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Air pollution exposure during pregnancy and childhood, cognitive function, and emotional and behavioral problems in adolescents

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ABSTRACT

Background: Exposure to air pollution may impact neurodevelopment during childhood, but current evidence on the association with cognitive function and mental health is inconclusive and primarily focusses on young children. Therefore, we aim to study the association of exposure to air pollution during pregnancy and childhood, with cognitive function and emotional and behavioral problems in adolescents.
Methods: We used data from 5170 participants of a birth cohort in Rotterdam, the Netherlands. Concentrations of fourteen air pollutants at participant's home addresses were estimated during pregnancy and childhood, using land use regression models. We included four cognitive domains (processing speed, working memory, fluid reasoning and verbal intelligence quotient (IQ)) and an estimated full-scale IQ. Internalizing, externalizing, and attention problems were self- and parent-reported. We used linear regression models to assess the association of each air pollutant, with cognitive function and emotional and behavioral problems, adjusting for socioeconomic status and lifestyle characteristics. Then, we performed multipollutant analyses using the Deletion/Substitution/Addition (DSA) algorithm.
Results: Air pollution exposure was not associated with full-scale IQ, working memory, or processing speed. Higher exposure to few air pollutants was associated with higher fluid reasoning and verbal IQ scores (e.g. 0.22 points of fluid reasoning (95%CI 0.00; 0.44) per 1 $\mu g/m^3$ increase in organic carbon during pregnancy). Higher exposure to some air pollutants was also associated with less internalizing, externalizing, and attention problems (e.g. −0.27 internalizing problems (95% CI -0.52; −0.02) per each 5 ng/m^3 increase in copper during pregnancy).
Conclusions: Higher exposure to air pollution during pregnancy and childhood was not associated with lower cognitive function or more emotional and behavioral problems in adolescents. Based on previous literature and biological plausibility, the observed protective associations are probably explained by negative residual confounding, selection bias, or chance and do not represent a causal relationship.

1. Introduction

The Global Burden of Disease study estimated that air pollution exposure was responsible for 254 million years of life lost worldwide in 2015 (Kassebaum et al., 2016; Landrigan et al., 2018). Air pollution has also been highlighted as a potential determinant that can influence neurodevelopment in children (Suades-González et al., 2015). Several studies in animals suggest that fine particles cross the blood brain barrier and cause elevated cytokine expression and oxidative stress in neuronal cells (Campbell et al., 2009; Levesque et al., 2011). These processes can already occur before birth, as prenatal protection against chemical hazards is poor and fine particles can transfer across the placenta to the fetal brain (Bové et al., 2019). Children and adolescents might be especially vulnerable to the neurotoxic effects of air pollution, due to development of neuronal structures and relatively poor protective mechanisms (Rice and Barone Jr, 2000).

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Previous studies on exposure to air pollution and cognitive function in children found mixed results (Chiu et al., 2016; Gonzalez-Casanova et al., 2018; Guxens et al., 2014; Harris et al., 2015, 2016; Lertxundi et al., 2019; Loftus et al., 2019; Porta et al., 2016; Saenen et al., 2016; Sentís et al., 2017). The evidence seems more consistent for a harmful effect of air pollution exposure on executive functions, including attentional function (Chiu et al., 2013, 2016; Sentís et al., 2017; Sunyer et al., 2015), working memory (Forns et al., 2017; Rivas et al., 2019; van Kempen et al., 2012), and inhibitory control (Guxens et al., 2018). Only a few studies investigated the association between air pollution exposure and emotional and behavioral problems, including internalizing, externalizing, and attention problems. The majority of these studies were conducted in school-aged children and did not find an association (Donzelli et al., 2019; Forns et al., 2016, 2018; Fuertes et al., 2016; Gong et al., 2014; Harris et al., 2016; Jorcano et al., 2019; McGuinn et al., 2020; Newman et al., 2013; Roberts et al., 2019). School-aged children might be too young for an association between air pollution and the occurrence of these problems to be detected, because especially depression, the most common internalizing problem, typically does not emerge until adolescence (Merikangas et al., 2010). Moreover, most previous studies only used parental or teacher reports to assess children's emotional and behavioral problems, since they were conducted in children aged 5-12-years (Donzelli et al., 2019; Forns et al., 2016, 2018; Fuertes et al., 2016; Gong et al., 2014; Harris et al., 2016; Jorcano et al., 2019; McGuinn et al., 2020; Newman et al., 2013). Thus, studies in adolescents, which include self-reporting of problems in addition to parental reports, might shed new light onto the relationship between air pollution and mental health.

As current evidence appears inconsistent and there are few studies in adolescents, the aim of this study is to investigate the association of exposure to air pollution during pregnancy and childhood with cognitive function, and emotional and behavioral problems in adolescents, using data from a large prospective birth-cohort study.

