Archival Report

Biological Psychiatry

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

Mònica Guxens, Małgorzata J. Lubczyńska, Ryan L. Muetzel, Albert Dalmau-Bueno, Vincent W.V. Jaddoe, Gerard Hoek, Aad van der Lugt, Frank C. Verhulst, Tonya White, Bert Brunekreef, Henning Tiemeier, and Hanan El Marroun

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

https://doi.org/10.1016/j.biopsych.2018.01.016

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

ISSN: 0006-3223

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