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Residential ambient air pollution exposure and the development of white matter microstructure throughout adolescence

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ABSTRACT

Background: Recent evidence suggests an association of air pollution exposure with brain development, but evidence on white matter microstructure in children is scarce. We investigated how air pollution exposure during pregnancy and childhood impacts longitudinal development of white matter microstructure throughout adolescence.

Methods: Our study population consisted of 4108 participants of Generation R, a large population-based birth cohort from Rotterdam, the Netherlands. Residential air pollution exposure to 14 air pollutants during pregnancy and childhood was estimated with land-use regression models. Diffusion tensor images were obtained around age 10 and 14, resulting in a total of 5422 useable scans (n = 3082 for wave 1 and n = 2340 for wave 2; n = 1314 for participants with data on both waves). We calculated whole-brain fractional anisotropy (FA) and mean diffusivity (MD) and performed single- and multi-pollutant analyses using mixed effects models adjusted for life-style and socioeconomic status variables.

Results: Higher exposure to $PM_{2.5}$ during pregnancy, and PM_{10}, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_X during childhood was associated with a consistently lower whole-brain FA throughout adolescence (e.g. -0.07×10^{-2} FA [95%CI -0.12; −0.02] per 1 standard deviation higher $PM_{2.5}$ exposure during pregnancy). Higher exposure to silicon (Si) in $PM_{2.5}$ and oxidative potential of $PM_{2.5}$ during pregnancy, and $PM_{2.5}$ during childhood was associated with an initial higher MD followed by a faster decrease in MD throughout adolescence (e.g. -0.02×10^{-5} mm^2/s MD [95%CI -0.03; −0.00] per year of age per 1 standard deviation higher Si exposure during pregnancy). Results were comparable when performing the analysis in children with complete data on the outcome for both neuroimaging assessments.

Conclusions: Exposure to several pollutants was associated with a consistently lower whole-brain FA throughout adolescence. The association of few pollutants with whole-brain MD at baseline attenuated throughout adolescence. These findings suggest both persistent and age-limited associations of air pollution exposure with white matter microstructure.

1. Introduction

Accumulating evidence suggests that exposure to air pollution affects neurodevelopment (Volk et al., 2021). Previous studies have shown that air pollutants can both trigger local neuroinflammation and oxidative stress in the brain, and lead to prolonged activation of the hypothalamus-pituitary-adrenal axis (Levesque et al., 2011; Thomson, 2019). Furthermore, exposure to pollutants has been suggested to alter placenta functioning in utero, including a decrease in the expression of placental genes implicated in fetal neurodevelopment (Bongaerts et al., 2022; Bové et al., 2019; Saenen et al., 2015, 2019). Research also showed that nanoparticles were present in fetal brains exposed to high

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air pollution levels (Calderón-Garcidueñas et al., 2022). Children are likely especially vulnerable to the adverse effects of air pollution due to a lack of mitigation abilities and due to the continuous neurodevelopment taking place (Grandjean and Landrigan, 2014).

Diffusion Tensor Imaging (DTI) allows visualisation of white matter tracts by detecting the magnitude and direction of water molecule diffusion. White matter tracts play a central role in learning processes, overall brain functioning, and communication between distal brain regions. Fiber architecture and organization of white matter tracts are mainly determined in utero, while myelination of fibers occurs primarily after birth and continues throughout childhood and adolescence (Dean et al., 2017; Dubois et al., 2014). Water molecules move more freely along the axis of a white matter tract, leading to directional oriented diffusion (i.e., anisotropic), while substances such as cerebrospinal fluid allow for freer diffusion of water molecules in all directions (i.e., isotropic). Two primary scalar measures of DTI are i) fractional anisotropy (FA), in which higher values indicate more anisotropic diffusion, and ii) mean diffusivity (MD), in which higher values indicate higher magnitude of diffusion, regardless of directionality.

Previous studies that looked at air pollution exposure and white matter DTI microstructure in children found conflicting results. A large study in the United States showed that higher levels of outdoor residential $PM_{2.5}$ were cross-sectionally associated with lower MD in several white matter tracts in 9- to 10-year-olds (Burnor et al., 2021). Children aged 8–12 years exposed to higher outdoor Copper (Cu) levels in $PM_{2.5}$ in Spanish schools showed higher FA in the caudate nucleus, but for nitrogen dioxide (NO_2) and elemental carbon (EC) no association was found (Pujol et al., 2016). Our previous work indicated that higher outdoor residential exposure to several pollutants, including $PM_{2.5}$, was associated with lower whole-brain FA and higher whole-brain MD in 9- to 12-year-olds from the Netherlands (Lubczyńska et al., 2020). Current literature only comprises studies that measured white matter microstructure at one time-point and lacks evidence on the effect of the constituents of $PM_{2.5}$ on white matter microstructure. A study design which follows participants throughout childhood and includes two neuroimaging assessments for each child would shed new light on whether the associations between air pollution and changes in white matter microstructure, persist, attenuate or worsen as white matter matures throughout childhood.

To our knowledge, this is the first study that aims to investigate the association between air pollution exposure and change in white matter microstructure in adolescence, with two neuroimaging assessments. We consider both pregnancy and childhood as exposure periods of air pollution and include fourteen different types of air pollutants.

2. Methods

2.1. Study design and population

We used data from the Generation R Study, a population-based birth cohort from Rotterdam, The Netherlands, which investigates children's health from fetal life onwards. A total of 9778 women were included and children were born between April 2002 and January 2006. All children were invited for neuroimaging assessments at median age 9.9 (range 8.6–13.0; wave 1) and 13.8 (range 12.6–17.1; wave 2). Air pollution and good quality neuroimaging data for at least one neuroimaging assessment were available for 4108 children: 3082 for wave 1 and 2340 for wave 2 (Fig. S1). This resulted in a total of 5422 good quality neuroimaging scans for children with air pollution data. For 1314 children data were available for both neuroimaging assessments. Not all children had data for both neuroimaging assessments, because they either choose to participate in only one assessment or because they did not have good quality neuroimaging scans for both neuroimaging assessments (e.g. due to the presence of dental braces). The study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants and their parents.