2. Methods

2.1. Study population

We used data from Generation R, a prospective population-based birth cohort based in Rotterdam, The Netherlands (Kooijman et al., 2016). A total of 8879 women were included during pregnancy and 899 women shortly after giving birth (Fig. S1). Children were born between April 2002 and January 2006. After exclusion of twin pregnancies, a total of 9610 children remained. All children still enrolled at age 13–16 were invited to complete questionnaires and participate in two assessments at the research center with their mothers. Among those with available data on exposure to air pollution, data was available for at least one of the outcomes for 5170 participants (4683 participants for cognitive function and 4645 participants for emotional and behavioral problems). Written informed consent was obtained from all participants.

2.2. Exposure to air pollution

We estimated the concentration of 14 air pollutants during pregnancy (i.e., from conception until birth) and during childhood (i.e., from birth until the last follow up, mean age 10.1 years) using a standardized procedure (Beelen et al., 2013; De Hoogh et al., 2013; Eeftens et al., 2012; Jedynska et al., 2014; Yang et al., 2015). Briefly, in the period between February 2009 and February 2010, nitrogen dioxide (NO_2) and nitrogen oxides (NO_x) were measured at 80 sites spread throughout the Netherlands and Belgium. Particulate matter (PM) with aerodynamic diameter <10 μm (PM_{10}) and <2.5 μm ($PM_{2.5}$), was measured at 40 sites within the same time period. PM between 10 μm and 2.5 μm (PM_{coarse}) was calculated by subtracting $PM_{2.5}$ from PM_{10}. The absorbance of $PM_{2.5}$ fraction ($PM_{2.5}$absorbance), the composition of $PM_{2.5}$ consisting of polycyclic aromatic hydrocarbons (PAHs), organic carbon (OC), copper (Cu), iron (Fe), silicon (Si), zinc (Zn), and the oxidative potential of $PM_{2.5}$ (OP) using two acellular methods (i.e., dithiothreitol (OP^{DTT}) and electron spin resonance (OP^{ESR})) were measured in the $PM_{2.5}$ filters. We calculated an annual mean concentration for each pollutant, averaging the results of the above measurements, while using data from a continuous reference site to adjust for temporal trends. Next, we created land-use regression models, by assessing which potential land use predictors explained most of the air pollutant concentrations. To obtain the final mean exposure concentration for each air pollutant during pregnancy and childhood, we weighted the air pollutant concentrations based on the time spent at each home address for all participants. We were unable to perform back- and forward extrapolation of the air pollution concentrations to match the exact time period of interest, due to a lack of historical data for most air pollutants. We assumed the concentrations to have remained reasonably stable over time, as Eeftens et al. (2011) previously indicated for a period of 8 years in the Netherlands (1999–2007) and Gulliver et al. (2013) for a period of 18 years in Great Britain (1991–2009).

2.3. Cognitive function

We measured cognitive function when children were 13- to 16-years-old using four core subsets of the Wechsler Intelligence Scale for Children-Fifth Edition (Kaufman et al., 2015). We measured processing speed using the Coding subtest, working memory using the Digit Span subtest, fluid reasoning (an important indicator of non-verbal IQ) using the Matrix Reasoning subtest, and verbal IQ using the Vocabulary subtest. The Digit Span and Vocabulary subtests were administered and scored by trained research assistants. The Coding and Matrix Reasoning subtests were performed on an iPad Air 2 and automatically scored using the Q-interactive system of Pearson (Daniel et al., 2014). For a few children (2.7%) a paper/pencil version was administered due to tablet malfunctioning. Raw scores from the four subtests were then converted to age-standardized T-scores using Dutch norm-scores (Dutch WISC-V manual Table A1), summed and converted to an estimated full-scale IQ.

2.4. Emotional and behavioral problems

We assessed emotional and behavioral problems with the Child Behavior Check List (CBCL) for ages 6–18 reported by the primary caretaker of the child, and the Youth Self-Report (YSR) reported by the child, when children were 13- to 16-years-old. The CBCL and YSR are validated scales for measuring emotional and behavioral problems (Achenbach and Rescorla, 2000). They are widely used and considered generalizable across multiple populations (Ivanova et al., 2010). The CBCL and YSR each consist of 112 items about the occurrence of emotional and behavioral problems over a period of the previous 6 months. For our study we used the internalizing problem (including anxious/depressed, withdrawn-depressed, and somatic complaints scores), externalizing problem (including aggressive behavior and rule-breaking behavior scores), and attention problem scales. In our analyses we used a sum of the raw CBCL and YSR scores for each problem scale. When either was missing for a participant (9.8%), the score of the one available scale was doubled.

