Environmental Research 235 (2023) 116557

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Prenatal and childhood exposure to ambient air pollution and cognitive function in school-age children: Examining sensitive windows and sex-specific associations

Ariane Guilbert [a,*], Jonathan Y. Bernard [b], Hugo Peyre [c,d,e], Nathalie Costet [f], Ian Hough [a,g,h], Emie Seyve [a], Christine Monfort [f], Claire Philippat [a], Rémy Slama [a], Itai Kloog [g], Cécile Chevrier [f], Barbara Heude [b], Franck Ramus [e], Johanna Lepeule [a,*]

[a] Team of Environmental Epidemiology Applied to Development and Respiratory Health, Institute for Advanced Biosciences (IAB), Université Grenoble Alpes, Inserm, CNRS, 38700, La Tronche, France
[b] Université Paris Cité and Université Sorbonne Paris Nord, Inserm, INRAE, Centre for Research in Epidemiology and StatisticS (CRESS), 75004, Paris, France
[c] Centre de Ressources Autisme Languedoc-Roussillon et Centre d'Excellence sur l'Autisme et les Troubles Neuro-développementaux, CHU Montpellier, 34090, Montpellier, France
[d] Université Paris-Saclay, UVSQ, Inserm, CESP, Team DevPsy, 94807, Villejuif, France
[e] Laboratoire de Sciences Cognitives et Psycholinguistique, Département d'Etudes Cognitives, Ecole Normale Supérieure, PSL University, EHESS, CNRS, 75005, Paris, France
[f] Team of Epidemiology and Exposure Science in Health and Environment, Research Center on Environmental and Occupational Health (IRSET), Inserm, Université Rennes, EHESP, 35000, Rennes, France
[g] Department of Geography and Environmental Development, Ben-Gurion University of the Negev, Be'er Sheva, Israel
[h] Institute of Environmental Geosciences (IGE), Université Grenoble Alpes, 38400, Saint Martin D'Hères, France

ARTICLE INFO

Handling Editor: Jose L Domingo

Keywords:
Neurodevelopment
IQ
NO_2
PM
Pregnancy
DLNM

ABSTRACT

Background: Combined effect of both prenatal and early postnatal exposure to ambient air pollution on child cognition has rarely been investigated and periods of sensitivity are unknown. This study explores the temporal relationship between pre- and postnatal exposure to PM_{10}, $PM_{2.5}$, NO_2 and child cognitive function.
Methods: Using validated spatiotemporally resolved exposure models, pre- and postnatal daily $PM_{2.5}$, PM_{10} (satellite based, 1 km resolution) and NO_2 (chemistry-transport model, 4 km resolution) concentrations at the mother's residence were estimated for 1271 mother-child pairs from the French EDEN and PELAGIE cohorts. Scores representative of children's General, Verbal and Non-Verbal abilities at 5–6 years were constructed based on subscale scores from the WPPSI-III, WISC-IV or NEPSY-II batteries, using confirmatory factor analysis (CFA). Associations of both prenatal (first 35 gestational weeks) and postnatal (60 months after birth) exposure to air pollutants with child cognition were explored using Distributed Lag Non-linear Models adjusted for confounders.
Results: Increased maternal exposure to PM_{10}, $PM_{2.5}$ and NO_2, during sensitive windows comprised between the 15^{th} and the 33^{rd} gestational weeks, was associated with lower males' General and Non-verbal abilities. Higher postnatal exposure to $PM_{2.5}$ between the 35^{th} and 52^{nd} month of life was associated with lower males' General, Verbal and Non-verbal abilities. Some protective associations were punctually observed for the very first gestational weeks or months of life for both males and females and the different pollutants and cognitive scores.
Discussion: These results suggest poorer cognitive function at 5–6 years among males following increased maternal exposure to PM_{10}, $PM_{2.5}$ and NO_2 during mid-pregnancy and child exposure to $PM_{2.5}$ around 3-4 years. Apparent protective associations observed are unlikely to be causal and might be due to live birth selection bias, chance finding or residual confounding.

* Corresponding authors. Institute for Advanced Biosciences (IAB) Allée des Alpes, 38700, La Tronche, France.
E-mail addresses: ariane.guilbert@univ-grenoble-alpes.fr (A. Guilbert), johanna.lepeule@univ-grenoble-alpes.fr (J. Lepeule).

https://doi.org/10.1016/j.envres.2023.116557
Received 18 April 2023; Received in revised form 16 June 2023; Accepted 3 July 2023
Available online 7 July 2023

1. Introduction

In 2020, 71% of the European urban population was exposed to PM_{10} levels exceeding the WHO recommendations (European Environment Agency, 2022; World Health Organization, 2022). The percentage reached 96% for $PM_{2.5}$ making this pollutant a major environmental contributor to human health burden (Chowdhury et al., 2022; Southerland et al., 2022).

Several experimental and epidemiological studies suggest that chronic exposure to particulate matter (PM) has neurodevelopmental toxicity (You et al., 2022) and may be associated with cognitive impairment (Chandra et al., 2022), affecting abilities to remember, learn, perceive the environment, communicate or reason. Developing fetuses and infants may be more specifically at risk (Spencer-Hwang et al., 2023; Yi et al., 2022). Indeed, *in vitro*, animal and epidemiological studies demonstrated the ability of air pollutants to distribute to multiple organs, including the brain, after crossing the blood-air, blood--brain and placental barriers (Bongaerts et al., 2020; Brockmeyer and D'Angiulli, 2016). These chemicals can trigger chronic oxidative stress and inflammation in the pregnant woman, the fetus and the child (Chen et al., 2021; Kelly, 2003). The developing brain is particularly susceptible to such toxicity due to its rapid evolution, high demand in oxygen and immature detoxification system (Brockmeyer and D'Angiulli, 2016; Ikonomidou and Kaindl, 2011). Brain development starts in the first weeks after conception and continues until adulthood (Gibb and Kovalchuk, 2018). Any disturbance in this tightly controlled process may lead to long-lasting neurodevelopmental impairments whose nature and severity are likely to vary according to the timing of exposure.

Both prenatal (Chiu et al., 2016; Girardi et al., 2021; Lertxundi et al., 2019; Loftus et al., 2019; Ni et al., 2022) and postnatal (Binter et al., 2022; Ni et al., 2022; Wang et al., 2017) chronic exposures to $PM_{2.5}$ or PM_{10} have been linked with lower total intellectual quotient (IQ) and various subscales related to verbal, memory, reasoning or attention skills in school-age children or adolescents. Long considered to be solely a marker of exposure to traffic-related air pollution, several studies now also highlight the intrinsic neurotoxicity of NO_2. In 2020, a systematic review and meta-analysis showed that prenatal exposure to NO_2 was associated with impaired neurodevelopment in children, with a specific decrease in global and fine psychomotor abilities (Shang et al., 2020). Effects may occur for exposure levels within the WHO limits (Spencer-Hwang et al., 2023). Some research suggests that neurodevelopmental effects of air pollutants might be sex-specific with males more vulnerable (Ha, 2021; Yi et al., 2022). However, several studies did not highlight significant adverse effects of PM or NO_2 on cognitive function (Freire et al., 2010; Gonzalez-Casanova et al., 2018; Harris et al., 2015; Porta et al., 2016) or showed significant effects associated with some specific exposure periods (Binter et al., 2022; Ni et al., 2022).

In this context, recent literature reviews refrain from drawing firm conclusions about the effect of PM or NO_2 exposure history on child cognition (Ha, 2021; Shang et al., 2020; Spencer-Hwang et al., 2023; Volk et al., 2021; Yi et al., 2022). They underline an insufficient number of studies, heterogeneity in methodological approaches and study design weaknesses. In particular, a limited number of studies assessed exposure on the long-term, taking into account the effect of both pre- and postnatal exposure, and very few shed light on sensitive windows of exposure at a fine temporal scale. Considering the robust associations observed between early cognitive skills and later performance (Chen et al., 1996; Johnson et al., 2010; Marchman and Fernald, 2008; Sajaniemi et al., 2001), this research area deserves further investigation. Besides, insights on potential sensitive windows of air pollution exposure are needed to better understand underlying biological mechanisms and improve prevention.

Based on the French EDEN and PELAGIE mother-child cohorts, this study aims to explore the temporal relationship of early life chronic exposure to ambient PM_{10}, $PM_{2.5}$ and NO_2 with male and female cognitive abilities at 5–6 years. To address previously mentioned weaknesses, this work relies on high-resolution exposure models and the implementation of sex-stratified distributed lag models, taking into account the effect of both pre- and postnatal exposure to identify sensitive windows at a fine temporal scale.

2. Materials and methods

2.1. Study population

The study sample was drawn from two French prospective mother-child cohorts: EDEN ("Étude des Déterminants pré-et postnatals du développement et de la santé de l'Enfant") and PELAGIE ("Perturbateurs Endocriniens, Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance"). The former recruited 2002 pregnant women (less than 24 weeks of amenorrhea) from the Nancy and Poitiers hospital maternity wards between 2003 and 2006 (Heude et al., 2016). The latter included 3421 pregnant women (less than 19 weeks of amenorrhea) from Britany between 2002 and 2006 recruited through gynecologists (Petit et al., 2010). In EDEN, all participants were eligible to attend the cognitive tests. In PELAGIE, only a sub-sample of children were eligible: they were randomly selected from the live-born singletons aged between 6 years and 6 years and 3 months, excluding those with gestational duration less than 35 weeks amenorrhea, neonatal disorders (e.g., severe hypoglycemia, low Apgar score), neonatal hospitalization or reanimation, genetic abnormalities, child or mother death or child who had previously undergone neuropsychological tests (to avoid retest effect and bias). This sub-sample was very similar to the initial PELAGIE cohort in terms of socioeconomic and maternal behavioral characteristics (Béranger et al., 2017).

Because the EDEN and PELAGIE cohorts were very similar in terms of population characteristics, data collection periods and exposure data available, they were pooled. This study focused on 1271 mother-child pairs with available data on exposure to air pollutants during the period of interest and cognitive function at 5–6 years (Fig. 1 and Table S1). It did not include premature children (with gestational duration less than 37 weeks amenorrhea) in order to assess the effect of air pollution itself (direct effect) on cognition and not a total effect that passes through the prematurity associated with the exposure.

2.2. Exposure assessment

Maternal home addresses, including any changes during the follow-up period, were geocoded using the software Mon Géocodeur from the National Institute of Geographic and Forest Information and Geocible. Over the 1003 EDEN participants and their 1702 geocoded addresses, 1529 addresses were geocoded at the street number level, 118 at the street level, 24 at the hamlet level and 31 at the city level. Among the 268 PELAGIE participants and their 448 geocoded addresses, 208 addresses were geocoded at the street number level, 101 at the street level, 119 at the hamlet level and 20 at the city level.

Daily PM_{10} and $PM_{2.5}$ exposures at home addresses were estimated at a 1 km spatial resolution using a hybrid satellite based multi-stage ensemble model covering the continental French territory (Hough et al., 2021). This model combines data on aerosol optical depth (AOD), meteorology (temperature, air pressure, cloud cover, etc.), vegetation (normalized difference vegetation index based on MODIS data) and other spatiotemporal predictors (land cover, road and railway density, elevation, population, climatic region) using three base learners (mixed models, Gaussian Markov random fields and random forests) ensembled using a generalized additive model. The model shows good performance with a mean absolute error of 4.26 $\mu g/m^3$ and $R^2 = 0.71$ for PM_{10}, and a mean absolute error of 2.72 $\mu g/m^3$ and $R^2 = 0.76$ for $PM_{2.5}$.

