HEI

STATEMENT

Synopsis of Research Report 209

HEALTH EFFECTS INSTITUTE

Air Pollution and Brain Outcomes in Children

BACKGROUND

Although several epidemiological studies have assessed the association between air pollution exposure during early life and child neurological development, it is yet unclear whether brain structural alterations underlie the observed associations. Advances in neuroimaging that allow in vivo investigation of brain structure and function have emerged. Such studies provide additional information about the possible mechanisms and add biological plausibility to the nervous system outcomes reported in epidemiological studies. So far, only a few studies have used magnetic resonance imaging techniques to evaluate the effect of air pollution on the developing brain.

Dr. Mònica Guxens of ISGlobal, a recipient of HEI's 2016 Walter A. Rosenblith New Investigator Award, and colleagues have assessed the possible relationship of early life air pollution exposure with brain outcomes using neuroimaging data in children.

APPROACH

The study by Dr. Guxens assessed the possible relationship of air pollution exposure during pregnancy and childhood with brain outcomes in children. Brain structural and functional measures were studied in Generation R — an existing birth cohort in Rotterdam, the Netherlands. Mother–child pairs were recruited during pregnancy or at birth from 2002–2006 and followed up until 2015.

Dr. Guxens and colleagues used air pollution data and high-resolution neuroimaging data collected in about 800 school-age children and in about 3,100 pre-adolescents. About 400 children underwent imaging at two time points. To increase statistical power in the first round, a potential sampling bias was introduced by deliberately selecting more school children with child behavior problems and with mothers who reported certain exposures during pregnancy (e.g., exposure to drugs, nicotine, alcohol, and psychiatric medication).

Early life exposure was estimated at the residential address level for various air pollutants using existing land-use regression models, mainly from the European ESCAPE project. Those models were based on air pollution measurements between February 2009 and February 2010 at 40 to 80 sites spread across the Netherlands and Belgium. Guxens and colleagues applied single pollutant regression models to assess the association between early life air pollution exposure and brain structural and functional measures corrected for important potential confounders, such as maternal smoking, prepregnancy body mass index, and socioeconomic status. Because the number of outcome measurements was very large, analyses of most brain outcomes were corrected for mul-

What This Study Adds

- The goal of the study was to assess whether early life air pollution exposure affects brain outcomes using neuroimaging data from an existing birth cohort (Generation R) in Rotterdam, the Netherlands.
- The study focused on brain structural and functional measures in children.
- Strengths of the study were the availability of high-resolution neuroimaging data for a large subset of the cohort, the wealth of individual-level covariate data, and estimation of a large suite of air pollution exposure metrics.
- The study found some evidence of associations between early life air pollution exposure and various measures of brain structural morphology, structural connectivity, and functional connectivity in children. For example, exposure to air pollution during early life was associated with a thinner cortex in various regions of the brain in both school-age children and pre-adolescents. The clinical relevance of the findings remains unclear.
- The results add to the limited evidence of air pollution effects on the developing brain, with only a few MRI studies in children so far.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Mònica Guxens at Barcelona Institute for Global Health, Barcelona, Spain, and colleagues. The complete report, *Associations of Air Pollution on the Brain in Children: A Brain Imaging Study* (© 2022 Health Effects Institute), can be obtained from HEI or our website (see last page).

tiple comparisons. Additionally, they used multipollutant models using a deletion/substitution/addition approach.

MAIN RESULTS AND INTERPRETATION

In its independent review of the study, the HEI Review Committee thought the research was well motivated and addressed important and novel questions about the potential relationships between air pollution and the developing brain. This type of research is emerging but remains distinctive — with only a few MRI studies in children so far. The availability of high-resolution neuroimaging data for a large subset of the cohort — the largest sample to date — was unprecedented; the wealth of individual-level covariate data and the large suite of air pollution exposure metrics estimated were strengths of the study.

The study documented associations between early life air pollution exposure and various measures of brain structural morphology, structural connectivity, and functional connectivity in children. For example, exposure to air pollution during early life was associated with a thinner cortex in various regions of the brain in both school-age children and pre-adolescents. Moreover, in pre-adolescents, exposure to air pollution during early life was associated with differences in region-specific brain volumes, such as a smaller volume in the hippocampus and corpus callosum. In addition, associations were documented between exposure and white matter microstructure and higher brain functional connectivity among several brain regions. Although the Review Committee broadly agrees with the investigators' conclusions, it noted a few limitations that should be considered when interpreting the results.

The Committee had concerns about the exposure assessment because of the substantial temporal and spatial misalignment of the data. That issue is particularly important when studying the developing brain, which is exceptionally complex with potentially critical time windows of development. Furthermore, all brain outcomes, including brain volume outcomes, should have been corrected for multiple comparisons because of the large number of analyses. The Committee was not convinced that the multipollutant approach added much, because, for example, it remains unclear how stable the identified specific exposure associations in the multipollutant analyses really are. High correlations were noted among many pollutants in the analyses and between prenatal and childhood exposure. Thus, it was not possible to tease out independent pollutant associations and identify a susceptible exposure window during pregnancy and early childhood. Additionally, some study design features affected the generalizability of the findings.

CONCLUSIONS

Overall, the insights drawn from the current study, along with a few other brain imaging studies in children, are noteworthy and should provide impetus for further research. Because the brain has a dynamic structure that is constantly evolving throughout life, longitudinal studies beginning as early as possible are the best means to assess the effect of air pollution on the developmental trajectories of the brain outcomes included in the current cross-sectional analysis. Also, further analyses should be encouraged, for example, to investigate whether children with worse brain outcomes showed poorer cognitive function or other adverse neurological development outcomes. Those analyses would shed light on whether the brain outcome findings are clinically relevant, but this so far remains unclear.

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