2.2. Exposures

The process used for the estimation of air pollutant concentrations at the home addresses of the participants with land-use regression models was previously described in detail by Guxens et al. (2022) and is summarized in Methods S1. For this study we used outdoor residential concentrations of particulate matter (PM) with aerodynamic diameter <10 μm (PM_{10}), <2.5 μm ($PM_{2.5}$), and between 10 μm and 2.5 μm ($PM_{2.5\text{-}10}$), the absorbance of $PM_{2.5}$ fraction ($PM_{2.5}$ absorbance), nitrogen dioxide (NO_2), nitrogen oxides (NO_x), the composition of $PM_{2.5}$, which consisted of polycyclic aromatic hydrocarbons (PAHs), organic carbon (OC), copper (Cu), iron (Fe), silicon (Si) and zinc (Zn), and the oxidative potential of $PM_{2.5}$ (OP), measured by two acellular methods (i.e., dithiothreitol (OP^{DTT}) and electron spin resonance (OP^{ESR})). We considered mean exposure to each air pollutant during pregnancy (i.e., from conception until birth) and during childhood (i.e., the period between birth and the first neuroimaging assessment) for each child, taking into account the changes in residences. Of note, a total of 2818 children (69% of study population) moved home address at least once between birth and the first neuroimaging assessment.

2.3. Magnetic resonance imaging

2.3.1. Image acquisition

Both neuroimaging assessments were done with a 3 T General Electric scanner (MR750W; GE) with an 8-channel receive-only head coil as previously described by White et al. (2018). The diffusion tensor imaging data were collected with an axial spin echo with 35-direction echo planar imaging sequence (see Methods S2 for full sequence parameters).

2.3.2. Image preprocessing and probalistic tractography

Preprocessing of the images was done using the FMRIB Software Library (FSL, v6.0.2) and the Camino diffusion MRI toolkit, as previously described by Dall'Aglio et al. (2023). Average weighted FA, MD, radial diffusivity (RD), and axial diffusivity (AD) values were calculated for each white matter tract. FA, capturing the amount of directional oriented diffusion of water molecules, and MD, capturing the total magnitude of diffusion of water molecules, were used for the main analyses. A loss of white matter microstructure organization is typically characterized by lower FA and higher MD values. As a follow-up analysis we included RD and AD, to gain insights into underlying pathophysiological mechanisms. RD describes the magnitude of the diffusion of water molecules perpendicular to the white matter tract, while AD describes the mean diffusion of water molecules parallel to the white matter tract. Generally speaking, higher RD suggests a loss of myelination, while lower AD suggests a loss of axonal structure. Then, 12 commonly defined white matter tracts were selected, namely the superior longitudinal fasciculus, inferior longitudinal fasciculus, corticospinal tract, cingulum bundle, uncinate fasciculus (one per hemisphere thus 10 in total), and the forceps major and the forceps minor (interhemispheric thus 2 in total). Based on the size of each tract, a weighted mean FA, MD, RD, and AD of the 12 tracts was calculated (Table S1).

2.3.3. Data quality assessment

Data quality assessment of raw images was performed using both visual inspection and automated software. For more information on this process see Dall'Aglio et al. (2023).

2.4. Statistical analysis

We first imputed missing values of the co-variates for all participants in our study population and created 25 complete datasets using the mice package from R (Spratt et al., 2010; Sterne et al., 2009). All co-variates

had less than 30% missing values except paternal education (37.4%) and maternal folic acid use (30.5%) (Table S2). Imputed and observed values were similar (data not shown). Parents of children included had an overall higher socioeconomic status, so we used inverse probability weighting in all analyses to mitigate potential selection bias (Table S2, Fig. S2) (Weisskopf et al., 2015; Weuve et al., 2012).

To investigate the association between each air pollutant and whole-brain FA and MD we used two approaches. First, we investigated whether exposure to each air pollutant was associated with a consistent lower or higher whole-brain FA and MD over both timepoints (Model $_{\text{overall associations}}$, Methods S3) to see whether there were persistent associations of air pollution exposure with white matter microstructure. We ran 56 single-pollutant analyses, using separate linear mixed models for each exposure period (i.e., exposure during pregnancy and exposure from birth to the first neuroimaging assessment) of each air pollutant with whole-brain FA and MD. Models included FA and MD at both timepoints and a random intercept for participant to take into account the within-subject correlation due to the repeated measures nature of our study. All models were adjusted for covariates selected based on a directed acyclic graph (Guxens et al., 2018), including child's sex, age and season of birth, maternal and paternal age at enrolment, national origin and education level, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status of the neighborhood, based on mean household income of the neighborhood, and proportion of households with low income, low educational level, and without paid work (NIPHE, 2017), and greenness, estimated with the Normalized Difference Vegetation Index (NDVI) in the surrounding area of 300 m of maternal home addresses (Fig. S3). NDVI represents the degree of land surface reflectance of light and was estimated using the Landsat 4–5 Thematic Mapper (TM), Landsat 7 Enhanced Thematic Mapper Plus (ETM+), and Landsat 8 Operational Land Imager (OLI)/-Thermal Infrared Sensor (TIRS) with 30m × 30m resolution. We used images from the greenest period of the year, only selected images with cloud cover less than 10%, and applied Standard Terrain Correction (Level 1T). Greenness was estimated from conception to birth for the pregnancy exposure models, and from birth to the age of the first neuroimaging assessment for the childhood exposure models. We selected a buffer of 300 m following the recommendation by the World Health Organization to provide access for everyone to at least 2 ha of green space within 300 m linear distance (corresponding to approximately 5 min' walk) (World Health Organization, 2016). Second, we ran the same linear mixed models with an interaction term between each air pollutant and age, which allowed us to investigate how exposure to each air pollutant was associated with a change in whole-brain FA and MD development with age (i.e. a faster or slower increase/decrease with age) (Model $_{\text{overall associations}}$, Methods S3). We centered age at the 5th percentile of age (9.6 years) to see whether a participant had lower or higher FA and MD at baseline. Assumptions for linear mixed models were fulfilled in all analyses (i.e., linearity between the exposure and outcome, normality of the residuals, homoscedasticity, and no collinearity). Finally, we performed the following sensitivity analyses to address potential bias related to how missing data are handled by the linear mixed models and the inclusion of air pollution exposure up until the first MRI only: (i) we imputed missing data in the outcome for those participants with data for only one of the neuroimaging assessments, using the mice package from R to generate 25 complete datasets (N = 4108 participants and 5422 scans) (Spratt et al., 2010; Sterne et al., 2009), (ii) we restricted the analyses to those participants with complete data on the exposure and outcome for both neuroimaging assessments only (N = 1314 participants and 2628 scans), and (iii) we restricted the analyses to those participants that had not moved home address in between the first and second neuroimaging assessment (N = 3437 participants and 4535 scans).