Daily NO_2 exposures at home addresses were estimated at a 4 km spatial resolution using a model combining measurements from the permanent monitoring network and the Chemistry Transport Model CHIMERE (Real et al., 2022). This approach relying on a kriging

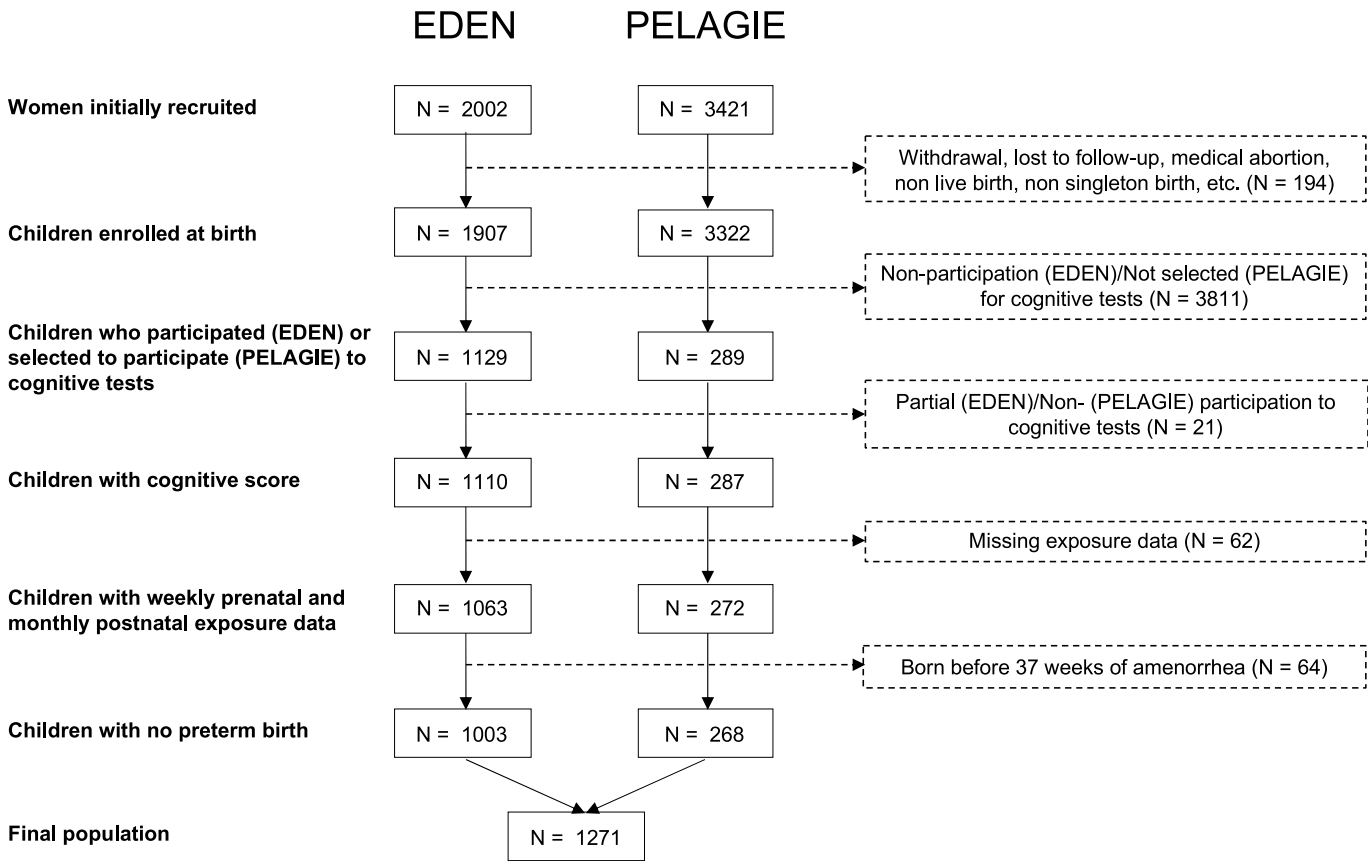

Fig. 1. Flow chart of the study population.
All EDEN participants were eligible to take the cognitive tests while in PELAGIE only a sub-sample were selected to take the cognitive tests.

procedure showed good performance in urban areas, with a bias not exceeding −3.5% but lower performance in rural areas with an overestimation by 60–80% depending on years due to a low number of monitoring stations.

2.3. Child cognitive function assessment

Child cognitive function was assessed with classic and well-validated tests in the two cohorts. In EDEN, the Wechsler Preschool and Primary Scale of Intelligence 3rd version (WPPSI-III (Wechsler, 2004)) battery and several subtests from the NEuroPSYchological Assessment 2nd version (NEPSY-II (Korkman and Kirk, 2007)) battery were administered at a median age of 5 years (InterQuartile Range [IQR]: 5.57, 5.72) by trained psychologists. The former covered the 7 main subtests (Block design, Information, Matrix reasoning, Vocabulary, Picture concepts, Word reasoning, Coding) while the latter included 4 subtests (Repetition of nonsense words, Phonological processing, Sentence repetition, Design copying). In PELAGIE, some parts of the Wechsler Intelligence Scale for Children 4th version (WISC-IV (Wechsler, 2005)) and of the NEPSY-II batteries were administered at 6 years (IQR: 6.04, 6.09) by trained psychologists. Six subtests from the WISC-IV (Block design, Similarities, Digit span, Vocabulary, Letter-number sequencing, Comprehension) and 8 subtests from the NEPSY-II (Design copying, Memory for faces, Tower, Auditory attention and response set, Arrows, Memory for names, Visual attention, Narrative memory) were used. Because the tests implemented by the two cohorts were partly different and administered at different ages, samples could not be pooled based on the cohort specific tests. Instead, scores similar to "g factors" (Spearman, 1946) were constructed separately within each cohort based on the standardized subtest scores using confirmatory factor analyses and the "lavaan" package (R; version 0.6–13). A two-factor second order structure was considered, distinguishing Verbal from Non-verbal abilities and assuming an underlying latent common factor representative of General abilities (Figs. S1 and S2). Individuals with data for fewer than two subtests per Verbal or Non-verbal scores were excluded (i.e., 19 participants in the EDEN population with cognitive data). Because the data contained some missing data (affecting 26 EDEN and 35 PELAGIE participants in the populations with cognitive score), "full information" maximum likelihood estimation was computed (estimation of an unrestricted model (Allison, 2003)). Modification indices were examined and additional residual correlations between subtests were included if they significantly improved the model fit in terms of chi-square test statistic. Model fits were assessed using the Comparative Fit Index (CFI) and the Root Mean Squared Error of Approximation (RMSEA) (Hooper et al., 2008). To additionally check the consistency of the constructs, the direction of the associations between the three scores and known predictors (e.g. maternal education, schooling, etc.) was analyzed.

2.4. Covariates

Covariates were identified based on literature and a directed acyclic graph (Fig. 2). Analyses were adjusted for the recruitment center ("Nancy", "Poitiers", "Brittany"), maternal education ("Baccalaureate or less", "Technology degree", "Bachelor or more"), maternal age at conception (continuous), maternal pre-pregnancy Body Mass Index (BMI; "Underweight", "Normal weight", "Overweight", "Obese", based on the WHO classification), maternal fish consumption before pregnancy ("Less than twice per week", "Twice per week or more"), parity ("Primiparous", "Non-primiparous"), child sex ("Female", "Male"), maternal smoking during pregnancy ("No", "Yes"), breastfeeding ("Breastfed less than 6 months", "Breastfed 6 months or more"), indicator of child stimulation at 24 months (based on weekly frequency of

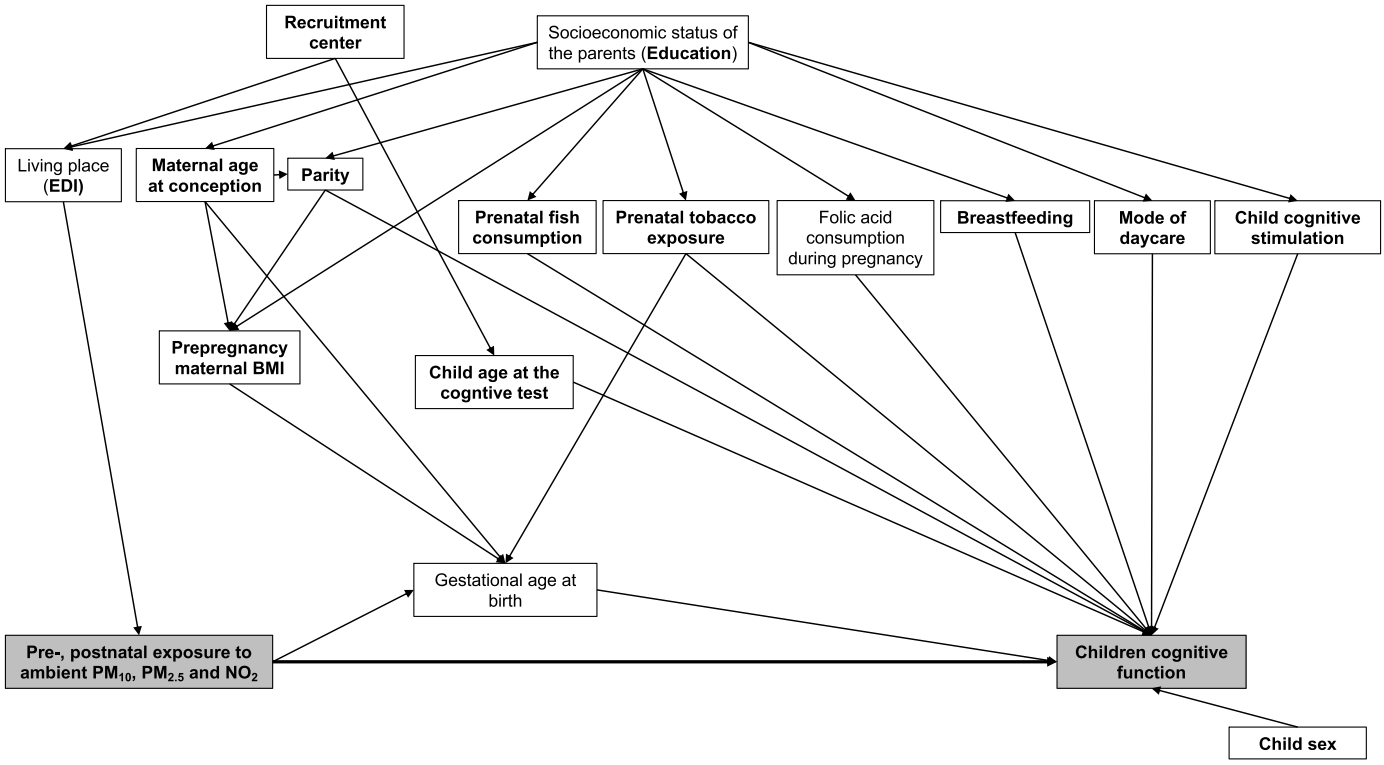

Fig. 2. Directed acyclic graph.
Description of the relationship between pre-, postnatal exposure to ambient pollution and children's cognitive function, in the framework of the EDEN and PELAGIE cohorts.
In **bold**: Exposure, outcome of interest and covariates included in the main analyses of the present study.

child-mother interactions including singing, reading story, playing games; continuous), Home Observation Measurement of the Environment at 5–6 years (HOME; continuous), method of child care ("Collective daycare facility", "Childminder or neighbor", "Family"), age at the cognitive test (continuous) and the French European Deprivation Index (EDI; at the neighborhood scale, for the 2007 year (Pornet et al., 2012); continuous score ranging from −17.3 to 51.1).