3. Covariates

We selected potential confounding variables for our study based on a direct acyclic graph, previous literature, and the availability of data within Generation R (Guxens et al., 2018; Lubczyńska et al., 2020). We collected information on maternal and paternal age at enrollment, national origin, education level, social class (based on occupation), marital status, and income level, and maternal parity, alcohol consumption, smoking, and folic acid use during pregnancy, through questionnaires during pregnancy. We calculated the parental body mass index (BMI), based on maternal and paternal self-reported pre-pregnancy weight and measured height in the first trimester of pregnancy. We assessed maternal and paternal psychological distress during pregnancy using the Brief Symptom Inventory (De Beurs, 2004). At the child's age of 6, we assessed maternal IQ using the Ravens Advanced Progressive Matrices Test, set I (Raven et al., 1962). We collected child's sex and season of birth from hospital records. We recorded the child's age at the assessment of the outcomes. We used the Normalized Difference Vegetation Index, based on the degree of land surface reflectance of light assessed by satellites, to estimate average exposure to greenness in the surrounding area of 100 m of maternal home addresses during pregnancy (i.e., from conception until birth) and during childhood (i.e. from birth until age 9). Values range from −1 to 1, with higher numbers suggesting more greenness, and negative numbers suggesting water bodies and tiled or sandy areas (Rhew et al., 2011). We used an area-level score indicative of mean household income, and proportion of population with low income, low educational level, and without paid work, from The Netherlands Institute for Social Research to assess socioeconomic status of the neighborhood during pregnancy for each participant, with lower scores representing lower socioeconomic status (NIPHE, 2017).

3.1. *Statistical analysis*

First, we performed multiple imputation using chained equations to obtain 25 complete datasets, by imputing missing values of potential confounders for all participants with available data on the exposures and outcomes (Spratt et al., 2010; Sterne et al., 2009). The percentage of missing values was below 30% for all variables, except for education of the father (36%), social class of the mother (45%) and the father (56%), folic acid use of the mother during pregnancy (30%), and parental psychological distress during pregnancy (33% for mothers, 49% for fathers) (Table S1). Descriptive statistics of imputed values were similar to observed values (data not shown).

Compared to parents enrolled at baseline but not included in this study, parents of children included in our study (N = 5170) generally had a higher socioeconomic status (Table S1). Thus, we performed inverse probability weighting to account for potential selection bias due to only including those participants with available data on exposures and outcomes (Weisskopf et al., 2015; Weuve et al., 2012). In brief, we selected the variables that were most predictive of participation in our study and used these to calculate the inverse of the probability of participation for each participant included (Table S2). This inverse probability was assigned as a weight for each participant and used in all subsequent analyses (Fig. S2).

The internalizing, externalizing, and attention problem variables were square root transformed to improve normal distribution of the residuals. To assess the association of exposure to air pollution during pregnancy and during childhood, with cognitive function, and with emotional and behavioral problems, linear regression models were run for each of the air pollutant exposures separately with each of the outcomes, adjusting for all the potential confounders described in the previous section (i.e. single-pollutant analysis). Next, we performed multi-pollutant analyses for each exposure period and outcome separately, using the Deletion/Substitution/Addition (DSA) algorithm. The DSA algorithm, which has been shown to perform relatively well in the trade-off between sensitivity and false discovery proportion (Agier et al., 2016), provides a selection of variables that are most predictive of the outcome and corrects for multiple testing, using v-fold cross-validation. The selection of variable combinations is based on achieving the lowest possible root-mean-square deviation and follows the sequence of (1) deletion of a variable, (2) substitution of variable with another variable, and (3) addition of a variable to the pending model. As the algorithm is based on a cross-validation process, which is subject to random variations, we ran each model 200 times. We adjusted all models for potential confounders and identified those combinations of pollutants that were selected at least 10% of the time. When two pollutants had a correlation of 0.90 or more, we excluded one of these pollutants from the analyses to ensure adequate performance of the DSA. In our study, we excluded PM_{10} as it had a correlation of 0.98 with $PM_{2.5}$ absorbance. Due to computational issues, we ran these analyses on a single imputed dataset (the final, 25th imputed dataset from the R package mice). Finally, to test the sensitivity of our results, single-pollutant and multi-pollutant analyses for the emotional and behavioral outcomes were rerun separately for the CBCL scores and the YSR scores, i.e. for primary caretaker of the child report and adolescent self-report.

Statistical tests of hypotheses were two-tailed with significance set at $p < 0.05$. All statistical analyses were carried out using R (version 4.0.3; R Development Core Team).

