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Nitrogen dioxide exposure, attentional function, and working memory in children from 4 to 8 years: Periods of susceptibility from pregnancy to childhood

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ABSTRACT

Background: Air pollution exposure during pregnancy and childhood has been linked to executive function impairment in children, however, very few studies have assessed these two exposure periods jointly to identify susceptible periods of exposure. We sought to identify potential periods of susceptibility of nitrogen dioxide (NO_2) exposure from conception to childhood on attentional function and working memory in school-aged children.

Methods: Within the Spanish INMA Project, we estimated residential daily NO_2 exposures during pregnancy and up to 6 years of childhood using land use regression models (n = 1,703). We assessed attentional function at 4–6 years and 6–8 years, using the Conners Kiddie Continuous Performance Test and the Attention Network Test, respectively, and working memory at 6–8 years, using the N-back task. We used distributed lag non-linear models to assess the periods of susceptibility of each outcome, adjusting for potential confounders and correcting for multiple testing. We also stratified all models by sex.

Results: Higher exposure to NO_2 between 1.3 and 1.6 years of age was associated with higher hit reaction time standard error (HRT-SE) (0.14 ms (95 % CI 0.05; 0.22) per 10 $\mu g/m^3$ increase in NO_2) and between 1.5 and 2.2 years of age with more omission errors (1.02 (95 % CI 1.01; 1.03) of the attentional function test at 4–6 years. Higher exposure to NO_2 between 0.3 and 2.2 years was associated with higher HRT-SE (10.61 ms (95 % CI 3.46;

Abbreviations: ANT, Attention Network Test; BMI, Body Mass Index; CIs, Confidence Intervals; d', d prime; DLNM, Distributed Lag Non-linear Models; HRT, Hit Reaction Time; HRT-SE, Hit Reaction Time Standard Error; INMA Project, INfancia y Medio Ambiente (Environment and Childhood) Project; IQR, Inter Quartile Range; ISCO88, International Standard Classification of Occupations; K-CPT, Conners Kiddie Continuous Performance Test; LUR, Land Use Regression; NDVI, Normalized Difference Vegetation Index; NO_2, Nitrogen dioxide; $PM_{2.5}$, Particular Matter with a diameter less than 2.5 μm; O_3, Ozone.

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17.75) at 6–8 years only in boys. We found no associations between exposure to NO_2 and working memory at 6–8 years.
Conclusion: Our findings suggest that NO_2 exposure during the first two years of life is associated with poorer attentional function in children from 4 to 8 years of age, especially in boys. These findings highlight the importance of exploring long-term effects of traffic-related air pollution exposure in older age groups.

1. Introduction

Air pollution has been widely recognized as one of the main global environmental public health hazards and it is the largest environmental health risk in Europe (European Environment Agency (EEA)., 2022; McDuffie et al., 2021). Within the European Union, particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$), nitrogen dioxide (NO_2) and ozone (O_3) were together responsible for an estimated 311,000 premature deaths in 2020 (European Environment Agency (EEA)., 2022). Children, a particularly vulnerable subset of the population, are disproportionately impacted by the consequences of air pollution. Alarmingly, 93 % of children worldwide reside in areas exceeding World Health Organization air quality guidelines (World Health Organization, 2018). During pregnancy, the placenta offers only limited protection from the influx of environmental toxicants and the foetus' detoxification systems are still immature (Liu et al., 2021; Rice & Barone, 2000). Consequently, when the mother is exposed to air pollution, air pollutants may affect the foetal brain development as a result of oxidative stress and systemic inflammation, resulting in persistent neuroinflammation, microglia activation, and neuronal migratory damage (Block et al., 2012; Ghazi et al., 2021). Postnatally, children remain susceptible to adverse health effects from air pollution due to rapid organ development and increased vulnerability to inflammation and oxidative stress-related damage (Brumberg et al., 2021). Moreover, children inhale more air per unit of body weight and have a longer lifespan, allowing latent diseases to manifest (Brumberg et al., 2021).