2.5. Statistical analysis

a) Imputation

Missing data in the exposure datasets were imputed only if they affected the prenatal period and did not exceed 10 weeks per participant (three participants affected for PM_{10} and $PM_{2.5}$ with up to two weeks of exposure imputed and four participants affected for NO_2 with up to 10 weeks of exposure imputed for one of them). Individuals with 11 weeks missing or more or missing data during the postnatal period were excluded from the analyses. Missing data were imputed by the mean of the previous and next values or by the nearest observation carried forward or backward in case the missing data affected the first or last windows of exposure.

To increase the statistical power of the analyses and avoid selection bias, missing data in the covariates were replaced using single imputation (predictive mean matching method) relying on prediction from exposure, covariates and outcome using the "mice" package (R; version 3.15.0). Imputed and non-imputed datasets were compared using bivariate analyses and did not significantly differ (Table S2).

b) DLNM analyses

Distributed Lag Non-linear Models (DLNM) were used to explore the relationships between exposure to ambient air pollution and child cognitive function (Gasparrini et al., 2010). A model including simultaneously 1) prenatal exposure, encompassing the first 35 gestational weeks as weekly average concentrations (1^{st} cross-basis) and 2) postnatal exposure, covering the first 60 months of life as monthly average concentrations (2^{nd} cross-basis) was fitted for each pollutant (PM_{10}, $PM_{2.5}$, NO_2) and each cognitive score (General, Verbal and Non-verbal abilities) using the "dlnm" package (version 2.4.7). This strategy allowed exposure matrices of the same length for all participants and clearly distinguished between pre- and postnatal exposure.

The dose-response relationship between ambient air pollutant exposure and cognitive scores was assumed to be linear. A non-linear lag-response was considered, using natural cubic splines with 4 degrees of freedom (based on the Akaike information criterion, unconstrained lag-response relationship and parsimony) for both cross-bases. The lag-response (β and 95% confidence interval (95%CI)) curves were modelled for an increase of 10 $\mu g/m^3$ of air pollutant exposure. A time period was considered as a sensitive window of exposure as long as the 95% CI of the lag-specific effect did not cross $\beta = 0$.

c) Sensitivity analyses

To assess the robustness of the results, analyses were repeated after restricting to mother-child pairs with no or very few uncertainties on residential history, no or very few date imputations and no geocoding at the city level (n = 1192).

Analyses were carried out using the R software (version 4.0.4).

3. Results

3.1. Population characteristics

Median mother's age was 29 years (IQR: 26.7, 32.6) at conception (Table 1). 36% of the mothers studied 3 years or more after the

Table 1
Characteristics of the study population (n = 1271, mother-child pairs from the EDEN and PELAGIE cohorts).

Characteristics	All n = 1271	Males n = 650	Females n = 621
	n (%)		
Cohort			
EDEN	1003 (79)	526 (81)	477 (77)
PELAGIE	268 (21)	124 (19)	144 (23)
Highest level of parental education			
Baccalaureate or less	502 (39)	263 (40)	239 (38)
Baccalaureate +1 or + 2 years	316 (25)	161 (25)	155 (25)
Baccalaureate + 3 years (bachelor) or more	453 (36)	226 (35)	227 (37)
Mother's BMI before pregnancy (kg/m^2)			
Underweight (<18.5)	100 (8)	49 (8)	51 (8)
Normal weight (≥18.5 and < 25)	843 (66)	434 (67)	409 (66)
Overweight (≥25 and < 30)	230 (18)	119 (18)	111 (18)
Obese (≥30)	98 (8)	48 (7)	50 (8)
Parity			
No child	563 (44)	287 (44)	276 (44)
One child or more	708 (56)	363 (56)	345 (56)
Mother's fish consumption before pregnancy			
Less than twice/week	978 (77)	501 (77)	477 (77)
Twice/week or more	293 (23)	149 (23)	144 (23)
Mother's tobacco consumption during pregnancy			
No	1000 (79)	505 (78)	495 (80)
Yes	271 (21)	145 (22)	126 (20)
Breastfeeding			
Breastfed less than 6 months	948 (75)	494 (76)	454 (73)
Breastfed 6 months or more	323 (25)	156 (24)	167 (27)
Mode of day care at 24 months			
Collective childcare facility	284 (22)	135 (21)	149 (24)
Childminder or neighbor	741 (58)	382 (59)	359 (58)
Family	246 (19)	133 (20)	113 (18)
	Median (IQR)		
Mother's age at conception (Years)	29.6 (26.7, 32.6)	29.5 (26.7, 32.7)	29.8 (26.6, 32.5)
Maternal stimulation at 24 months	4.3 (4.0, 5.0)	4.5 (3.7, 5.0)	4.3 (4.0, 5.0)
HOME score at 5–6 years	0.2 (−0.5, 0.8)	0.2 (−0.5, 0.8)	0.3 (−0.5, 0.8)
Child age at the cognitive test (Years)	5.7 (5.6, 5.9)	5.7 (5.6, 5.9)	5.7 (5.6, 6.0)
Neighborhood deprivation index	−1.8 (−3.3, 0.0)	−2.0 (−3.4, 0.0)	−1.7 (−3.2, 0.1)
PM_{10} concentration ($\mu g/m^3$)[a]	19.3 (18.3, 20.0)	19.3 (18.4, 20.0)	19.3 (18.2, 20.0)
$PM_{2.5}$ concentration ($\mu g/m^3$)[a]	12.4 (11.6, 13.1)	12.4 (11.7, 13.1)	12.4 (11.6, 13.1)
NO_2 concentration ($\mu g/m^3$)[a]	16.9 (15.5, 19.7)	16.9 (15.5, 19.5)	16.9 (15.6, 19.8)
General abilities	0.1 (−0.4, 0.5)	0.1 (−0.5, 0.5)	0.1 (−0.4, 0.6)
Verbal abilities	0.1 (−0.9, 1.1)	0.1 (−1.0, 1.1)	0.2 (−0.9, 1.0)
Non-verbal abilities	0.1 (−0.8, 1.0)	0.1 (−0.9, 1.0)	0.1 (−0.7, 1.0)

Abbreviations: BMI: Body Mass Index; IQR: InterQuartile Range.
[a] Average from the conception until the 60th month of life.

baccalaureate. Median child's age at assessment was 5 years (IQR: 5.6, 5.9). Almost 80% had not been exposed to prenatal maternal smoking and 75% were breastfed less than six months.

Median ambient air pollution levels over the pre- and postnatal follow-up were on average 19.3 $\mu g/m^3$ (IQR: 18.3, 20.0) for PM_{10}, 12.4 $\mu g/m^3$ (IQR: 11.6, 13.1) for $PM_{2.5}$ and 16.9 $\mu g/m^3$ (IQR: 15.5, 19.7) for NO_2 (Table 1). Estimated concentrations tended to be lower during the summer season compared with the winter season, especially for NO_2 (Fig. 3). Exposure levels were comparable for males and females. Moderate to high Spearman correlations were observed between PM_{10} and $PM_{2.5}$ ($\rho = 0.92$), PM_{10} and NO_2 ($\rho = 0.58$), $PM_{2.5}$ and NO_2 ($\rho = 0.55$) as well as between prenatal and postnatal exposure: PM_{10} ($\rho = 0.50$), $PM_{2.5}$ ($\rho = 0.58$) and NO_2 ($\rho = 0.85$).

The two-factor second order CFA provided reasonable to good fit models to describe cognitive abilities: for EDEN, the CFI and RMSEA reached 0.96 and 0.06, respectively while for PELAGIE, the CFI and RMSEA were 0.92 and 0.06, respectively. General, Verbal and Non-verbal abilities distribution did not significantly differ by sex (P-value >0.05; Fig. S3).

Participants included in the present study lived in places with significantly higher PM_{10}, $PM_{2.5}$ and NO_2 levels and in more deprived areas than participants not included. Included mothers were more frequently overweight or obese, more often breastfed 6 months or more and were more likely to use a collective childcare facility to look after their child. The EDEN cohort was also significantly more represented than the PELAGIE cohort among included participants (Table S1).

3.2. Ambient air pollution and child cognitive function

Because trends in lag-responses observed for males and females differed, sex-specific results are presented in the next paragraphs (Figs. S5–S7 for non-sex-stratified results).

In males, increased maternal exposure (10 $\mu g/m^3$) to PM_{10} during the end of the second and early third trimesters of pregnancy was significantly associated with lower General and Non-verbal abilities (Fig. 4). Significant sensitive windows ranged between the 24th and 33rd weeks of gestation. In particular, an increased exposure (10 $\mu g/m^3$) of PM_{10} at the peak of the window (weeks 28-29 after conception) was associated with a 0.07 point (95%CI: -0.13; -0.01) decrease in the General score derived from CFA. Similarly, higher maternal exposure to $PM_{2.5}$ between the 17th and 30th weeks of gestation was related to lower General and Non-verbal abilities (Fig. 5). Maternal exposure to NO_2 was adversely associated with the three cognitive abilities, with sensitive windows occurring slightly earlier than PM, during the second trimester of pregnancy (Figure S4). Sensitive windows of exposure more specifically encompassed the 15th and 22nd weeks of gestation. Of note, maternal exposure to PM_{10} before the 11th week of gestation was related to higher scores for the three cognitive abilities (Fig. 4), with an increased exposure (10 $\mu g/m^3$) of PM_{10} at the peak of the window (weeks 4-5 after conception) associated with a 0.09 point (95%CI: 0.02; 0.16) increase in the General score derived from CFA. Regarding postnatal exposure, significant sensitive windows were only observed for $PM_{2.5}$. Higher child exposure to $PM_{2.5}$ between the 35th and 52nd months of life (i.e. 3-4 years) was associated with lower General, Verbal and Non-verbal abilities (Fig. 5).

Among females, an adverse relationship was only highlighted for $PM_{2.5}$ and Non-verbal abilities for exposure occurring between the 28th and 32nd gestational weeks (Figure 5). Apparent protective associations were observed for exposure occurring before the 3rd gestational week between NO_2 and General and Verbal abilities (Figure S4) as well as for exposure occurring before the 6th month of child life between $PM_{2.5}$ and all the three cognitive abilities (Figure 5).

3.3. Sensitivity analysis

When restricting to participants with no or very few residential history uncertainties (n = 1192), the curves of the lag-response relationships were highly similar to the main analyses (Figs. S8–S10, Figs. S11–S13 for non-sex-stratified results). The significance and the length of the sensitive windows of the associations observed in the main analyses varied very little in the sensitivity analyses. Consistent with the main results, increased mid-pregnancy exposure to PM_{10}, $PM_{2.5}$and NO_2 exposure as well as $PM_{2.5}$child exposure at 3-4 years tended to be associated with lower cognitive abilities in males. Sensitivity analyses further suggested some adverse effects of $PM_{2.5}$ exposure at 2-3 years on General and Nonverbal abilities on females.