4. Results

4.1. *Descriptive results*

Average maternal age at enrollment was 31 years, 52.8% of mothers had higher education, and 73.7% of mothers had never smoked during pregnancy (Table 1). Median air pollution concentrations during pregnancy were 26.7 $\mu g/m^3$ for PM_{10}, 16.8 $\mu g/m^3$ for $PM_{2.5}$, 1.6 10^{-5m-1} for $PM_{2.5}$absorbance, and 34.1 $\mu g/m^3$ for NO_2 (Table 2). Concentrations during childhood were slightly lower. Correlations between air pollution exposure during pregnancy and childhood were moderate (e.g. 0.49 for NO_2 and 0.63 for $PM_{2.5}$). Correlations between the different air pollutants varied from −0.08 (between NO_2 and PAH exposure during childhood) to 0.98 (between PM_{10} and $PM_{2.5}$ absorbance exposure) (Fig. S3).

4.2. *Cognitive function*

Exposure to air pollution during pregnancy or childhood was not associated with full-scale IQ (e.g. 0.77 points (95% CI -2.24; 3.78) per each 5 μg/m3 increase in $PM_{2.5}$ during pregnancy) (Fig. 1, Tables S3 and S4). In the single-pollutant analysis, exposure to higher OC during pregnancy and childhood was associated with a higher fluid reasoning score, and this association remained in the multi-pollutant analysis (e.g. 0.22 points (95%CI 0.00; 0.44) per 1 $\mu g/m^3$ increase in OC during pregnancy) (Tables S3–S5). Higher exposure to several air pollutants during pregnancy, but not during childhood, was associated with a higher verbal IQ score in the single-pollutant analysis (Tables S3 and S4). In the multi-pollutant analysis, only OP^{ESR} exposure during pregnancy remained positively associated with verbal IQ (0.84 points (95% CI 0.39; 1.30) per 1000 units/m^3 increase in OP^{ESR}) (Table S5). Pregnancy or childhood air pollution exposure was not associated with the processing speed and working memory subscales (Tables S3 and S4).

4.3. *Emotional and behavioral problems*

In the single-pollutant analysis, higher exposure to few air pollutants during pregnancy and childhood was associated with less internalizing problems (Fig. 2, Table S6). In the multi-pollutant analysis,higher exposure to Cu during pregnancy and higher exposure to Fe during childhood remained associated with less internalizing problems (−0.27 (95% CI -0.52; −0.02) per each 5 ng/m^3 increase in Cu during pregnancy, and −0.35 (95%CI -0.56; −0.15) per each 100 ng/m^3 increase of Fe during childhood) (Table S6, Table S7).

Exposure to air pollutants during pregnancy was not associated with externalizing problems. Higher exposure to some air pollutants during childhood was associated with less externalizing problems in the single-pollutant analysis. In the multi-pollutant analysis, higher exposure to Cu during childhood remained associated with less externalizing problems (−0.35 (95% CI -0.63; −0.08) per each 5 ng/m^3 increase in Cu).

In the single-pollutant analysis, a higher exposure to some air pollutants during pregnancy and childhood was associated with less attention problems. In the multi-pollutant analysis, exposure to Cu during pregnancy, and exposure to PM_{COARSE} and Cu during childhood remained associated with less attention problems (e.g. −0.24 (95% CI

Table 1
Maternal characteristics of the study participants (N = 5170).

Participant characteristics	Distribution
Age at enrollment (years)	31.1 (4.9)
National origin	
Dutch	59.5
Moroccan	4.7
Surinamese	7.0
Turkish	5.4
European, other	7.8
Non-European, other	15.5
Education level at enrollment	
Higher or above	52.8
Secondary	29.4
Primary or lower	17.8
Social class at enrollment	
Managers/Technicians	60.9
Skilled manual and non-manual	34.7
Semi-skilled/unskilled	4.4
Household income at enrollment	
>2200€	64.2
1600–2200€	14.4
900–1600€	13.8
<900€	7.6
Marital status at enrollment	
Married	50.7
Living together	38.4
No partner	10.9
Parity	
0 children	57.9
1 child	30.0
2+ child	12.1
Pre-pregnancy body mass index (kg/m^2)	22.5 (20.8; 25.1)
Alcohol during pregnancy	
Never	39.2
Until pregnancy known	13.9
Occasional use during pregnancy	37.3
Frequent use during pregnancy	9.7
Smoking during pregnancy	
Never	73.7
Until pregnancy known	8.3
Continued during pregnancy	18.0
Folic acid use during pregnancy	
Start preconceptional	48.0
Start in the first 10 weeks of pregnancy	31.7
None periconceptional	20.4
Intelligence quotient	100 (90; 107)
Psychological distress	0.2 (0.1; 0.4)
Socioeconomic status neighborhood	
high	10.5
high-middle	12.1
middle	12.2
low-middle	11.2
low	54.0
Greenness pregnancy	0.4 (0.1)

Values are percentages for categorical variables, mean (standard deviation) for normally-distributed continuous variables, and median (25th percentile; 75th percentile) for non-normally-distributed continuous variables.