Next, we performed a multi-pollutant analysis for the main outcomes (i.e., whole-brain FA and MD) with which we observed an association in the single-pollutant analyses, using the Least Absolute Shrinkage and Selection Operator (LASSO) for mixed models. LASSO is a shrinkage model that takes the correlation between exposures into account. It aids in identifying those pollutants which explain the most variance in your outcome after accounting for all other pollutants, by penalizing certain variables of the model towards zero, based on the regularization parameters in the model (i.e. the lambda parameter). In all models, only the exposures and interaction terms between exposure and age (i.e., indicating an association with change) were penalized. Models were run separately for exposure during pregnancy and childhood. LASSO is merely a variable-selection model, but has previously been shown to have a relatively low false discovery rate in comparison to the Bonferroni-type correction or other multi-pollutant models and it can be utilized with linear mixed models (Agier et al., 2016). We only interpreted those associations that remained in the multi-pollutant analyses and therefore did not correct the single-pollutant analyses with a formal multiple testing correction method.

As follow-up analyses, in case we observed an association between air pollution and whole-brain FA in the multi-pollutant analyses, we explored how the identified pollutant was associated with whole-brain RD and AD, to gain insights into the underlying pathophysiological mechanism. Additionally, in the case that an association was found between a specific pollutant and whole-brain FA or MD in the multi-pollutant analyses, linear mixed models were run for each of the twelve white matter tracts to investigate whether the association showed regional specificity.

Finally, to account for multiple testing over the two main outcomes (whole brain FA and MD), we calculated the number of effective tests, following the method that was recommended by Galwey (2009). In short, this method calculates the number of effective tests by extracting eigenvalues from individual-level matrix of phenotype data, which led to a number of effective tests of 1.75 for the two main outcomes. We then divided $p < 0.05$ by the number of effective tests (1.75), which resulted in a corrected p-value of <0.03. All statistical analyses were carried out using R (version 4.0.3; R Development Core Team).

3. Results

3.1. Descriptive results

The majority of mothers in our study population were of Dutch national origin (56.1%) and had never smoked during pregnancy (72.5%) (Table 1). Median air pollution exposure during pregnancy was 17.1 μg/m^3 for $PM_{2.5}$, 1.6 × 10^{-5m-1} for $PM_{2.5}$ absorbance and 33.9 μg/m^3 for NO_2 (Table 2). Concentrations were slightly lower during childhood. Correlations between air pollutants varied between 0.01 ($PM_{2.5}$ and PAH in $PM_{2.5}$) and 0.95 (PM_{10} and $PM_{2.5}$ absorbance) (Fig. S4).

Overall associations: stable association between air pollution exposure and white matter microstructure over time (Model $_{\text{overall associations}}$)

In the single-pollutant analyses we observed an association of higher exposure to several pollutants during pregnancy and childhood with a consistently lower whole-brain FA over the two neuroimaging assessments. In the multi-pollutant analyses, higher exposure to $PM_{2.5}$ during pregnancy, and PM_{10}, $PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_X during childhood remained associated with a consistently lower whole-brain FA, after correction for multiple testing over the outcomes (e.g. –0.07 × 10^{-2} FA [95% CI −0.12; −0.02] per 1 standard deviation (SD) higher $PM_{2.5}$ exposure during pregnancy) (N = 4108 participants and 5422 scans) (Table 3, Fig. S5). No associations were found for exposure to Cu, Fe, Si, Zn, PAH, OC, OP^{DTT} and OP^{ESR}. Exposure to air pollution was not associated with a consistent difference in whole-brain MD over the two timepoints. Follow-up analyses showed that higher exposure to $PM_{2.5}$, $PM_{2.5\text{-}10}$, and NO_X during childhood was associated with higher whole-brain RD, but not with whole-brain AD (Table S3). Although the above-mentioned associations did not reach significance in all of the white

Table 1
Characteristics of the study participants (N = 4108).

Participant characteristics	Distribution
Maternal age at enrolment (years)	31.1 ± 4.9
Maternal national origin	
Dutch	56.1
Moroccan	5.4
Surinamese	8.0
Turkish	6.4
European, other	7.6
Non-European, other	16.4
Maternal educational level at enrolment	
Higher or above	49.5
Secondary	30.7
Primary or lower	19.8
Monthly household income at enrolment	
>2200€	58.3
1600–2200€	15.3
900-1600€	16.1
<900€	10.3
Marital status at enrolment	
Married	50.7
Living together	38.0
No partner	11.3
Maternal parity	
0 children	56.4
1 child	30.9
≥2 children	12.7
Maternal pre-pregnancy BMI (kg/m^2)	23.6 ± 4.2
Maternal alcohol use during pregnancy	
Never	41.9
Until pregnancy known	13.7
Occasional use during pregnancy	35.1
Frequent use during pregnancy	9.4
Maternal smoking during pregnancy	
Never	72.5
Until pregnancy known	8.8
Continued during pregnancy	18.7
Maternal folic acid use during pregnancy	
Start preconceptional	45.3
Start in the first 10 weeks of pregnancy	31.3
None periconceptional	23.4
Maternal intelligence quotient	96.9 ± 15.1
Socioeconomic status neighborhood during pregnancy	−0.9 ± 1.4
Residential greenness pregnancy	0.4 ± 0.1

Values are percentages for categorical variables, mean (standard deviation) for continuous variables.

matter tracts in the follow-up analyses, the pattern of associations suggests a global association (Fig. 1, Tables S4–S5).

Interaction associations: association between air pollution exposure and the change in white matter microstructure with age (Model $_{\text{interaction associations}}$)

Exposure to air pollution during pregnancy and childhood was not associated with a faster or slower increase in whole-brain FA with age (N = 4108 participants and 5422 scans) (Table S6). However, higher exposure to several pollutants was associated with higher whole-brain MD around age 10, followed by a faster decrease in MD (Table S7). In the multi-pollutant analyses and after correction for multiple testing, Si and OP^{DDT} in $PM_{2.5}$ during pregnancy and $PM_{2.5}$ during childhood were associated with a change in whole brain MD (e.g. -0.02×10^{-5} mm^2/s MD [95% CI −0.03; −0.00] per year of age per 1 SD higher Si exposure) (Fig. 2, Table S7). No associations were found for exposure to PM_{10}, PAH and OC. Although the above-mentioned associations reached significance in only the cingulate gyrus part of the cingulum and inferior longitudinal fasciculus of the left hemisphere, and the superior longitudinal fasciculus and uncinate fasciculus of both hemispheres (e.g. -0.02×10^{-5} mm^2/s MD for the left superior longitudinal fasciculus [95% CI -0.03; −0.00] per year of age per 1 SD higher Si exposure), the pattern of associations suggests a global association (Fig. 3, Tables S8–S9).