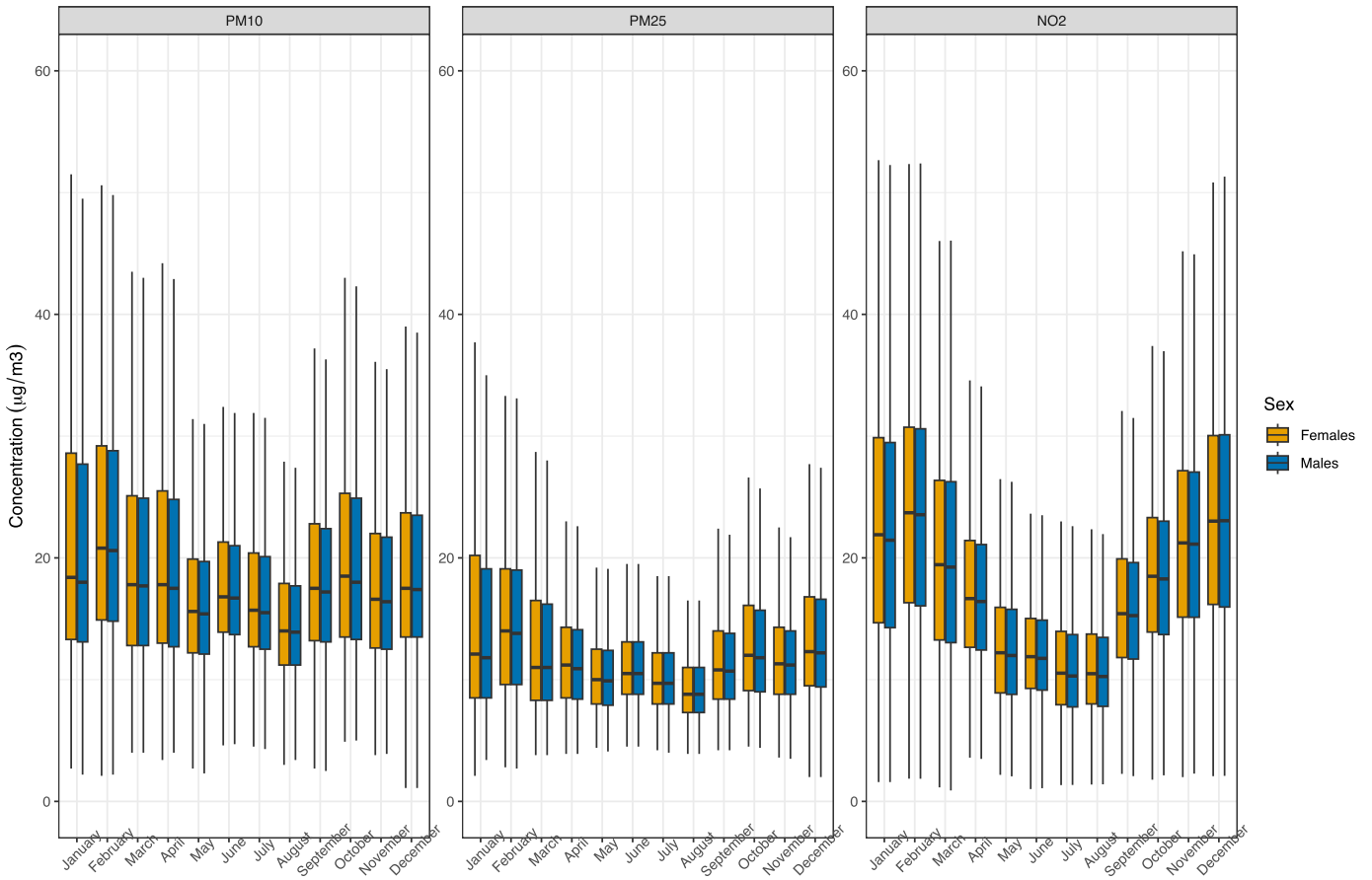

Fig. 3. Distribution of daily PM_{10}, $PM_{2.5}$ and NO_2 concentrations (µg/m^3) aggregated by month, for the period covering the first 35 gestational weeks and first 60 months after birth.
The top and the bottom of the boxes show the 25th and the 75th percentiles, the middle line inside the box indicates the median, the whiskers display the minimum and maximum values within 1.5 times the interquartile range from the first and third quartiles.
n = 1271 mother-child pairs from the EDEN and PELAGIE cohorts.

Of note, participants excluded for the sensitivity analysis were more frequently from the PELAGIE cohort, took the cognitive tests at a slightly older age and were exposed to lower levels of air pollution than the included participants (Table S3).

4. Discussion

This study explored the temporal relationship of pre- and postnatal exposure to PM_{10}, $PM_{2.5}$ and NO_2 based on fine resolution PM exposure models with three scores of cognitive abilities among 1271 children from the French EDEN and PELAGIE mother-child cohorts. Lower males' General and Non-verbal abilities in relationship with increased exposure to PM_{10}, $PM_{2.5}$ and NO_2 during mid-pregnancy was observed. Prenatal exposure to NO_2 was related to lower males' Verbal abilities too. In addition, increased males' exposure to $PM_{2.5}$ around 3-4 years was associated with lower General, Verbal and Non-verbal abilities. In females, an adverse association was solely highlighted between increased $PM_{2.5}$ exposure during end-pregnancy and Non-verbal abilities. Some protective associations were punctually observed for the very first gestational weeks or months of life for both males and females, the different pollutants and cognitive scores.

Air pollution is pervasive and current research suggests that there is no safe level of air pollution exposure for human health (Marks, 2022). In this work, participating women and children were exposed to PM and NO_2 concentrations largely exceeding the WHO recommendations (PM_{10}: 15 µg/m^3; $PM_{2.5}$: 5 µg/m^3; NO_2: 10 µg/m^3 annual mean): 19.3 µg/m^3 (IQR: 18.3, 20.0) for PM_{10}, 12.4 µg/m^3 (IQR: 11.6, 13.1) for $PM_{2.5}$ and 16.9 µg/m^3 (IQR: 15.5, 19.7) for NO_2 (Table 1). In France, the sources of PM_{10} distribute as follows: 36% from the residential and tertiary sectors, 26% from industry, 25% from agriculture and 14% from transport. $PM_{2.5}$ are mainly released by the residential and tertiary sectors (57%) while NOx are mainly attributed to transport (53%) (Boullanger et al., 2022).

Increased exposure to PM_{10} between the 24th and the 33rd weeks of gestation was related to lower males' General, Non-verbal abilities in the main analysis. A few past studies observed adverse associations between prenatal PM_{10} exposure and similar cognitive measurements but also for other abilities. Loftus et al. concluded that prenatal exposure to PM_{10} was related to lower full-scale IQ, verbal IQ, fluid reasoning and quantitative reasoning scores at 4–6 years in American children (Loftus et al., 2019). In Italy, lower cognitive scores assessed at 5–8 years through the Developmental Profile 3 were noticed for increased maternal exposure to PM_{10} during the second, third trimesters and overall pregnancy (Girardi et al., 2021). Of note, distributed lag models implemented in the Southern California Mother's Milk Study highlighted adverse associations between PM_{10} exposure during the 5th and 6th months of pregnancy (a sensitive window close to ours) and composite cognitive score assessed through the Bayley-III scale in 2-year-old children (Morgan et al., 2023). Such detrimental association was not detected in a large study based on six European birth cohorts which followed younger children, assessed exposure at birth and used various neuropsychological batteries (Guxens et al., 2014).

Higher maternal exposure to $PM_{2.5}$ between the end of the second and early third trimesters (17th - 30th gestational weeks) was

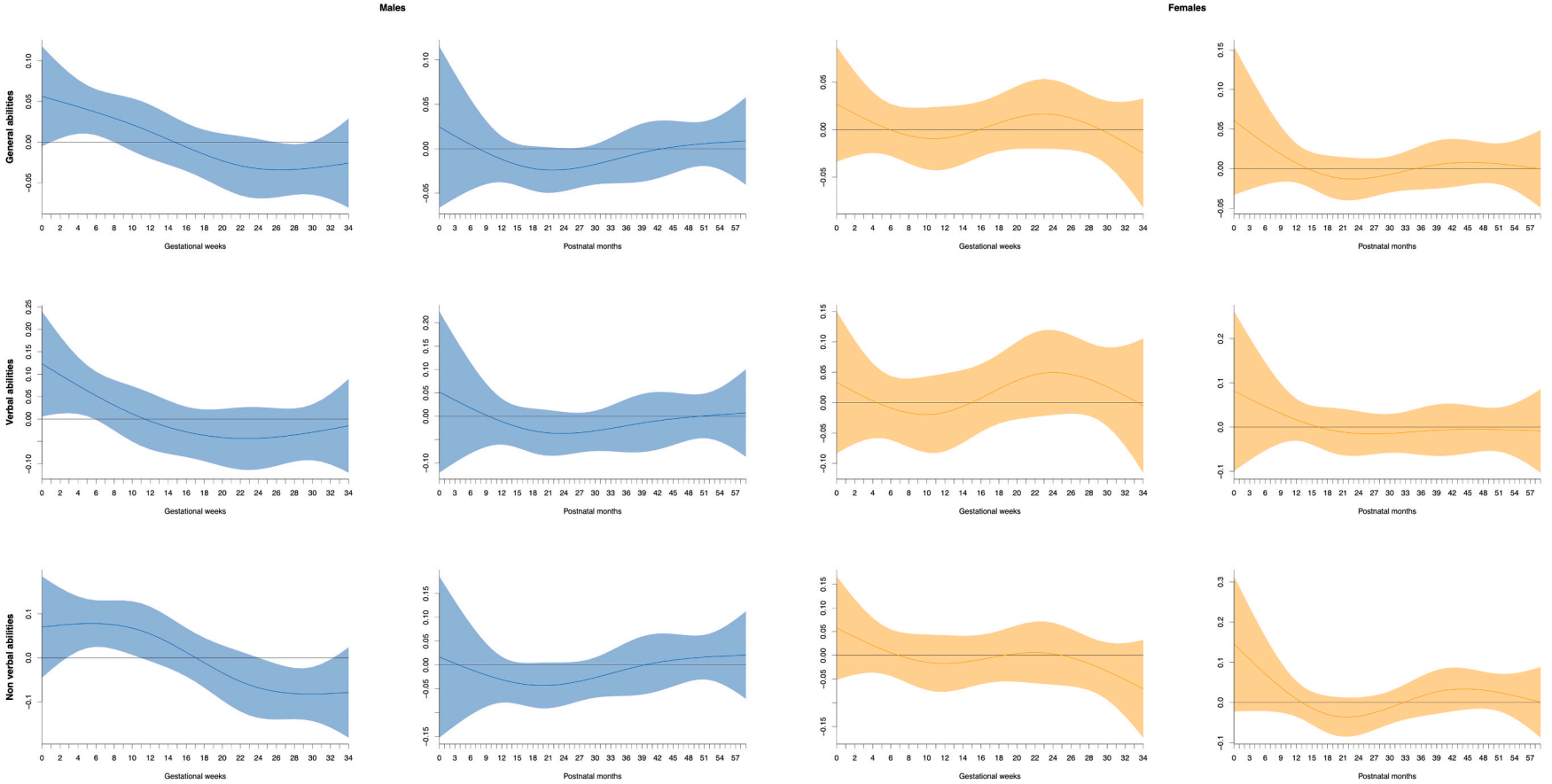

Fig. 4. Sex-stratified lag-specific effect of a 10 μg/m^3 increase in PM_{10} concentration on children's cognitive abilities - Main analyses.
Shaded areas represent the 95% CI of the estimate.
Abbreviations: CI: Confidence Interval.
Models adjusted for the recruitment center, maternal education, maternal age at conception, maternal prepregnancy body mass index, maternal fish consumption before pregnancy, parity, child prenatal tobacco exposure, breastfeeding, child stimulation through maternal interactions, Home Observation Measurement of the Environment, method of child care, age at the cognitive test and the French European Deprivation Index.
n = 1271 mother-child pairs from the EDEN and PELAGIE cohorts.