-0.43; −0.05) per each 5 ng/m^3 increase in Cu during pregnancy, and −0.29 (95% CI -0.51; −0.08) per each 5 ng/m^3 increase in Cu during childhood).

Result were similar when analyzing the CBCL scores and the YSR scores separately as a sensitivity analysis (data not shown).

5. Discussion

In this prospective population-based birth cohort we did not observe an association between air pollution and full-scale IQ, working memory, or processing speed. However, higher exposure to few air pollutants, such as Cu and less consistently OC, OP^{ESR}, Fe, and PM_{COARSE}, was associated with higher scores of fluid reasoning and verbal IQ, and with less internalizing, externalizing, and attention problems.

In line with our results on full-scale IQ, working memory, and processing speed, many studies did not find that higher exposure to air pollution during pregnancy or childhood was associated with cognitive functioning (Freire et al., 2010; Gonzalez-Casanova et al., 2018; Guxens et al., 2014; Harris et al., 2015, 2016; Sentís et al., 2017). In contrast, some other studies suggested that higher air pollution exposure was associated with lower overall cognitive function (Chiu et al., 2016; Loftus et al., 2019; Perera et al., 2009), fluid reasoning (Wang et al., 2017) and working memory (Rivas et al., 2019). However, three of these studies only found an association when looking at specific time windows, for example exposure during 31–38 weeks of gestation, but not when considering the entire pregnancy period or a longer exposure period during childhood (Chiu et al., 2016; Rivas et al., 2019; Wang et al., 2017). This might suggest that air pollution exposure only has an effect during specific vulnerable periods. One other study that reported an association used personal monitoring, which includes pollutant sources other than traffic, and might therefore not be comparable to our study (Perera et al., 2009). We also found that higher exposure to some air pollutants was associated with higher scores on the fluid reasoning and verbal IQ scale. Considering evidence from previous studies and the absence of hypotheses on mechanisms underlying a potential protective association, we do not expect this to represent a true causal relationship. To our knowledge, only Harris et al. (2015) previously reported an association of higher exposure to air pollution with higher cognitive function (i.e. black carbon exposure during childhood with non-verbal IQ) in an urban sample.

So far, few studies have reported an association between higher exposure to air pollution and more emotional and behavioral problems, and some of these had a small sample size (Donzelli et al., 2019; Perera et al., 2012; Yorifuji et al., 2017). Most studies did not find an association between exposure to air pollution during pregnancy or childhood and emotional and behavioral problems (Forns et al., 2018; Gong et al., 2014; Harris et al., 2016; Jorcano et al., 2019; McGuinn et al., 2020; Newman et al., 2013). When studying these associations, the age at which the outcome is assessed could be an important factor. Forns et al. (2018) and Jorcano et al. (2019) included Generation R as one of the 8 population-based birth cohorts, but assessed emotional and behavioral problems at a younger age of 3–11 years. Since internalizing problems typically initiate from adolescence onwards (Merikangas et al., 2010), it is important to investigate if an association between exposure to air pollution and the occurrence of these problems appears at a later age. However, in our study we also did not find that higher exposure to air pollution was associated with more internalizing problems at 13–16 years old. This age group might still be too young to detect a relationship, as Roberts et al. (2019) found an association between air pollution exposure at age 12 and depressive disorder at age 18, but not for depressive symptoms at age 12. A second important factor is by whom the emotional and behavioral problems are reported (i.e. teachers, parents or self-reports). Most previous studies are conducted in younger children, and thus only few used self-reported data (Donzelli et al., 2019; Roberts et al., 2019). Other studies have shown that adolescents themselves tend to report more internalizing and less externalizing problems as compared to their parents reporting on the adolescent's problems (Angold et al., 1987; Edelbrock et al., 1985; van der Ende et al., 2012). Since multi-informant data on emotional and behavioral problems is generally considered most reliable, we used a sum score of the CBCL and YSR in our study. However, our multi-informant approach did not seem to influence our results, as the results of the combined scores were similar to those of the CBCL and YSR scores separately. We also found that for some air pollutants higher exposure was associated with less emotional and behavioral problems. To our knowledge, only Harris et al. (2016) previously reported a similar protective association (i.e. higher exposure to black carbon was associated with a lower overall emotional and behavioral problems). We also do not expect the associations between few air pollutants and less emotional and behavioral problems to represent true causal relationships.

The results of this study should be interpreted in the context of

Table 2
Air pollution exposure concentrations during pregnancy and during childhood with Spearman's correlations for each air pollution exposure between the two time periods.