3.2. Sensitivity analyses

Results were comparable when using multiple imputation to generate 25 complete datasets of the outcomes before running the linear mixed models (N = 4108 participants and 5422 scans), when restricting the analyses to those participants with complete data on the exposure and outcome for both neuroimaging assessments (N = 1314 participants and 2628 scans), and when restricting the analyses to those children that did not move home address in between the 2 neuroimaging assessments (N = 3437 participants and 4535 scans) (Tables S10–12).

4. Discussion

This is the first population-based birth cohort to our knowledge that investigated how air pollution exposure during both pregnancy and childhood was associated with longitudinal development of white matter microstructure across adolescence. We have demonstrated an association of higher exposure to $PM_{2.5}$ during pregnancy, and higher exposure to $PM_{2.5}$, PM_{10}, $PM_{2.5\text{-}10}$, and NO_X during childhood with a

Table 2
Air pollution exposure concentrations during pregnancy and childhood (N = 4108 participants).

	Pregnancy				Childhood				Spearman's correlation
	median	p25	p75	mean (SD)	median	p25	p75	mean (SD)	
PM_{10} (μg/m^3)	27.1	26.3	29.0	27.8 (2.1)	26.6	25.9	28.0	27.1 (1.9)	0.55
$PM_{2.5}$ (μg/m^3)	17.1	16.6	17.7	17.3 (0.8)	16.9	16.6	17.4	17.1 (0.6)	0.64
$PM_{2.5\text{-}10}$ (μg/m^3)	10.7	9.8	11.2	10.4 (1.2)	10.1	8.9	10.8	9.9 (1.2)	0.53
$PM_{2.5}$ absorbance (10^{-5m-1})	1.6	1.5	1.8	1.7 (0.3)	1.5	1.4	1.7	1.6 (0.2)	0.52
NO_2 (μg/m^3)	33.9	31.2	37.6	34.8 (5.4)	32.0	29.1	35.3	32.3 (5.3)	0.49
NO_X (μg/m^3)	50.8	43.5	69.8	57.1 (18.0)	46.4	40.8	58.4	51.4 (16.0)	0.57
Cu (ng/m^3)	4.6	4.5	5.0	4.8 (0.9)	4.5	4.2	4.8	4.6 (0.7)	0.53
Fe (ng/m$^{3)}$	119.7	114.1	129.0	124.1 (21.0)	116.7	107.0	124.6	116.8 (19.5)	0.52
Si (ng/m$^{3)}$	88.8	87.9	90.7	92.9 (14.2)	88.7	87.6	90.6	91.4 (11.6)	0.60
Zn (ng/m$^{3)}$	19.5	17.9	23.8	21.6 (5.4)	19.3	17.8	22.5	21.0 (5.2)	0.59
PAH (ng/m$^{3)}$	0.9	0.8	1.1	0.9 (0.3)	0.9	0.8	1.1	0.9 (0.2)	0.67
OC (μg/m^3)	1.8	1.5	2.0	1.7 (0.4)	1.6	1.4	1.9	1.6 (0.4)	0.60
OP^{DTT} (nmol DTT/min/m^3)	1.3	1.2	1.3	1.2 (0.1)	1.2	1.2	1.3	1.2 (0.1)	0.61
OP^{ESR} (units/m^3)	1046.6	1008.4	1119.1	1101.2 (191.0)	1027.0	973.9	1091.9	1049.0 (146.4)	0.58

Abbreviations: Cu, elemental copper; Fe, elemental iron; NO_X, nitrogen oxides; NO_2, nitrogen dioxide; OC, organic carbon; OP, oxidative potential (evaluated using two acellular methods: OP^{DTT}, dithiothreitol and OPESR, electron spin resonance); p25, 25th percentile; p75, 75th percentile; PAH, polycyclic aromatic hydrocarbons; PM, particulate matter with different aerodynamic diameters: less than 10 μm (PM_{10}); between 10 μm and 2.5 μm ($PM_{2.5\text{-}10}$); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$ absorbance, absorbance of $PM_{2.5}$ filters; SD, standard deviation; Si, elemental silicon; Zn, elemental zinc. We considered mean exposure to each air pollutant during pregnancy (i.e., from conception until birth) and during childhood (i.e., the period between birth and the first neuroimaging assessment) for each child, taking into account the changes in residences.

Table 3
Model $_{\text{overall association}}$: Adjusted beta estimates of each air pollutant with whole-brain fractional anisotropy and mean diffusivity for exposure during pregnancy and childhood (N = 4108 participants and 5422 scans).

