ratios have already been linked to brain alterations as seen on MRI (Benedetti et al., 2021; Nam et al., 2022; Nam et al., 2017; Xiao et al., 2023) as well as with other environmental pollutant exposures in both children and adults (H. Zhang et al., 2022; L. Zhao et al., 2022; Dai et al., 2019; S. Zhang et al., 2019). Therefore, these immune ratios may be especially useful to consider in probing how immune function may map onto air pollution and brain health in males and females during development.

To address these knowledge gaps, the goal of the current study was to explore associations between air pollution exposure, blood-based immune markers, and functional and structural brain connectivity at ages 11-13 years-old. To do so, we leveraged sex-stratified data from the large, regionally diverse, US-based Adolescent Brain Cognitive Development℠ (ABCD) Study® cohort and applied a partial least squares correlation (PLSC), a multivariate data-driven method previously used in neuroimaging research (Krishnan et al., 2011) that allows for both multivariate predictors and outcomes to identify significant reliable patterns (i.e., latent dimensions) and the variables driving them. Importantly, PLSC can handle multicollinearity, allowing for the

quantification of both joint and independent effects of highly correlated variables (Hamra and Buckley 2018), particularly important when exploring co-exposures of pollutants and multiple related immune components. Thus, we performed PLSCs to investigate: 1) the associations between prenatal and childhood air pollution exposure and both structural and functional connectivity (measured by rsFC and RSI, respectively) at ages 11–13 years (i.e., concurrent with immune marker measurements), 2) the associations between prenatal and childhood air pollution exposure and immune markers, and 3) the associations between temporally linked immune markers and both structural and functional connectivity at ages 11–13 years. We then performed post-hoc exploratory stepwise regression analyses to assess potential cognitive relevance of brain outcomes identified from PLSC analyses. Given the known sex-specific effects in environmental neurotoxicity (Gade et al. 2021), innate and adaptive immunity (Klein and Flanagan 2016; Wilkinson et al., 2022), and adolescent brain development (Lenroot and Giedd 2010; Giedd et al., 2012; Kaczkurkin et al. 2019), as well as PLSC's inability to handle interaction terms, we opted to examine these relationships in each sex separately, reducing the potential for bias (Buckley et al., 2017). Given the exploratory nature of this research, we did not have specific hypotheses. Rather, we aimed to conduct this hypothesis-generating research to uncover potentially novel patterns of association between different types of data within each sex, in hopes of identifying potential links between air pollution, cellular immune markers, and the adolescent brain connectome for further, future inquiry.

2. Methods

2.1. Study population

The current study uses data collected as part of the ongoing longitudinal ABCD Study®, which enrolled 11,876 children between the ages of 9–10 years across 21 study sites in the United States (Volkow et al., 2018). Participants included in this study were ≤10 years-old at their initial visit, and English language proficient. Exclusion criteria were as follows: diagnosis of schizophrenia, moderate/severe autism spectrum disorder, intellectual disability, alcohol/substance use disorder, major medical or neurological conditions, history of traumatic brain injury, and contraindications to MRI scanning (Garavan et al., 2018). All study procedures were approved by the centralized institutional review board at the University of California San Diego; each study site also obtained approval from their institutional review boards. Participants provided written assent and legal guardians provided written consent.

By study design, data collection within the ABCD Study varies as a function of annual study visits (Garavan et al., 2018). As such, the current study used a subset of data, including air pollution from the prenatal period and baseline assessment (i.e., when children were 9–10 years), as well as blood analytes, neuroimaging, and demographic data collected at the second annual study visit when the participants were approximately 11–13 years-old. Given that blood-based biomarkers were introduced into the ABCD Study beginning at the second annual visit, we chose to use MRI data from the 2-year follow-up visit to temporally align with these data. Each subset of data used in respective PLSC analyses were stratified by sex and varied depending on data availability (please see Table 1 and Supplemental Tables 1-3). All data used here were obtained from ABCD's 5.0 data release (http://doi.org/10.15154/8873-zj65).

2.2. Ambient air pollution estimates

Geocoded information about participants' residential addresses was used to define the locations where prenatal and one-year childhood daily $PM_{2.5}$, daily NO_2, and 8-hour maximum O_3 exposures were estimated (C.C. Fan et al., 2021). Primary residential addresses at study enrollment (i.e., when participants were 9–10 years-old) were collected in-person from the participant's caregiver during the study visit between October 2016 to October 2018. At the second-year study visit, additional previous residential addresses were collected retrospectively by the participant's caregiver. All residential addresses were then geocoded by the ABCD consortium's Data Analytics Information and Resource Center

Table 1
Descriptive statistics per each sex-stratified PLSC analysis. Abbreviations: restriction spectrum imaging (RSI), resting-state functional connectivity (rsFC), fine particulate matter ($PM_{2.5}$), ground-level ozone (O_3), nitrogen dioxide (NO_2), systemic immune-inflammation index (SII), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), white blood cell count (WBC).

Cohort Characteristics		
	Female	Male
Total N	2279	2809
Demographics		
Mean Age, *months* (SD)	142.88 (7.74)	143.38 (7.77)
Pubertal Development Scale, N (%)		
1	103 (4.5%)	1028 (36.6%)
2	228 (10%)	1005 (35.8%)
3	1057 (46.4%)	535 (19%)
4	738 (32.4%)	112 (4%)
5	33 (1.4%)	3 (0.1%)
Missing	120 (5.3%)	126 (4.5%)
Race/Ethnicity, N (%)		
Non-Hispanic White	1368 (60%)	1761 (62.7%)
Non-Hispanic Black	248 (10.9%)	287 (10.2%)
Hispanic	383 (16.8%)	461 (16.4%)
Non-Hispanic Asian	42 (1.8%)	46 (1.6%)
Multi-Racial/Other*	238 (10.5%)	254 (9.1%)
Handedness, N (%)		
Right	1798 (78.9%)	2146 (76.4%)
Left	135 (5.9%)	223 (7.9%)
Mixed	308 (13.5%)	373 (13.3%)
Missing	38 (1.7%)	67 (2.4%)
Highest Household Education, N (%)		
Post Graduate Degree	856 (37.5%)	1088 (38.7%)
Bachelor	638 (28%)	802 (28.6%)
Some College	547 (24%)	650 (23.1%)
HS Diploma/GED	164 (7.2%)	189 (6.7%)
< HS Diploma	72 (3.2%)	77 (2.7%)
Missing	2 (0.1%)	3 (0.1%)
Overall Income, N (%)		
≥100 K	982 (43.1%)	1245 (44.3%)
≥50 K & <100 K	661 (29%)	785 (28%)
<50 K	487 (21.4%)	587 (20.9%)
Don't Know/Refuse	149 (6.5%)	192 (6.8%)
Mean Pollutants (SD)		
N	2219	2709
Prenatal $PM_{2.5}$, $\mu g/m^3$	10.97 (2.41)	10.87 (2.44)
Childhood $PM_{2.5}$, $\mu g/m^3$	7.58 (1.51)	7.49 (1.56)
Prenatal O_3, *ppb*	40.04 (4.51)	40.06 (4.68)
Childhood O_3, *ppb*	41.33 (4.31)	41.34 (4.37)
Prenatal NO_2, *ppb*	26.05 (9.76)	26.34 (9.93)
Childhood NO_2, *ppb*	18.58 (5.92)	18.58 (5.9)
Mean Immune Markers (SD)		
N	294	391
SII	457.36 (239.35)	445.56 (280.68)
LMR	5.45 (2.16)	5.24 (2.54)
PLR	137.6 (44.01)	137.13 (43.12)
NLR	1.42 (0.69)	1.41 (0.77)
WBC	6.55 (1.7)	6.45 (1.79)
MRI Precision Variables		
Mean Frame Displacement (SD)		
RSI (N = 2188)	1.17 (0.34)	1.21 (0.43)
rsFC (N = 2054)	0.15 (0.15)	0.19 (0.17)
MRI Manufacturer, N (%)		
N	2241	2742
Siemens	1418 (63.3%)	1768 (64.5%)
GE	574 (25.6%)	658 (24%)
Philips	249 (11.1%)	316 (11.5%)

*"Other" race/ethnicity category includes participants identified by their caregiver as American Indian/Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan, Other Pacific Islander, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian not listed, or Other Race not listed.

(DAIRC) (C.C. Fan et al., 2021). Daily ambient air pollution concentration estimates for $PM_{2.5}$, NO_2, and O_3 were then estimated for the entire continental U.S. as previously described (Di et al., 2019, 2020; Requia et al., 2020). In brief, hybrid spatiotemporal models were leveraged to first derive daily air pollution estimates at a 1-km^2 resolution, utilizing satellite remote sensing, land-use regression, and chemical transport models (Di et al., 2019, 2020; Requia et al., 2020). Daily estimates were subsequently averaged over the 2016 calendar year, corresponding with participant study enrollment (when children were aged 9–10 years). One-year annual average concentrations during childhood were then assigned to primary residential addresses for each participant. Prenatal exposure was assigned by averaging across the daily exposure estimates for 9 months of pregnancy based on the child's birthdate [birth years 2005–2009] and the address that corresponded to the child's birth year. If multiple addresses overlapped with the birthdate of the child, the prenatal average exposure values for each residence were weighted by the reported percent of time spent at that residence, after which the sum of these weighted exposure averages was divided by the sum of all reported percentages. To reduce potential misclassification bias, subjects were excluded from the analyses if the percentage of time reported across the multiple addresses overlapping with the child's birthdate totaled below 90% or above 110%. Lastly, quality-controlled prospective residential addresses are not currently available in the ABCD consortium. Therefore, we assumed the spatial contrast remained constant between the study enrollment period and the annual 2-year follow-up study period, which has been demonstrated using these ensemble-based models from 2000 to 2016 (Di et al., 2019, 2020; Requia et al., 2020). Spearman correlations between prenatal and childhood exposures are presented in Supplemental Figure 1.

2.3. Restriction spectrum imaging (RSI)

The ABCD Study utilizes a harmonized neuroimaging protocol, due to site-to-site differences in scanner manufacturer (3T; Siemens Prisma, Phillips, or GE 750) (Casey et al., 2018). Multi-shell diffusion-weighted images were acquired in 1.7 mm^3 resolution, implemented multiband EPI (Moeller et al., 2010; Setsompop et al., 2012) with slice acceleration factor 3, and included a field map scan for B0 distortion correction. The ABCD Study collected seven b = 0 frames and 96 total diffusion directions at 4 b-values (6 with b = 500 s/mm^2, 15 with b = 1000 s/mm^2, 15 with b = 2000 s/mm^2, and 60 with b = 3000 s/mm^2) (Hagler et al., 2019). Following distortion, bias field, and motion correction, manual and automated quality control were conducted on all images (Hagler et al., 2019). Utilizing all 96 directions in ABCD's multi-shell acquisition protocol (Casey et al., 2018), RSI allows for biophysical modeling of diffusion-weighted images to estimate both the intra- and extracellular compartments of tissue within the brain (White et al., 2013). Selected RSI model outputs are unitless on a scale of 0–1 and included both restricted (intracellular) normalized isotropic (RNI) and directional (RND) signal fractions of white matter fiber tract ROIs created with AtlasTrack (Hagler et al., 2009). RNI measures intracellular diffusion in all directions, while RND measures intracellular diffusion in a single direction. Although this technique is unable to directly assess cellular processes, RNI is thought to potentially reflect diffusion within glial cells or other round structures, whereas RND is likely to reflect diffusion along an axon or other elongated process (White et al., 2013; Palmer et al., 2021). We opted to include all individual tracts, excluding summary tracts (14 per hemisphere and 3 traversing both hemispheres, totaling 31 tracts). Specific tracts included the right and left fornix, cingulate cingulum, parahippocampal cingulum, corticospinal tract, anterior thalamic radiations, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, temporal and parietal superior longitudinal fasciculus, frontal and parietal superior corticostriate, striatal to inferior frontal cortex, and inferior frontal to superior frontal cortex, as well as the forceps major, minor, and corpus callosum. Brain images were only included if deemed absent of clinically significant incidental findings (*mrif_score* = 1 or 2) and passed all ABCD quality-control parameters (*imgincl_dmri_include* = 1).

2.4. Resting-state functional connectivity (rsFC)

Scans were collected on Siemens Prisma, Philips, or GE 750 3T MRI scanners using harmonized acquisition procedures specific to ABCD, as previously described by Casey et al. (2018). Twenty cumulative minutes of resting-state data was collected from each participant using two blocks of two 5-min acquisition periods. During acquisition, subjects were instructed to keep their eyes open and fixed on a crosshair in order to maximize the probability of collecting enough low-motion data per ABCD's standards (>12.5 min of data with framewise displacement (FD) < 0.2 mm) (Power et al., 2014). Sixty slices of resting-state scans were acquired with an echo-planar imaging sequence in the axial plane (TR = 800 ms, TE = 30 ms, flip angle = 90°, voxel size = 2.4 mm^3). Images without clinically significant incidental findings (*mrif_score* = 1 or 2) that passed all ABCD quality-control parameters (*imgincl_rsfmri_include* = 1) were included for analysis. Image processing steps used in the current study have been previously described by Hagler et al. (2019). Networks of interest were defined using rsFC patterns as described by Gordon et al. (2016). Intra-, inter-, and subcortical-to-network correlations were calculated for each subject. Intra-network correlations were calculated by averaging the pairwise correlations for ROIs within that network. Inter-network correlations were calculated by averaging the pairwise correlations between ROIs belonging to one network and ROIs belonging to another distinct network. Subcortical-to-network correlations were calculated by averaging the pairwise correlations between ROIs within a specific network and a given subcortical ROI (Gordon et al., 2016). Networks of interest included the salience network (SN), frontoparietal network (FPN), and default mode network (DMN); subcortical ROIs included both right and left amygdalae and hippocampi.