There has been growing concern about the effects of air pollution exposure on brain development, particularly in children (Health Effects Institute Panel on the Health Effects of Long-Term Exposure to Traffic-Related Air Pollution, 2022). An important component of brain development that might be affected by air pollution is executive function. Executive function generally refers to a range of cognitive processes, including planning, working memory, attentional function, cognitive flexibility, and inhibitory control, that manage and control actions, thoughts, and emotions to achieve a goal or objective (Gartland et al., 2022). These cognitive processes emerge early in life and have a critical period of development from an age of 6 to 10 years (Gui et al., 2020). Executive functions are especially important for academic achievement, social functioning, and they form the basis of a child's ability to learn (Gartland et al., 2022). A recent systematic review on the effects of air pollution on neurodevelopmental skills in preschool- and school-aged-children found that air pollution has a deleterious influence on both executive function and academic achievement during childhood (Castagna et al., 2022). The findings suggest a particularly pronounced association between air pollution exposure during pregnancy and executive function, but some adverse effects are also seen with exposure during childhood (Castagna et al., 2022). Chiu et al. (2016) examined susceptible periods of prenatal air pollution exposure on executive functions and found susceptible periods between mid and late pregnancy, however they did not include childhood in their analyses. Rivas et al. (2019) were the first to our knowledge studying susceptible periods from conception till an age of 7 years and found periods of susceptibility between 5 and 7 years of age. Exploring susceptible periods of exposure is important because this can avoid potential biases inherent in earlier studies stemming from the averaging of extended intervals and inadequate adjustments across diverse time segments (Buckley et al., 2019). Furthermore, associations at different time intervals may elucidate specific biological mechanisms rooted in known underlying developmental processes, such as the intricate neural pathways encompassing brain regions in development and neural processes (Buckley et al., 2019). Chiu et al. (2016) and Rivas et al. (2019) also observed that sex-differential susceptibility played a significant role in the association of air pollution with executive function. For instance, Chiu et al. (2016) identified an association of air pollution with attentional function, particularly in boys, while Rivas et al. (2019) found an association with working memory, specifically in boys. This could be explained by enhanced regulation of oxidative stress balance in the female brain (Guevara et al., 2009).

Therefore, this study aims to identify potential periods of susceptibility to NO_2 exposure from conception to early childhood on attentional function at the age of 4 to 6 years and 6 to 8 years, and working memory at the age of 6 to 8 years.

2. Methods and materials

2.1. Study population

We utilized data from the INfancia y Medio Ambiente (INMA) Project, a Spanish-based multi-site prospective birth cohort that recruited pregnant women from 1997 to 2008 to explore pre- and post-natal environmental effects on child health, growth, and development (Guxens et al., 2012). Women were included during the first trimester of pregnancy and had to meet the following criteria: (1) resident in one of the study areas, (2) minimum age of 16 years, (3) a singleton pregnancy, (4) no programme for assisted reproduction, (5) intent to deliver in the recruitment hospital, (6) first pre-natal visit between 10 and 13 weeks of gestation, and (7) no communication problems. In this study, we included data from pregnant women and their children from the regions of Asturias, Gipuzkoa, Sabadell, and Valencia, who were enrolled between the years 2003 and 2007 based on data availability, comprising a total of 2,764 women (Supplemental Material, Figure S1). We included mother-infant pairs with children born after 32 weeks of gestation that had a complete exposure assessment from conception to the child's age of 4 years (for neuropsychological assessment at ages 4 to 6 years) or to the child's age of 6 years (for neuropsychological assessment at ages 6 to 8 years), and assessment of at least one outcome at ages 4 to 6 years or 6 to 8 years. This resulted in an inclusion of 1,703 mother–child pairs in the present analysis (Supplemental Material, Figure S1). The INMA Project was approved by the ethics committees of the different reference hospitals and informed consent regarding the prenatal period was collected from all mothers and in each phase of the childhood period further consent was collected by one of the parents or a legal representative.

2.2. Assessment of the exposure to NO_2

We estimated residential exposure to NO_2 for each participant using temporally-adjusted land use regression (LUR) models based on a standardized method that has been described previously (Estarlich et al., 2011). Briefly, NO_2 levels were measured during numerous 7-days sampling periods using passive samplers distributed throughout the study areas according to geographic criteria. NO_2 levels were measured during times covering the gestational periods of women recruited in each region as well as when children were around 4 years or age in the Gipuzkoa and Valencia regions. We estimated annual NO_2 levels at each participant's home address with LUR models using predictor variables such as distance to local sources of pollution, land coverage, population

density, roads, and topography, taking into account the residential mobility of participants during pregnancy and childhood. For each participant, to enhance temporal precision, we utilized daily data from background monitoring sites to extrapolate the air pollution levels to the specific residency periods at each address (Brunekreef, 2012). This approach resulted in daily air pollution levels for all addresses where participants resided from conception until the time of the neuropsychological assessment. Subsequently, daily levels were combined as arithmetic averages providing exposure levels for periods of 4-weeks for the entire pregnancy and for childhood from birth until 6 years old. We considered that 4-week periods of exposure had sufficient fine temporal resolution for identifying windows of susceptibility in our time series analysis.

2.3. Attentional function

To assess the attentional function of the children, two different validated computerized tests were used. When children were 4 to 6 years of age, attentional function was measured using the 2nd edition of the Conners Kiddie Continuous Performance Test (K-CPT) (Conners, 2015) and when children were 6 to 8 years of age, the Attention Network Test (ANT) was administered (Forns et al., 2014; Posner, 2017). In the K-CPT, children responded swiftly to images on a computer screen, pressing the space bar unless the image depicted a ball. In the ANT, children indicated the direction a central fish was pointing using arrow keys. For both tests, the primary outcomes of interest were: the hit reaction time (HRT), a measure of speed processing, for correct targets; the hit reaction time standard error (HRT-SE), a measure of speed consistency throughout the test, for correct targets; and the number of omission errors, which is the absence of answers to targets, a measure of selective attention. We additionally evaluated the number of commission errors, which is an incorrect answer to non-targets, a measure of impulsivity, for the K-CPT; we did not have enough variability in the commission errors of the ANT, so we did not include this outcome in these analyses. Higher scores in all the aforementioned outcomes indicate a poorer attentional function.

