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Air Pollution Exposure During Fetal Life, Brain Morphology, and Cognitive Function in School-Age Children

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ABSTRACT

BACKGROUND: Air pollution exposure during fetal life has been related to impaired child neurodevelopment, but it is unclear if brain structural alterations underlie this association. The authors assessed whether air pollution exposure during fetal life alters brain morphology and whether these alterations mediate the association between air pollution exposure during fetal life and cognitive function in school-age children.

METHODS: We used data from a population-based birth cohort set up in Rotterdam, The Netherlands (2002–2006). Residential levels of air pollution during the entire fetal period were calculated using land-use regression models. Structural neuroimaging and cognitive function were performed at 6 to 10 years of age (n = 783). Models were adjusted for several socioeconomic and lifestyle characteristics.

RESULTS: Mean fine particle levels were 20.2 $\mu g/m^3$ (range, 16.8–28.1 $\mu g/m^3$). Children exposed to higher particulate matter levels during fetal life had thinner cortex in several brain regions of both hemispheres (e.g., cerebral cortex of the precuneus region in the right hemisphere was 0.045 mm thinner (95% confidence interval, 0.028–0.062) for each 5-$\mu g/m^3$ increase in fine particles). The reduced cerebral cortex in precuneus and rostral middle frontal regions partially mediated the association between exposure to fine particles and impaired inhibitory control. Air pollution exposure was not associated with global brain volumes.

CONCLUSIONS: Exposure to fine particles during fetal life was related to child brain structural alterations of the cerebral cortex, and these alterations partially mediated the association between exposure to fine particles during fetal life and impaired child inhibitory control. Such cognitive impairment at early ages could have significant long-term consequences.

Keywords: Child development, Cognition, Cohort studies, Environmental pollution, Neuroimaging, Particulate matter

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Air pollution is a global risk factor for various adverse health effects in humans (1–7). There is increasing evidence indicating that air pollution exposure is also related to an impairment of the central nervous system through chronic neuroinflammation and microglia activation, which can lead to neuronal damage (8). Because pregnancy and the first years of life are critical windows of developmental vulnerability for the brain, exposure to air pollution during this period could cause permanent changes in the brain even at low levels of exposure (9,10).

Several epidemiological studies have assessed the association between air pollution exposure during early life and child neurodevelopment (11–16). These studies have found that air pollution exposure during pregnancy or during the first years of life was associated with lower cognitive or psychomotor function and higher behavior problems, including autism spectrum disorder. However, they mainly used neuropsychological or clinical instruments to evaluate child neurodevelopment, limiting our understanding of which brain structural and functional alterations underlie these associations. Only a few small studies have started using magnetic resonance imaging (MRI) techniques to assess relationships with air pollution (17–20). Three studies found an association between higher exposure to air pollution at home during fetal life or early childhood and white matter abnormalities in children at 7 to 13 years of age (17–19). A fourth study in children 8 to 12 years of age showed a relationship between air pollution exposure at school and lower functional integration and segregation in key brain networks (20). Despite the fact that prior studies have not found an association between air pollution exposure and cortical thickness, the study of brain morphology is key in providing insights in the underlying neurobiological pathways.

Therefore, the aims of the present study were to assess 1) the association between air pollution exposure during fetal life and brain morphology in school-age children and 2) the mediation role of brain morphology on the association

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between air pollution exposure during fetal life and cognitive function in school-age children. Cognitive function is the result of integration of functions of many different brain regions, and thus there was no a priori hypothesis on which specific brain regions would be affected by air pollution exposure during fetal life, as no other similar studies have been performed so far. Thus, we used an exploratory approach to examine the association of exposure to air pollutants and brain surface measures.

METHODS AND MATERIALS

Population and Study Design

This study was embedded in the Generation R Study, a population-based birth cohort study from fetal life onward in Rotterdam, The Netherlands (21). A total of 8879 pregnant women were enrolled and children were born between April 2002 and January 2006. A subgroup of children between 6 and 10 years of age participated in an MRI substudy (22). Briefly, a total of 1932 children were invited to participate in this substudy. Children were oversampled based on certain maternal exposures during pregnancy (i.e., cannabis, nicotine, selective serotonin reuptake inhibitors, depressive symptoms, and plasma folate levels) and child behavior problems (i.e., attention-deficit/hyperactivity disorder, pervasive developmental problems, dysregulation problems, and aggressive problems). Exclusion criteria comprised contradictions for the MRI procedure, severe motor or sensory disorders, neurological disorders, head injuries with loss of consciousness, and claustrophobia. Among those invited, 155 did not answer the invitation call, 447 refused to participate, and 5 could not participate owing to contraindications for the MRI procedure. Among the 1325 that attended the MRI visit, after excluding those with poor MRI data quality and major abnormalities, MRI measurements were available for 1070 children. Finally, after excluding those without air pollution estimations during fetal life, 783 children were included in the present study. This study was approved by the Medical Ethics Committee of the Erasmus Medical Centre in Rotterdam, The Netherlands. Written informed consent was obtained from parents.