	Pregnancy			Childhood			Spearman 's
	median	p25	p75	median	p25	p75	correlation
PM_{10} (μg/m^3)	26.7	26.0	27.9	26.3	25.6	27.2	0.54
$PM_{2.5}$ (μg/m^3)	16.8	16.6	17.2	16.7	16.5	17.0	0.62
PM_{COARSE} (μg/m^3)	10.1	9.2	10.6	9.5	8.7	10.3	0.57
$PM_{2.5abs}$ (10^{-5m-1})	1.6	1.5	1.8	1.5	1.4	1.7	0.54
NO_2 (μg/m^3)	34.1	31.9	36.7	32.3	29.4	34.9	0.49
NO_X (μg/m^3)	46.4	40.8	57.8	43.2	38.5	51.5	0.57
Cu (ng/m^3)	4.6	4.5	5.0	4.5	4.2	4.8	0.54
Fe (ng/m$^{3)}$	119.7	114.2	129.0	116.3	106.7	124.4	0.51
Si (ng/m$^{3)}$	88.8	87.9	90.7	88.6	87.6	90.6	0.62
Zn (ng/m$^{3)}$	18.9	17.6	21.3	18.8	17.5	20.9	0.57
PAH (ng/m$^{3)}$	0.9	0.8	1.1	0.9	0.8	1.1	0.68
OC (μg/m^3)	1.8	1.5	2.0	1.7	1.4	1.9	0.59
OP^{DTT} (nmol DTT/min/m^3)	1.3	1.3	1.4	1.3	1.2	1.4	0.59
OP^{ESR} (units/m^3)	1037.0	999.9	1101.0	1015.5	965.6	1071.9	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 OP^{ESR}, 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_{COARSE}); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5abs}$, absorbance of $PM_{2.5}$ filters; Si, elemental silicon; Zn, elemental zinc.