2.4. Working memory

To evaluate the working memory of the children at an age of 6 to 8 years, the N-Back Task was used (Coulacoglou & Saklofske, 2017). This task involved tracking numbers or colours on a laptop screen and responding when a presented number or colour matched the number or colour from one to three trials earlier (1-back to 3-back) (Forns et al., 2014). We used the d prime (d') and HRT as the main outcomes of the N-Back Task. D' is a measure of detection derived from signal detection theory computed by subtraction of the z-score of the false alarm rate (incorrect answers to the non-targets) from the z-score of the hit rate (correct answers to the target) (Forns et al., 2014). HRT was only captured when the child correctly responded to the targets and is a measure of speed processing. In this study, we evaluated the 3-back load of both the numbers and colours tests, to assess the highest demands on working memory. Thus, we used 4 outcomes, namely, d' and HRT for the 3-back test of numbers and colours. A lower d' indicates less accurate test performance, that is to say, poorer working memory function. A higher HRT indicates lower brain processing velocity, as it means poorer working memory function.

2.5. Potential confounding variables

Interviewer-administered questionnaires were carried out during pregnancy and at child's age of 4 years (Guxens et al., 2012) to collect information on a range of covariates. Existing literature was used to select potential confounding variables (Chen et al., 2023; Julvez et al., 2021; Sentís et al., 2017; Sunyer et al., 2015) for the present study. Based upon this evidence and availability of the data, a direct acyclic graph (DAG) (Supplemental Material, Figure S2) was used to inform variables to be included in our models (Weisskopf et al., 2015.). We included the following variables informing about the socioeconomic status of the family: maternal and paternal education level at enrolment (primary / secondary / higher); parental social class during pregnancy defined from the Spanish adaptation of International Standard Classification of Occupations (ISCO88) (managers & technicians / skilled manual & non-manual / semiskilled & unskilled & others); and maternal and paternal country of birth (Spain / foreign). Furthermore, we included the variable maternal intelligence quotient, assessed at child's age 4 to 6 using the Wechsler Adult Intelligence Scale, third edition (continuous). Related to the parental health and lifestyle we included the following variables: maternal and paternal age at enrolment (years); month and year of conception; maternal parity at birth (nulliparous / multiparous); maternal pre-pregnancy body mass index (BMI) (kg/m^2); paternal BMI (kg/m^2); maternal smoking during pregnancy (never / stopped when pregnancy known / continued); second-hand smoke exposure at home during pregnancy (yes / no); alcohol consumption during pregnancy (yes / no); maternal mean daily consumption of lean fish, large fatty fish, and fruit and vegetables at 12 weeks of pregnancy (high / medium / low); and maternal intake and supplementation of folic acid at 12 weeks of pregnancy (high / medium / low). In addition, maternal circulating blood levels of vitamin D were measured during the first trimester of pregnancy and deseasonalized (ηg/mL) (Morales et al., 2012). Related to the child's characteristics the following covariates were collected: exact age of child at the neuropsychological assessment (years) and the child's biological sex at birth (female / male). Finally, regarding residence characteristics the following confounding variables were obtained: urbanicity of the living area at birth (urban / semi-urban and rural); normalized difference vegetation index (NDVI) during pregnancy, a near-infrared spectroscopy index and indicator of residential surrounding greenness within 300 m; cooking stove (electricity / other); and heating gas appliances at home (yes / no). We did not include marital status as a confounding variable in our models due to its low variability (Table 1).

2.6. Statistical analyses

Missing values of covariates ranged from 0.1 to 9.8 %. These missing values were imputed to mitigate attrition bias and enhance research validity (Sterne et al., 2009), utilizing the expectation–maximization algorithm (Amelia R package). We assumed that the variables were missing at random and the imputed values resembled original dataset distributions (Supplemental Material, Table S1, S2 and S3). As only participants with available exposure and outcome data were studied, inverse probability weighting was used to account for potential selection bias (Seaman & White, 2013). Parents of included participants were more likely to have higher education, higher social class, and be Spanish, as compared to parents of participants that were not included (Supplemental Material, Table S4, S5 and S6). We imputed missing values for all eligible subjects (N = 2764) and identified covariates associated with likelihood of participation, utilizing their inverse probabilities for calculating the weights. This approach ensured representativeness of the initial cohort, addressing underrepresentation of characteristics of subjects who were lost to follow-up (Seaman & White, 2013; Weuve et al., 2012). Imputation and inverse probability weighting were performed for each region and outcome separately.