Air Pollution Exposure

Air pollution levels at mothers' home addresses for the entire fetal period were estimated following a standardized procedure described elsewhere (23–25). Briefly, air pollution monitoring campaigns of three 2-week periods of nitrogen dioxide (NO_2) in 80 sites and particulate matter (PM) with aerodynamic diameters <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$ or fine particles), and absorbance of fine particles (a proxy for elemental carbon) in 40 sites were performed in 2009 to 2010 across The Netherlands and Belgium (26,27). Coarse particle concentration was calculated as the difference between PM_{10} and $PM_{2.5}$. The three measurements were averaged, adjusting for temporal variation using data from a centrally located background monitoring site with year-round monitoring. Land-use regression models were developed using predictor variables on nearby traffic intensity, population/household density, and land use derived from geographic information systems to explain spatial variation of annual average concentrations (23–25). These models were then used to assign air pollution levels at mothers' home addresses during the entire fetal period using the exact geographical x and y coordinates that corresponded to the addresses reported by each participant. Seven available routine background monitoring network sites were simultaneously used to back-extrapolate to the exact fetal period (6,25), accounting for the changes of home address during pregnancy (Supplemental Methods S1). This resulted in a single, time-adjusted mean air pollution concentration for each participant for the entire fetal period. Previous research supports stability of measured and modeled spatial contrast in air pollutants for periods up to 18 years (28).

Magnetic Resonance Imaging

Structural MRI scans were obtained on a 3T scanner (Discovery MR750, GE Healthcare, Milwaukee, WI). Using an 8-channel head coil, a whole-brain high-resolution T1-weighted inversion recovery fast spoiled gradient recalled sequence was obtained. The scan parameters were the following: repetition time = 10.3 ms, echo time = 4.2 ms, inversion time = 350 ms, flip angle = 16°, 186 contiguous slices with a thickness of 0.9 mm, and in-plane resolution = 0.9 × 0.9 mm.

To minimize movement, children participated in a mock scanning session before the actual MRI scanning to introduce them to the scanning environment (22). In the scanner, care was taken that children were comfortable, and soft cushions were used to assist with head immobilization. However, it was still possible that children moved in the scanner. Image quality assurance was performed in two steps. First, a visual inspection of the image quality of the T1 sequence was done at the scanner. If the image quality was poor or unusable, the scan was repeated with extra instructions for children to lie still. Second, a visual inspection of the surface reconstruction quality was done after the images were processed through the FreeSurfer pipeline. Both steps of quality control had to be passed successfully for data to be included in the analyses.

Cortical reconstruction and volumetric segmentation of global brain measures was performed with the FreeSurfer image analysis suite, version 5.1.0 (http://surfer.nmr.mgh.harvard.edu/). Briefly, cortical thickness at each vertex was measured by calculating the shortest distance from the white matter to the pial surface. Procedures for the measurement of cortical thickness have been validated against histological analysis and manual measurements (29). Volumetric measures included total brain volume, cortical gray matter volume, cortical white matter volume, subcortical gray matter volumes (i.e., caudate, putamen, pallidum, accumbens, hippocampus, amygdala, and thalamus), and ventricular volume. FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (30). All FreeSurfer output was visually inspected and rated for quality.

Cognitive Function

Children's cognitive function was assessed on the day of the scanning or shortly after using an array of subtasks from the Dutch version of the Developmental Neuropsychological Assessment (31). A detailed description of the test has been published previously (22). Briefly, the subtasks were chosen to

tap into specific domains, including attention and executive functioning, language, memory and learning, sensorimotor function, and visuospatial processing. Children were individually tested in a quiet room by trained investigators.

Potential Confounding Variables

Potential confounding variables were defined a priori based on direct acyclic graph (Supplemental Figure S1) and on previous literature (11,12,25). Parental characteristics during pregnancy were collected by questionnaires: parental educational levels, monthly household income, parental countries of birth, parental ages, maternal prenatal smoking, maternal prenatal alcohol use, maternal parity, family status, and maternal psychological distress (using the Brief Symptom Inventory). Parental weights and heights were measured or self-reported at the first trimester of pregnancy in the research center. Prepregnancy body mass index (kg/m^2) was calculated. Child's gender and date of birth were obtained from hospital or national registries. Child genetics ancestry was estimated based on the genome-wide single nucleotide polymorphism data from whole blood at birth, and four principal components of ancestry were included to better correct for population stratification (32,33). Maternal IQ was assessed at 6 years of age with the Ravens Advanced Progressive Matrices Test, set I. Child's age at scanning was also collected.