2.5. Blood-based biomarkers of cellular immune activation

Starting at the 2-year follow-up visit, whole blood for the complete blood count (CBC) with differential was collected using a purple top EDTA tube and processed at ambient temperature. ABCD 5.0 Release Notes state that some ambient shipments may not have been processed within the recommended 24–48 h for CBC stability and thus, sample integrity and resultant values are not assured. Unfortunately, there is no indication of time from collection to time of assay in the publicly available dataset and as such, no way to remove potentially compromised samples. Caution should be exercised when interpreting these results.

Biomarkers of immune activation were derived from immune cell counts from the CBC. Specifically, systemic immune inflammation index (SII) was calculated using the following equation:

$$SII = (platelet\ count \times neutrophil\ count) \div lymphocyte\ count$$

In addition to SII, three additional ratios were calculated: 1) platelet-to-lymphocyte (PLR), 2) neutrophil-to-lymphocyte (NLR), and 3) lymphocyte-to-monocyte (LMR). Lastly, we used white blood cell count (WBC) directly from the CBC. SII considers peripheral lymphocyte, neutrophil, and platelet counts and is described as an excellent integrated indicator of both inflammatory and immune status (Hu et al., 2014), reflecting the balance between innate and adaptive immune activity (J. Zhao et al., 2022; Nam et al., 2022). PLR represents immune and autonomic dysregulation (Kurtul et al., 2014; Haskó and Szabó 1998), whereas NLR is a validated marker for stress and systemic inflammation and is indicative of cellular immune activation and more aggressive pathology (Zahorec 2021). LMR is another measure of systemic inflammation and cellular immune activation (Chan et al., 2017; Eo et al., 2016; Ji et al., 2016). Spearman correlations between markers of cellular immune activation are presented in Supplemental Figure 2.

2.6. Covariates

Time invariant covariates were taken from enrollment at the baseline visit, and included sex at birth, race/ethnicity (*non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian,* or *Multi-Racial/Other*), total household income in USD (*≥100 K, ≥50 & <100 K, <50 K,* or *Don't Know/Refuse to Answer*), and highest household education (*Post-Graduate, Bachelor, Some College, High School Diploma/GED,* or *< High School Diploma*). Race/ethnicity and socioeconomic factors were included since pollution levels are higher in minority communities and those from disadvantaged social status backgrounds (Hajat, Hsia, and O'Neill 2015). We also included precision variables from the year-2 follow-up study visit that were related to both the child and MRI collection, including the child's age, Pubertal Development Scale (PDS) (*1–5*, based on Tanner staging), and handedness (*right, left,* or *mixed*), as well as scanner manufacturer (*Siemens*, *Philips*, *GE*) to account for differences in both scanner hardware and software, and average framewise displacement (*mm*) to account for head motion. To account for the shared variance between siblings, we additionally controlled for family relationships (*0 = single, 1 = sibling, 2 = twin, 3 = triplet*).

2.7. Partial least squares correlations

A series of partial least squares correlation (PLSC) analyses were employed as previously reported (Sukumaran et al., 2023) (see also Supplemental material). Briefly, PLSC is a multivariate statistical approach that compares two multidimensional data blocks with possible cross-correlated features (McIntosh et al., 1996) revealing shared covariance patterns between these data blocks, termed *latent dimensions*. PLSC identifies the relationship between two datasets by maximizing the covariance between them and deduces sets of solutions that best model this relationship. As such, in each sex we examined five associations using PLSC. First, we examined the association between (i) air pollution and white matter RSI and (ii) air pollution and rsFC. Next, we examined associations between (iii) air pollution and immune markers. Lastly, we examined the relationships between (iv) immune markers and white matter RSI as well as (v) immune markers and rsFC. Given PLSC is applicable on complete case data only, listwise deletion of data was performed prior to each analysis. Statistical significance of PLSC models and each latent dimension was determined using 10,000 permutations, and the reliability of the specific variable loadings was determined using bootstrapping (n = 10,000), with a bootstrap ratio >2.5 (corresponding to $p<0.01$) deemed reliable and significant. Notably, the sample size for this study exceeds the minimum required for stable and replicable results in PLSCs (Helmer et al., 2024). Because PLSCs involve one decomposition procedure for two matrices, we did not conduct multiple comparison correction as it is only one test per latent dimension.

2.8. Additional sensitivity and post-hoc exploratory analyses

While our *a priori* approach included covarying for household socioeconomic factors, ethnic minority and lower income communities are exposed to both higher air pollution levels and neighborhood socioeconomic factors. Moreover, neighborhood socioeconomic factors have also been found to be associated with brain outcomes in the ABCD Study (Rakesh et al., 2021; Hackman et al., 2021). Thus, we conducted a sensitivity analysis where we also adjusted for neighborhood disadvantage (see Supplemental Methods). Lastly, to investigate the potential functional consequences of our PLSC findings and as part of the revision process, we conducted a series of post-hoc exploratory stepwise regression analyses to assess the relationship between the PLSC-identified white matter tracts and rsFC networks and performance in the cognitive domains of processing speed and cognitive control using the NIH Toolbox (Luciana et al., 2018; see Supplemental Methods).

3. Results

3.1. Air pollution and brain connectivity

3.1.1. Female adolescents

One significant latent dimension was identified in the relationship between air pollution exposure and measures of white matter microstructural integrity in female adolescents (variance explained = 61%). Bootstrap ratios revealed that the right fornix RNI (i.e., intracellular isotropic diffusion) and right frontal superior corticostriate RND (i.e., intracellular directional diffusion) were the most influential variables. However, for the air pollution loadings, bootstrap ratios of the contributions were not found to be stable (Figure 1A). Thereby, while we can conclude that although there is a significant positive relationship between these white matter tracts and the air pollution variables, we are unable to determine which air pollution variables reliably contribute to this pattern. For the relationship between rsFC and air pollution in female adolescents, the scree plot revealed two latent dimensions; however, permutation tests showed that these dimensions were not significant (Supplemental Figure 3).

3.1.2. Male adolescents

One significant latent dimension was identified in the relationship between air pollution exposure and measures of white matter microstructural integrity in male adolescents (variance explained = 62%). Bootstrap ratios for the RSI loadings showed that RNI (i.e., intracellular isotropic diffusion) of the left corticospinal tract and the left uncinate fasciculus as well as RND (i.e., intracellular directional diffusion) of the right inferior frontal to superior frontal cortex, forceps minor, and corpus callosum were the most influential variables. Again, however, while there is a significant negative relationship between these white matter tracts and the air pollution variables, bootstrap ratios for the air pollution loadings did not determine any of these contributions as reliable (Figure 1B). For the relationship between rsFC and air pollution in male adolescents, results were analogous to those in female adolescents. The scree plot revealed two latent dimensions; however, permutation tests showed that these dimensions were not significant (Supplemental Figure 3).

3.2. Air pollution and cellular immune markers

3.2.1. Female adolescents

For the relationship between air pollution and cellular immune markers in female adolescents, two latent dimensions were identified, but permutation tests showed that these dimensions were not significant.

3.2.2. Male adolescents

For the relationship between air pollution and cellular immune markers in male adolescents, one dimension was found to be significant (variance explained = 69%). This dimension was characterized by a reliable correlation between WBC positive loadings and childhood NO_2 negative loadings (Figure 2).

3.3. Cellular immune markers and brain connectivity

3.3.1. Female adolescents

One significant latent dimension was identified in the relationship between cellular immune markers and measures of white matter microstructural integrity in female adolescents (variance explained = 71%). This dimension was characterized by a reliable positive correlation between SII and PLR immune markers and RND (i.e., intracellular directional diffusion) of bilateral frontal superior corticostriate, bilateral inferior fronto-occipital, and left striatal to inferior frontal cortex tracts (Figure 3Ai.).

Two significant latent dimensions were identified in the relationship

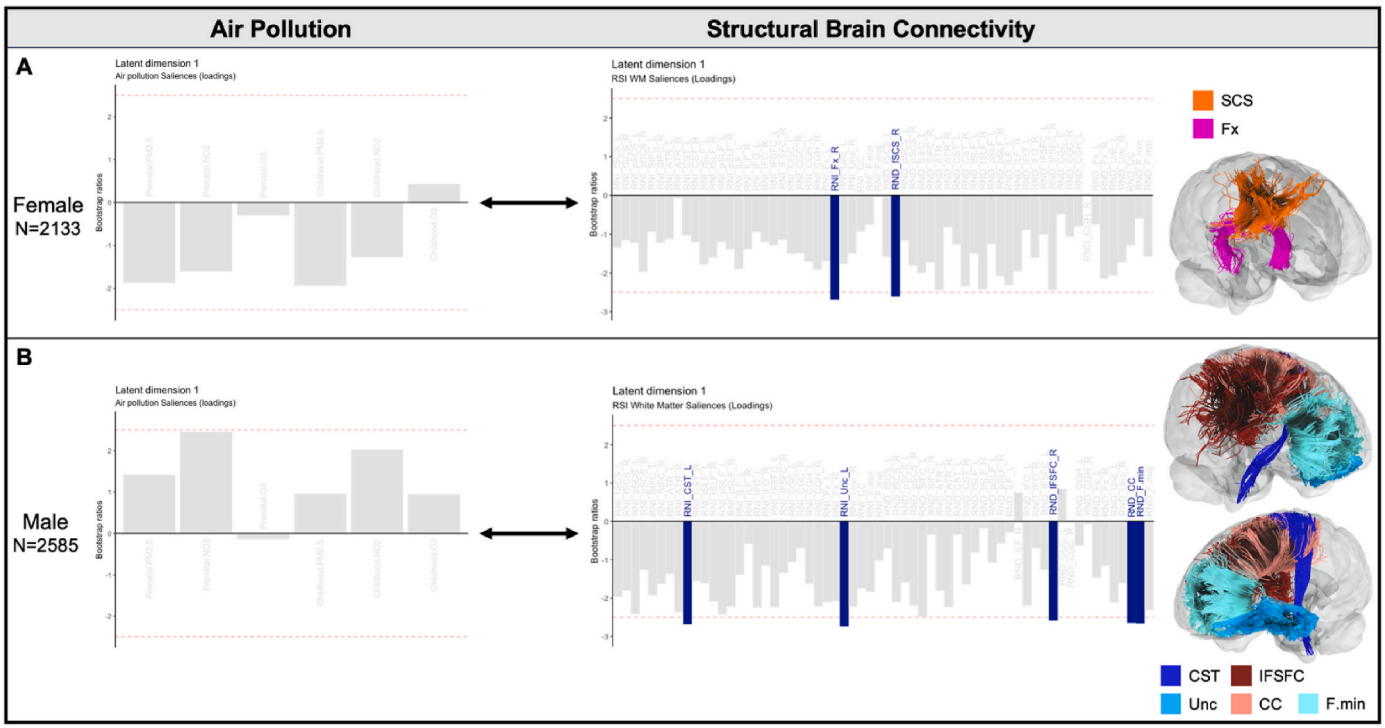

Fig. 1. Bar plots depicting bootstrap ratios of air pollution and structural brain connectivity loadings for the identified latent dimension in female and male adolescents. Abbreviations: restriction spectrum imaging (RSI), restricted normalized isotropic diffusion (RNI), restricted normalized directional diffusion (RND), right hemisphere (R), left hemisphere (L), Fornix (Fx), superior corticostriate (SCS), corticospinal tract (CST), uncinate fasciculus (Unc), inferior frontal to superior frontal cortex (IFSFC), forceps minor (F.min), and corpus callosum (CC).