	FA (10^{-2}) beta [95% CI]	p-value	MD (10^{-5} mm^2/s) beta [95% CI]	p-value
Pregnancy				
PM_{10} (Δ 2.1 μg/m^3)	**−0.05 [-0.11; 0.00]** [a]	**0.039**	0.01 [-0.05; 0.08]	0.666
$PM_{2.5}$ (Δ 0.8 μg/m^3)	**−0.07 [-0.12; -0.02]** [b]	**0.007**	0.02 [-0.04; 0.08]	0.462
$PM_{2.5\text{-}10}$ (Δ 1.2 μg/m^3)	−0.05 [-0.10; 0.01]	0.083	0.03 [-0.03; 0.10]	0.356
$PM_{2.5}$ absorbance (0.3 × 10^{-5m-1})	**−0.07 [-0.12; -0.01]**	**0.013**	0.03 [-0.03; 0.09]	0.319
NO_2 (Δ 5.4 μg/m^3)	−0.04 [-0.09; 0.01]	0.136	0.02 [-0.04; 0.09]	0.459
NO_X (Δ 18.0 μg/m^3)	−0.05 [-0.10; 0.00]	0.057	0.02 [-0.04; 0.08]	0.536
Cu (Δ 0.9 ng/m^3)	−0.04 [-0.09; 0.02]	0.174	0.02 [-0.04; 0.08]	0.468
Fe (Δ 21.0 ng/m^3)	−0.02 [-0.08; 0.03]	0.348	0.04 [-0.02; 0.10]	0.222
Si (Δ 14.2 ng/m^3)	−0.03 [-0.08; 0.02]	0.228	0.04 [-0.02; 0.10]	0.180
Zn (Δ 5.4 ng/m^3)	−0.03 [-0.08; 0.02]	0.274	0.02 [-0.04; 0.08]	0.511
PAH (Δ 0.3 ng/m^3)	−0.01 [-0.06; 0.05]	0.839	−0.02 [-0.08; 0.04]	0.571
OC (Δ 0.4 μg/m^3)	−0.03 [-0.08; 0.02]	0.282	0.05 [-0.01; 0.11]	0.124
OP^{DTT} (Δ 0.1 nmol DTT/min/m^3)	0.00 [-0.05; 0.06] [a]	0.950	0.02 [-0.05; 0.09]	0.521
OP^{ESR} (Δ 191.0 units/m^3)	−0.03 [-0.08; 0.03]	0.317	0.03 [-0.03; 0.09]	0.302
Childhood				
PM_{10} (Δ 1.9 μg/m^3)	**−0.06 [-0.11; -0.01]** [b]	**0.013**	0.03 [-0.03; 0.09]	0.266
$PM_{2.5}$ (Δ 0.6 μg/m^3)	**−0.07 [-0.12; -0.02]** [b]	**0.009**	0.05 [-0.01; 0.11]	0.131
$PM_{2.5\text{-}10}$ (Δ 1.2 μg/m^3)	**−0.08 [-0.13; -0.02]** [b]	**0.007**	0.06 [-0.01; 0.12]	0.086
$PM_{2.5}$ absorbance (0.2 × 10^{-5m-1})	**−0.06 [-0.11; -0.00]** [a]	**0.032**	0.04 [-0.02; 0.10]	0.208
NO_2 (Δ 5.3 μg/m^3)	**−0.06 [-0.11; 0.00]** [a]	**0.040**	0.03 [-0.03; 0.09]	0.356
NO_X (Δ 16.0 μg/m^3)	**−0.07 [-0.12; -0.02]** [b]	**0.006**	0.05 [-0.01; 0.11]	0.122
Cu (Δ 0.7 ng/m^3)	−0.02 [-0.07; 0.03] [a]	0.414	0.00 [-0.06; 0.06]	0.931
Fe (Δ 19.5 ng/m^3)	−0.03 [-0.08; 0.02]	0.272	0.01 [-0.05; 0.07]	0.805
Si (Δ 11.6 ng/m^3)	−0.03 [-0.08; 0.02]	0.295	0.01 [-0.05; 0.07]	0.640
Zn (Δ 5.2 ng/m^3)	−0.03 [-0.08; 0.02]	0.229	0.06 [0.00; 0.12]	0.054
PAH (Δ 0.2 ng/m^3)	0.03 [-0.02; 0.08] [a]	0.259	−0.02 [-0.08; 0.05]	0.627
OC (Δ 0.4 μg/m^3)	−0.04 [-0.10; 0.01] [a]	0.113	0.05 [-0.01; 0.11]	0.134
OP^{DTT} (Δ 0.1 nmol DTT/min/m^3)	−0.01 [-0.07; 0.05] [a]	0.663	0.01 [-0.06; 0.08]	0.793
OP^{ESR} (Δ 146.4 units/m^3)	−0.01 [-0.06; 0.04] [a]	0.656	0.02 [-0.04; 0.08]	0.536

Abbreviations: Cu, elemental copper; FA, fractional anisotropy; Fe, elemental iron; MD, mean diffusivity; NO_X, nitrogen oxides; NO_2, nitrogen dioxide; OC, organic carbon; OP, oxidative potential (evaluated using two acellular methods: OP^{DTT}, dithiothreitol and OP^{ESR}, electron spin resonance); PAH, polycyclic aromatic hydrocarbons; PM, particulate matter with different aerodynamic diameters: less than 10 μm (PM_{10}); between 10 μm and 2.5 μm ($PM_{2.5\text{-}10}$); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$ absorbance, absorbance of $PM_{2.5}$ filters; Si, elemental silicon; Zn, elemental zinc. Beta coefficients and 95% CI from linear mixed models, including a random intercept for participant and adjusted for child's sex, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status neighborhood, and greenness. Beta estimates are reported per 1 standard deviation increase in exposure. Beta estimate of age in months was 0.013 × 10^{-2} in the model of exposure to $PM_{2.5}$ during pregnancy. In bold, associations with p-value <0.05.

[a] Associations that were selected by the LASSO.

[b] Associations that were selected by the LASSO and survived correction for multiple testing over the outcomes.

lower whole-brain FA throughout adolescence in an urban population. In contrast, children exposed to higher Si and OP^{DTT} in $PM_{2.5}$ during pregnancy, and $PM_{2.5}$ during childhood had higher whole-brain MD around age 10, but this difference was attenuated by the time of the second assessment at age 14. This suggests both persistent and age-limited associations of air pollution exposure with white matter microstructure.

Few studies have previously looked at the association between air pollution exposure and white matter microstructure in children (Burnor et al., 2021; Peterson et al., 2022; Pujol et al., 2016). Peterson et al. (2022) found that higher outdoor residential exposure to $PM_{2.5}$ and personal exposure to PAH during pregnancy was associated with higher FA in the basal ganglia, thalamus, and anterior cingulate gyrus in 6- to 14-year-olds, and Pujol et al. (2016) found that higher outdoor exposure to Cu in $PM_{2.5}$ at schools was associated with higher FA in the caudate nucleus in 8- to 12-year-olds. However, comparison with our results is difficult because we did not study these exact same regions. Furthermore, Pujol et al. (2016) considered air pollution exposure at schools, while we looked at residential air pollution exposure. A large cohort study from the United States did include a summed FA and MD value per hemisphere and found a cross-sectional association between residential exposure to $PM_{2.5}$ and lower MD for each hemisphere in children aged 10 years (Burnor et al., 2021), while no association was found for FA. The differences in $PM_{2.5}$ concentrations, $PM_{2.5}$ composition, genetics, and diffusion-MRI parameters might explain the discrepancies with our results.