Statistical Analyses

We performed whole-brain, vertexwise statistics using the FreeSurfer QDEC (query, design, estimate, contrast) module for each air pollutant adjusting for child's gender and age. As there are many vertices per hemisphere (~160,000), analyses were corrected for multiple testing using the built-in Monte Carlo null-*Z* simulations with 10,000 iterations ($p < .01$). Due to limitations in modeling strategy with QDEC (types of variables, number of confounding variables, and inability to impute missingness in confounding variables), subject-level data from the identified regions associated with each air pollutant were imported into Stata version 14 (StataCorp, College Station, TX) for the following analysis.

Among children with available data on air pollution, neuroimaging, and cognitive function, we performed multiple imputation of missing values of potential confounding variables using chained equations to generate 25 complete datasets (34). The percentage of missing values was relatively low and distributions in imputed datasets were similar to those observed (Supplemental Table S1). Children included in the analysis (n = 783) were more likely to have mothers from a higher socioeconomic position compared with those that were not included, among children selected for the MRI substudy (n = 1149) (Supplemental Table S2). This was also the case when we compared our study population with the not-included children from the full cohort recruited in pregnancy (n = 8097) (Supplemental Table S3). We used inverse probability weighting to correct for lost to follow-up, i.e., to account for potential selection bias when including only participants with available data as compared with the full cohort recruited at pregnancy (35).

We used linear regression analyses to assess the associations between 1) exposure to each air pollutant and global brain measures and 2) exposure to each air pollutant and the cortical thickness of each identified region in the QDEC analysis. Models were adjusted for all potential confounding variables described in the previous section.

Next, we selected the tasks that assessed the cognitive function involved with each identified region based on the literature. We assessed whether both air pollution exposure and the cortical thinness of these regions were associated with the selected cognitive functions using adjusted negative binomial or linear regression models depending on the distribution of the outcome. We then applied causal mediation analysis providing estimation of the natural direct effect (NDE), the natural indirect effect (NIE), and the total effect (Supplemental Methods S2) (36). Briefly, we assessed the direct and indirect effects of air pollution exposure during fetal life on cognitive function. We tested whether part of the indirect effect was mediated by cortical thinness (Supplemental Figure S1). We used negative binomial regression for the outcome regression model and linear regression for the mediator regression model. Standard errors were calculated using bootstrapping. All models were adjusted for all potential confounding variables described in the previous section. The total effect results as the product of the NDE and NIE. We also calculated the proportion mediated as incidence rate ratio $(IRR)^{NDE}(IRR^{NIE} - 1)/(IRR^{NDE}IRR^{NIE} - 1)$.

We performed sensitivity analysis of the association between air pollutants and the cortical thickness of each identified region in the whole-brain analysis: 1) we restricted the analysis to those children without attention-deficit/hyperactivity disorder, pervasive developmental problems, dysregulation problems, and aggressive problems; and 2) we restricted the analysis to those children from nonsmoking mothers during pregnancy.

RESULTS

Participant characteristics of the study population are shown in Table 1 and Supplemental Table S4. Mean residential air pollution exposure during fetal life was 39.3 μg/m^3 for NO_2 (range, 25.3–73.3 μg/m^3) and 20.2 μg/m^3 for fine particles (range, 16.8–28.1 μg/m^3). The correlation between air pollutants was between 0.43 and 0.79 (Supplemental Table S5). Mothers exposed to higher air pollution levels during fetal life were more likely to have a higher level of education, to have a higher household income, and to be Dutch compared with those exposed to lower levels (Supplemental Tables S6–9).

We did not find significant associations between air pollution exposure during fetal life and global brain volume measures (Table 2). Children exposed to higher particulate matter levels during fetal life had thinner cortices in several brain regions in both hemispheres (Figure 1). Sizes of associated brain regions varied between 532 and 2995 mm^2 (Supplemental Table S10). Mean thickness of these brain regions was between 2.31 and 3.17 mm^2 (with a minimum thickness of 1.61–2.23 mm^2 and a maximum thickness of 3.23–3.97 mm^2). After adjusting for potential confounding variables, exposure to particulate matter levels remained strongly associated with thinner cortices of all identified regions (e.g., cerebral cortex of the precuneus region was 0.045 mm thinner (95% confidence interval [CI], 0.028 to 0.062) for each 5-μg/m^3 increase in fine