To explore the susceptible periods of exposure to NO_2 on the studied outcomes we used distributed lag non-linear models (DLNM). These models depict exposure-outcome relationships across time, addressing limitations of analysing averaged exposures over prolonged periods (Gasparrini, 2014). We selected a linear shape for all exposure–response relationships after visually inspecting the association of each averaged exposure during the whole pregnancy and childhood period with each outcome. We employed a natural cubic B-spline with a lag-response intercept, assuming smooth variation in exposure-outcome association across lags, with a 4-week period lag. All children were assigned 9 4-

Table 1
Characteristics of the study population for each outcome assessment.

Variable	Distribution at K-CPT (n = 1253)	Distribution at ANT (n = 1476)	Distribution at N-back (n = 1407)
Child́s gender (female vs. male)	50.8	49.9	48.5
Maternal age at enrolment (years)	30.9 (4.0)	31.1 (4.0)	31.1 (3.9)
Paternal age at enrolment (years)	32.9 (4.8)	33.2 (4.8)	33.1 (4.8)
Maternal parity (nulliparous vs. multiparous)	57.6	58.1	58.5
Maternal educational level at enrolment			
Primary or lower	21.5	18.7	19.2
Secondary	41.9	41.2	41.3
Higher	36.6	40.1	39.5
Paternal educational level at enrolment			
Primary or lower	35.1	31.4	32.1
Secondary	43.4	45.0	44.3
Higher	21.5	23.6	23.6
Maternal IQ score	99.4 (15.0)	100.2 (14.7)	99.9 (14.7)
Maternal social class during pregnancy			
Managers & Technicians	23.8	25.8	25.7
Skilled manual & non-manual	27.0	26.8	26.4
Semiskilled & unskilled & others	49.2	47.4	47.9
Paternal social class during pregnancy			
Managers & Technicians	20.3	22.2	22.3
Skilled manual & non-manual	18.9	18.4	18.4
Semiskilled & unskilled & others	60.8	59.4	59.3
Maternal country of birth (Spain vs. others)	94.0	94.9	95.2
Paternal country of birth (Spain vs. others)	93.2	94.3	94.1
Marital status (Parents living together vs. parents not living together)	98.9	99.0	98.9
Maternal pre-pregnancy BMI (kg/m^2)	23.5 (4.2)	23.4 (4.1)	23.5 (4.1)
Paternal BMI at enrolment (kg/m^2)	26.0 (3.5)	26.0 (3.4)	26.0 (3.4)
Maternal smoking during pregnancy			
Never	46.2	47.7	47.6
Stopped when pregnancy known	23.0	23.3	23.2
Continued	30.8	29.0	29.2
Maternal second-hand smoke exposure during pregnancy (yes vs. no)	29.8	27.2	28.0
Maternal alcohol consumption during pregnancy (yes vs. no)	12.3	11.4	11.6
Maternal deseasonalized blood levels of vitamin D during pregnancy (ng/mL)	0.6 (10.9)	0.01 (10.7)	0.01 (10.7)
Maternal total folic acid intake and supplementation during pregnancy			
High (>1000 μg/day)	36.9	39.5	38.8
Medium (400–1000 μg/day)	49.9	46.6	46.8
Low (<400 μg/day)	13.2	13.9	14.4
Maternal consumption of lean (white) fish during pregnancy			
High	31.0	33.7	33.6
Medium	34.9	34.1	34.3
Low	34.1	32.2	32.1
Maternal consumption large fatty (blue) fish during pregnancy			
High	34.6	34.9	35.0
Medium	33.3	33.9	34.1
Low	32.1	31.2	30.9
Maternal consumption of fruit and vegetables during pregnancy			
High	29.6	33.5	33.3
Medium	34.7	34.1	34.0
Low	35.7	32.4	32.7
Cooking stove appliances at home (electricity vs. others)	55.8	59.9	60.3
Heating with gas at home (yes vs. no)	54.8	59.5	59.6
Urbanicity of the living area (urban vs. semiurban/rural)	82.3	80.6	81.2
Residential surrounding greenness within 300 m	0.3 (0.1)	0.3 (0.1)	0.3 (0.1)

Values are percentages for categorical variables and mean (standard deviation) for continuous variables.

week prenatal lags since exposures during pregnancy were considered having the same length. For children born between 33 and 36 gestational weeks, the 9th 4-week lag included exposures averaged across fewer than 4 weeks; exposures beyond 36 weeks were disregarded. The childhood period comprised from birth until the age of 4, when we assessed K-CPT (i.e., attentional function test at 4 to 6 years), and from birth until the age of 6, when we assessed ANT and N-back (i.e., attentional function and working memory tests at 6 to 8 years), corresponding to 52 4-week lags and 78 4-week lags, respectively. We considered both prenatal and childhood exposures as a continuous temporal frame, due to the high correlation between the periods. Since there is no *a priori* knowledge of the number and location of knots in the cross-basis matrix, we decided the number and location of knots by visual inspection. To do that, we conducted individual adjusted linear or negative binomial regressions for each exposure lag and the continuous (i.e., HRT and HRT-SE for attentional function and d' and HRT for working memory) or count outcomes (i.e., commissions and omissions for attentional function), respectively. We then plotted each of the beta coefficients along with their 95 % confidence intervals (CIs) for each lag. Three researchers (ACB, KLHAC, MG) assessed these plots independently, considering slope changes and the parsimony principle, reconciling knot placements through discussion (Martin & Hine, 2008). For outcomes of attentional function at ages 4 to 6 years and working memory at ages 6 to 8 years, no knots were placed; for attentional function at ages 6 to 8 years, a knot was placed at lag 51 (Supplemental material, Figure S3 and S4). After running the DLNMs, we identified susceptible periods to NO_2 exposure of attentional function and working memory as consecutive periods where the 95 % CIs excluded the null. The DLNMs were conducted after pooling the data from all regions, adjusting for region and all other covariates listed above, and executed using the R package "dlnm".