Our previous research within the Generation R cohort indicated that exposure to several pollutants during pregnancy and childhood was associated with lower whole-brain FA in 9- to 12-year-olds (Lubczyńska et al., 2020), and in the current work we showed that these associations persisted at older ages. Myelination of axons, and axonal structure and packaging continuously develop throughout childhood and adolescence (Kostović and Jovanov-Milošević, 2006). Axon structure and packing density are believed to be the primary determinants of FA, although myelination does play a modulating role, and lower FA values generally indicate a loss of white matter organization (Beaulieu, 2002). We observed that the association between air pollution exposure and whole-brain FA was accompanied by higher RD, but not by a difference in AD. Since a reduction in myelination is related to an increase in perpendicular diffusion and trace diffusion (for which RD is an indicator), this could suggest that the association between air pollution exposure and lower whole-brain FA is more likely the result of changes in myelin than in axonal structure and packing density (for which AD is an indicator). Although the exact mechanism through

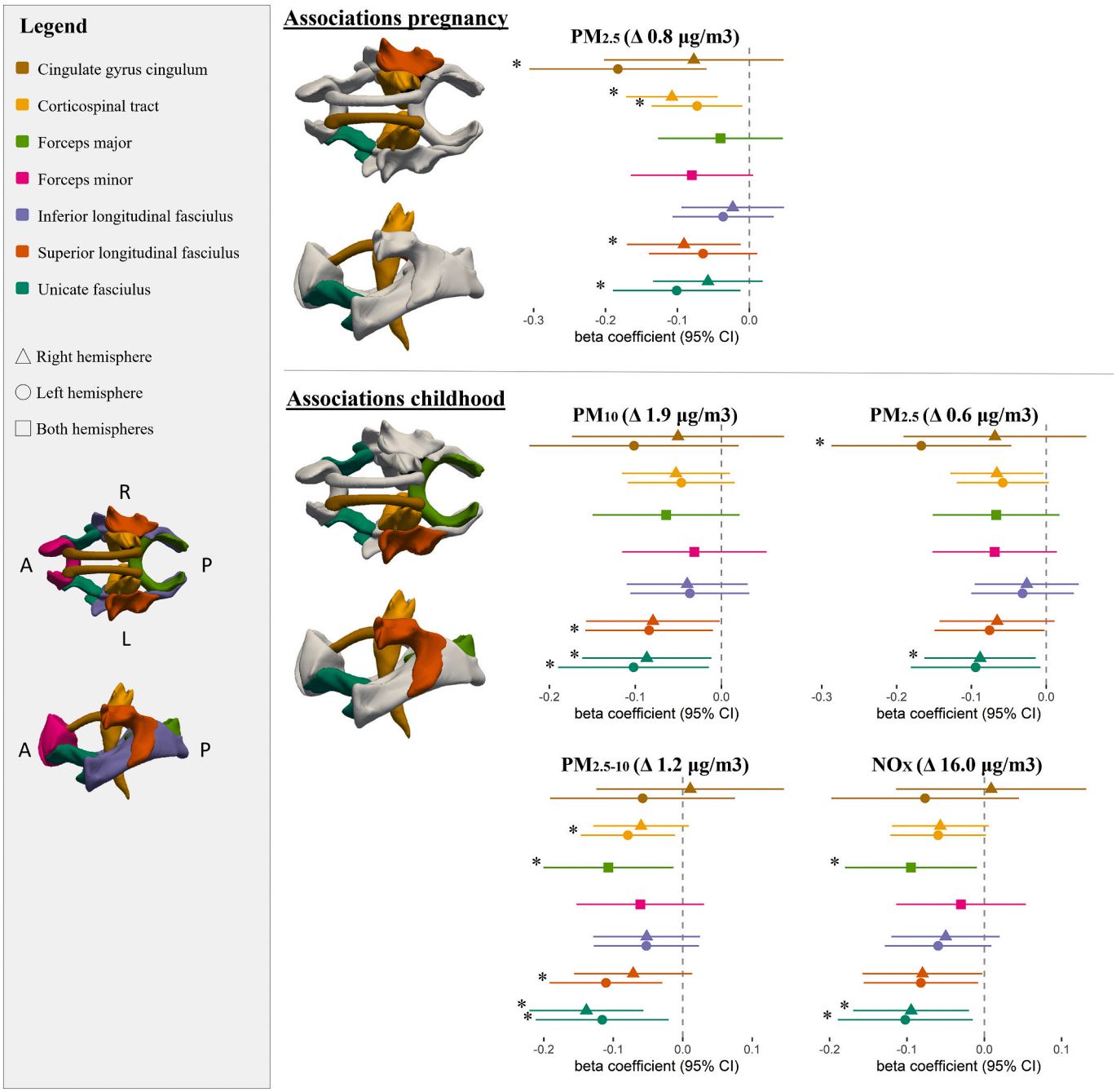

Fig. 1. Model $_{\text{overall association}}$: Adjusted linear regression analyses of fractional anisotropy in twelve individual white matter tracts in relation to exposure to $PM_{2.5}$ during pregnancy, and PM_{10}, $PM_{2.5}$, $PM_{2.5\text{-}10}$ and NO_X exposure during childhood (N=4108 participants and 5422 scans). Abbreviations: ; NO_X, nitrogen oxides; PM, particulate matter with different aerodynamic diameters: less than 10 µm (PM_{10}); between 10 µm and 2.5 µm ($PM_{2.5\text{-}10}$); less than 2.5 µm ($PM_{2.5}$). Beta coefficients and 95% CI from linear mixed models, including a random intercept for participant and adjusted for child's sex, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status neighborhood, and greenness. For wave 2, 5 and 6 scans were excluded for the corticospinal tract of the left and right hemisphere, respectively, due to insufficient data to calculate FA and MD. FA was multiplied by 10^2 to improve readability. *associations present at $p < 0.03$.

which pollution particles impact myelin are not yet fully understood, several mechanisms have been proposed through which air pollution might lead to neurodegeneration (Genc et al., 2012). Small particles could translocate to the brain directly or trigger the release of inflammatory mediators from entry organs like the lungs, which would lead to systemic inflammation and the release of proinflammatory cytokines (Levesque et al., 2011; Thomson, 2019). Together this could invoke neuroinflammation, oxidative stress, and protein aggregation, eventually leading to neuronal death. Indeed, research in animals suggests an effect of exposure to PM on the myelination of axons through either impairment of the maturation of myelin-producing oligodendrocytes or oxidative stress-mediated oligodendrocyte cell death (Morris et al., 2021).