Table 1. Participant Characteristics and Air Pollution Levels During Fetal Life

Participant Characteristics	Distribution
Maternal Education Level, %	
Primary education	7.0
Secondary education	44.8
University education	48.2
Paternal Education Level, %	
Primary education	5.7
Secondary education	40.9
University education	53.4
Monthly Household Income, %	
<1,200€	14.1
1,200€–2,000€	17.7
>2,000€	68.1
Maternal Country of Birth, %	
The Netherlands	65.2
Cape Verde	4.7
Morocco	4.7
Surinam	6.5
Turkey	4.5
Other country of birth	14.5
Paternal Country of Birth, %	
The Netherlands	72.7
Cape Verde	2.6
Morocco	1.9
Surinam	5.0
Turkey	3.4
Other country of birth	14.4
Maternal Age, Years, Mean (SD)	30.7 (4.9)
Paternal Age, Years, Mean (SD)	32.9 (5.3)
Family Status (Monoparental vs. Biparental), %	13.5
Maternal Parity (Multiparous vs. Nulliparous), %	39.5
Maternal Smoking Use During Pregnancy, %	
Never	75.8
Smoking use until pregnancy known	6.5
Continued smoking use during pregnancy	18.2
Maternal Alcohol Use During Pregnancy, %	
Never	37.6
Alcohol use until pregnancy known	14.3
Continued alcohol use during pregnancy	48.1
Maternal Prepregnancy BMI, kg/m^2, Mean (SD)	24.6 (4.3)
Paternal Prepregnancy BMI, kg/m^2, Mean (SD)	25.3 (3.3)
Maternal Height, cm, Mean (SD)	168.6 (7.4)
Paternal Height, cm, Mean (SD)	182.9 (7.3)
Maternal Overall Psychological Distress, Mean (SD)	0.3 (0.4)
Maternal IQ Score, Mean (SD)	98.4 (13.9)
Air Pollution Levels During Fetal Life, Median (Min-Max)	
NO_2, μg/m^3	39.3 (25.3–73.3)
Fine particles, μg/m^3	20.2 (16.8–28.1)
Coarse particles, μg/m^3	11.8 (9.2–17.8)
Absorbance of fine particles (10^{-5} m^{-1})	1.9 (1.2–3.6)

BMI, body mass index; Max, maximum; Min, minimum; NO_2, nitrogen dioxide.

Table 2. Fully Adjusted Association Between Air Pollution Exposure During Fetal Life and Global Brain Volume Measures at 6–10 Years of Age

	Coefficient[a]	95% CI	*p* Value
NO_2			
Total brain volume	124	−1118 to 1375	.84
Cortical gray matter volume	−60	−853 to 733	.88
Cortical white matter volume	199	−287 to 685	.42
Subcortical gray matter volume	36	−17 to 89	.18
Ventricular volume	4	−57 to 64	.90
Fine Particles			
Total brain volume	−3079	−7790 to 1632	.20
Cortical gray matter volume	−2598	−5583 to 387	.09
Cortical white matter volume	−268	−2096 to 1559	.77
Subcortical gray matter volume	−60	−258 to 138	.55
Ventricular volume	−96	−323 to 131	.40
Coarse Particles			
Total brain volume	−4868	−10337 to 822	.09
Cortical gray matter volume	−3542	−7059 to 8	.05
Cortical white matter volume	−1129	−3215 to 1127	.34
Subcortical gray matter volume	−92	−325 to 148	.46
Ventricular volume	−100	−372 to 168	.45
Absorbance of Fine Particles			
Total brain volume	−2861	−18745 to 24467	.79
Cortical gray matter volume	−2683	−16377 to 11012	.70
Cortical white matter volume	5807	−2566 to 14180	.17
Subcortical gray matter volume	418	−497 to 1334	.36
Ventricular volume	−64	−1108 to 979	.90

CI, confidence interval; NO_2, nitrogen dioxide.

[a]Beta coefficient (95% CI) from linear regression model adjusted for parental educational levels; monthly household income; parental countries of birth; parental ages; maternal prenatal smoking, maternal prenatal alcohol use; parental body mass indices and heights; maternal parity; marital status; maternal psychological distress; maternal IQ; and child gender, age, and genetic ancestry. Coefficients represent the differences in volume (cm^3) per each increase of 10 μg/m^3 of NO_2, 5 μg/m^3 of fine particles, 5 μg/m^3 of coarse particles, and 10^{-5} m^{-1} of absorbance of fine particles.

particles) (Table 3). We observed similar results in the different sensitivity analysis (Supplemental Tables S11 and S12).