Lastly, we explored potential sex-specific effects by stratifying all analyses based on the child's biological sex. The *p*-values for all analyses were adjusted for multiple testing, considering 1 exposure, 7 attentional function indicators, and 4 working memory indicators. To estimate the effective number of tests and the independence among different outcomes and exposure, we extracted eigenvalues from individual-level

phenotype data matrix using the meff function from the R package "poolr". The effective test count was estimated at 9 out of 11 outcomes, following Galwey's recommended approach (Galwey, 2009). This led to a new p-value threshold of 0.006 (=0.05/9). All statistical analyses were executed using R (version 4.3.0; R Development Core Team).

3. Results

3.1. Characteristics of the study population

The characteristics of the included mother–child pairs are shown in Table 1. Approximately half of the children were female. Pregnant women were on average 31.0 years old at the time of recruitment, with an age range between 16 and 43 years old, 3 of them under 18 years old, and 4 between 18 and 20 years old. Fathers were on average 33.1 years old, with an age range between 17 and 64 years old, 1 of them under 18 years old, and 3 between 18 and 20 years old. Maternal education varied from 20.7 % completing primary education or lower, 41.3 % secondary education, and 38 % higher degrees. Fathers' educational distribution differed slightly with 33.3 % completing primary education or lower, 44.4 % secondary education, and 22.2 % higher degrees. Most mothers (94.1 %) and fathers (93.3 %) were born in Spain, with the majority residing in urban areas (81.0 %). The distributions of each outcome are shown in Table 2. The attentional function outcomes had a low correlation between the two different time points (Supplemental material, Figure S5).

NO_2 levels decreased from the conception to childhood period, as shown in Fig. 1. For example, the median NO_2 concentrations were 27.6 (interquartile range (IQR) 18.3–39.2) μg/m^3 during the first 4 weeks of pregnancy, 24.7 (IQR 16.6–34.7) μg/m^3 during the last 4 weeks of the 4th year of life, and 21.0 (IQR 13.8–31.0) μg/m^3 during the last 4 weeks of the 6th year of life (Fig. 1). The Pearson coefficients between NO_2 concentrations in the different time periods (4-week lags) for the pregnancy and childhood period were moderate to high (between 0.46 and 0.88 for pregnancy and between 0.34 and 0.92 for childhood; Supplemental Material, Figure S6 and S7).

3.2. Association between NO_2 and attentional function

We observed some periods of susceptibility to NO_2 for attentional function at 4 to 6 years of age after correction for multiple testing (Fig. 2). We found that higher NO_2 levels between 1.3 and 1.6 years of age were associated with higher HRT-SE (0.14 ms (95 % CI 0.05 to 0.22) per 10 μg/m^3 increase in NO_2) and between 1.5 and 2.2 years of age with more omission errors (1.02 (95 % CI 1.01 to 1.03) per 10 μg/m^3 increase in NO_2). After stratifying by sex and correcting for multiple testing, we observed similar periods of susceptibility to NO_2 exposure for higher HRT-SE and more omission errors only in boys (Supplemental Material, Figure S8).

We observed no periods of susceptibility to NO_2 for attentional function at 6 to 8 years in the overall analyses (Fig. 2). However, we found a period of susceptibility to NO_2 levels between 0.3 and 2.2 years for higher HRT-SE (10.61 ms (95 % CI 3.46 to 17.75) per 10 μg/m^3 increase in NO_2) at 6 to 8 years only in boys, after correcting for multiple testing (Supplemental Material, Figure S8).

Table 2
Distribution of attentional function and working memory scores.

Variable	Distribution
Attentional Function Scores at 4–6 years (K-CPT)	n = 1253
Child's age at test (years)	5.0 (0.7)
Hit reaction time (ms)	725.86 (135.13)
Hit reaction time standard error (ms)	30.54 (13.96)
Omission errors (number)	18 (9, 34)
Commission errors (number)	21 (13, 29)
Attentional Function Scores at 6–8 years (ANT)	n = 1476
Child's age at test (years)	7.7 (0.6)
Hit reaction time (ms)	936.99 (186.38)
Hit reaction time standard error (ms)	301.96 (80.65)
Omission errors (number)	2 (0, 5)
Working Memory Scores at 6–8 years (N-back)	n = 1407
Child's age at test (years)	7.6 (0.6)
3-back numbers	n = 1278
d prime	1.35 (0.86)
Hit reaction time (ms)	813.19 (258.88)
3-back colours	n = 1213
d prime	1.20 (0.71)
Hit reaction time (ms)	824.52 (262.02)

ANT = Attention Network Test. K-CPT = Connors Kiddie Continuous Performance Test. NO_2 = Nitrogen Dioxide.
Values are mean (standard deviation) for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous variables.