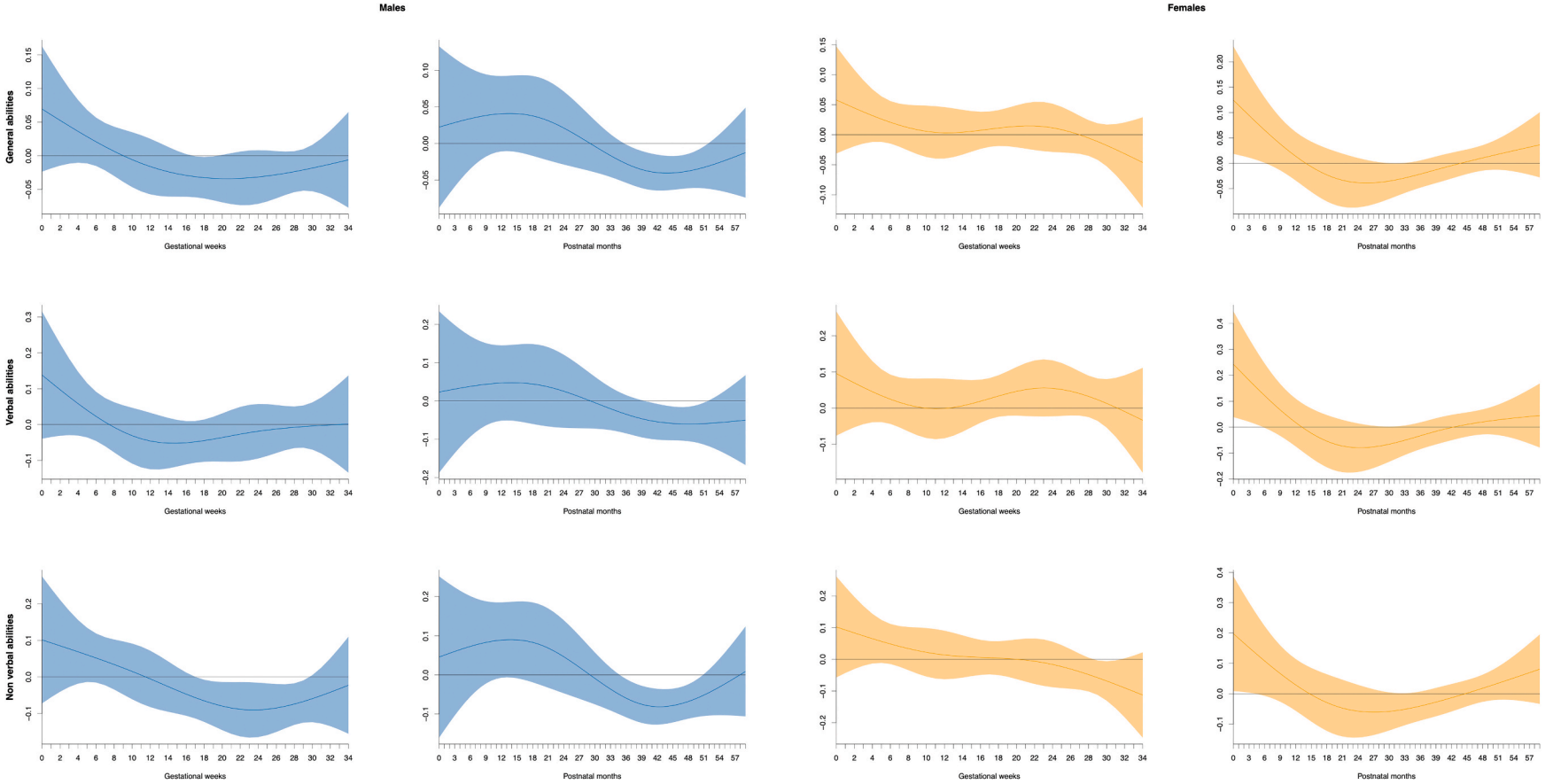

Fig. 5. Sex-stratified lag-specific effect of a 10 μg/m^3 increase in $PM_{2.5}$ concentration on children's cognitive abilities - Main analyses.
Shaded areas represent the 95% CI of the estimate.
Abbreviations: CI: Confidence Interval.
Models adjusted for the recruitment center, maternal education, maternal age at conception, maternal prepregnancy body mass index, maternal fish consumption before pregnancy, parity, child prenatal tobacco exposure, breastfeeding, child stimulation through maternal interactions, Home Observation Measurement of the Environment, method of child care, age at the cognitive test and the French European Deprivation Index.
n = 1271 mother-child pairs from the EDEN and PELAGIE cohorts.

significantly associated with lower males' General and Non-verbal abilities, which tends to be consistent with PM_{10} results. A significant sensitive window at the same period was observed among females for Non-verbal abilities solely. An American multi-cohort study showed significant relationship between higher exposure to $PM_{2.5}$ during the second trimester and lower IQ in 4-6-year-old males (Ni et al., 2022). Also, higher exposure to $PM_{2.5}$ around 20–40 weeks gestation has been associated with lower IQ and attention among 6-year-old American males while increased exposure around 8–27 weeks gestation was related to lower visual memory, attention-concentration and general memory scores among females (Chiu et al., 2016). Similarly, increased $PM_{2.5}$ exposure between the 6^{th} and 8^{th} months of pregnancy was associated with lower composite cognitive score in 2-year-old children from the Southern California Mother's Milk Study (Morgan et al., 2023). In the INMA cohort, average exposure during pregnancy has been related to lower verbal and memory scores at 4-6-years among males (Lertxundi et al., 2019). For its part, postnatal exposure to $PM_{2.5}$ at age 3-4 years was related to lower males' scores for all three cognitive abilities investigated in the present study. Of note, significant sensitive windows were observed for postnatal exposure to $PM_{2.5}$ at 2-3-year and General, Non-verbal abilities among females in sensitivity analyses. Such exposure assessed at school 2–3 years before cognitive tests has been linked with decreasing working memory in 11-years old Spanish children (Forns et al., 2017) while postnatal exposure measured at home 1–2 years before cognitive tests was related to diminished performance IQ (through the matrix reasoning subscale) or the verbal IQ similarities subscale among 9–20 years old American (Wang et al., 2017). Using distributed lag models covering both pregnancy and the first seven years of life, Rivas et al. showed deleterious associations between exposure at 6–7 years to $PM_{2.5}$ and lower working memory in males, and executive attention assessed in males and females at 8 years (Rivas et al., 2019). Of note, a trend for protective associations was observed between prenatal and early life exposure to $PM_{2.5}$ and attentiveness. One study analyzing both pre- and postnatal exposure highlighted lower cognitive measurements among 4–5 years children for postnatal exposure only (with no sex-stratification (Binter et al., 2022)). Some past works did not highlight significant association between pre- or postnatal exposure to $PM_{2.5}$ and child cognitive function (Guxens et al., 2014; Harris et al., 2015; Porta et al., 2016).

Maternal exposure to NO_2 between the 15^{th} and 22^{nd} weeks of gestation was consistently associated with General, Verbal and Non-verbal abilities among males. A recent meta-analysis showed significant association between prenatal exposure to NO_2 and lower global and fine psychomotor abilities but no significant relationship with language and cognitive development (Shang et al., 2020).

Unexpectedly, our results showed punctual protective associations between early pregnancy or postnatal exposure to PM_{10}, $PM_{2.5}$ or NO_2 and the three cognitive measurements in males and females. To the best of our knowledge, no biological hypothesis supports a favorable effect of air pollution exposure on cognitive function. These positive associations are unlikely to be causal. Protective associations observed for prenatal exposure might be attributed to chance or live-birth bias. Such bias has been frequently observed and described when examining prenatal environmental exposure and developmental outcomes, including in studies linking NO_2 exposure and autism (Leung et al., 2021; Raz et al., 2018) or perfluoroalkyl substances and attention-deficit/hyperactivity disorder (Liew et al., 2015). It may also have occurred in a study very similar to the present work, which highlighted, among others, a protective association between average exposure to NO_2 during pregnancy and Verbal IQ and no significant association for PM_{10} and $PM_{2.5}$ in teenagers from the Dutch Generation R cohort (Kusters et al., 2022). Indeed, the inevitable restriction of the analyses to live births may have excluded the most vulnerable fetuses as well as those exposed to both high air-pollution levels and other unmeasured causes of reduced fetal survival and cognitive function (known as collider) leading to distorted associations. Interestingly, increased risk of stillbirth has been associated with PM exposure (Sarovar et al., 2020; Xue et al., 2022). Also, the fetus may be more sensitive to air pollution in the first weeks of gestation, leading to a more noticeable live-birth bias for exposure in early pregnancy than later pregnancy. Indeed, it is estimated that around 80% of all cases of pregnancy loss occur within the first trimester (Wang et al., 2003; Wilcox et al., 1988). The protective associations may also be partly due to residual confounding by socioeconomic factors and parents' intelligence. Large cities may concentrate high air pollution levels but also families with high educational attainments and income as well as stimulating extra-curricular activities. More generally, the results of this study may be affected by chance leading to spurious associations.

The ability of PM and NO_2 to induce oxidative stress and inflammation have been identified as key mechanisms underpinning their neurotoxicity by *in vitro*, animal and epidemiological studies (Costa et al., 2014; Kelly, 2003). These mechanisms may occur in the mother, in the developing fetus and in the child and may be both systemic and localized in the brain after pollutants crossed the blood-air, blood--placental and blood-brain barriers or directly crossed the nasal olfactory mucosa (Bongaerts et al., 2020; Brockmeyer and D'Angiulli, 2016; Costa et al., 2020). Oxidative stress and inflammation can impair the placenta function and subsequently fetal development including brain structures and circuits, with lifelong consequences (Saenen et al., 2019; Yi et al., 2022). Alterations are diverse including placental epigenic changes (Abraham et al., 2018; Saenen et al., 2019), release of pro-inflammatory cytokines, neurotransmitter imbalance partly mediated by microglial activation (which modulates, among others, neurogenesis and angiogenesis) and astrocytes, oligodendrocytes dysfunction, white matter changes (Allen et al., 2017; Morimoto and Nakajima, 2019; Morris et al., 2021). These alterations may possibly be amplified by mitochondrial dysfunction (Morris et al., 2021).

The developing fetus and the young child are particularly vulnerable because of the rapid neural development, the high metabolic demand of brain, its rich lipid composition, its antioxidant deficiencies and child's higher respiratory rate to body size, specific behavior, etc. (Ha, 2021; Xu et al., 2016). Because of the sequential development of the brain, any disruption in the process may successively affect various structural regions and different cognitive domains depending on the timing, the dose of exposure and the sensitivity of the regions (Herting et al., 2019; Volk et al., 2021). This may support differential effects across cognitive abilities (Peyre et al., 2016).

Consistently with past reviews (Ha, 2021; Yi et al., 2022), adverse significant associations were mainly observed for males in the present study. Sexual dimorphism in brain structure, function development and neurodevelopmental disorders has been widely documented and males' greater vulnerability to certain factors is established (Geschwind and Galaburda, 1985; López-Ojeda and Hurley, 2021; Pallayova et al., 2019; Yi et al., 2022). The underlying biological mechanisms are still speculative; they may be linked with the sex chromosomes and hormones. In particular, in females, estrogens exert anti-inflammatory activity that might regulate inflammation initiated in response to air pollution (Shivers et al., 2015). Besides, animal studies suggested neurodevelopmental disorder and cognitive impairment may be linked with changes in gene expression notably related to serotonin signaling, endocytosis, Gαi, cAMP signaling, as well as inflammatory pathways in males specifically (Yi et al., 2022). Differences in male and female microglia (morphology and number) may also partly explain sex-differences (Hanamsagar and Bilbo, 2016). More generally, it has been demonstrated that male embryos show a greater vulnerability to environmental factors which may be related to a lower immune compatibility in maternal-fetal interactions compared with female embryos, leading to a possible higher immune response and proinflammatory state in male fetuses (Capriati et al., 2023).