Based on the cognitive functions involved with each identified region, we selected the attention and executive functioning tasks for all regions except for the fusiform region, where we selected the memory for faces tasks (Supplemental Methods S3). Fine particles exposure during fetal life was associated with a higher number of inhibition errors of the response set task (IRR, 1.07; 95% CI, 1.01 to 1.14 per each 5-μg/m^3 increase in fine particles) (Table 4). No significant associations were observed for the other relationships. A thinner cortex in the precuneus region and the rostral middle frontal region was also associated with a higher number of inhibition errors in those tasks (IRR, 1.32; 95% CI, 1.00 to 1.77 per each 1-mm decrease of the cortex in the precuneus region; and IRR, 1.69; 95% CI, 1.09 to 2.61 per each 1-mm decrease of the cortex in the rostral middle frontal region) (Table 5). We finally

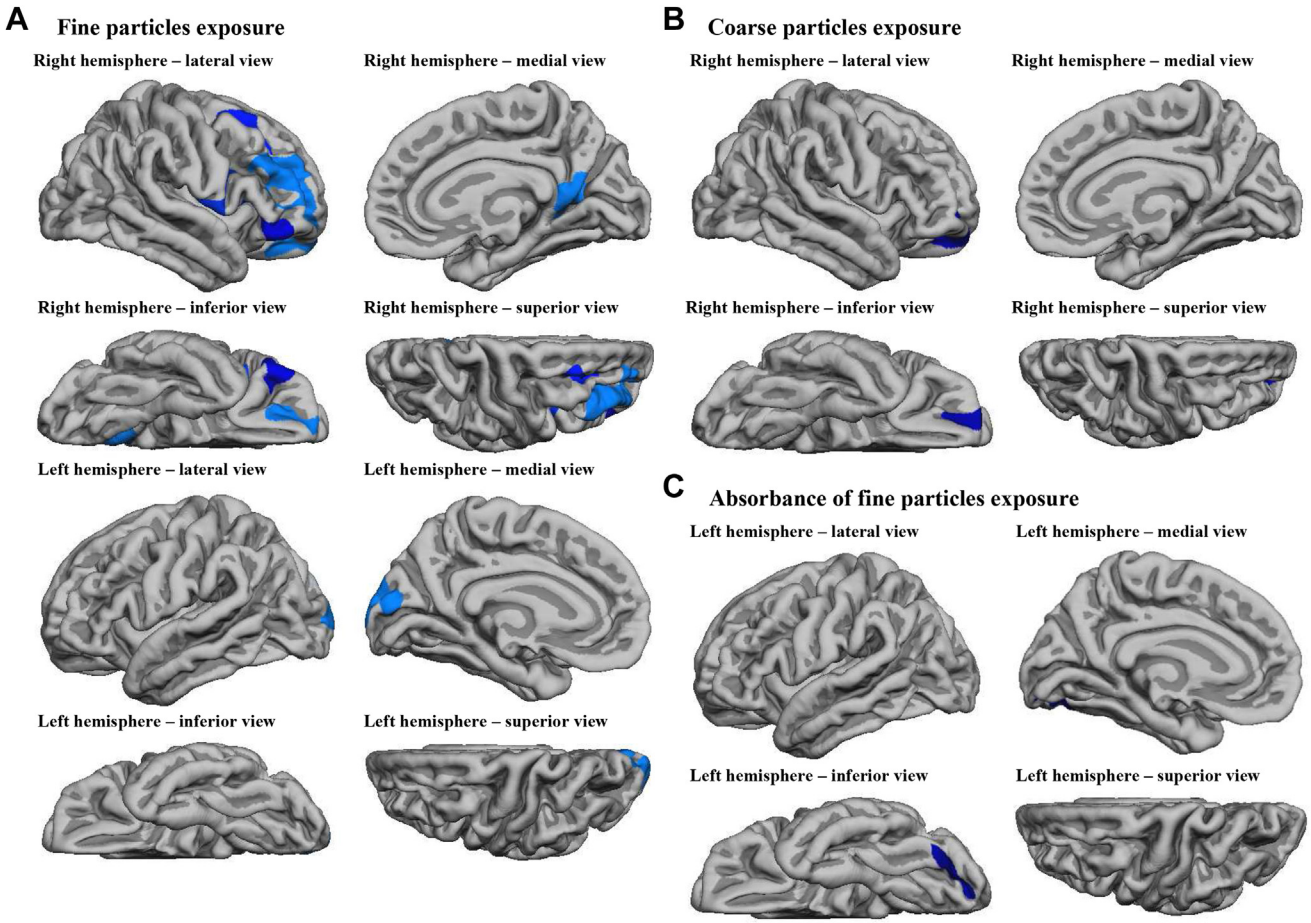


Figure 1. Differences in cortical thickness at 6–10 years of age associated with air pollution exposure during fetal life: **(A)** fine particles exposure, **(B)** coarse particles exposure, and **(C)** absorbance of fine particles exposure. The colored regions on the surface map represent brain regions that are thinner in relation to higher exposure to air pollution during fetal life in the right and left hemisphere (darker color indicates stronger association). Analyses were adjusted for child's gender and age. All brain regions survived the correction (Monte Carlo null-*Z* simulation with 10,000 iterations) for multiple comparisons ($p < .01$).