In this study sample, we observed a 0.01×10^{-2} increase in FA for each 1-month increase in age. In comparison, we observed a 0.06–0.08 $\times 10^{-2}$ decrease in FA with each 1 SD increase in exposure to air

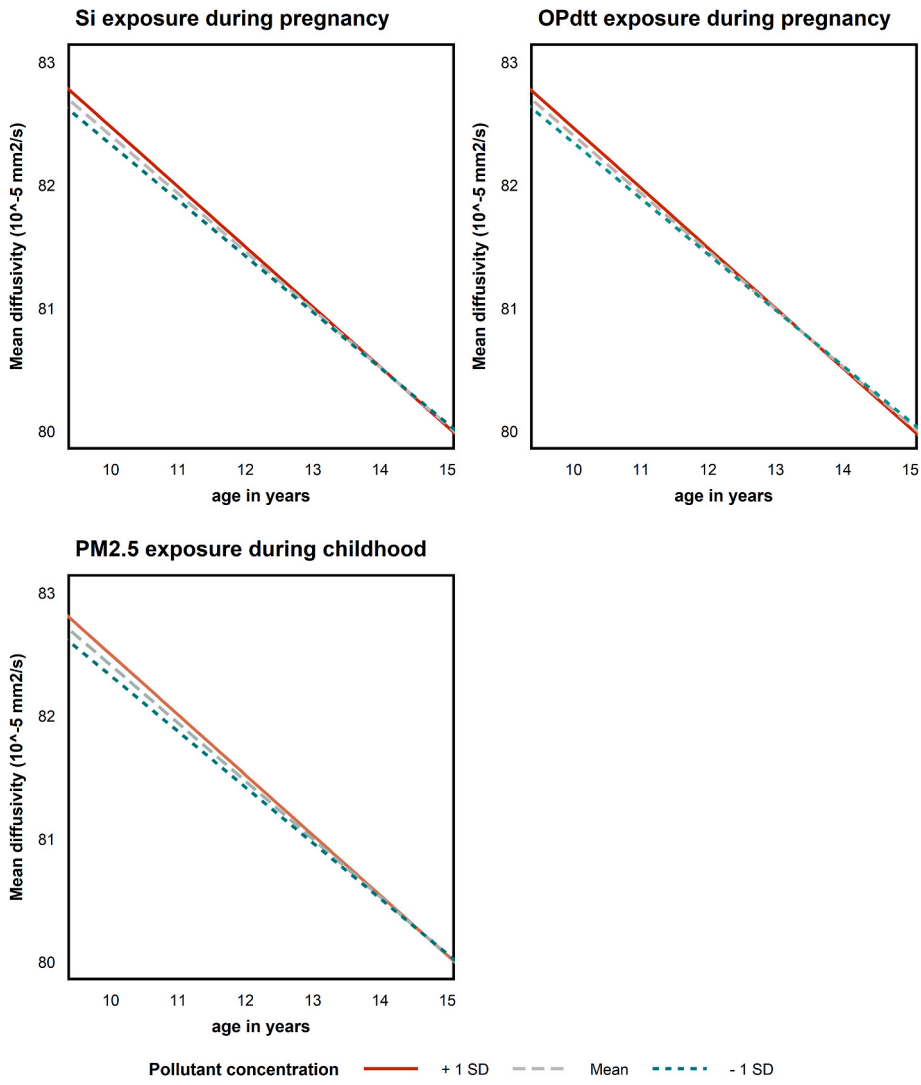

Fig. 2. Model $_{\text{interaction association}}$: Association of low and high Si in $PM_{2.5}$ and OP^{DTT} in $PM_{2.5}$ exposure during pregnancy, and $PM_{2.5}$ exposure during childhood (one standard deviation below and above the mean, respectively) with changes in predicted whole-brain mean diffusivity values from childhood into adolescence, based on the fully adjusted mixed-effects models (N=4108 participants and 5422 scans). Categorization into low and high air pollutant exposure was performed for depiction purposes only (i.e., metrics were not dichotomized in analyses). The x-axis depicts the 5 percentile – 95 percentile of age. Abbreviations: Si, elemental silicon; OP^{DTT}, oxidative potential evaluated using dithiothreitol; $PM_{2.5}$, particulate matter with aerodynamic diameters less than 2.5 μm; SD, standard deviation.

pollution, which represent more than a 5-month delay in the development of FA. We found significant associations for exposure to air pollution in multiple tracts, including the uncinate fasciculus, which plays a role in learning and memory (Von Der Heide et al., 2013), but the similar direction of estimates over all tracts suggests a more global association. Therefore, caution is warranted when drawing conclusions about regionally specific associations of air pollution with white matter microstructure and its functional implications. Still, we would like to stress that air pollution exposure associated delays in FA development, even if effects sizes were small, can potentially translate to meaningful impact on a population scale.

In our study population we also showed that the association of exposure to several pollutants during pregnancy and childhood with higher whole-brain MD at age 9–12 years attenuated as white matter tracts further developed throughout adolescence. At birth, the majority of axons are already in place and during the post-natal period a process of axonal pruning and myelination occurs, with myelination being known to continue far into adolescence (Kostović and Jovanov-Milošević, 2006). Increases in white matter volume with age are most likely originating from increases in axon calibre and/or thickness of the myelin sheath (Paus, 2010). Although children exposed to higher air pollution concentrations thus no longer had higher MD values around age 14, diverging from normal development by showing a faster decrease in MD might still have an adverse effect on brain functioning. Looking at the individual white matter tracts, we saw similar trends of a faster decrease in MD with age in all tracts, even though the interaction term of pollutant with age was not always significant. Future studies are warranted to investigate the potential impact of the faster decrease in MD seen in our study on neuropsychological functioning.

The main strength of this study is the longitudinal nature of the design with 2 repeated neuroimaging assessments. This allowed us to investigate the association between air pollution exposure during 2 time periods with the development of white matter microstructure with age in a large cohort. However, several limitations should be considered when interpreting our results. First, in our study we only included air pollution exposure concentrations estimated at the participant's residential address, due to data unavailability of air pollution concentrations at schools. Since children spend a significant part of their waking hours in schools, it would be interesting for future studies to consider both air pollution concentrations at schools and at home addresses.