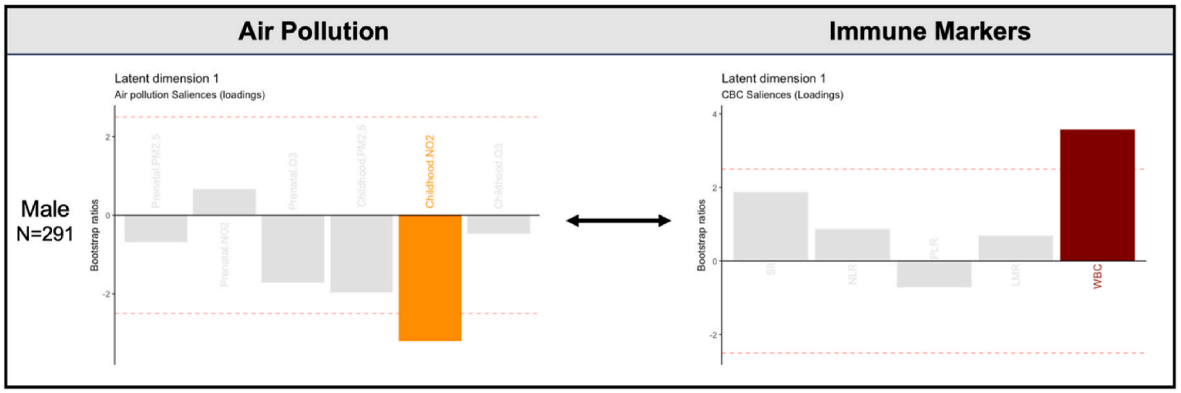

Fig. 2. Bar plots depicting bootstrap ratios of air pollution and complete blood count loadings for the identified latent dimension in male adolescents. Abbreviations: complete blood count (CBC), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), white blood cell count (WBC).

between cellular immune markers and measures of rsFC in female adolescents. In the first dimension (variance explained = 51%), bootstrap ratios revealed a negative relationship between LMR and intra-DMN connectivity. In the second dimension (variance explained = 32%), bootstrap ratios showed that PLR and WBC were the most important variables for the immune marker loadings. However, for the air pollution loadings, the bootstrap ratios of the contributions were not found to be stable (Figure 3Aii.).

3.3.2. *Male adolescents*

One significant latent dimension was identified in the relationship between cellular immune markers and measures of white matter microstructural integrity in male adolescents (variance explained = 73%). The bootstrap ratios showed a reliable positive relationship between WBC and RNI (i.e., intracellular isotropic diffusion) of the left cingulate cingulum, right parietal superior longitudinal fasciculus, and right inferior longitudinal fasciculus, as well as RND (i.e., intracellular directional diffusion) of the right parietal superior corticostriate, the forceps major, and the corpus callosum (Figure 3Bi.).

One significant latent dimension was identified in the relationship between cellular immune markers and rsFC in male adolescents (variance explained = 68%). The bootstrap ratios showed that salience network to left hippocampus connectivity was negatively associated with SII, NLR, and PLR and positively associated with LMR (Figure 3Bii.).

3.4. *Sensitivity and post-hoc exploratory analyses*

In sensitivity analyses also adjusting for neighborhood disadvantage, the results remained nearly identical, apart from minor differences in

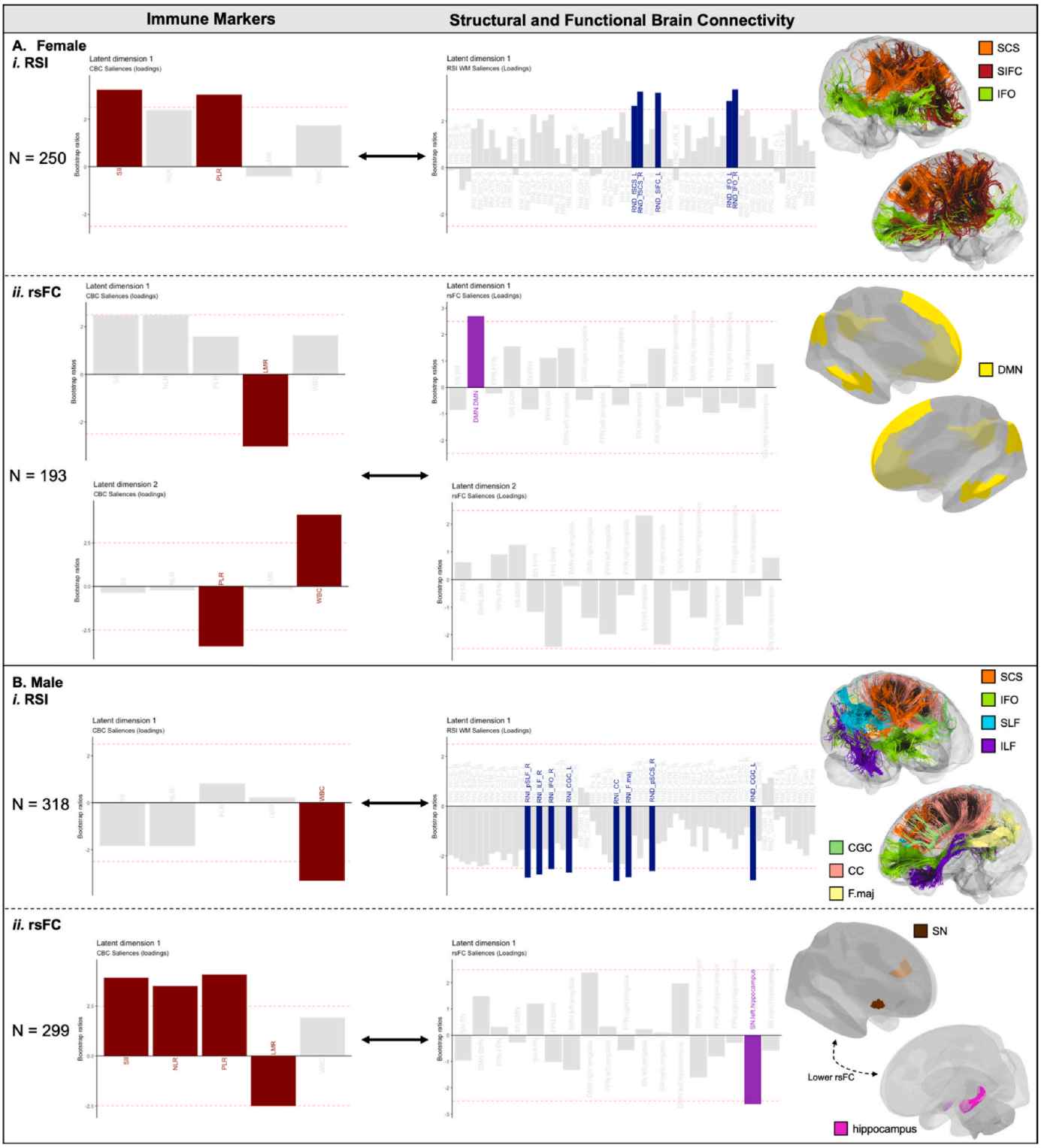

Fig. 3. Bar plots depicting bootstrap ratios of complete blood count loadings and structural and functional brain connectivity loadings for the identified latent dimensions in both female and male adolescents. Abbreviations: complete blood count (CBC), systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), white blood cell count (WBC), restriction spectrum imaging (RSI), restricted normalized isotropic diffusion (RNI), restricted normalized directional diffusion (RND), resting-state functional connectivity (rsFC), right hemisphere (R), left hemisphere (L), frontal superior corticostriate (fSCS), striatal to inferior frontal cortex (SIFC), inferior frontal occipital fasciculus (IFO), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), cingulate cingulum (CGC), corpus callosum (CC), forceps major (F.maj), default mode network (DMN), salience network (SN).

which a few loadings were exceptionally similar but no longer deemed 'significant' based on bootstrapping (Supplemental FIgures 4-6). In stepwise regression analyses, we found that the PLSC-identified white matter tracts related to cognition in females. Specifically, higher RND (i.e., intracellular directional diffusion) in the right inferior frontal to superior frontal cortex tract and RNI (i.e., intracellular isotropic diffusion) in the left corticospinal tract were associated with faster processing speed, whereas higher RND in the corpus callosum and higher RNI in the right fornix, right inferior frontal occipital fasciculus, and right inferior longitudinal fasciculus were associated with better cognitive control in females (Supplemental Table 4). In males, PLSC-identified white matter tracts and rsFC were found to relate to processing speed, but not cognitive control. In particular, higher RND in the corpus callosum, RNI in the left corticospinal tract, and intra-DMN rsFC were associated with faster processing speed (Supplemental Figures 4-6).

4. Discussion

The current cross-sectional study explored the relationships between air pollution exposure at different developmental periods (i.e., pregnancy and childhood), structural and functional brain connectivity, and cellular immune markers in male and female adolescents at ages 11–13 years-old. In doing so, three prominent patterns emerged. Prenatal and childhood exposure related to structural, but not functional, connectivity, albeit with distinct patterns of exposure and implicated white matter tracts seen in male and female adolescents. Air pollution and immune function were related in males (but not females), which was primarily driven by a negative association between childhood NO_2 exposure and white blood cell count. Moreover, immune function was found to be associated with both structural and functional connectivity in both male and female adolescents, albeit again with different immune and brain connectome markers identified by sex. Lastly, exploratory analyses found that as a whole, white matter microstructure and resting-state connectivity in identified brain regions related to processing speed and cognitive control, suggesting these findings may be important to consider in future work focused on understanding potential biological links between air pollution exposure, innate immune function, and neurodevelopment. Below, we expand upon each of these results in terms of the existing literature and potential importance in further studying these complex processes between air pollution, immune function, and brain connectivity during adolescence.

4.1. Co-exposures to prenatal and childhood ambient pollution relates to structural connectivity and cellular immune profiles in adolescents in a sex-stratified manner

Previous studies by our research team have identified links between childhood air pollution and brain connectivity in adolescents from the ABCD Study (Burnor et al., 2021; Sukumaran et al., 2023; Cotter et al., 2023b; Cotter et al., 2023a). The current analyses build upon these initial studies to include prenatal estimates in addition to childhood exposure, and utilizes a multivariate approach that allows for quantification of both joint and independent effects of highly correlated variables, such as co-exposures of different criterion pollutants from two different periods of neurodevelopment. In females, higher overall pollution exposure was linked to both greater isotropic and directional intracellular diffusion at ages 11-13 years-old in the right fornix, the main tract connecting the hippocampus to the frontal cortex, and the right superior corticostriate, which connects the striatum to the frontal cortex. While RSI cannot directly measure cellular properties in humans, it has been histologically validated in animal models (White et al., 2013). As such, it is thought that higher isotropic intracellular diffusion might indicate an increase in quantity, size, and/or morphology of glial cells such as microglia, astrocytes, and oligodendrocytes, whereas higher intracellular directional diffusion may reflect higher myelination, axon caliber, or axon density (White et al., 2013; Palmer et al., 2021). Generally, both intracellular isotropic and directional diffusion increase with age during adolescence (Palmer et al., 2021), and thus our results in female adolescents could represent potentially maladaptive precocious brain development or alternatively, a compensatory mechanism in response to pollution exposure. In males, there was a negative correlation between pollutant exposure and both intracellular isotropic and directional diffusion in large tracts spanning both hemispheres. Based on histology and RSI studies in rodents (White et al., 2013) and the animal exposure literature (Costa et al., 2014), we have hypothesized that lower intracellular isotropic diffusion could represent a reduction in glial cells, potentially damaged and depleted due to neurotoxic air pollution exposure effects. Lower intracellular directional diffusion, on the other hand, may result from damage to the myelin sheath, an indication of reduced white matter microstructural integrity (Palmer et al., 2022). Interestingly, no one pollutant or exposure window was found to be driving the air pollution latent dimension in either sex. This suggests that generally and perhaps cumulatively, various pollutants at different developmental periods may contribute to notable differences in white matter microstructural integrity in adolescents, with obvious sex-specific effects.

Theorized mechanisms as to how air pollution affects health include increased cortisol levels, systemic and neuroinflammation, oxidative stress, endoplasmic reticulum stress, epigenetic alterations, and disrupted function of the hypothalamic-pituitary-adrenal axis (Morgan et al., 2011; Yan et al., 2015; Levesque et al., 2011a; Levesque et al., 2011b; Levesque et al., 2013; H. Li et al., 2012; Chen et al., 2021). In the current study, we explored if air pollution related to cellular immune markers in each sex separately. Interestingly, we found air pollution to be linked to immune markers in male, but not female, adolescents. This association was found to be driven by higher childhood NO_2 exposure relating to lower white blood cell counts, consistent with adult studies showing a negative association between NO_2 exposure and white blood cell subtypes (Steenhof et al., 2014b; Frampton et al., 2002; Hung et al., 2021). It is feasible that inhalation of NO_2 (or another noxious gas or substance) induces recruitment of white blood cell subtypes from the periphery to the lung, increasing the number of bronchoalveolar white blood cells and reducing their levels in the blood. Beyond white blood cells being recruited away from the periphery, NO_2 exposure could also lead to pathologically high leukocyte infection and destruction, resulting in a lower white blood cell counts and ultimately hampering the body's ability to efficiently mount a response to foreign pathogens (i.e., a reduction of macrophage activation (Ural et al., 2022) or neutrophil respiratory burst (Phelps et al., 2023)). Additionally, one rodent study (Li et al., 2012) discovered that NO_2 exposure significantly increased anxiety and depression-like behaviors, damaged myelin content, and increased pro-inflammatory cytokines in male compared to female rats. These results are possibly partly attributed to NO_2-mediated increases in prolactin expression in female compared to male rats, a biologically active hormone and cytokine known for its role in stress-induced immunoregulation and its anti-inflammatory properties (Li et al., 2012; Borba et al., 2018; Freeman et al., 2000; Jara et al., 2011). This tracks with our results demonstrating a potentially protective effect of female sex on associations of pollutant exposure with white matter microstructure noted above as well as a putative effect of male sex on the relationship between pollutant exposure, particularly NO_2, and white matter microstructure as well as immune markers. However, it is important to note that air pollution exposures are not time-locked with blood collection in the current study. As such, the potential acute effects of air pollution exposure on cellular immune markers in adolescents remains unclear. Nonetheless, this initial analysis suggests characterizing sex differences in the effects of both acute and chronic air pollution exposure on these blood-based immune function biomarkers is an important area of future research.