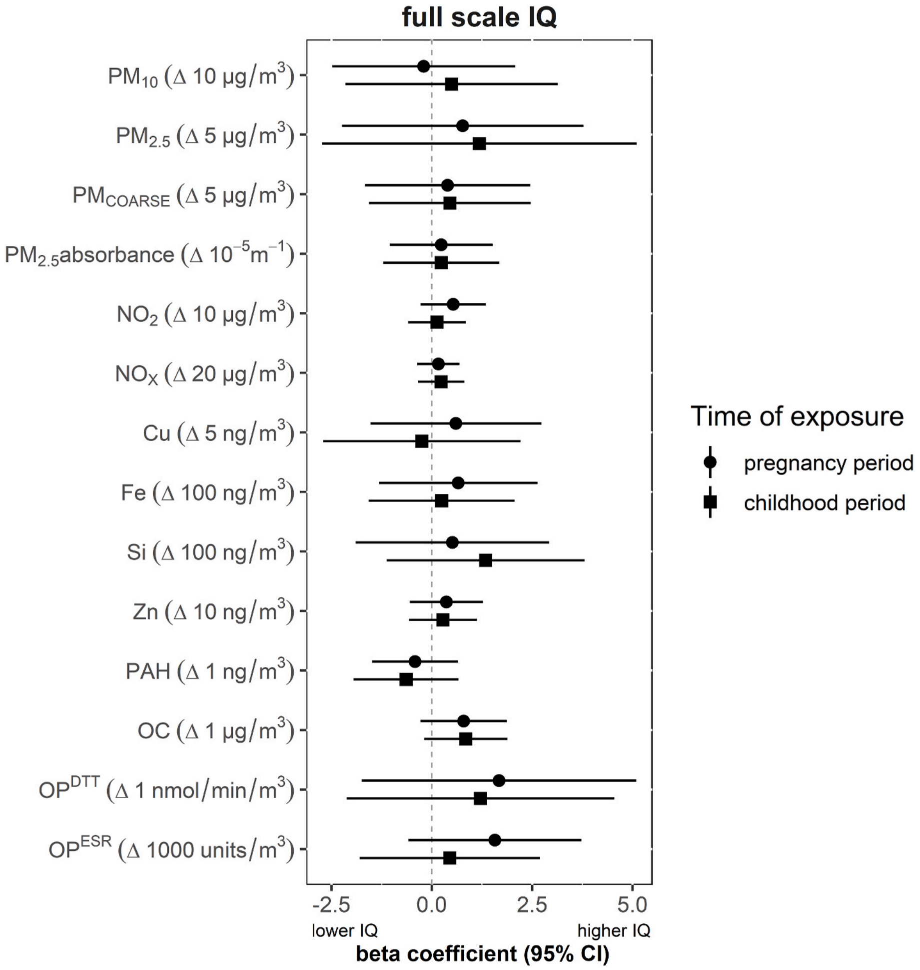

Fig. 1. Adjusted associations of exposure during pregnancy (round bullet) and during childhood (square bullet) to various air pollutants with full scale IQ in adolescents aged 13–16.
Abbreviations: CI, confidence intervals; Cu, elemental copper; Fe, elemental iron; NO_X, nitrogen oxides; NO_2, nitrogen dioxide; OC, organic carbon; OP, oxidative potential (evaluated using two acellular methods: OP^{DTT} – dithiothreitol and 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_{COARSE}); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$absorbance, absorbance of $PM_{2.5}$ filters; Si, elemental silicon; Zn, elemental zinc. Coefficient and 95% CI were estimated through linear regression analysis, adjusted for child's gender, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, maternal and paternal social class, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index and height, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligent quotient, maternal and paternal psychosocial distress, socioeconomic status neighborhood, and greenness.

several limitations. Although we adjusted for many potential confounders, including individual socioeconomic variables and a neighborhood socioeconomic status score, we suspect that some negative residual confounding remained, which could underly the observed protective findings. Negative residual confounding is confounding that causes an underestimation of the effect and if the confounding is sufficiently strong, it might even reverse the apparent association (McNamee, 2003). In our case, negative residual confounding would have been caused by factors related to both higher air pollution exposure and higher cognitive function/less emotional and behavioral problems or

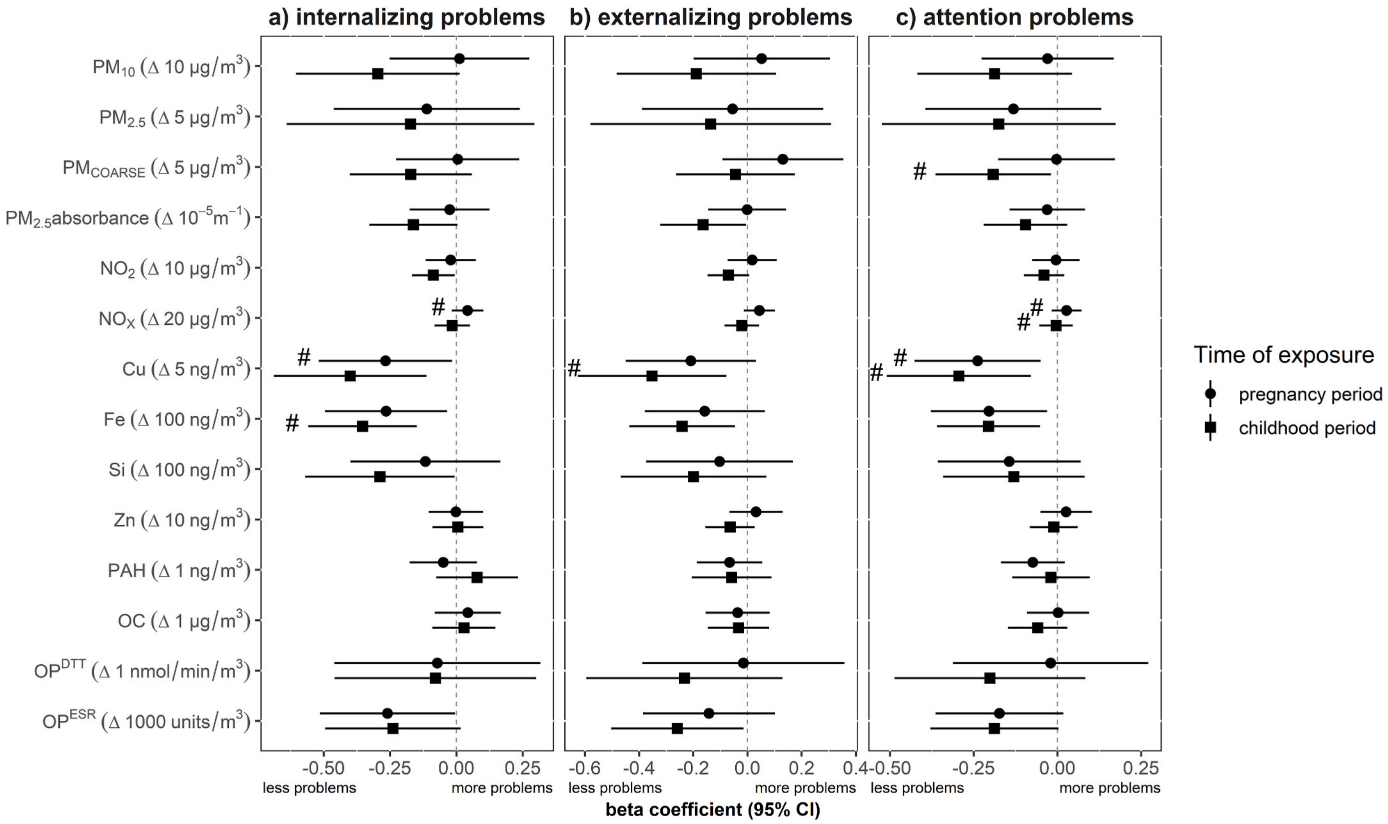

Fig. 2. Adjusted associations of exposure during pregnancy (round bullet) and during childhood (square bullet) to various air pollutants with (a) internalizing problems, (b) externalizing problems and (c) attention problems in adolescents aged 13–16.