3.3. Association between NO_2 and working memory

We observed no periods of susceptibility to NO_2 exposure for working memory overall or stratifying by sex (Fig. 3 and Supplemental Material, Figure S9).

4. Discussion

In this study, we found a susceptible period of NO_2 exposure between 1.5 and 2 years of age for attentional function in 4- to 6-year-olds, and another between 0.5 and 2 years of age for attentional function in 6- to 8-year-olds but only in boys. Exposure to NO_2 during pregnancy and childhood was not associated with working memory in 6- to 8-year-olds.

Attentional function is a critical factor in achieving proper development of executive functions and the first 10 years of life play a crucial role in this development (Garon et al., 2008; Gui et al., 2020). The prefrontal cortex, one of the brain regions with the slowest rate of development, has been closely linked to executive functions (Garon et al., 2008). Since the prefrontal cortex is still in development during pregnancy and childhood, it might be especially susceptible to air pollution exposure during this period. Animal studies provided evidence that the brain reacts to traffic-related emissions with enhanced neuroinflammation, oxidative stress responses, and an impaired energy metabolism (Salvi et al., 2020; Xu et al., 2022). Different results have been published on the association between air pollution and attentional function in a large cohort of school-going children in Barcelona, Spain (Rivas et al., 2019; Sunyer et al., 2015). Sunyer et al. (2015) found that the development of inattentiveness over a 12-month period was reduced in children aged 7 to 10 years who were exposed to higher levels of traffic-related air pollutants at school, specifically elemental carbon and ultrafine particle number, with boys appearing more susceptible. Rivas et al. (2019) studied the susceptible periods of residential $PM_{2,5}$ exposure on attentional function at an age of 7 to 10 years old and identified a susceptible period around 6 to 7 years of age. Of note, they did not identify a susceptible period at a younger age as we did. This might be attributed to employment of year-long lags in their study as opposed to our 4-week lags, dissimilar knot placement, exposure to a different air pollutant, or a more extended period of exposure. Another study in the United States looked at susceptible periods of residential $PM_{2.5}$ exposure only during pregnancy on attentional function in 6- to 7-year-olds and found a susceptible period in mid-to-late pregnancy but only in boys (Chiu et al., 2016). However, this study did not additionally consider exposures experienced in childhood, which would have led to a more comprehensive understanding of the exposure windows of susceptibility across the entire period of attentional function development in children.

Neuroplasticity is the central nervous system's essential dynamic biological potential to mature, alter physically and functionally in response to experience, and adapt following damage (Ismail et al., 2017). This mechanism might contribute to attenuation of the association between NO_2 exposure and attentional function between the two