In contrast to structural connectivity, we did not find an association between prenatal and childhood exposure and resting-state functional connectivity at ages 11–13 years-old in the current study. While initially

surprising given our previous study showing childhood air pollution exposure related to longitudinal changes in resting-state functional connectivity (Cotter et al., 2023b), it is important to recognize the multivariate PLSC analyses used here investigates a fundamentally distinct question as compared to a more traditional univariate multi-pollutant analysis. First, in the current study we assessed the variance explained between co-exposures (including prenatal exposure, which was not included in our previous work) and a group of resting-state patterns. Thus, unlike our previous research that showed childhood exposures explained *unique* variance in the age-related *changes* over time on a single outcome (i.e., slope), this study suggests co-exposure to air pollution does not account for shared variance in resting-state patterns when assessed at the single timepoint when participants were aged 11–13 years. This further highlights the nuances and importance of examining the relationship between air pollution and brain development at different ages, considering the windows of exposure (i.e., prenatal, childhood, etc.), and the inherent limitations and inferences that can be made with cross-sectional versus longitudinal data. Future work should aim to further explore exposure windows in different vulnerable developmental stages as well as the potential cumulative effects of lifetime pollution exposure on longitudinal outcomes in samples with wider age ranges.

4.2. Immune profiles are related to structural and functional connectivity during adolescence in both sexes

While SII and NLR have previously been associated with white matter hyperintensities and altered resting-state functional connectivity in older adults (Del Brutto et al., 2023; Nam et al., 2022; Nam et al., 2017; McIntosh et al., 2022), to our knowledge, this is the first study to find that immune function profiles from CBC are linked to both white matter microstructural integrity and resting-state functional connectivity in healthy male and female adolescents. In both sexes, higher values of immune markers were correlated with differences in intracellular white matter microstructure in various tracts across the brain, albeit with different patterns seen in male and female adolescents. Higher SII, PLR, NLR, WBC, and lower LMR values are typically associated with poor health outcomes as they are often used in prognosis for cancer and stroke (Li et al., 2021; Lu et al., 2023; Tian et al., 2022; Wei et al., 2023). In female adolescents, higher SII and PLR were primarily related to greater intracellular directional diffusion in projection (i.e., left striatal to inferior frontal cortex) and association (i.e., bilateral frontal superior corticostriate tract) fibers. In male adolescents, higher white blood cell counts were associated with both intracellular isotropic and directional diffusion in specific projection (i.e., parietal superior longitudinal fasciculus, inferior longitudinal fasciculus), association (i.e., parietal superior corticostriate), and commissural (i.e., corpus callosum) white matter bundles. In terms of immune response, cytokine infiltration from the periphery to the brain in response to lung-associated immune activation can induce glial cell activation (John et al. 2003), which could result in the higher intracellular isotropic diffusion we observe in males. However, if this homeostatic balance is tipped by errant inflammation, persistently activated glial cells can become maladaptive. Potential mechanisms that could explain the positive relationship between markers of immune activation and intracellular directional diffusion, which may reflect differences in myelination, axon caliber, or axon density, are less certain. There is some evidence to suggest that a degree of inflammation is important for myelin repair processes in a context-dependent way, in that it plays a role in promoting oligodendrocyte lineage progression, debris clearance, and iron regulation (necessary for myelin synthesis) (Goldstein et al., 2016)

In terms of the correlations between immune markers and resting-state functional connectivity, decreased LMR (i.e., lower lymphocyte counts and higher monocyte counts, potentially indicating increased inflammation) was associated with increased intra-DMN connectivity in female adolescents. In male adolescents, we found that elevated SII, NLR, PLR, and decreased LMR (i.e., typically linked with poor health outcomes) were related to less connectivity between the salience network and the left hippocampus. Resting-state brain network development doctrine suggests that regions within networks become more correlated (i.e., undergo integration) while regions from different networks become less correlated (i.e., undergo segregation) with age during adolescence (Dosenbach et al., 2010). In our previous research using longitudinal data from the ABCD Study cohort, we found intra-DMN connectivity increased (i.e., reflecting within-network integration) and subcortical-to-network connectivity, including the left hippocampus to SN, decreased (i.e., reflecting between-network segregation) over time from ages 9-13 years-old (Cotter et al., 2023b). Thus, the current findings suggest that unique profiles of immune activity are linked with differences in DMN integration and SN-to-hippocampus segregation during a prime period of adolescent neurodevelopment.

PLSC methods do not allow for us to directly test for significant differences in males and females (i.e., interaction terms, see also limitations section), but notable sex differences exist in both the innate and adaptive immune response, with important changes seen at the time of puberty (Klein and Flanagan 2016) that might account for the sex-specific effects observed between immune markers and neuroimaging outcomes in the current study. For example, within our sample, 85% of the females were in the mid-to-late stages, whereas 70% of males were in the pre-to-early stages of pubertal development. While pubertal status was regressed out prior to PLSC analyses to reduce confounding, and physical pubertal development and sex steroid levels are correlated and change in tandem, there is still substantial variation in sex steroid levels between individuals at the same pubertal stage (Shirtcliff et al. 2009). Therefore, some variance due to sex steroids unaccounted for by the puberty variable in our analysis may be contributing to the sex-specific results seen here. Therefore, it is feasible that differences in sex hormones, as well as sex chromosomes, may have contributed to these findings, especially given the role of sex steroids in oxidative stress (Bhatia et al., 2012; Cruz-Topete et al., 2020; Rattanasopa et al., 2019), endothelial integrity (Filipe et al., 2008), and inflammation (Chen et al., 2021). Future research is necessary to further characterize how biological sex influences cellular immune markers and adolescent brain development.

4.3. Potential relevance to cognitive performance?

Understanding how neural correlates via neuroimaging map onto human behavior is a complex field of study (Fernandez-Iriondo et al., 2022), as differences in brain structure and function may exist with or without overt changes in behavior for various reasons (i.e., tempo and magnitude of brain plasticity changes detected by the spatial limits of MRI, a plethora of unmeasured neural compensatory mechanisms as the entire brain is involved in complex human behaviors, limited brain phenotypes usually studied in specified regions of interest, etc.). However, given the relative novelty of the neuroimaging markers used here and the exploratory nature of the current research, we also explored if the PLSC-identified brain features related to neurocognitive performance on the NIH Toolbox. We found that higher intracellular white matter microstructure (isotropic and/or directional) in the right inferior frontal to superior frontal cortex (in females), left corticospinal tract (both sexes), and corpus callosum (in males) related to faster processing speed, as did the intra-network integration of the DMN (in males). In terms of cognitive control, better performance in females was found to be associated with intracellular isotropic and directional diffusion in the corpus callosum, right fornix, right inferior frontal occipital fasciculus, and right inferior longitudinal fasciculus. These findings align with previous literature suggesting a role for these association and projection white matter tracts in goal-directed behaviors (Haber 2016), integration of information from several functional domains (i.e., visuospatial processing, executive function) (Benedictis et al., 2021), and motor control (Javed et al. 2023; Seiler et al., 2017; Von Der Heide et al., 2013; El-Baba

and Schury 2023). Previous studies have also linked information processing speed with brain activation in the DMN with stronger effects noted in males (Dhamala et al., 2021). Thus, our findings support some of the more widely accepted functions of these tracts and networks to be related to immune markers and air pollution exposure. However, given the complexities mentioned above, it is difficult to extrapolate how air pollution exposure and immune dysfunction may have effects on brain outcomes that would, or would not, directly map to better or worse cognitive performance, especially considering the dynamic neural changes adolescents undergo at this developmental stage. As such, it is beyond the scope of this current study to disentangle the possible mediating or moderating effects of exposures and alterations in immune function on cognitive outcomes, and we recommend caution be exercised when interpreting these associations. Nonetheless, it is clear from this post-hoc analysis that white matter tracts and functional brain networks that are associated with both air pollution exposure and immune profiles may also play a role in cognitive changes in adolescents.

4.4. Strengths and limitations

While the current study leverages a large and regionally diverse ABCD Study sample with >2000 subjects in each sex for the air pollution and brain analyses, only a smaller subset of ABCD participants had available blood samples to assess immune markers. The current study also utilizes a cross-sectional approach and has limited lifetime air pollution exposure, which curtails our ability to investigate how lifetime and/or acute periods of exposure to air pollution might affect the current findings. However, we were able to include air pollution exposure for two critical developmental windows – gestation and childhood – alongside biomarkers of brain and immune function at ages 11–13 years. Another strength of this study is the use of the novel RSI technique that may allow for a more in-depth assessment of white matter microstructure, particularly in the context of inflammation. Due to its multi-compartmental nature, RSI can distinguish between intracellular, extracellular, and free water spaces (White et al., 2013). Additionally, this biophysical model is better able to quantify spherical or elongated shapes, representing glial cells and axons, respectively, in turn allowing for a more precise characterization of white matter microstructure (White et al., 2013). Lastly, the current study also included immune biomarkers such as SII, PLR, NLR, LMR, and WBC, which are easily derived from a complete blood count (CBC). The use of these markers represents a novel approach to studying immune function in the field of development. As compared to the canonical inflammatory markers (i.e., CRP, inflammatory cytokines) commonly used in research, these CBC-derived immune measures are inexpensive, clinically accessible, and highly scalable, making them an attractive and easily adoptable method for assaying immune function in various populations. These markers are limited, however, in that they are also sensitive to transient immune activation, making it difficult to discern whether a subject with high immune markers is experiencing transient and/or chronic inflammation/immune activation. Therefore, additional research is needed using repeated measures of these markers to confirm the relationships between air pollution, immune responses, and brain outcomes noted in the current study. Given the cross-sectional study design and relatively small sample size with immune measures, we were not adequately powered to test a formal mediation of immune components on the relationships between pollutants and brain outcomes. However, we hope these exploratory associations between air pollution exposure, immune markers, and neural outcomes may help generate new hypotheses aimed at understanding the important mechanistic pathways by which air pollution can harm brain health during adolescence. Lastly, our analyses were stratified by sex due to the inability of our chosen methodology to accommodate a formal test of sex differences (i.e., a by-sex interaction term). As such, the differential patterns we find by sex may not be statistically significant and future work should probe this potential interaction.

Of note, more broad limitations are inherent in using the publicly available ABCD Study dataset. Concerns exist in how overuse of public datasets may contribute to issues of generalizability, as multiple published papers reporting on the same dataset can inflate the literature and perpetuate sample nuances and bias into a field of study (Mroczek et al., 2022). While the characteristics of the PLSC method, including permutation tests and bootstrap ratios, improve the likelihood that our findings may be more robust as they rely on subsampling the data thousands of times, the ABCD Study sample itself is not generalizable to the entire population of American adolescents. It should therefore be noted that the inherent sampling bias within the ABCD sample has resulted in the over-representation of youth from wealthier and more educated families and the under-representation of both Black and Asian youth as compared to the U.S. population at the time of study conception. As such, these findings necessitate replication in various diverse samples to assess the replicability and generalizability of these effects across various populations.

4.5. Summary and conclusions

In summary, our findings build upon an emerging literature to: 1) demonstrate that prenatal and childhood co-exposure to $PM_{2.5}$, NO_2, and O_3 is related to structural brain networks at ages 11-13 years-old in opposite directions per sex, 2) identify a new link between childhood NO_2 exposure and immune components in male adolescents, and 3) identify relationships between immune function profiles and both structural and functional brain network connectivity in both sexes during adolescence. Together, these exploratory multivariate analyses identified novel links between air pollution, immune function, and brain connectivity, as well as demonstrate the potential value CBC assays may hold in investigating these relationships. Future research is necessary to build upon these relationships and more formally explore the possible mediating role of immune function as it pertains to the relationship between air pollution exposure and brain development.

CRediT authorship contribution statement

Devyn L. Cotter: Writing – review & editing, Writing – original draft, Visualization, Formal analysis, Conceptualization. **Jessica Morrel:** Writing – review & editing, Writing – original draft. **Kirthana Sukumaran:** Writing – review & editing, Methodology, Formal analysis. **Carlos Cardenas-Iniguez:** Writing – review & editing, Methodology, Formal analysis. **Joel Schwartz:** Writing – review & editing, Methodology, Funding acquisition, Data curation. **Megan M. Herting:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Dr. Megan Herting, PhD reports financial support was provided by National Institute of Environmental Health Sciences. Dr. Joel D. Schwartz, PhD reports financial support was provided by United States Environmental Protection Agency.

Data availability

The data is publicly available to all.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100799.