Limitations should be acknowledged. First, as previously mentioned, bias due to selection on live births, residual confounding or chance finding may have occurred. Second, covariates were not always

collected with the same degree of detail for EDEN and PELAGIE which often resulted in a loss of information during pooling. Despite the implementation of a dedicated pooling approach for cognitive data, one should keep in mind that child intelligence was assessed using different tests and at slightly different ages in the two cohorts. Maternal IQ was not available for the two cohorts and therefore could not be adjusted for. Third, measurement error in the air pollutant estimates exists. Change in the measurement techniques used by the national air quality monitoring stations to include semi-volatile PM in 2007 for PM_{10} and in 2008–2009 for $PM_{2.5}$ resulted in an underestimation of PM concentrations before these dates (Hough et al., 2021). This change may have affected the postnatal trajectory of exposure to PM and our ability to detect significant sensitive windows. Also, the NO_2 model spatial resolution was lower (4 km) and tended to overestimate concentrations in rural areas (Real et al., 2022). Besides, exposure was assessed at participants' home address solely, without taking into account pregnant women and their child's travel or indoor pollution. All these elements may lead to non-differential error resulting in an underestimation of the risk. Fourth, this work did not consider PM chemical composition that may vary geographically (van Donkelaar et al., 2019) and may differently affect health (Park et al., 2018). Due to the correlation between PM and NO_2 levels and to model complexity, the present work also did not implement multi-pollutant models to rule out co-pollutant confounding. It did not adjust for noise because of a lack of valid data.

This work shows several strengths, however. This is one of the first studies considering air pollution exposure on the long term, taking into account both pre- and postnatal exposure at a fine temporal resolution (weeks and months). Both air pollution models covered the EDEN and PELAGIE cohorts homogeneously in time and space. The PM models notably rely on an innovative multi-stage ensemble model showing good performance (with a mean absolute error of 4.26 $\mu g/m^3$ and $R^2 = 0.71$ for PM_{10}, and a mean absolute error of 2.72 $\mu g/m^3$ and $R^2 = 0.76$ for $PM_{2.5}$ (Hough et al., 2021);). DLNM make use of these data to explore sensitive windows, with no a priori, dealing with the correlation of exposure over time and lagged effects. Second, child cognitive function was assessed using several standardized and validated neuropsychological testing tools, implemented by trained psychologists, according to rigorous protocols. Finally, the analyses took advantage of two distinct French mother-child cohorts with highly similar protocols. Pooling these two cohorts improved the representativity of the sample in terms of participants' characteristics, exposure levels and also increased the sample size and so the statistical power.

5. Conclusion

This work expands research on the effect of early life exposure to air pollution on child cognitive development. Analyzing the time dimension of the exposure-response relationship, it suggests deleterious associations between PM_{10}, $PM_{2.5}$ and NO_2 exposure during mid-pregnancy and to $PM_{2.5}$ around 3-4years and General, Verbal and Non-verbal abilities in school-age males. It shows also unexpected protective associations possibly due to live-birth bias, residual confounding or chance finding. The effects could be substantial at the population level considering the ubiquitous exposure to air pollution.

Individual contributions

Ariane Guilbert: Methodology; Software; Formal analysis; Writing - original draft; Visualization. Jonathan Y. Bernard: Methodology; Writing - review & editing. Hugo Peyre: Methodology; Writing - review & editing. Nathalie Costet: Methodology; Writing - review & editing. Ian Hough: Methodology; Software; Writing - review & editing. Emie Seyve: Software; Writing - review & editing. Christine Monfort: Software; Writing - review & editing. Claire Philippat: Conceptualization; Writing - review & editing. Rémy Slama: Writing - review & editing. Itai Kloog: Writing - review & editing. Cécile Chevrier: Conceptualization; Funding acquisition; Methodology; Writing - review & editing. Barbara Heude: Conceptualization; Writing - review & editing. Franck Ramus - Conceptualization; Methodology; Writing - review & editing. Johanna Lepeule - Conceptualization; Funding acquisition; Methodology; Writing - original draft; Supervision; Project administration.

Funding source

This work as well as AG were funded by the Fondation de France (PAND-Alp grant 00089597).

The EDEN cohort was supported by the Foundation for Medical Research, the National Agency for Research, the National Institute for Research in Public Health (IRESP: TGIR cohorte santé. 2008 program), the French Ministry of Health, the French Ministry of Research, the Inserm Bone and Joint Diseases National Research and Human Nutrition National Research Programs, Paris-Sud University, Nestlé, the French National Institute for Population Health Surveillance, the French National Institute for Health Education, the European Union FP7 programs (FP7/2007–2013, HELIX, ESCAPE, ENRIECO, Medall projects), the Diabetes National Research Program (through a collaboration with the French Association of Diabetic Patients), the French Agency for Environmental Health Safety, Mutuelle

Générale de l'Education Nationale, the French National Agency for Food Security and the French-speaking Association for the Study of Diabetes and Metabolism.

This study in the PELAGIE cohort was mainly supported by Inserm, the French National Research Agency (ANR-2010-PRSP-007) and the French Agency for Food, Environmental and Occupational Health and Safety (ANSES APR EST, 2009). The initial fundings of the PELAGIE cohort were Inserm, the French Ministries of Health, Labor, and Research, the French National Institute for Public Health Surveillance, the National Agency for Research, the French Agency for Environmental Health Safety (Afsset/ANSES), the European programs Hi-WATE and ENRIECO, and the Research Institute of Public Health.

FR and HP received support under the program "Investissements d'Avenir" launched by the French Government and implemented by ANR with the references ANR-17-EURE-0017 and ANR-10-IDEX-0001-02.

The funders contributed to data collection but had no role in the design and conduct of the study; analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The opinions, results, and conclusions herein are those of the authors and do not reflect the official policy or position of the funding sources.

ETHICS

The EDEN and PELAGIE cohorts were reviewed and approved prior to their conduct by ethical committees (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale du Kremlin Bicêtre, Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé) and the Data Protection Authority (Commission Nationale de l'Informatique et des Libertés). All participating women gave informed written consent for themselves and their future child at enrollment.

Data sharing statement

The EDEN and PELAGIE datasets analyzed in the present study are not publicly available as they are containing information that could compromise the research participant's privacy/consent and are property of the research institutes. However, they are available on reasonable request and with permission from the EDEN Steering Committee by filling the questionnaire at http://eden.vjf.inserm.fr/en/page/25/submit-a-research-project or the PELAGIE Steering Committee, after examination according to the French ethical rules and the

European individual data protection regulations.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Ariane Guilbert reports financial support was provided by Fondation de France. Franck Ramus & Hugo Peyre reports financial support was provided by Agence nationale de la recherche.

Data availability

Data will be made available on request.

Acknowledgement

We acknowledge the commitment of the EDEN mother-child cohort study group: I. Annesi-Maesano, J.Y. Bernard, J. Botton, M.A. Charles, P. Dargent-Molina, B. de Lauzon-Guillain, P. Ducimetire, M. de Agostini, B. Foliguet, A. Forhan, X. Fritel, A. Germa, V. Goua, R. Hankard, B. Heude, M. Kaminski, B. Larroque, N. Lelong, J. Lepeule, G. Magnin, L. Marchand, C. Nabet, F. Pierre, R. Slama, M.J. Saurel-Cubizolles, M. Schweitzer and O. Thiebaugeorges. We express our sincere thanks to the participants of the EDEN study. We are also grateful to the midwives, obstetricians, gynecologists, ultrasonographers, pediatricians, and families who participated in the PELAGIE study. We thank V. Villalon, C. Nouyrigat, V. Dardier, and S. Le Sourn-Bissaoui for their help, M. Mordelet and O. Martin for conducting neuropsychological testing, and T. Serrano-Chavez for the geocoding in PELAGIE.

We thank the INERIS (French Institute for Industrial Environment and Risks) for making available in open data the air pollutant concentrations data from which NO_2 analyzed in this study were used: "https://www.ineris.fr/fr/recherche-appui/risques-chroniques/mesure-prevision-qualite-air/qualite-air-france-metropolitaine". We also acknowledge the MapInMed platform for providing the European Deprivation Index data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.116557.

References

Abraham, E., Rousseaux, S., Agier, L., Giorgis-Allemand, L., Tost, J., Galineau, J., Hulin, A., Siroux, V., Vaiman, D., Charles, M.-A., Heude, B., Forhan, A., Schwartz, J., Chuffart, F., Bourova-Flin, E., Khochbin, S., Slama, R., Lepeule, J., EDEN mother-child cohort study group, 2018. Pregnancy exposure to atmospheric pollution and meteorological conditions and placental DNA methylation. Environ. Int. 118, 334–347. https://doi.org/10.1016/j.envint.2018.05.007.

Allen, J.L., Klocke, C., Morris-Schaffer, K., Conrad, K., Sobolewski, M., Cory-Slechta, D. A., 2017. Cognitive effects of air pollution exposures and potential mechanistic underpinnings. Curr. Environ. Health Rep. 4, 180–191. https://doi.org/10.1007/s40572-017-0134-3.

Allison, P.D., 2003. Missing data techniques for structural equation modeling. J. Abnorm. Psychol. 112, 545–557. https://doi.org/10.1037/0021-843X.112.4.545.

Béranger, R., Garlantézec, R., Le Maner-Idrissi, G., Lacroix, A., Rouget, F., Trowbridge, J., Warembourg, C., Monfort, C., Le Gléau, F., Jourdin, M., Multigner, L., Cordier, S., Chevrier, C., 2017. Prenatal exposure to glycol ethers and neurocognitive abilities in 6-year-old children: the PELAGIE cohort study. Environ. Health Perspect. 125, 684–690. https://doi.org/10.1289/EHP39.

Binter, A.-C., Bernard, J.Y., Mon-Williams, M., Andiarena, A., González-Safont, L., Vafeiadi, M., Lepeule, J., Soler-Blasco, R., Alonso, L., Kampouri, M., Mceachan, R., Santa-Marina, L., Wright, J., Chatzi, L., Sunyer, J., Philippat, C., Nieuwenhuijsen, M., Vrijheid, M., Guxens, M., 2022. Urban environment and cognitive and motor function in children from four European birth cohorts. Environ. Int. 158, 106933 https://doi.org/10.1016/j.envint.2021.106933.

Bongaerts, E., Nawrot, T.S., Van Pee, T., Ameloot, M., Bové, H., 2020. Translocation of (ultra)fine particles and nanoparticles across the placenta; a systematic review on the evidence of in vitro, ex vivo, and in vivo studies. Part. Fibre Toxicol 17, 56. https://doi.org/10.1186/s12989-020-00386-8.

Boullanger, C., Bouzidi, H., Cesbron, O., Clincke, A.-S., Crunaire, S., Gandar, S., Le Bihan, O., Le Moullec, A., Mahé-Deckers, C., Meleux, F., Morice, Y., 2022. Bilan de la qualité de l'air extérieur en France en 2021. Le service des données et études statistiques (SDES).