Table 3. Fully Adjusted Association Between Air Pollution Exposure During Fetal Life and Cortical Thickness at 6–10 Years of Age

	Hemisphere	Size Brain Region (mm^2)	Coefficient[a]	95% CI	*p* Value
Fine Particles Exposure					
Precuneus region	Right	936	−0.045	−0.062 to −0.028	<.001
Pars opercularis region	Right	753	−0.024	−0.033 to −0.014	<.001
Pars orbitalis region	Right	651	−0.028	−0.043 to −0.012	.001
Rostral middle frontal region	Right	2995	−0.029	−0.041 to −0.018	<.001
Superior frontal region	Right	722	−0.029	−0.043 to −0.016	<.001
Cuneus region	Left	843	−0.022	−0.035 to −0.009	.002
Coarse Particles Exposure					
Lateral orbitofrontal region	Right	565	−0.037	−0.059 to −0.016	.001
Absorbance of Fine Particles Exposure					
Fusiform region	Left	532	−0.105	−0.160 to −0.049	<.001

CI, confidence interval.

[a]Beta coefficient (95% CI) from linear regression model adjusted for parental educational levels, monthly household income, parental countries of birth, parental ages, maternal prenatal smoking, maternal prenatal alcohol use, parental body mass indices and heights, maternal parity, family status, maternal psychological distress, maternal IQ, and child gender, age, and genetic ancestry. Coefficients represent the differences in thickness (mm) per each increase of 5 $\mu g/m^3$ of fine particles, 5 $\mu g/m^3$ of coarse particles, and 10^{-5} m^{-1} of absorbance of fine particles.

Table 4. Adjusted Association Between Air Pollution Levels During Fetal Life and Cognitive Function at 6–10 Years of Age

	IRR[a]	95% CI	*p* Value
Fine Particles Exposure			
Auditory attention task			
Correct responses	1.00	0.99 to 1.01	.61
Commission errors	1.00	0.89 to 1.16	.95
Omission errors	0.98	0.92 to 1.03	.38
Inhibition errors	1.10	0.63 to 1.93	.73
Response set task			
Correct responses	1.01	1.00 to 1.02	.17
Commission errors	1.00	0.96 to 1.04	.79
Omission errors	0.97	0.94 to 1.00	.07
Inhibition errors	1.07	1.01 to 1.14	.02
Coarse Particles Exposure			
Auditory attention task			
Correct responses	1.00	0.99 to 1.01	.71
Commission errors	0.99	0.87 to 1.13	.88
Omission errors	0.98	0.92 to 1.05	.63
Inhibition errors	0.98	0.55 to 1.76	.95
Response set task			
Correct responses	1.01	0.99 to 1.02	.39
Commission errors	0.97	0.92 to 1.02	.19
Omission errors	0.98	0.94 to 1.02	.28
Inhibition errors	1.04	0.97 to 1.12	.24
	Coefficient[a]	95% CI	*p* Value
Absorbance of Fine Particles Exposure			
Memory for faces task	0.22	−0.24 to 0.69	.34
Memory for faces delayed task	0.29	−0.23 to 0.81	.27

CI, confidence interval; IRR, incidence rate ratio.

[a]IRR values (95% CI) from negative binomial regression model or beta coefficients (95% CI) from linear regression model adjusted for parental educational levels; monthly household income; parental countries of birth; parental ages; maternal prenatal smoking; maternal prenatal alcohol use; parental body mass indices and heights; maternal parity; family status; maternal psychological distress; maternal IQ; and child gender, age, and genetic ancestry.

Table 5. Adjusted Association Between Thinner Cortical Thickness and Total Number of Inhibition Errors of the Response Set Task at 6–10 Years of Age

	IRR[a]	95% CI	*p* Value
Precuneus Region	1.32	1.00 to 1.77	.05
Pars Opercularis Region	0.83	0.49 to 1.42	.49
Pars Orbitalis Region	1.16	0.83 to 1.61	.38
Rostral Middle Frontal Region	1.69	1.09 to 2.61	.02
Superior Frontal Region	1.28	0.89 to 1.86	.18

CI, confidence interval; IRR, incidence rate ratio.

[a]IRR values (95% CI) from negative binomial regression model adjusted for parental educational levels; monthly household income; parental countries of birth; parental ages; maternal prenatal smoking; maternal prenatal alcohol use; parental body mass indices and heights; maternal parity; family status; maternal psychological distress; maternal IQ; and child gender, age, and genetic ancestry.