References

Armijos, Rodrigo X., Margaret Weigel, M., Myers, Orrin B., Li, Wen-Whai, Racines, Marcia, Berwick, Marianne, 2015. Residential exposure to urban traffic is associated with increased carotid intima-media thickness in children. Journal of Environmental and Public Health 2015 (January), e713540. https://doi.org/10.1155/2015/713540.

Barraza-Villarreal, Albino, Sunyer, Jordi, Hernandez-Cadena, Leticia, Escamilla-Nuñez, Maria Consuelo, Sienra-Monge, Juan Jose, Ramírez-Aguilar, Matiana, Cortez-Lugo, Marlene, et al., 2008. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. Environ. Health Perspect. 116 (6), 832–838. https://doi.org/10.1289/ehp.10926.

Benedetti, Francesco, Palladini, Mariagrazia, Paolini, Marco, Melloni, Elisa, Vai, Benedetta, De Lorenzo, Rebecca, Furlan, Roberto, Rovere-Querini, Patrizia, Falini, Andrea, Mazza, Mario Gennaro, 2021. Brain correlates of depression, post-traumatic distress, and inflammatory biomarkers in COVID-19 survivors: a multimodal magnetic resonance imaging study. Brain, Behavior, & Immunity - Health 18 (December), 100387. https://doi.org/10.1016/j.bbih.2021.100387.

Benedictis DE, Alessandro, Marras, Carlo E., Petit, Laurent, Sarubbo, Silvio, 2021. The inferior fronto-occipital fascicle: a century of controversies from anatomy theaters to operative neurosurgery. J. Neurosurg. Sci. 65 (6), 605–615. https://doi.org/10.23736/S0390-5616.21.05360-1.

Bhatia, K., Elmarakby, A.A., El-Remessy, A.B., Sullivan, J.C., 2012. Oxidative stress contributes to sex differences in angiotensin II-mediated hypertension in spontaneously hypertensive rats. American journal of physiology. Regulatory, integrative and comparative physiology 302 (2), R274–R282. https://doi.org/10.1152/ajpregu.00546.2011.

Binter, Anne-Claire, Kusters, Michelle S.W., van den Dries, Michiel A., Alonso, Lucia, Lubczyńska, Małgorzata J., Hoek, Gerard, White, Tonya, Iñiguez, Carmen, Tiemeier, Henning, Guxens, Mònica, 2022. Air pollution, white matter microstructure, and brain volumes: periods of susceptibility from pregnancy to preadolescence. Environ. Pollut. 313 (November), 120109 https://doi.org/10.1016/j.envpol.2022.120109.

Borba, V.V., Zandman-Goddard, G., Shoenfeld, Y., 2018. Prolactin and Autoimmunity. Frontiers in immunology 9, 73. https://doi.org/10.3389/fimmu.2018.00073.

Bové, Hannelore, Bongaerts, Eva, Slenders, Eli, Bijnens, Esmée M., Saenen, Nelly D., Gyselaers, Wilfried, Van Eyken, Peter, et al., 2019. Ambient Black carbon particles reach the fetal side of human placenta. Nat. Commun. 10 (1), 3866. https://doi.org/10.1038/s41467-019-11654-3.

Brancher, Marlon, 2021. Increased ozone pollution alongside reduced nitrogen dioxide concentrations during vienna's first COVID-19 lockdown: significance for air quality management. Environ. Pollut. 284 (September), 117153 https://doi.org/10.1016/j.envpol.2021.117153.

Brown, Meredith S., Sarnat, Stefanie Ebelt, DeMuth, Karen A., Brown, Lou Ann S., Whitlock, Denise R., Brown, Shanae W., Tolbert, Paige E., Fitzpatrick, Anne M., 2012. Residential proximity to a major roadway is associated with features of asthma control in children. PLoS One 7 (5), e37044. https://doi.org/10.1371/journal.pone.0037044.

Brunst, Kelly J., Ryan, Patrick H., Brokamp, Cole, Bernstein, David, Reponen, Tiina, Lockey, James, Khurana Hershey, Gurjit K., Levin, Linda, Grinshpun, Sergey A., LeMasters, Grace, 2015. Timing and duration of traffic-related air pollution exposure and the risk for childhood wheeze and asthma. Am. J. Respir. Crit. Care Med. 192 (4), 421–427. https://doi.org/10.1164/rccm.201407-1314OC.

Buckley, Jessie P., Doherty, Brett T., Keil, Alexander P., Engel, Stephanie M., 2017. Statistical approaches for estimating sex-specific effects in endocrine disruptors research. Environ. Health Perspect. 125 (6), 067013 https://doi.org/10.1289/EHP334.

Burnor, Elisabeth, Cserbik, Dora, Cotter, Devyn L., Palmer, Clare E., Ahmadi, Hedyeh, Eckel, Sandrah P., Berhane, Kiros, et al., 2021. Association of outdoor ambient fine particulate matter with intracellular white matter microstructural properties among children. JAMA Netw. Open 4 (12), e2138300. https://doi.org/10.1001/jamanetworkopen.2021.38300.

Calderón-Garcidueñas, Lilian, Mora-Tiscareño, Antonieta, Francolira, Maricela, Torres-Jardón, Ricardo, Peña-Cruz, Bernardo, Palacios-López, Carolina, Zhu, Hongtu, et al., 2013. Exposure to urban air pollution and bone health in clinically healthy six-year-old children. Arh. Hig. Rad. Toksikol. 64 (1), 23–34. https://doi.org/10.2478/10004-1254-64-2013-2219.

Casey, B.J., Cannonier, Tariq, Conley, May I., Cohen, Alexandra O., Barch, Deanna M., Heitzeg, Mary M., Soules, Mary E., et al., 2018. The adolescent brain cognitive development (ABCD) study: imaging acquisition across 21 sites. Developmental Cognitive Neuroscience 32 (August), 43–54. https://doi.org/10.1016/j.dcn.2018.03.001.

Chan, Joseph C.Y., Chan, David L., Diakos, Connie I., Engel, Alexander, Nick, Pavlakis, Gill, Anthony, Clarke, Stephen J., 2017. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann. Surg. 265 (3), 539–546. https://doi.org/10.1097/SLA.0000000000001743.

Chen, Xiangchuan, Beltran, Diana J., Tsygankova, Valeriya D., Woolwine, Bobbi J., Patel, Trusharth, Baer, Wendy, Felger, Jennifer C., Miller, Andrew H., Ebrahim, Haroon, 2021. Kynurenines increase MRS metabolites in basal ganglia and decrease resting-state connectivity in frontostriatal reward circuitry in depression. Transl. Psychiatry 11 (1), 456. https://doi.org/10.1038/s41398-021-01587-1.

Clark, Nina Annika, Demers, Paul A., Karr, Catherine J., Koehoorn, Mieke, Lencar, Cornel, Tamburic, Lillian, Brauer, Michael, 2010. Effect of early life exposure to air pollution on development of childhood asthma. Environ. Health Perspect. 118 (2), 284–290. https://doi.org/10.1289/ehp.0900916.

Costa, Lucio G., Cole, Toby B., Coburn, Jacki, Chang, Yu-Chi, Dao, Khoi, Roque, Pamela, 2014. Neurotoxicants are in the air: convergence of human, animal, and in vitro studies on the effects of air pollution on the brain. BioMed Res. Int. 2014, 736385 https://doi.org/10.1155/2014/736385.

Costa, Lucio G., Cole, Toby B., Coburn, Jacki, Chang, Yu-Chi, Dao, Khoi, Roqué, Pamela J., 2017. Neurotoxicity of traffic-related air pollution. Neurotoxicology 59 (March), 133–139. https://doi.org/10.1016/j.neuro.2015.11.008.

Costa, Lucio G., Cole, Toby B., Dao, Khoi, Chang, Yu-Chi, Coburn, Jacki, Garrick, Jacqueline M., 2020. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. Pharmacol. Therapeut. 210 (June), 107523 https://doi.org/10.1016/j.pharmthera.2020.107523.

Cotter, Devyn, Ahmadi, Hedyeh, Cardenas-Iniguez, Carlos, Bottenhorn, Katherine, James Gauderman, W., McConnell, Rob, Berhane, Kiros, et al., 2023a. Sex-specific effects in how childhood exposures to multiple ambient air pollutants affect white matter microstructure development across early adolescence. https://doi.org/10.21203/rs.3.rs-3213618/v1.

Cotter, Devyn L., Campbell, Claire E., Sukumaran, Kirthana, McConnell, Rob, Berhane, Kiros, Schwartz, Joel, Hackman, Daniel A., Ahmadi, Hedyeh, Chen, Jiu-Chiuan, Herting, Megan M., 2023b. Effects of ambient fine particulates, nitrogen dioxide, and ozone on maturation of functional brain networks across early adolescence. Environ. Int. 177 (July), 108001 https://doi.org/10.1016/j.envint.2023.108001.

Cruz-Topete, D., Dominic, P., Stokes, K.Y., 2020. Uncovering sex-specific mechanisms of action of testosterone and redox balance. Redox biology 31, 101490. https://doi.org/10.1016/j.redox.2020.101490.

Dadouli, Katerina, Janho, Michel B., Hatziefthimiou, Apostolia, Voulgaridi, Ioanna, Piaha, Konstantina, Anagnostopoulos, Lemonia, Ntellas, Panagiotis, et al., 2022. Neutrophil-to-Lymphocyte, monocyte-to-lymphocyte, platelet-to-lymphocyte ratio and systemic immune-inflammatory index in different states of bipolar disorder. Brain Sci. 12 (8), 1034. https://doi.org/10.3390/brainsci12081034.

Dai, Yifeng, Huo, Xia, Cheng, Zhiheng, Wang, Qihua, Zhang, Yuling, Xu, Xijin, 2019. Alterations in platelet indices link polycyclic aromatic hydrocarbons toxicity to low-grade inflammation in preschool children. Environ. Int. 131 (October), 105043 https://doi.org/10.1016/j.envint.2019.105043.

Del Brutto, Oscar, H., Mera, Robertino M., Rumbea, Denisse A., Del Brutto, Victor J., 2023. Systemic immune-inflammation index and progression of white matter hyperintensities of presumed vascular origin. A longitudinal population study in community-dwelling older adults living in rural Ecuador. J. Neurol. Sci. 452 (September), 120741 https://doi.org/10.1016/j.jns.2023.120741.

Dhamala, Elvisha, Jamison, Keith W., Jaywant, Abhishek, Kuceyeski, Amy, 2021. Shared functional connections within and between cortical networks predict cognitive abilities in adult males and females. Hum. Brain Mapp. 43 (3), 1087–1102. https://doi.org/10.1002/hbm.25709.

Di, Qian, Amini, Heresh, Shi, Liuhua, Kloog, Itai, Silvern, Rachel, Kelly, James, Benjamin Sabath, M., et al., 2019. An ensemble-based model of PM2.5 concentration across the contiguous United States with high spatiotemporal resolution. Environ. Int. 130 (September), 104909 https://doi.org/10.1016/j.envint.2019.104909.

Di, Qian, Amini, Heresh, Shi, Liuhua, Kloog, Itai, Silvern, Rachel, Kelly, James, Benjamin Sabath, M., et al., 2020. Assessing NO2 concentration and model uncertainty with high spatiotemporal resolution across the contiguous United States using ensemble