Brockmeyer, S., D'Angiulli, A., 2016. How air pollution alters brain development: the role of neuroinflammation. Transl. Neurosci. 7, 24–30. https://doi.org/10.1515/tnsci-2016-0005.

Capriati, M., Hao, C., D'Cruz, S.C., Monfort, C., Chevrier, C., Warembourg, C., Smagulova, F., 2023. Genome-wide analysis of sex-specific differences in the mother–child PELAGIE cohort exposed to organophosphate metabolites. Sci. Rep. 13, 8003. https://doi.org/10.1038/s41598-023-35113-8.

Chandra, M., Rai, C.B., Kumari, N., Sandhu, V.K., Chandra, K., Krishna, M., Kota, S.H., Anand, K.S., Oudin, A., 2022. Air pollution and cognitive impairment across the life course in humans: a systematic review with specific focus on income level of study area. Int. J. Environ. Res. Publ. Health 19, 1405. https://doi.org/10.3390/ijerph19031405.

Chen, C., Lee, S., Stevenson, H.W., 1996. Long-term prediction of academic achievement of American, Chinese, and Japanese adolescents. J. Educ. Psychol. 88, 750–759. https://doi.org/10.1037/0022-0663.88.4.750.

Chen, H., Oliver, B.G., Pant, A., Olivera, A., Poronnik, P., Pollock, C.A., Saad, S., 2021. Particulate matter, an intrauterine toxin affecting foetal development and beyond. Antioxidants 10, 732. https://doi.org/10.3390/antiox10050732.

Chiu, Y.-H.M., Hsu, H.-H.L., Coull, B.A., Bellinger, D.C., Kloog, I., Schwartz, J., Wright, R. O., Wright, R.J., 2016. Prenatal particulate air pollution and neurodevelopment in urban children: examining sensitive windows and sex-specific associations. Environ. Int. 87, 56–65. https://doi.org/10.1016/j.envint.2015.11.010.

Chowdhury, S., Pozzer, A., Haines, A., Klingmüller, K., Münzel, T., Paasonen, P., Sharma, A., Venkataraman, C., Lelieveld, J., 2022. Global health burden of ambient PM2.5 and the contribution of anthropogenic black carbon and organic aerosols. Environ. Int. 159, 107020 https://doi.org/10.1016/j.envint.2021.107020.

Costa, L.G., Cole, T.B., Coburn, J., Chang, Y.-C., Dao, K., Roque, P., 2014. Neurotoxicants are in the air: convergence of human, animal, and in vitro studies on the effects of air pollution on the brain. BioMed Res. Int. 2014, 736385. https://doi.org/10.1155/2014/736385.

Costa, L.G., Cole, T.B., Dao, K., Chang, Y.-C., Coburn, J., Garrick, J.M., 2020. Effects of air pollution on the nervous system and its possible role in neurodevelopmental and neurodegenerative disorders. Pharmacol. Ther. 210, 107523 https://doi.org/10.1016/j.pharmthera.2020.107523.

European Environment Agency, 2022. Europe's Air Quality Status 2022. https://www.eea.europa.eu/. https://www.eea.europa.eu/publications/status-of-air-quality-in-Europe-2022/europes-air-quality-status-2022. accessed 9.5.22.

Forns, J., Dadvand, P., Esnaola, M., Alvarez-Pedrerol, M., López-Vicente, M., Garcia-Esteban, R., Cirach, M., Basagaña, X., Guxens, M., Sunyer, J., 2017. Longitudinal association between air pollution exposure at school and cognitive development in school children over a period of 3.5 years. Environ. Res. 159, 416–421. https://doi.org/10.1016/j.envres.2017.08.031.

Freire, C., Ramos, R., Puertas, R., Lopez-Espinosa, M.-J., Julvez, J., Aguilera, I., Cruz, F., Fernandez, M.-F., Sunyer, J., Olea, N., 2010. Association of traffic-related air pollution with cognitive development in children. J. Epidemiol. Community Health 64, 223–228. https://doi.org/10.1136/jech.2008.084574.

Gasparrini, A., Armstrong, B., Kenward, M.G., 2010. Distributed lag non-linear models. Stat. Med. 29, 2224–2234. https://doi.org/10.1002/sim.3940.

Geschwind, N., Galaburda, A.M., 1985. Cerebral lateralization: biological mechanisms, associations, and pathology: I. A hypothesis and a program for research. Arch. Neurol. 42, 428–459. https://doi.org/10.1001/archneur.1985.04060050026008.

Gibb, R., Kovalchuk, A., 2018. Chapter 1 - brain development. In: Gibb, R., Kolb, B. (Eds.), The Neurobiology of Brain and Behavioral Development. Academic Press, pp. 3–27. https://doi.org/10.1016/B978-0-12-804036-2.00001-7.

Girardi, P., Lanfranchi, S., Mastromatteo, L.Y., Stafoggia, M., Scrimin, S., 2021. Association between exposure to particulate matter during pregnancy and multidimensional development in school-age children: a cross-sectional study in Italy. Int. J. Environ. Res. Publ. Health 18, 11648. https://doi.org/10.3390/ijerph182111648.

Gonzalez-Casanova, I., Stein, A.D., Barraza-Villarreal, A., Feregrino, R.G., DiGirolamo, A., Hernandez-Cadena, L., Rivera, J.A., Romieu, I., Ramakrishnan, U., 2018. Prenatal exposure to environmental pollutants and child development trajectories through 7 years. Int. J. Hyg Environ. Health 221, 616–622. https://doi.org/10.1016/j.ijheh.2018.04.004.

Guxens, M., Garcia-Esteban, R., Giorgis-Allemand, L., Forns, J., Badaloni, C., Ballester, F., Beelen, R., Cesaroni, G., Chatzi, L., de Agostini, M., de Nazelle, A., Eeftens, M., Fernandez, M.F., Fernández-Somoano, A., Forastiere, F., Gehring, U., Ghassabian, A., Heude, B., Jaddoe, V.W.V., Klümper, C., Kogevinas, M., Krämer, U., Larroque, B., Lertxundi, A., Lertxuni, N., Murcia, M., Navel, V., Nieuwenhuijsen, M., Porta, D., Ramos, R., Roumeliotaki, T., Slama, R., Sørensen, M., Stephanou, E.G., Sugiri, D., Tardón, A., Tiemeier, H., Tiesler, C.M.T., Verhulst, F.C., Vrijkotte, T., Wilhelm, M., Brunekreef, B., Pershagen, G., Sunyer, J., 2014. Air pollution during pregnancy and childhood cognitive and psychomotor development: six European birth cohorts. Epidemiol. Camb. Mass 25, 636–647. https://doi.org/10.1097/EDE.0000000000000133.

Ha, S., 2021. Air pollution and neurological development in children. Dev. Med. Child Neurol. 63, 374–381. https://doi.org/10.1111/dmcn.14758.

Hanamsagar, R., Bilbo, S.D., 2016. Sex differences in neurodevelopmental and neurodegenerative disorders: focus on microglial function and neuroinflammation during development. J. Steroid Biochem. Mol. Biol. 160, 127–133. https://doi.org/10.1016/j.jsbmb.2015.09.039.

Harris, M.H., Gold, D.R., Rifas-Shiman, S.L., Melly, S.J., Zanobetti, A., Coull, B.A., Schwartz, J.D., Gryparis, A., Kloog, I., Koutrakis, P., Bellinger, D.C., White, R.F., Sagiv, S.K., Oken, E., 2015. Prenatal and childhood traffic-related pollution exposure and childhood cognition in the project viva cohort (Massachusetts, USA). Environ. Health Perspect. 123, 1072–1078. https://doi.org/10.1289/ehp.1408803.

Herting, M.M., Younan, D., Campbell, C.E., Chen, J.-C., 2019. Outdoor air pollution and brain structure and function from across childhood to young adulthood: a methodological review of brain MRI studies. Front. Public Health 7, 332. https://doi.org/10.3389/fpubh.2019.00332.

Heude, Barbara, Forhan, Anne, Slama, Rémy, Douhaud, L., Bedel, S., Saurel-Cubizolles, M.-J., Hankard, Régis, Thiebaugeorges, Olivier, De Agostini, M., Annesi-Maesano, Isabella, Kaminski, Monique, Charles, Marie-Aline, Annesi-Maesano, I., Bernard, J., Botton, J., Charles, M.-A., Dargent-Molina, P., de Lauzon-Guillain, B., Ducimetière, P., de Agostini, M., Foliguet, B., Forhan, A., Fritel, X., Germa, A., Goua, V., Hankard, R., Heude, B., Kaminski, M., Larroque, B., Lelong, N., Lepeule, J., Magnin, G., Marchand, L., Nabet, C., Pierre, F., Slama, R., Saurel-Cubizolles, M., Schweitzer, M., Thiebaugeorges, O., on behalf of the EDEN mother-child cohort study group, 2016. Cohort Profile: the EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. Int. J. Epidemiol. 45, 353–363. https://doi.org/10.1093/ije/dyv151.

Hooper, D., Coughlan, J., Mullen, M., 2008. Structural Equation Modelling: Guidelines for Determining Model Fit. https://doi.org/10.21427/D7CF7R. Articles.

Hough, I., Sarafian, R., Shtein, A., Zhou, B., Lepeule, J., Kloog, I., 2021. Gaussian Markov random fields improve ensemble predictions of daily 1 km PM2.5 and PM10 across France. Atmos. Environ. 264, 118693 https://doi.org/10.1016/j.atmosenv.2021.118693.

Ikonomidou, C., Kaindl, A.M., 2011. Neuronal death and oxidative stress in the developing brain. Antioxidants Redox Signal. 14, 1535–1550. https://doi.org/10.1089/ars.2010.3581.

Johnson, C.J., Beitchman, J.H., Brownlie, E.B., 2010. Twenty-year follow-up of children with and without speech-language impairments: family, educational, occupational, and quality of life outcomes. Am. J. Speech Lang. Pathol 19, 51–65. https://doi.org/10.1044/1058-0360(2009/08-0083.

Kelly, F.J., 2003. Oxidative stress: its role in air pollution and adverse health effects. Occup. Environ. Med. 60, 612–616. https://doi.org/10.1136/oem.60.8.612.

Korkman, M., Kirk, U., 2007. NEPSY—Second Edition (NEPSY-II). Harcourt Assess.

Kusters, M.S.W., Essers, E., Muetzel, R., Ambrós, A., Tiemeier, H., Guxens, M., 2022. Air pollution exposure during pregnancy and childhood, cognitive function, and emotional and behavioral problems in adolescents. Environ. Res. 214, 113891 https://doi.org/10.1016/j.envres.2022.113891.

Lertxundi, A., Andiarena, A., Martínez, M.D., Ayerdi, M., Murcia, M., Estarlich, M., Guxens, M., Sunyer, J., Julvez, J., Ibarluzea, J., 2019. Prenatal exposure to PM2.5 and NO2 and sex-dependent infant cognitive and motor development. Environ. Res. 174, 114–121. https://doi.org/10.1016/j.envres.2019.04.001.

Leung, M., Kioumourtzoglou, M.-A., Raz, R., Weisskopf, M.G., 2021. Bias due to selection on live births in studies of environmental exposures during pregnancy: a simulation study. Environ. Health Perspect. 129, 047001 https://doi.org/10.1289/EHP7961.

Liew, Z., Olsen, J., Cui, X., Ritz, B., Arah, O.A., 2015. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. Int. J. Epidemiol. 44, 345–354. https://doi.org/10.1093/ije/dyu249.