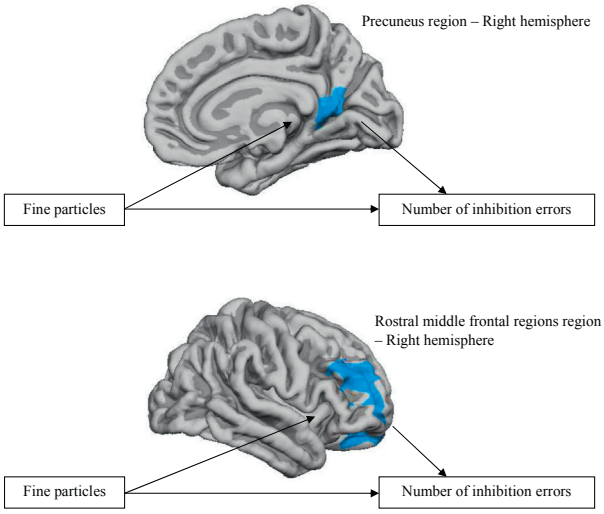
found that the reduced cortical thickness in the precuneus and rostral middle frontal regions partially mediated the observed association between fine particles exposure during fetal life and the increase number of inhibition errors (NIE: IRR, 1.01; 95% CI, 1.00 to 1.02 per each 1-mm decrease of the cortex in the precuneus region and in the rostral middle frontal region) (Figure 2). The proportion mediated through the reduced cortical thickness in each of the regions was estimated to be 15%.

DISCUSSION

The present study suggests that particulate matter exposure during fetal life was associated with a thinner cortex in several brain regions and with an impaired inhibitory control in school-age children. The structural alterations in the precuneus and the rostral middle frontal regions partially mediated the association between fine particles exposure and impaired inhibitory control. No association was found between air pollution exposure and global brain volume measures.

Several epidemiological studies have found that air pollution exposure during fetal life is associated with lower cognitive function (11–14). However, very few studies have investigated which brain structural and functional alterations underlie these associations. A child's cognitive function is the result of integration of functions of many different brain regions, and thus we did not have an a priori hypothesis on which specific brain regions could be affected by air pollution exposure during fetal life. In our study, we identified that some specific brain regions had a thinner cortex in relation to air pollution exposure during fetal life. We do not have a hypothesis regarding why air pollution exposure during fetal life is affecting the gray matter of specific brain regions instead of having a more widespread effect. One explanation would be that this is due to the different development of each brain region across adolescence. For example, cortical volume of the frontal lobe showed a relatively stable trajectory in late childhood and an accelerated thinning in adolescence, while decelerating trajectories with increasing age were seen for thickness in the parietal and occipital lobes (37). Further longitudinal studies are warranted to better understand the potential associations at different ages.

To date, only one small study assessed the relationship between air pollution exposure during fetal life and structural brain morphology in 40 children at 7 to 9 years of age from New York City, taking also an exploratory approach, as we did in our study (17). Peterson *et al.* (17) did not find an association between personal polycyclic aromatic hydrocarbons exposure during the third trimester of pregnancy and any measure of cortical thickness. However, they found an association between higher personal polycyclic aromatic hydrocarbons exposure during the third trimester of pregnancy and a lower white matter surface, almost exclusively to the left hemisphere of the brain (17). In contrast with this previous study, we did not find a relationship between exposure to air pollutants during fetal life and white matter volume using a much larger sample of children at a similar age. As there is indication that white matter could be one of the brain structures affected by air pollution exposure during fetal life, future research should focus on white matter microstructure, which could uncover deficits that are not apparent with simple white matter volumetric measures.



	IRR	(95% CI)
Natural direct effect	1.06	(1.00 to 1.12)
Natural indirect effect	1.01	(1.00 to 1.02)
Total effect	1.07	(1.00 to 1.13)

Figure 2. Causal mediation analyses between air pollution exposure during fetal life, cortical thickness (in mm) in the precuneus and rostral middle frontal regions, and the number of inhibition errors of the response set task at 6–10 years of age. Incidence rate ratio (IRR) (95% confidence interval [CI]) from negative binomial regression models adjusted for parental educational levels, monthly household income, parental countries of birth, parental ages, maternal prenatal smoking, maternal prenatal alcohol consumption, parental body mass indices and heights, maternal parity, family status, maternal psychological distress, maternal IQ, and child gender, age, and genetic ancestry. As results for both causal mediation analyses were identical rounded to 2 decimal places, only one table is presented.