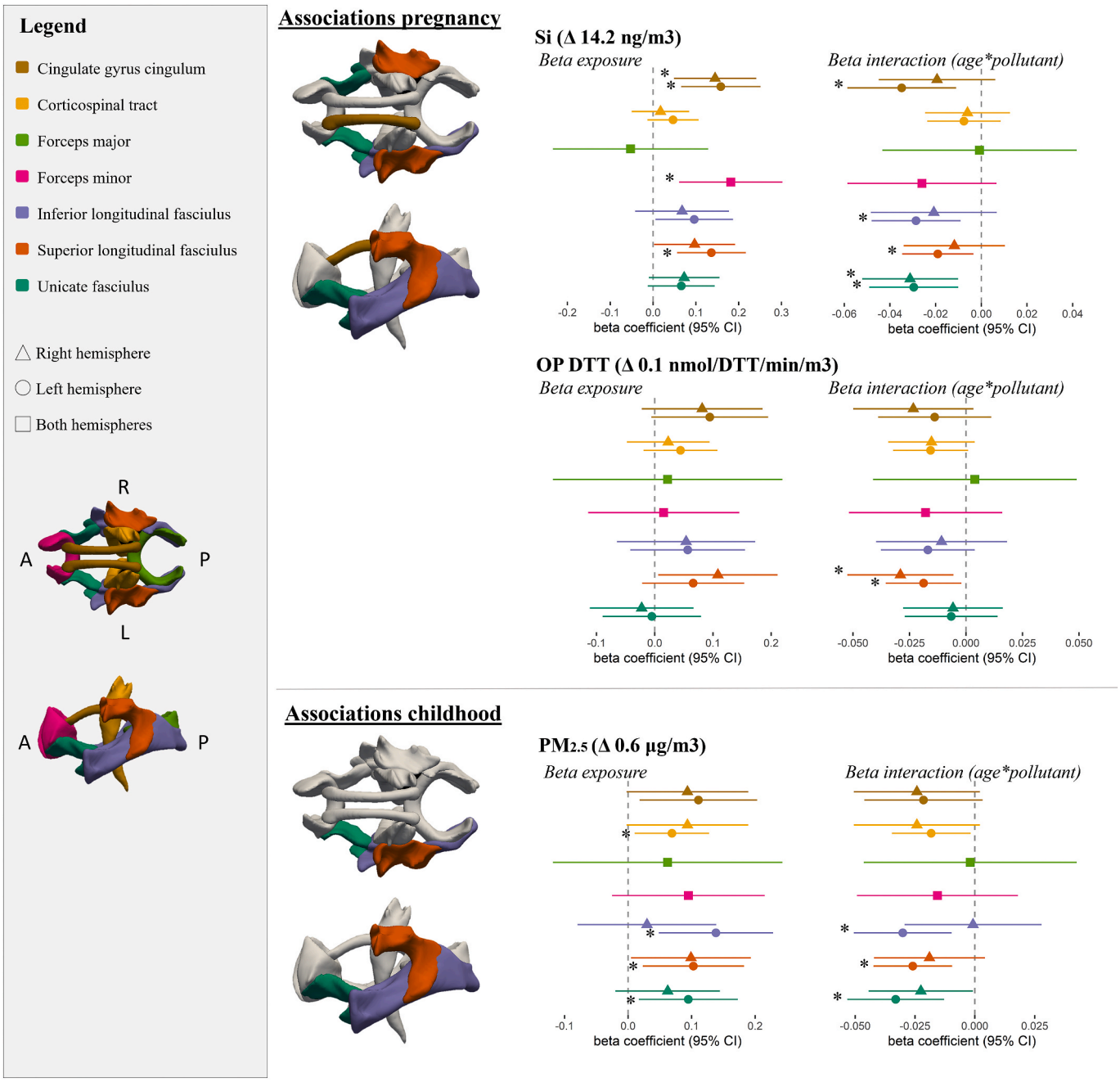

Fig. 3. Model $_{\text{interaction association}}$: Adjusted linear regression analyses of mean diffusivity in twelve individual white matter tracts in relation to exposure to Si and OP^{DTT} during pregnancy, and $PM_{2.5}$ exposure during childhood (N=4108 participants and 5422 scans). Abbreviations: OP^{DTT}, oxidative potential evaluated using dithiothreitol; PM, particulate matter with aerodynamic diameter less than 2.5 μm ($PM_{2.5}$); Si, elemental silicon. Beta coefficients and 95% CI from linear mixed models, including a random intercept for participant and adjusted for child's sex, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, socioeconomic status neighborhood, and greenness. Age was centered at the 5th percentile. For wave 2, 5 and 6 scans were excluded for the corticospinal tract of the left and right hemisphere, respectively, due to insufficient data to calculate FA and MD. MD was multiplied by 10^5 to improve readability. *associations present at $p < 0.03$.

Second, for the majority of children we did not have imaging data for both neuroimaging assessments and this might have introduced some bias. However, performing a complete case analysis with subjects that had data on both neuroimaging assessments indicated robustness of our results. Third, air pollution estimates were based on sampling measurements that took place during one year (i.e., between February 2009 and February 2010) when the participants were aged 3–9 years and we did not have sufficient historical pollutant data for all pollutants to perform back-extrapolation to the specific periods of interest (i.e., from conception until the first neuroimaging assessment which corresponded to the period between April 2002 and November 2015). Thus, we assumed that the spatial contrast remained stable over time. This assumption was supported by one study from the Netherlands that demonstrated this for a period up to 8 years (1999–2007) (Eeftens et al., 2011) and one from the United Kingdom for a period up to 18 years (1991–2009) (Gulliver et al., 2013). Lastly, in our study, we observed associations for only a selection of the investigated pollutants, even though all pollutants were indicators of traffic. This could be related to

characteristics of our multi-pollutant analysis model, LASSO, which might select only one of several associated pollutants when they are highly correlated, in order to achieve a more parsimonious model. It could also be related to relatively limited variability in air pollutant concentrations in our study population. This might have reduced the probability of observing significant associations and could decrease external validity of our results. Therefore, we recommend replication of this study in other cohorts with different air pollutant concentration distributions.

In conclusion, even though we found an attenuation of the initial association between air pollution and higher MD in early adolescence, residential outdoor air pollution exposure during pregnancy and childhood was also associated with lasting changes in white matter microstructure across adolescence. Specifically, one SD increase in exposure to air pollution corresponded to more than a 5-month delay in the development of FA. Since these findings were present in children exposed to $PM_{2.5}$ and PM_{10} concentrations above the currently recommended maximum values by the World Health Organization (World Health Organization, 2021), but below those recommended by the European Union (EU, 2008), our study provides support for more stringent European guidelines on acceptable levels of air pollution.

CRediT authorship contribution statement

Michelle S.W. Kusters: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Mónica López-Vicente:** Writing – review & editing, Formal analysis. **Ryan L. Muetzel:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Anne-Claire Binter:** Writing – review & editing, Methodology. **Sami Petricola:** Writing – review & editing, Methodology. **Henning Tiemeier:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mònica Guxens:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2024.119828.

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