Loftus, C.T., Hazlehurst, M.F., Szpiro, A.A., Ni, Y., Tylavsky, F.A., Bush, N.R., Sathyanarayana, S., Carroll, K.N., Karr, C.J., LeWinn, K.Z., 2019. Prenatal air pollution and childhood IQ: preliminary evidence of effect modification by folate. Environ. Res. 176, 108505 https://doi.org/10.1016/j.envres.2019.05.036.

López-Ojeda, W., Hurley, R.A., 2021. Sexual dimorphism in brain development: influence on affective disorders. J. Neuropsychiatry Clin. Neurosci. 33 (A4), 85–89. https://doi.org/10.1176/appi.neuropsych.20100269.

Marchman, V.A., Fernald, A., 2008. Speed of word recognition and vocabulary knowledge in infancy predict cognitive and language outcomes in later childhood. Dev. Sci. 11, F9–F16. https://doi.org/10.1111/j.1467-7687.2008.00671.x.

Marks, G.B., 2022. Misuse of pollution reference standards: No safe level of air pollution. Am. J. Respir. Crit. Care Med. 205, 984–985. https://doi.org/10.1164/rccm.202201-0160ED.

Morgan, Z.E.M., Bailey, M.J., Trifonova, D.I., Naik, N.C., Patterson, W.B., Lurmann, F.W., Chang, H.H., Peterson, B.S., Goran, M.I., Alderete, T.L., 2023. Prenatal exposure to ambient air pollution is associated with neurodevelopmental outcomes at 2 years of age. Environ. Health 22, 11. https://doi.org/10.1186/s12940-022-00951-y.

Morimoto, K., Nakajima, K., 2019. Role of the immune system in the development of the central nervous system. Front. Neurosci. 13, 916. https://doi.org/10.3389/fnins.2019.00916.

Morris, R.H., Counsell, S.J., McGonnell, I.M., Thornton, C., 2021. Early life exposure to air pollution impacts neuronal and glial cell function leading to impaired neurodevelopment. Bioessays 43, 2000288. https://doi.org/10.1002/bies.202000288.

Ni, Y., Loftus, C.T., Szpiro, A.A., Young, M.T., Hazlehurst, M.F., Murphy, L.E., Tylavsky, F.A., Mason, W.A., LeWinn, K.Z., Sathyanarayana, S., Barrett, E.S., Bush, N.R., Karr, C.J., 2022. Associations of pre- and postnatal air pollution exposures with child behavioral problems and cognitive performance: a U.S. Multi-cohort study. Environ. Health Perspect. 130, 67008 https://doi.org/10.1289/EHP10248.

Pallayova, M., Brandeburova, A., Tokarova, D., 2019. Update on sexual dimorphism in brain structure–function interrelationships: a literature review. Appl. Psychophysiol. Biofeedback 44, 271–284. https://doi.org/10.1007/s10484-019-09443-1.

Park, M., Joo, H.S., Lee, K., Jang, M., Kim, S.D., Kim, I., Borlaza, L.J.S., Lim, H., Shin, H., Chung, K.H., Choi, Y.-H., Park, S.G., Bae, M.-S., Lee, J., Song, H., Park, K., 2018. Differential toxicities of fine particulate matters from various sources. Sci. Rep. 8, 17007 https://doi.org/10.1038/s41598-018-35398-0.

Petit, C., Chevrier, C., Durand, G., Monfort, C., Rouget, F., Garlantezec, R., Cordier, S., 2010. Impact on fetal growth of prenatal exposure to pesticides due to agricultural activities: a prospective cohort study in Brittany, France. Environ. Health 9, 71. https://doi.org/10.1186/1476-069X-9-71.

Peyre, H., Bernard, J.Y., Hoertel, N., Forhan, A., Charles, M.-A., De Agostini, M., Heude, B., Ramus, F., 2016. Differential effects of factors influencing cognitive development at the age of 5-to-6 years. Cognit. Dev. 40, 152–162. https://doi.org/10.1016/j.cogdev.2016.10.001.

Pornet, C., Delpierre, C., Dejardin, O., Grosclaude, P., Launay, L., Guittet, L., Lang, T., Launoy, G., 2012. Construction of an adaptable European transnational ecological deprivation index: the French version. J. Epidemiol. Community Health 66, 982–989. https://doi.org/10.1136/jech-2011-200311.

Porta, D., Narduzzi, S., Badaloni, C., Bucci, S., Cesaroni, G., Colelli, V., Davoli, M., Sunyer, J., Zirro, E., Schwartz, J., Forastiere, F., 2016. Air pollution and cognitive development at age 7 in a prospective Italian birth cohort. Epidemiol. Camb. Mass 27, 228–236. https://doi.org/10.1097/EDE.0000000000000405.

Raz, R., Kioumourtzoglou, M.-A., Weisskopf, M.G., 2018. Live-birth bias and observed associations between air pollution and autism. Am. J. Epidemiol. 187, 2292–2296. https://doi.org/10.1093/aje/kwy172.

Real, E., Couvidat, F., Ung, A., Malherbe, L., Raux, B., Gressent, A., Colette, A., 2022. Historical reconstruction of background air pollution over France for 2000–2015. Earth Syst. Sci. Data 14, 2419–2443. https://doi.org/10.5194/essd-14-2419-2022.

Rivas, I., Basagaña, X., Cirach, M., López-Vicente, M., Suades-González, E., Garcia-Esteban, R., Álvarez-Pedrerol, M., Dadvand, P., Sunyer, J., 2019. Association between early life exposure to air pollution and working memory and attention. Environ. Health Perspect. 127, 57002 https://doi.org/10.1289/EHP3169.

Saenen, N.D., Martens, D.S., Neven, K.Y., Alfano, R., Bové, H., Janssen, B.G., Roels, H.A., Plusquin, M., Vrijens, K., Nawrot, T.S., 2019. Air pollution-induced placental alterations: an interplay of oxidative stress, epigenetics, and the aging phenotype? Clin. Epigenet. 11, 124. https://doi.org/10.1186/s13148-019-0688-z.

Sajaniemi, N., Hakamies-Blomqvist, L., Katainen, S., von Wendt, L., 2001. Early cognitive and behavioral predictors of later performance: a follow-up study of ELBW children from ages 2 to 4. Early Child. Res. Q. 16, 343–361. https://doi.org/10.1016/S0885-2006(01)00107-7.

Sarovar, V., Malig, B.J., Basu, R., 2020. A case-crossover study of short-term air pollution exposure and the risk of stillbirth in California, 1999–2009. Environ. Res. 191, 110103 https://doi.org/10.1016/j.envres.2020.110103.

Shang, L., Yang, L., Yang, W., Huang, L., Qi, C., Yang, Z., Fu, Z., Chung, M.C., 2020. Effects of prenatal exposure to NO2 on children's neurodevelopment: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. Int. 27, 24786–24798. https://doi.org/10.1007/s11356-020-08832-y.

Shivers, K.-Y., Amador, N., Abrams, L., Hunter, D., Jenab, S., Quiñones-Jenab, V., 2015. Estrogen alters baseline and inflammatory-induced cytokine levels independent from hypothalamic-pituitary-adrenal axis activity. Cytokine 72, 121–129. https://doi.org/10.1016/j.cyto.2015.01.007.

Southerland, V.A., Brauer, M., Mohegh, A., Hammer, M.S., Donkelaar, A. van, Martin, R. V., Apte, J.S., Anenberg, S.C., 2022. Global urban temporal trends in fine particulate matter (PM2·5) and attributable health burdens: estimates from global datasets. Lancet Planet. Health 6, e139–e146. https://doi.org/10.1016/S2542-5196(21)00350-8.

Spearman, C., 1946. Theory of general Factor1. Br. J. Psychol. Gen. Sect. 36, 117–131. https://doi.org/10.1111/j.2044-8295.1946.tb01114.x.

Spencer-Hwang, R., Hwang, J., Sinclair, R., Dennis, S., Montgomery, S., 2023. Adverse health outcomes in early childhood (birth to 5 years) and ambient air pollutant exposures: a systematic review. Air Qual. Atmosphere Health 16, 913–944. https://doi.org/10.1007/s11869-023-01308-1.

van Donkelaar, A., Martin, R.V., Li, C., Burnett, R.T., 2019. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. Environ. Sci. Technol. 53, 2595–2611. https://doi.org/10.1021/acs.est.8b06392.

Volk, H.E., Perera, F., Braun, J.M., Kingsley, S.L., Gray, K., Buckley, J., Clougherty, J.E., Croen, L.A., Eskenazi, B., Herting, M., Just, A.C., Kloog, I., Margolis, A., McClure, L. A., Miller, R., Levine, S., Wright, R., Environmental influences on Child Health Outcomes, 2021. Prenatal air pollution exposure and neurodevelopment: a review and blueprint for a harmonized approach within ECHO. Environ. Res. 196, 110320 https://doi.org/10.1016/j.envres.2020.110320.

Wang, P., Tuvblad, C., Younan, D., Franklin, M., Lurmann, F., Wu, J., Baker, L.A., Chen, J.-C., 2017. Socioeconomic disparities and sexual dimorphism in neurotoxic effects of ambient fine particles on youth IQ: a longitudinal analysis. PLoS One 12, e0188731. https://doi.org/10.1371/journal.pone.0188731.

Wang, X., Chen, C., Wang, L., Chen, D., Guang, W., French, J., 2003. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil. Steril. 79, 577–584. https://doi.org/10.1016/s0015-0282(02)04694-0.

Wechsler, D., 2005. WISC-IV: Echelle d'Intelligence de Wechsler pour Enfants (No. 4e édition). Editions du Centre de Psychologie Appliquée.

Wechsler, D., 2004. WPPSI-III: Échelle d'intelligence de Wechsler pour la période préscolaire et primaire (No. 3e édition). Editions du Centre de Psychologie Appliquée.

Wilcox, A.J., Weinberg, C.R., O'Connor, J.F., Baird, D.D., Schlatterer, J.P., Canfield, R.E., Armstrong, E.G., Nisula, B.C., 1988. Incidence of early loss of pregnancy. N. Engl. J. Med. 319, 189–194. https://doi.org/10.1056/NEJM198807283190401.

World Health Organization, 2022. Billions of People Still Breathe Unhealthy Air: New WHO Data. https://www.who.int/. https://www.who.int/news/item/04-04-2022-billions-of-people-still-breathe-unhealthy-air-new-who-data. accessed 9.2.22.

Xu, X., Ha, S.U., Basnet, R., 2016. A review of epidemiological research on adverse neurological effects of exposure to ambient air pollution. Front. Public Health 4, 157. https://doi.org/10.3389/fpubh.2016.00157.

Xue, T., Tong, M., Li, Jiajianghui, Wang, R., Guan, T., Li, Jiwei, Li, P., Liu, H., Lu, H., Li, Y., Zhu, T., 2022. Estimation of stillbirths attributable to ambient fine particles in 137 countries. Nat. Commun. 13, 6950. https://doi.org/10.1038/s41467-022-34250-4.

Yi, C., Wang, Q., Qu, Y., Niu, J., Oliver, B.G., Chen, H., 2022. In-utero exposure to air pollution and early-life neural development and cognition. Ecotoxicol. Environ. Saf. 238, 113589 https://doi.org/10.1016/j.ecoenv.2022.113589.

You, R., Ho, Y.-S., Chang, R.C.-C., 2022. The pathogenic effects of particulate matter on neurodegeneration: a review. J. Biomed. Sci. 29, 15. https://doi.org/10.1186/s12929-022-00799-x.