During pregnancy, the detoxification mechanisms of the developing fetus are still immature and the placenta grants only a partial protection against the entry of environmental toxicants (9,10). Hence, when the mother is exposed to air pollution, air pollutants may alter the prenatal brain development as a result of oxidative stress and systemic inflammation, leading to chronic neuroinflammation, microglia activation, and neuronal migration damage (8). Early disturbances in neuronal path finding, abnormalities in cell proliferation, and differentiation eventually result in a thinner cortex during childhood. Although the prenatal period is considered a particularly vulnerable period for brain development, the brain continues to develop until adolescence, and postnatal air pollution exposure could also play a role on brain development (8,11,12). In the New York City study, the authors also explored the relationship between postnatal urinary polycyclic aromatic hydrocarbon metabolites and structural brain morphology, not finding an association with cortical thickness, but rather showing a lower white matter surface in dorsal prefrontal regions bilaterally (17). Two small studies including around 30 children at 6 to 14 years of age found that children living in Mexico City had lower white matter volumes and higher rates of subcortical prefrontal white matter hyperintensities compared with those living in a low-polluted city in Mexico (18,19). Again, white matter seems to be influenced by air pollution exposure. Furthermore, in 263 children 8 to 12 years of age from Barcelona, Spain, higher elemental carbon and NO_2 exposure at school was not associated with brain structure, but rather with lower functional integration and segregation in key brain networks relevant to both inner mental processes and stimulus-driven mental operations (20). That study was the first to show that air pollution exposure may also alter brain functionality, which leads to a slower brain maturation. Overall, air pollution exposure in both prenatal and postnatal periods has been shown to impair brain development. Further studies are needed to disentangle the specific brain alterations due to prenatal and postnatal air pollution exposure.

Interestingly, our study is the first study to show that fine particles exposure during fetal life was associated with an impaired inhibitory control in school-age children and that a thinner cortex in the precuneus and the rostral middle frontal regions partially mediated this association. Inhibitory control, a key component of executive functions, regulates the self-control of resisting temptations and acting impulsively, and selective attention (38). Impaired inhibitory control has been related to several mental health problems such as addictive behaviors (39) or attention-deficit/hyperactivity disorder (40). The previous study carried out in New York City found that the white matter disruption partially mediated the association between prenatal polycyclic aromatic hydrocarbons exposure and a slower information processing speed in children (17). Therefore, we hypothesize that air pollution exposure during fetal life could lead to brain structural changes, and then to specific cognitive delays.

In our study, mean residential NO_2 levels during fetal life were just at the European Union (EU) limit of 40 $\mu g/m^3$, with 45% of our population having higher levels. Regarding fine particles, mean residential levels were clearly below the EU limit of 25 $\mu g/m^3$, with only 0.5% of our population above this limit (41). Similarly to our study, other studies have found relationships between fine particle levels below the current EU limit and several health end points including natural-cause mortality, cardiovascular and respiratory diseases, cognitive decline, and fetal growth development (1–7). Therefore, we cannot warrant that this limit is safe. The World Health Organization set a lower limit of 10 $\mu g/m^3$ for fine particles (42), and in our study, all of our population was above this limit. Further health effects research needs to bring greater insight into the safety of the current air pollution levels in our cities.

The strengths of our study are the large number of study participants with imaging data, the prospective and longitudinal nature of the study, the detailed information of air pollution estimations at the individual level during the entire fetal period, and the availability of adjusting the imaging analysis for a large number of socioeconomic and lifestyle factors known to be associated with both air pollution exposure and brain development. Nevertheless, we cannot discard that our results may still be affected by residual confounding, owing to the unavailability of other relevant potential confounding variables. Another limitation of our study was that children with exposure and outcome data were more likely to have mothers from a higher socioeconomic position than were those children without these data, but who were recruited at the beginning of the cohort in early pregnancy, which could have led to

selection bias in our results. To reduce this possible selection bias, we used advanced statistical methods, including multiple imputation combined with inverse probability weighting. However, we could have missed variables related to this potential selection bias that would have had a stronger effect on the results. In addition, there is the possibility of chance findings in the observed associations in the current study. The imaging analysis was corrected for multiple testing of the whole-brain, vertexwise statistics, as we had many vertices per hemisphere. However, the causal mediation analysis was hypothesis driven, and we decided not to correct for multiple testing, as this could have increased type II error (43,44). Instead, our conclusions were based on the general patterns of associations observed in the study. This is the first study to show that brain structural alterations seem to partially mediate the association between air pollution exposure during fetal life and impaired cognitive function. Further studies are warranted to replicate these findings and better understand this association.

Conclusions

We showed that fine particles exposure during fetal life was related to both child brain structural alterations of the cerebral cortex and impairment of an essential executive function such as inhibitory control. Moreover, the identified structural alterations in two specific regions partially mediated the association between fine particles exposure during fetal life and impaired inhibitory control. Such cognitive impairment at early ages could have significant long-term consequences, including increased risk of mental disorders, low academic achievement, and diminished economic productivity (38), in particular due to the ubiquity of the exposure.

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MG and HEM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MG, HEM, and HT were involved in concept and design. MG, RLM, VWVJ, GH, AvdL, FCV, TW, BB, HT, and HEM were involved in acquisition, analysis, or interpretation of data. MG and HEM were involved in drafting of the manuscript. All authors were involved in the critical revision of the manuscript for important intellectual content. MG, AD-B, and HEM were involved in statistical analysis. VWVJ, GH, AvdL, FCV, TW, BB, and HT obtained funding. All authors contributed administrative, technical, or material support. MG and HEM supervised.

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