model averaging. Environ. Sci. Technol. 54 (3), 1372–1384. https://doi.org/10.1021/acs.est.9b03358.
Dosenbach, Nico U.F., Nardos, Binyam, Cohen, Alexander L., Fair, Damien A., Power, Jonathan D., Church, Jessica A., Nelson, Steven M., et al., 2010. Prediction of individual brain maturity using fMRI. Science 329 (5997), 1358–1361. https://doi.org/10.1126/science.1194144.
"Effect of air pollution on the human immune system.". Nat. Med. 28 (12), 2022, 2482–2483. https://doi.org/10.1038/s41591-022-02093-7.
El-Baba, Rami M., Schury, Mark P., 2023. Neuroanatomy, frontal cortex. In: *StatPearls*. Treasure Island (FL). StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK554483/.
Eo, Wan Kyu, Chang, Hye Jung, Kwon, Sang Hoon, Koh, Suk Bong, Kim, Young Ok, Ji, Yong Il, Kim, Hong-Bae, et al., 2016. The lymphocyte-monocyte ratio predicts patient survival and aggressiveness of ovarian cancer. J. Cancer 7 (3), 289–296. https://doi.org/10.7150/jca.13432.
Fan, Chun Chieh, Marshall, Andrew, Smolker, Harry, Gonzalez, Marybel R., Tapert, Susan F., Barch, Deanna M., Sowell, Elizabeth, et al., 2021. Adolescent brain cognitive development (ABCD) study linked external data (LED): protocol and practices for geocoding and assignment of environmental data. Developmental Cognitive Neuroscience 52 (December), 101030. https://doi.org/10.1016/j.dcn.2021.101030.
Fan, Chun Chieh, Loughnan, Robert, Makowski, Carolina, Pecheva, Diliana, Chen, Chi-Hua, Hagler, Donald J., Thompson, Wesley K., et al., 2022a. Multivariate genome-wide association study on tissue-sensitive diffusion metrics highlights pathways that shape the human brain. Nat. Commun. 13 (1), 2423. https://doi.org/10.1038/s41467-022-30110-3.
Fan, Hueng-Chuen, Chen, Chuan-Mu, Tsai, Jeng-Dau, Chiang, Kuo-Liang, Tsai, Stella Chin-Shaw, Huang, Ching-Ying, Lin, Cheng-Li, Hsu, Chung Y., Chang, Kuang-Hsi, 2022b. Association between exposure to particulate matter air pollution during early childhood and risk of attention-deficit/hyperactivity disorder in taiwan. Int. J. Environ. Res. Publ. Health 19 (23), 16138. https://doi.org/10.3390/ijerph192316138.
Fernandez-Iriondo, Izaro, Jimenez-Marin, Antonio, Sierra, Basilio, Aginako, Naiara, Bonifazi, Paolo, Cortes, Jesus M., 2022. Brain mapping of behavioral domains using multi-scale networks and canonical correlation analysis. Front. Neurosci. 16 (June) https://doi.org/10.3389/fnins.2022.889725.
Filipe, C., Lam Shang Leen, L., Brouchet, L., Billon, A., Benouaich, V., Fontaine, V., Gourdy, P., Lenfant, F., Arnal, J.F., Gadeau, A.P., Laurell, H., 2008. Estradiol accelerates endothelial healing through the retrograde commitment of uninjured endothelium. American journal of physiology. Heart and circulatory physiology 294 (6), H2822–H2830. https://doi.org/10.1152/ajpheart.00129.2008.
Frampton, Mark W., Boscia, Joseph, Roberts, Norbert J., Mitra, Azadniv, Torres, Alfonso, Cox, Christopher, Morrow, Paul E., et al., 2002. Nitrogen dioxide exposure: effects on airway and blood cells. Am. J. Physiol. Lung Cell Mol. Physiol. 282 (1), L155–L165. https://doi.org/10.1152/ajplung.2002.282.1.L155.
Freeman, M.E., Kanyicska, B., Lerant, A., Nagy, G., 2000. Prolactin: structure, function, and regulation of secretion. Physiological reviews 80 (4), 1523–1631. https://doi.org/10.1152/physrev.2000.80.4.1523.
Gade, Meethila, Comfort, Nicole, Re, Diane B., 2021. Sex-specific neurotoxic effects of heavy metal pollutants: epidemiological, experimental evidence and candidate mechanisms. Environ. Res. 201 (October), 111558 https://doi.org/10.1016/j.envres.2021.111558.
Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R.Z., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., Zahs, D., 2018. Recruiting the ABCD sample: design considerations and procedures. Developmental Cognitive Neuroscience, The Adolescent Brain Cognitive Development (ABCD) Consortium: Rationale, Aims, and Assessment Strategy 32 (August), 16–22. https://doi.org/10.1016/j.dcn.2018.04.004.
García-Serna, Azahara M., Martín-Orozco, Elena, Jiménez-Guerrero, Pedro, Hernández-Caselles, Trinidad, Pérez-Fernández, Virginia, Cantero-Cano, Esther, Muñoz-García, María, et al., 2022. Cytokine profiles in cord blood in relation to prenatal traffic-related air pollution: the NELA cohort. Pediatr. Allergy Immunol. 33 (2), e13732 https://doi.org/10.1111/pai.13732.
Giedd, Jay N., Raznahan, Armin, Mills, Kathryn L., Lenroot, Rhoshel K., 2012. Review: magnetic resonance imaging of male/female differences in human adolescent brain anatomy. Biol. Sex Differ. 3 (1), 19. https://doi.org/10.1186/2042-6410-3-19.
Glencross, Drew A., Ho, Tzer-Ren, Camiña, Nuria, Hawrylowicz, Catherine M., Pfeffer, Paul E., 2020. Air pollution and its effects on the immune system. Free Radical Biol. Med. 151 (May), 56–68. https://doi.org/10.1016/j.freeradbiomed.2020.01.179.
Goldstein, Evan Z., Church, Jamie S., Hesp, Zoe C., Popovich, Phillip G., McTigue, Dana M., 2016. A silver lining of neuroinflammation: beneficial effects on myelination. Experimental Neurology, Myelin Repair 283 (September), 550–559. https://doi.org/10.1016/j.expneurol.2016.05.001.
Gordon, Evan M., Laumann, Timothy O., Adeyemo, Babatunde, Huckins, Jeremy F., Kelley, William M., Petersen, Steven E., 2016. Generation and evaluation of a cortical area parcellation from resting-state correlations. Cerebr. Cortex 26 (1), 288–303. https://doi.org/10.1093/cercor/bhu239. New York, N.Y.: 1991.
Grayson, David S., Fair, Damien A., 2017. Development of large-scale functional networks from birth to adulthood: a guide to the neuroimaging literature. Neuroimage 160 (October), 15–31. https://doi.org/10.1016/j.neuroimage.2017.01.079.
Guxens, Mònica, Lubczyńska, Małgorzata J., Pérez-Crespo, Laura, Muetzel, Ryan L., El Marroun, Hanan, Basagaña, Xavier, Hoek, Gerard, Tiemeier, Henning, 2022. Associations of air pollution on the brain in children: a brain imaging study. Res. Rep. Health Eff. Inst. 209, 2022 (February).
Haber, Suzanne N., 2016. Corticostriatal circuitry. Dialogues Clin. Neurosci. 18 (1), 7–21.
Hackman, Daniel A., Cserbik, Dora, Chen, Jiu-Chiuan, Berhane, Kiros, Minaravesh, Bita, McConnell, Rob, Herting, Megan M., 2021. Association of local variation in neighborhood disadvantage in metropolitan areas with youth neurocognition and brain structure. JAMA Pediatr. 175 (8), e210426 https://doi.org/10.1001/jamapediatrics.2021.0426.
Hagler, Donald J., Ahmadi, Mazyar E., Kuperman, Joshua, Holland, Dominic, McDonald, Carrie R., Halgren, Eric, Dale, Anders M., 2009. Automated white-matter tractography using a probabilistic diffusion tensor atlas: application to temporal lobe epilepsy. Hum. Brain Mapp. 30 (5), 1535–1547. https://doi.org/10.1002/hbm.20619.
Hagler, Donald J., Hatton, SeanN., Daniela Cornejo, M., Makowski, Carolina, Fair, Damien A., Dick, Anthony Steven, Sutherland, Matthew T., et al., 2019. Image processing and analysis methods for the adolescent brain cognitive development study. Neuroimage 202 (November), 116091. https://doi.org/10.1016/j.neuroimage.2019.116091.
Hahn, Jill, Gold, Diane R., Coull, Brent A., McCormick, Marie C., Finn, Patricia W., Perkins, David L., Rifas Shiman, Sheryl L., Oken, Emily, Kubzansky, Laura D., 2021. Air pollution, neonatal immune responses, and potential joint effects of maternal depression. Int. J. Environ. Res. Publ. Health 18 (10), 5062. https://doi.org/10.3390/ijerph18105062.
Hajat, Anjum, Hsia, Charlene, O'Neill, Marie S., 2015. Socioeconomic disparities and air pollution exposure: a global review. Current Environmental Health Reports 2 (4), 440–450. https://doi.org/10.1007/s40572-015-0069-5.
Hamra, Ghassan B., Buckley, Jessie P., 2018. Environmental exposure mixtures: questions and methods to address them. Current Epidemiology Reports 5 (2), 160–165. https://doi.org/10.1007/s40471-018-0145-0.
Haskó, G., Szabó, C., 1998. Regulation of cytokine and chemokine production by transmitters and Co-transmitters of the autonomic nervous system. Biochem. Pharmacol. 56 (9), 1079–1087. https://doi.org/10.1016/s0006-2952(98)00153-1.
Heidari Nejad, Sayeh, Takechi, Ryusuke, Mullins, Benjamin J., Giles, Corey, Larcombe, Alexander N., Bertolatti, Dean, Rumchev, Krassi, Dhaliwal, Satvinder, Mamo, John, 2015. The effect of diesel exhaust exposure on blood-brain barrier integrity and function in a murine model. J. Appl. Toxicol.: J. Anal. Toxicol. 35 (1), 41–47. https://doi.org/10.1002/jat.2985.
Helmer, Markus, Warrington, Shaun, Mohammadi-Nejad, Ali-Reza, Ji, Jie Lisa, Howell, Amber, Benjamin, Rosand, Anticevic, Alan, Sotiropoulos, Stamatios N., Murray, John D., 2024. On the stability of canonical correlation analysis and partial least squares with application to brain-behavior associations. Commun. Biol. 7 (1), 1–15. https://doi.org/10.1038/s42003-024-05869-4.
Herting, Megan M., Younan, Diana, Campbell, Claire E., Chen, Jiu-Chiuan, 2019. Outdoor air pollution and brain structure and function from across childhood to young adulthood: a methodological review of brain MRI studies. Front. Public Health 7, 332. https://doi.org/10.3389/fpubh.2019.00332.
Hu, Bo, Yang, Xin-Rong, Xu, Yang, Sun, Yun-Fan, Sun, Chao, Guo, Wei, Zhang, Xin, et al., 2014. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin. Cancer Res.: An Official Journal of the American Association for Cancer Research 20 (23), 6212–6222. https://doi.org/10.1158/1078-0432.CCR-14-0442.
Hung, Shih-Chiang, Cheng, Hsiao-Yuan, Yang, Chen-Cheng, Lin, Chia-I, Ho, Chi-Kung, Lee, Wen-Huei, Cheng, Fu-Jen, Li, Chao-Jui, Chuang, Hung-Yi, 2021. The association of white blood cells and air pollutants—a population-based study. Int. J. Environ. Res. Publ. Health 18 (5), 2370. https://doi.org/10.3390/ijerph18052370.
Jara, L.J., Medina, G., Saavedra, M.A., Vera-Lastra, O., Navarro, C., 2011. Prolactin and autoimmunity. Clinical reviews in allergy & immunology 40 (1), 50–59. https://doi.org/10.1007/s12016-009-8185-3.
Javed, Kinaan, Reddy, Vamsi, Lui, Forshing, 2023. Neuroanatomy, lateral corticospinal tract. In: *StatPearls*. Treasure Island (FL). StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK534818/.
Jerrett, Michael, Shankardass, Ketan, Berhane, Kiros, James Gauderman, W., Künzli, Nino, Avol, Edward, Gilliland, Frank, et al., 2008. Traffic-related air pollution and asthma onset in children: a prospective cohort study with individual exposure measurement. Environ. Health Perspect. 116 (10), 1433–1438. https://doi.org/10.1289/ehp.10968.
Ji, Hongfei, Xuan, Qijia, Yan, Caichuan, Liu, Tao, Nanding, Abiyasi, Zhang, Qingyuan, 2016. The prognostic and predictive value of the lymphocyte to monocyte ratio in luminal-type breast cancer patients treated with CEF chemotherapy. Oncotarget 7 (23), 34881–34889. https://doi.org/10.18632/oncotarget.8993.
John, Gareth R., Lee, Sunhee C., Brosnan, Celia F., 2003. Cytokines: powerful regulators of glial cell activation. Neuroscientist: A Review Journal Bringing Neurobiology, Neurology and Psychiatry 9 (1), 10–22. https://doi.org/10.1177/1073858402239587.
Kaczkurkin, Antonia N., Raznahan, Armin, Satterthwaite, Theodore D., 2019. Sex differences in the developing brain: insights from multimodal neuroimaging. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology 44 (1), 71–85. https://doi.org/10.1038/s41386-018-0111-z.
Kang, You Jung, Tan, Hsih-Yin, Lee, Charles Y., Cho, Hansang, 2021. An air particulate pollutant induces neuroinflammation and neurodegeneration in human brain models. Adv. Sci. 8 (21), 2101251 https://doi.org/10.1002/advs.202101251.
Klein, Sabra L., Flanagan, Katie L., 2016. Sex differences in immune responses. Nat. Rev. Immunol. 16 (10), 626–638. https://doi.org/10.1038/nri.2016.90.
Klümper, Claudia, Krämer, Ursula, Lehmann, Irina, Berg, Andrea von, Dietrich, Berdel, Herberth, Gunda, Beckmann, Christina, et al., 2015. Air pollution and cytokine