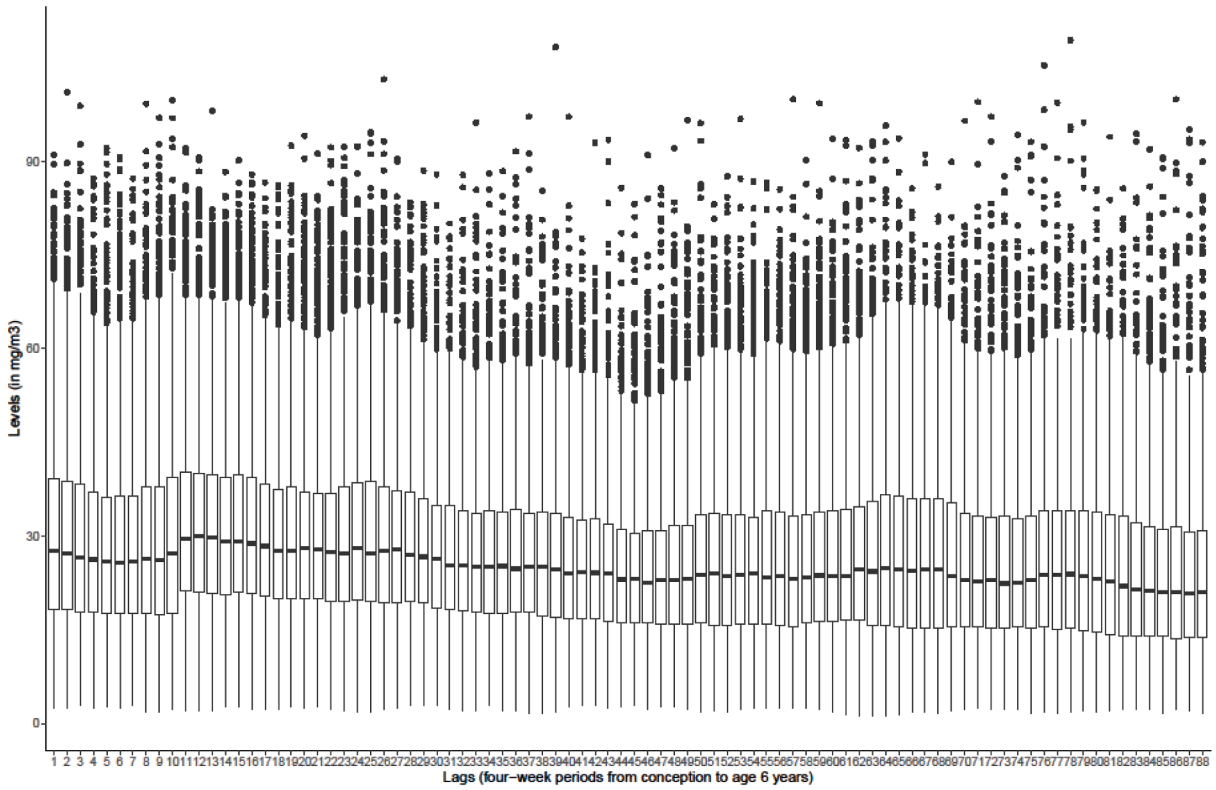

Fig. 1. *Boxplot of NO_2 levels during different periods of time* Note. NO_2 = Nitrogen Dioxide. Concentrations at different time windows that the participants (n = 1,703) are exposed to during pregnancy and childhood. The concentrations were estimated at home address for each 4 weeks (lag) from the temporally adjusted LUR model. Central line represents the median; lower and upper bound of the boxes correspond to the 25th and 75th percentile, respectively; bars outside the box represent the 1.5 × interquartile range; and dots are outliers.

ages (i.e., 4 to 6 years versus 6 to 8 years), possibly suggesting a delay in the maturation of attentional function (Pujol et al., 2016). The slower maturation of the male brain might account for the persisting association in boys, potentially due to a reduced safeguarding effect of neuroplasticity, resulting in a prolonged adverse impact on attentional function (Laureys et al., 2021). However, the older age range (i.e., 7–10 years) of participants in the study by Sunyer et al. (2015) suggests that the observed effect is less likely to be completely attenuated by age-related factors in our younger cohort. For future studies, a longitudinal approach is essential to unravel the interplay of age and sex differences in the association between air pollution and attentional function, including exploration of associations among older age groups.

Working memory is another important task of executive function that requires maintaining and manipulating information through time delays, especially in the presence of interruption (Gilbert & Burgess, 2008). Working memory evolves in the same brain regions as attentional function, however, the rapid development happens later in childhood (Anderson, 2002). Lertxundi et al. (2019) examined the relationship between prenatal NO_2 and $PM_{2.5}$ exposure and working memory in children from the INMA Project aged 4 to 6 years, revealing an association only in boys for both pollutants. Freire et al. (2010) found no cross-sectional association between NO_2 exposure and working memory at the age of 4 years; however, they did not explore sex-stratification. Sunyer et al. (2015) also studied development of working memory over a 12-month period in children from 7 to 10 years and found a decrease in development in children exposed to higher levels of elemental carbon, NO_2 and ultrafine particle number, with boys appearing more susceptible than girls. Forns et al. (2017) extended the study of Sunyer et al. (2015) by affirming that the observed association remained over a longer period of 3.5 years. van Kempen et al. (2012) found an adverse association between NO_2 exposure at school and working memory in children around 10 years old, but not for NO_2 exposure at residency. Conversely, Gui et al. (2020) did find an association between residential air pollution exposure and working memory in their cross-sectional study with 5028 participants aged 6 to 12 years, however not for NO_2 but only for $PM_{2.5}$ and PM_{10}. Although the majority of previous studies assessed NO2 exposure as we did, results have not been consistent. However, they do underscore the necessity of investigating the influence of long-term air pollution exposure on working memory in older age groups, considering assessments of air pollution exposure both at residency and school.

This study has several strengths. To begin with, it has a large sample size from a population-based multi-centre cohort and we adjusted for many socioeconomic and lifestyle variables known to be associated with NO_2 exposure and with child brain development. Moreover, we use a standardized and validated method of back-extrapolation to assess NO_2 exposure at the individual level from pregnancy to 6 years of age in a fine time scale. Besides, we have a prospective assessment of the development of executive functions using standardized and validated neuropsychological tests at different ages (Forns et al., 2014). Furthermore, we used imputation and inverse probability weighting to mitigate potential biases and enhance the validity of our findings. Lastly, we used an advanced statistical method, DLNM, to estimate the association of NO_2 exposure on attentional function and working memory from pregnancy to early childhood with unbiased estimates, to consider each 4-week period separately, and to identify periods of susceptibility without defining arbitrary periods *a priori.* Another benefit of DLNM is the cross-basis, which allows for the simultaneous examination of the lag-exposure-outcome link, hence avoiding the difficulty of numerous comparisons of an averaged exposure method with repeated measurements.