Abbreviations: CI, confidence intervals; 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 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_{COARSE}); less than 2.5 μm ($PM_{2.5}$); $PM_{2.5}$absorbance, absorbance of $PM_{2.5}$ filters; Si, elemental silicon; Zn, elemental zinc. Coefficient and 95% CI were estimated through linear regression analysis, adjusted for child's gender, age and season of birth, maternal and paternal age at enrollment, maternal and paternal education level, maternal and paternal social class, household income, marital status, maternal parity, maternal and paternal pre-pregnancy body mass index and height, maternal alcohol consumption, smoking and folic acid use during pregnancy, maternal intelligence quotient, maternal and paternal psychosocial distress, socioeconomic status neighborhood, and greenness.

Pollutant selected by the multipollutant analysis.

vice versa, that we failed to adjust for. For example, we observed that participants from Turkish national origin were more likely to live in areas with higher levels of pollutants such as Cu and Fe, and reported less emotional and behavioral problems, when compared to participants from Dutch national origin. In addition, we might not have been able to fully mitigate the presence of selection bias, since loss to follow-up was strongly related to socioeconomic status and national origin. We performed inverse probability weighting to adjust for this, but we might have missed important predictors for participation in our study. Also, although we ran the DSA algorithm to account for multiple testing among the exposures, this did not adjust for multiple testing across the outcomes. Therefore, our few protective findings could be chance findings. In our study we only used air pollution concentrations at home addresses, because we did not have data available for exposure concentrations at schools. A previous cross-sectional study in the Netherlands did not find an association of NO_2 exposure at home addresses with working memory and processing speed, but did find an association between NO_2 exposure at schools and working memory (van Kempen et al., 2012). Similarly, studies embedded in a large birth-cohort in Barcelona, that looked specifically at air pollution exposure at schools, found associations with lower working memory, lower attentional function, and more externalizing and attention problems (Alemany et al., 2018; Basagaña et al., 2016; Forns et al., 2016, 2017; Sunyer et al., 2015). Considering the fact that children are usually at school when traffic, and thus air pollution levels, are highest, future studies could combine air pollution measurements at home addresses with measurements at schools. In addition, although median exposure concentrations of the majority of air pollutants exceeded the safety thresholds set by the World Health Organization (World Health Organization. Regional Office for Europe., 2021), associations might only be apparent at higher air pollution concentrations well above the WHO limits. Yet, three large European studies, which included cohorts that were exposed to a relatively high pollution concentration, also did not find any association with cognitive function or emotional and behavioral problems (Forns et al., 2018; Guxens et al., 2014; Jorcano et al., 2019). Furthermore, we had sampling of air pollutants available for a period of 3.5–9 years and had insufficient data to extrapolate the concentrations of all air pollutants to the specific period of interest. However, one study from the Netherlands and another from the UK found that air pollution concentrations remained spatially stable over time (Eeftens et al., 2011; Gulliver et al., 2013). The differences between the air pollution concentrations during pregnancy and childhood in our study were a consequence of participants moving and changing home address during the course of the study.

One of the main strengths of our study is that we had data available from a large prospective birth-cohort. We assessed cognitive function and emotional and behavioral problems in adolescents, a group that has been relatively understudied, but undergoes vast neurodevelopmental changes over a relatively short time-span and is considered vulnerable for the development of mental disorders (Merikangas et al., 2010). We also reduced the risk of informant bias, by combining self-reported data with parental-reported data. In addition to an estimated full-scale IQ, we had data available on several specific cognitive functions which have been previously associated with air pollution. Lastly, we included 14 different air pollutants in our study, covering different sources of traffic air pollution (e.g. tailpipe emissions from diesel fuel, tire wear, or brake linings), and explored both exposure during pregnancy and during childhood as periods of susceptibility.

6. Conclusion

In conclusion, we did not find that higher exposure to air pollution during pregnancy or childhood was associated with lower cognitive function or with more emotional and behavioral problems in children aged 13- to 16-years-old. A few air pollutants were associated with higher scores of fluid reasoning and verbal IQ, and with less internalizing, externalizing, and attention problems. Based on previous literature and biological plausibility, we argue that these associations are explained by negative residual confounding, selection bias, or chance and do not represent a causal relationship.

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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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113891.

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