responsiveness in asthmatic and non-asthmatic children. Environ. Res. 138 (April), 381–390. https://doi.org/10.1016/j.envres.2015.02.034.
Krishnan, Anjali, Williams, Lynne J., McIntosh, Anthony Randal, Abdi, Hervé, 2011. Partial least squares (pls) methods for neuroimaging: a tutorial and review. Neuroimage 56 (2), 455–475. https://doi.org/10.1016/j.neuroimage.2010.07.034.
Kurtul, Alparslan, Murat, Sani Namik, Yarlioglues, Mikail, Duran, Mustafa, Ergun, Gokhan, Acikgoz, Sadik Kadri, Demircelik, Muhammed Bora, et al., 2014. Association of platelet-to-lymphocyte ratio with severity and complexity of coronary artery disease in patients with acute coronary syndromes. Am. J. Cardiol. 114 (7), 972–978. https://doi.org/10.1016/j.amjcard.2014.07.005.
Latzin, Philipp, Frey, Urs, Armann, Jakob, Kieninger, Elisabeth, Fuchs, Oliver, Röösli, Martin, Schaub, Bianca, 2011. Exposure to moderate air pollution during late pregnancy and cord blood cytokine secretion in healthy neonates. PLoS One 6 (8), e23130. https://doi.org/10.1371/journal.pone.0023130.
Laumann, Timothy O., Snyder, Abraham Z., Mitra, Anish, Gordon, Evan M., Gratton, Caterina, Adeyemo, Babatunde, Gilmore, Adrian W., et al., 2017. On the stability of BOLD fMRI correlations. Cerebr. Cortex 27 (10), 4719–4732. https://doi.org/10.1093/cercor/bhw265.
Lee, Pei-Chen, Raaschou-Nielsen, Ole, Lill, Christina M., Bertram, Lars, Sinsheimer, Janet S., Hansen, Johnni, Ritz, Beate, 2016. Gene-environment interactions linking air pollution and inflammation in Parkinson's disease. Environ. Res. 151 (November), 713–720. https://doi.org/10.1016/j.envres.2016.09.006.
Lenroot, Rhoshel K., Giedd, Jay N., 2010. Sex differences in the adolescent brain. Brain Cognit. 72 (1), 46. https://doi.org/10.1016/j.bandc.2009.10.008.
Levesque, Shannon, Surace, Michael J., Jacob, McDonald, Block, Michelle L., 2011a. Air pollution & the brain: subchronic diesel exhaust exposure causes neuroinflammation and elevates early markers of neurodegenerative disease. J. Neuroinflammation 8 (August), 105. https://doi.org/10.1186/1742-2094-8-105.
Levesque, Shannon, Taetzsch, Thomas, Lull, Melinda E., Kodavanti, Urmila, Stadler, Krisztian, Wagner, Alison, Johnson, Jo Anne, et al., 2011b. Diesel exhaust activates and primes microglia: air pollution, neuroinflammation, and regulation of dopaminergic neurotoxicity. Environ. Health Perspect. 119 (8), 1149–1155. https://doi.org/10.1289/ehp.1002986.
Levesque, Shannon, Taetzsch, Thomas, Lull, Melinda E., Johnson, Jo Anne, McGraw, Constance, Block, Michelle L., 2013. The role of MAC1 in diesel exhaust particle-induced microglial activation and loss of dopaminergic neuron function. J. Neurochem. 125 (5), 756–765. https://doi.org/10.1111/jnc.12231.
Li, Hongyan, Chen, Liqun, Guo, Zhen, Sang, Nan, Li, Guangke, 2012. In vivo screening to determine neurological hazards of nitrogen dioxide (NO2) using wistar rats. J. Hazard Mater. 225–226 (July), 46–53. https://doi.org/10.1016/j.jhazmat.2012.04.063.
Li, Xinwei, Zhang, Xiao, Zhang, Zhiqiang, Han, Lianyu, Gong, Deping, Li, Jie, Wang, Ting, et al., 2019. Air pollution exposure and immunological and systemic inflammatory alterations among schoolchildren in China. Sci. Total Environ. 657 (March), 1304–1310. https://doi.org/10.1016/j.scitotenv.2018.12.153.
Li, Li-Hua, Chen, Chung-Ting, Chang, Yun-Chin, Chen, Ying-Ju, Lee, I.-Hui, How, Chorng-Kuang, 2021. Prognostic role of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic immune inflammation index in acute ischemic stroke: a STROBE-compliant retrospective study. Medicine 100 (25), e26354. https://doi.org/10.1097/MD.0000000000026354.
Liao, Minyu, Braunstein, Zachary, Rao, Xiaoquan, 2023. Sex differences in particulate air pollution-related cardiovascular diseases: a review of human and animal evidence. Sci. Total Environ. 884 (August), 163803 https://doi.org/10.1016/j.scitotenv.2023.163803.
Lin, Cheng-Kuan, Chang, Yuan-Ting, Lee, Fu-Shiuan, Chen, Szu-Ta, Christiani, David, 2021. Association between exposure to ambient particulate matters and risks of autism spectrum disorder in children: a systematic review and exposure-response meta-analysis. Environ. Res. Lett. 16 (6), 063003 https://doi.org/10.1088/1748-9326/abfcf7.
Lu, You, Kwong, Katherine, Wells, James, Edwards, Andrea, Zhong, Chen, Tseng, Tung-Sung, Zhang, Kun, 2023. Quitting smoking after a cancer diagnosis is associated with high-risk neutrophil-to-lymphocyte ratio among tobacco use-related cancer survivors. Sci. Rep. 13 (February), 2745. https://doi.org/10.1038/s41598-023-27624-1.
Lubczyńska, Małgorzata J., Muetzel, Ryan L., El Marroun, Hanan, Basagaña, Xavier, Strak, Maciej, Denault, William, Jaddoe, Vincent W.V., et al., 2020. Exposure to air pollution during pregnancy and childhood, and white matter microstructure in preadolescents. Environ. Health Perspect. 128 (2), 27005 https://doi.org/10.1289/EHP4709.
Lubczyńska, Małgorzata J., Muetzel, Ryan L., El Marroun, Hanan, Hoek, Gerard, Kooter, Ingeborg M., Thomson, Errol M., Hillegers, Manon, et al., 2021. Air pollution exposure during pregnancy and childhood and brain morphology in preadolescents. Environ. Res. 198 (July), 110446 https://doi.org/10.1016/j.envres.2020.110446.
Luciana, M., Bjork, J.M., Nagel, B.J., Barch, D.M., Gonzalez, R., Nixon, S.J., Banich, M.T., 2018. Adolescent neurocognitive development and impacts of substance use: overview of the adolescent brain cognitive development (ABCD) baseline neurocognition battery. Developmental Cognitive Neuroscience 32 (August), 67–79. https://doi.org/10.1016/j.dcn.2018.02.006.
Mazza, Mario Gennaro, De Lorenzo, Rebecca, Conte, Caterina, Poletti, Sara, Vai, Benedetta, Bollettini, Irene, Melloni, Elisa Maria Teresa, et al., 2020. Anxiety and depression in COVID-19 survivors: role of inflammatory and clinical predictors. Brain Behav. Immun. 89 (October), 594–600. https://doi.org/10.1016/j.bbi.2020.07.037.
McIntosh, A.R., Bookstein, F.L., Haxby, J.V., Grady, C.L., 1996. Spatial pattern analysis of functional brain images using partial least squares. Neuroimage 3 (3 Pt 1), 143–157. https://doi.org/10.1006/nimg.1996.0016.
McIntosh, Roger C., Lobo, Judith, Paparozzi, Jeremy, Goodman, Zach, Kornfeld, Salome, Nomi, Jason, 2022. Neutrophil to lymphocyte ratio is a transdiagnostic biomarker of depression and structural and functional brain alterations in older adults. J. Neuroimmunol. 365 (April), 577831 https://doi.org/10.1016/j.jneuroim.2022.577831.
Moeller, Steen, Yacoub, Essa, Olman, Cheryl A., Auerbach, Edward, Strupp, John, Harel, Noam, Uğurbil, Kâmil, 2010. Multiband multislice GE-EPI at 7 tesla, with 16-fold acceleration using partial parallel imaging with application to high spatial and temporal whole-brain fMRI. Magn. Reson. Med. 63 (5), 1144–1153. https://doi.org/10.1002/mrm.22361.
Morgan, Todd E., Davis, David A., Iwata, Nahoko, Tanner, Jeremy A., Snyder, David, Ning, Zhi, Kam, Winnie, et al., 2011. Glutamatergic neurons in rodent models respond to nanoscale particulate urban air pollutants in vivo and in vitro. Environ. Health Perspect. 119 (7), 1003–1009. https://doi.org/10.1289/ehp.1002973.
Nam, Ki-Woong, Kwon, Hyung-Min, Jeong, Han-Yeong, Park, Jin-Ho, Kim, Sang Hyuck, Jeong, Su-Min, Yoo, Tae Gon, Kim, Shinhye, 2017. High neutrophil to lymphocyte ratio is associated with white matter hyperintensity in a healthy population. J. Neurol. Sci. 380 (September), 128–131. https://doi.org/10.1016/j.jns.2017.07.024.
Mroczek, D.K., Weston, S.J., Graham, E.K., Willroth, E.C., 2022. Data overuse in aging research: Emerging issues and potential solutions. Psychology and Aging 37 (1), 141–147. https://doi.org/10.1037/pag0000605.
Nam, Ki Woong, Kwon, Hyung Min, Han, Yeong Jeong, Park, Jin Ho, Kwon, Hyuktae, 2022. Systemic immune-inflammation index is associated with white matter hyperintensity volume. Sci. Rep. 12 (1) https://doi.org/10.1038/s41598-022-11575-0.
Nishimura, Katherine K., Galanter, Joshua M., Roth, Lindsey A., Oh, Sam S., Thakur, Neeta, Nguyen, Elizabeth A., Thyne, Shannon, et al., 2013. Early-life air pollution and asthma risk in minority children. The GALA II and SAGE II studies. Am. J. Respir. Crit. Care Med. 188 (3), 309–318. https://doi.org/10.1164/rccm.201302-0264OC.
Palmer, Clare E., Pecheva, Diliana, Iversen, John R., Hagler, Donald J., Sugrue, Leo, Nedelec, Pierre, Fan, Chun Chieh, Thompson, Wesley K., Jernigan, Terry L., Dale, Anders M., 2021. Microstructural development from 9 to 14 Years: evidence from the ABCD study. Developmental Cognitive Neuroscience 53 (December), 101044. https://doi.org/10.1016/j.dcn.2021.101044.
Palmer, Clare E., Pecheva, Diliana, Iversen, John R., Hagler, Donald J., Sugrue, Leo, Nedelec, Pierre, Fan, Chun Chieh, Thompson, Wesley K., Jernigan, Terry L., Dale, Anders M., 2022. Microstructural development from 9 to 14 Years: evidence from the ABCD study. Developmental Cognitive Neuroscience 53 (February), 101044. https://doi.org/10.1016/j.dcn.2021.101044.
Pérez-Crespo, Laura, Kusters, Michelle S.W., López-Vicente, Mónica, Lubczyńska, Małgorzata J., Foraster, Maria, White, Tonya, Hoek, Gerard, Tiemeier, Henning, Muetzel, Ryan L., Guxens, Mònica, 2022. Exposure to traffic-related air pollution and noise during pregnancy and childhood, and functional brain connectivity in preadolescents. Environ. Int. 164 (June), 107275 https://doi.org/10.1016/j.envint.2022.107275.
Peters, A., Liu, E., Verrier, R.L., Schwartz, J., Gold, D.R., Mittleman, M., Baliff, J., et al., 2000. Air pollution and incidence of cardiac arrhythmia. Epidemiology 11 (1), 11–17. https://doi.org/10.1097/00001648-200001000-00005.
Peterson, Bradley S., Bansal, Ravi, Sawardekar, Siddhant, Nati, Carlo, Elgabalawy, Eman R., Hoepner, Lori A., Garcia, Wanda, et al., 2022. Prenatal exposure to air pollution is associated with altered brain structure, function, and metabolism in childhood. J. Child Psychol. Psychiatry Allied Discip. 63 (11), 1316–1331. https://doi.org/10.1111/jcpp.13578.
Phelps, Drake W., Palekar, Anika I., Conley, Haleigh E., Ferrero, Giuliano, Driggers, Jacob H., Linder, Keith E., Kullman, Seth W., et al., 2023. Legacy and emerging per- and polyfluoroalkyl substances suppress the neutrophil respiratory burst. J. Immunot. 20 (1), 2176953 https://doi.org/10.1080/1547691X.2023.2176953.
Pope, C. Arden, Burnett, Richard T., Thurston, George D., Thun, Michael J., Calle, Eugenia E., Krewski, Daniel, Godleski, John J., 2004. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. Circulation 109 (1), 71–77. https://doi.org/10.1161/01.CIR.0000108927.80044.7F.
Power, Jonathan D., Cohen, Alexander L., Nelson, Steven M., Wig, Gagan S., Barnes, Kelly Anne, Church, Jessica A., Vogel, Alecia C., et al., 2011. Functional network organization of the human brain. Neuron 72 (4), 665–678. https://doi.org/10.1016/j.neuron.2011.09.006.
Power, Jonathan D., Mitra, Anish, Laumann, Timothy O., Snyder, Abraham Z., Schlaggar, Bradley L., Petersen, Steven E., 2014. Methods to detect, characterize, and remove motion artifact in resting state fMRI. Neuroimage 84 (January), 320–341. https://doi.org/10.1016/j.neuroimage.2013.08.048.
Pujol, Jesus, Fenoll, Raquel, Macià, Dídac, Martínez-Vilavella, Gerard, Alvarez-Pedrerol, Mar, Rivas, Ioar, Forns, Joan, et al., 2016a. Airborne copper exposure in school environments associated with poorer motor performance and altered basal ganglia. Brain and Behavior 6 (6), e00467. https://doi.org/10.1002/brb3.467.
Pujol, Jesus, Martínez-Vilavella, Gerard, Macià, Dídac, Fenoll, Raquel, Alvarez-Pedrerol, Mar, Rivas, Ioar, Forns, Joan, et al., 2016b. Traffic pollution exposure is associated with altered brain connectivity in school children. Neuroimage 129 (April), 175–184. https://doi.org/10.1016/j.neuroimage.2016.01.036.
Rakesh, Divyangana, Seguin, Caio, Zalesky, Andrew, Cropley, Vanessa, Whittle, Sarah, 2021. Associations between neighborhood disadvantage, resting-state functional connectivity, and behavior in the adolescent brain cognitive development study: the moderating role of positive family and school environments. Biol. Psychiatr.:

Cognitive Neuroscience and Neuroimaging 6 (9), 877–886. https://doi.org/10.1016/j.bpsc.2021.03.008.
Rattanasopa, C., Kirk, J.A., Bupha-Intr, T., Papadaki, M., de Tombe, Wattanapermpool, J., 2019. Estrogen but not testosterone preserves myofilament function from doxorubicin-induced cardiotoxicity by reducing oxidative modifications. American journal of physiology. Heart and circulatory physiology 316 (2), H360–H370. https://doi.org/10.1152/ajpheart.00428.2018.
Requia, Weeberb J., Di, Qian, Silvern, Rachel, Kelly, James T., Koutrakis, Petros, Mickley, Loretta J., Sulprizio, Melissa P., Amini, Heresh, Shi, Liuhua, Schwartz, Joel, 2020. An ensemble learning approach for estimating high spatiotemporal resolution of ground-level ozone in the contiguous United States. Environ. Sci. Technol. 54 (18), 11037–11047. https://doi.org/10.1021/acs.est.0c01791.
Reuben, Aaron, Arseneault, Louise, Beddows, Andrew, Beevers, Sean D., Moffitt, Terrie E., Ambler, Antony, Latham, Rachel M., et al., 2021. Association of air pollution exposure in childhood and adolescence with psychopathology at the transition to adulthood. JAMA Netw. Open 4 (4), e217508. https://doi.org/10.1001/jamanetworkopen.2021.7508.
Sanders, Ashley F.P., Harms, Michael P., Kandala, Sridhar, Scott, Marek, Somerville, Leah H., Bookheimer, Susan Y., Dapretto, Mirella, et al., 2023. Age-related differences in resting-state functional connectivity from childhood to adolescence. Cerebr. Cortex, bhad011. https://doi.org/10.1093/cercor/bhad011. February.
Satterthwaite, Theodore D., Wolf, Daniel H., Roalf, David R., Ruparel, Kosha, Erus, Guray, Vandekar, Simon, Gennatas, Efstathios D., et al., 2015. Linked sex differences in cognition and functional connectivity in youth. Cerebr. Cortex 25 (9), 2383–2394. https://doi.org/10.1093/cercor/bhu036. New York, N.Y.: 1991.
Schulz, Kalynn M., Sisk, Cheryl L., 2016. The organizing actions of adolescent gonadal steroid hormones on brain and behavioral development. Neuroscience & Biobehavioral Reviews, The Adolescent Brain 70 (November), 148–158. https://doi.org/10.1016/j.neubiorev.2016.07.036.
Seiler, S., Pirpamer, L., Gesierich, B., Hofer, E., Duering, M., Pinter, D., Jouvent, E., et al., 2017. Lower magnetization transfer ratio in the forceps minor is associated with poorer gait velocity in older adults. Am. J. Neuroradiol. 38 (3), 500–506. https://doi.org/10.3174/ajnr.A5036.
Setsompop, Kawin, Gagoski, Borjan A., Polimeni, Jonathan R., Witzel, Thomas, Wedeen, Van J., Wald, Lawrence L., 2012. Blipped-controlled aliasing in parallel imaging for simultaneous multislice echo planar imaging with reduced g-factor penalty. Magn. Reson. Med. 67 (5), 1210–1224. https://doi.org/10.1002/mrm.23097.
Shi, Y., Toga, A.W., 2017. Connectome imaging for mapping human brain pathways. Mol. Psychiatr. 22 (9), 1230–1240. https://doi.org/10.1038/mp.2017.92.
Shirtcliff, Elizabeth A., Dahl, Ronald E., Pollak, Seth D., 2009. Pubertal development: correspondence between hormonal and physical development. Child Dev. 80 (2), 327–337. https://doi.org/10.1111/j.1467-8624.2009.01263.x.
Smith, Stephen M., Fox, Peter T., Miller, Karla L., Glahn, David C., Mickle Fox, P., Mackay, Clare E., Filippini, Nicola, et al., 2009. Correspondence of the brain's functional architecture during activation and rest. Proc. Natl. Acad. Sci. USA 106 (31), 13040–13045. https://doi.org/10.1073/pnas.0905267106.
Steenhof, Maaike, Janssen, Nicole A.H., Strak, Maciej, Hoek, Gerard, Gosens, Ilse, Mudway, Ian S., Kelly, Frank J., et al., 2014a. Air pollution exposure affects circulating white blood cell counts in healthy subjects: the role of particle composition, oxidative potential and gaseous pollutants - the RAPTES Project. Inhal. Toxicol. 26 (3), 141–165. https://doi.org/10.3109/08958378.2013.861884.
Steenhof, Maaike, Janssen, Nicole A.H., Strak, Maciej, Hoek, Gerard, Gosens, Ilse, Mudway, Ian S., Kelly, Frank J., et al., 2014b. Air pollution exposure affects circulating white blood cell counts in healthy subjects: the role of particle composition, oxidative potential and gaseous pollutants – the RAPTES Project. Inhal. Toxicol. 26 (3), 141–165. https://doi.org/10.3109/08958378.2013.861884.
Sukumaran, Kirthana, Cardenas-Iniguez, Carlos, Burnor, Elisabeth, Bottenhorn, Katherine L., Hackman, Daniel A., McConnell, Rob, Berhane, Kiros, Schwartz, Joel, Chen, Jiu-Chiuan, Herting, Megan M., 2023. Ambient fine particulate exposure and subcortical gray matter microarchitecture in 9- and 10-year-olds children across the United States. iScience 106087. https://doi.org/10.1016/j.isci.2023.106087. January.
Tian, Bao-Wen, Yang, Ya-Fei, Yang, Chun-Cheng, Yan, Lun-Jie, Ding, Zi-Niu, Liu, Hui, Xue, Jun-Shuai, et al., 2022. Systemic immune-inflammation index predicts prognosis of cancer immunotherapy: systemic review and meta-analysis. Immunotherapy 14 (18), 1481–1496. https://doi.org/10.2217/imt-2022-0133.
Tripathy, Sheila, Marsland, Anna L., Kinnee, Ellen J., Tunno, Brett J., Manuck, Stephen B., Gianaros, Peter J., Clougherty, Jane E., 2021. Long-term ambient air pollution exposures and circulating and stimulated inflammatory mediators in a cohort of midlife adults. Environ. Health Perspect. 129 (5), 57007 https://doi.org/10.1289/EHP7089.
Ural, Basak B., Caron, Daniel P., Dogra, Pranay, Wells, Steven B., Szabo, Peter A., Granot, Tomer, Senda, Takashi, et al., 2022. Inhaled particulate accumulation with age impairs immune function and architecture in human lung lymph nodes. Nat. Med. 28 (12), 2622–2632. https://doi.org/10.1038/s41591-022-02073-x.
US EPA, OAR, 2016a. Basic information about NO2. Overviews and Factsheets. July 6, 2016. https://www.epa.gov/no2-pollution/basic-information-about-no2.
US EPA, OAR, 2016b. Health and Environmental Effects of Particulate Matter (PM). Overviews and Factsheets. https://www.epa.gov/pm-pollution/health-and-environmental-effects-particulate-matter-pm. (Accessed 26 April 2016).
US EPA, OAR, 2015. Ground-Level Ozone Basics. Overviews and Factsheets. https://www.epa.gov/ground-level-ozone-pollution/ground-level-ozone-basics. (Accessed 29 May 2015).
Volkow, Nora D., George, F. Koob, Croyle, Robert T., Bianchi, Diana W., Gordon, Joshua A., Koroshetz, Walter J., Pérez-Stable, Eliseo J., et al., 2018. The conception of the ABCD study: from substance use to a broad NIH collaboration. Developmental Cognitive Neuroscience, The Adolescent Brain Cognitive Development (ABCD) Consortium: Rationale, Aims, and Assessment Strategy 32 (August), 4–7. https://doi.org/10.1016/j.dcn.2017.10.002.
Von Der Heide, Rebecca J., Skipper, Laura M., Klobusicky, Elizabeth, Olson, Ingrid R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 136 (6), 1692–1707. https://doi.org/10.1093/brain/awt094.
Wei, Yanyan, Wang, Tingting, Li, Guoguang, Feng, Junhui, Deng, Lianbang, Xu, Haiting, Yin, Lu, Ma, Jinbao, Chen, Dongning, Chen, Jingxu, 2022. Investigation of systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. Front. Psychiatr. 13. https://www.frontiersin.org/articles/10.3389/fpsyt.2022.941728.
Wei, Chan-Juan, Xue, Juan-Juan, Zhou, Xiao, Xia, Xiao-Shuang, Li, Xin, 2023. Systemic immune-inflammation index is a prognostic predictor for patients with acute ischemic stroke treated with intravenous thrombolysis. Neurol. https://doi.org/10.1097/NRL.0000000000000508. June.
White, Nathan S., Leergaard, Trygve B., D'Arceuil, Helen, Bjaalie, Jan G., Dale, Anders M., 2013. Probing tissue microstructure with restriction spectrum imaging: histological and theoretical validation. Hum. Brain Mapp. 34 (2), 327–346. https://doi.org/10.1002/hbm.21454.
Wilkinson, Nicole M., Chen, Ho-Chung, Lechner, Melissa G., Su, Maureen A., 2022. Sex differences in immunity. Annu. Rev. Immunol. 40 (1), 75–94. https://doi.org/10.1146/annurev-immunol-101320-125133.
Xiao, Yining, Teng, Zhenjie, Xu, Jing, Qi, Qianqian, Guan, Tianyuan, Jiang, Xin, Chen, Huifang, Xie, Xiaohua, Dong, Yanhong, Lv, Peiyuan, 2023. Systemic immune-inflammation index is associated with cerebral small vessel disease burden and cognitive impairment. Neuropsychiatric Dis. Treat. 19 (February), 403–413. https://doi.org/10.2147/NDT.S401098.
Yan, Wei, Ji, Xiaotong, Shi, Jing, Li, Guangke, Sang, Nan, 2015. Acute nitrogen dioxide inhalation induces mitochondrial dysfunction in rat brain. Environ. Res. 138 (April), 416–424. https://doi.org/10.1016/j.envres.2015.02.022.
Yeo, B. T. Thomas, Krienen, Fenna M., Sepulcre, Jorge, Sabuncu, Mert R., Lashkari, Danial, Hollinshead, Marisa, Roffman, Joshua L., et al., 2011. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (3), 1125–1165. https://doi.org/10.1152/jn.00338.2011.
Zahorec, R., 2021. Neutrophil-to-Lymphocyte ratio, past, present and future perspectives. Bratisl. Lek. Listy 122 (7), 474–488. https://doi.org/10.4149/BLL_2021_078.
Zhang, Shaocheng, Huo, Xia, Zhang, Yu, Huang, Yu, Zheng, Xiangbin, Xu, Xijin, 2019. Ambient fine particulate matter inhibits innate airway antimicrobial activity in preschool children in E-waste areas. Environ. Int. 123 (February), 535–542. https://doi.org/10.1016/j.envint.2018.12.061.
Zhang, Honglong, Yan, Jun, Niu, Jingping, Wang, Haiping, Li, Xun, 2022. Association between lead and cadmium Co-exposure and systemic immune inflammation in residents living near a mining and smelting area in NW China. Chemosphere 287 (January), 132190. https://doi.org/10.1016/j.chemosphere.2021.132190.
Zhao, Ji, Lv, Haichen, Yin, Da, Zhou, Xuchen, Zhu, Hao, Guo, Lei, Wang, Junjie, 2022a. Systemic immune-inflammation index predicts long-term outcomes in patients with three-vessel coronary disease after revascularization: results from a large cohort of 3561 patients. J. Inflamm. Res. 15 (September), 5283–5292. https://doi.org/10.2147/JIR.S385990.
Zhao, Lei, Liu, Miao, Liu, Linlin, Guo, Wenting, Yang, Huihua, Chen, Shuang, Yu, Jie, et al., 2022b. The association of Co-exposure to polycyclic aromatic hydrocarbon and phthalates with blood cell-based inflammatory biomarkers in children: a panel study. Environ. Pollut. 307 (August), 119479 https://doi.org/10.1016/j.envpol.2022.119479. Barking, Essex: 1987.