However, our study also has a number of limitations. Firstly, there might be a nondifferential misclassification of exposure due to our sampling approach focusing on home addresses only. This excludes

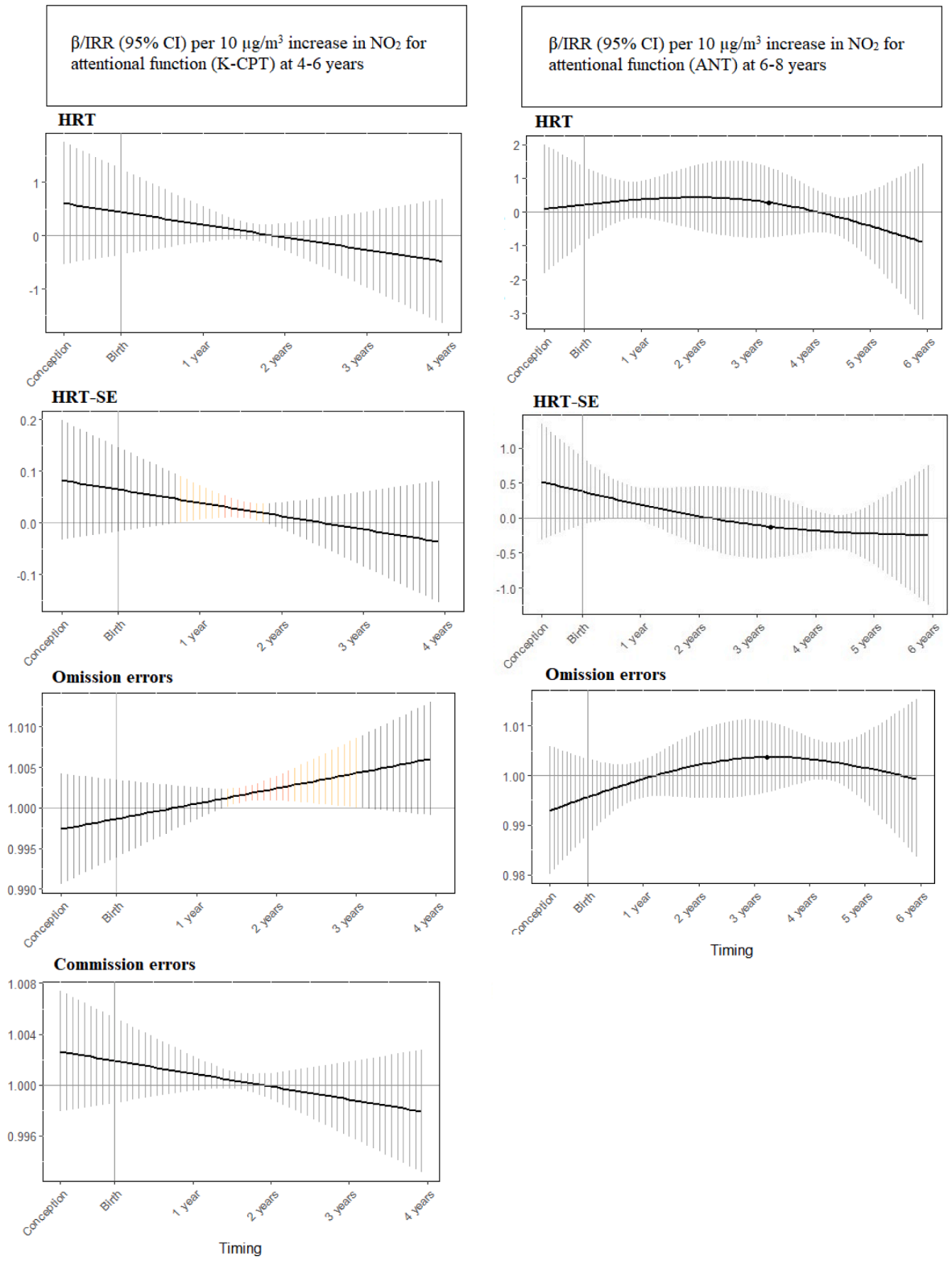

Fig. 2. *Fully-adjusted associations between 4-week NO_2 levels from conception until childhood and attentional function at 4–6 years of age and at 6–8 years of age. Note.* ANT = Attention Network Test. β = beta coefficient for HRT and HRT-SE. 95 % CI = 95 % confidence interval. HRT = Hit reaction time (ms). HRT-SE = Hit reaction time standard error (ms). IRR = Incidence-rate ratio for commission and omission errors. K-CPT = Connors Kiddie Continuous Performance Test. NO_2 = Nitrogen dioxide. The associations are presented for n = 1253 (at 4–6 years) and n = 1476 participants (at 6–8 years). Models were adjusted for parental education level, parental social class, parental country of birth, maternal intelligence quotient, maternal pre-pregnancy body mass index, paternal body mass index, parental age at pregnancy, maternal smoking, second-hand smoke exposure and alcohol consumption during pregnancy, maternal folic acid and Vitamin D blood levels during pregnancy, maternal consumption of fish, fruit and vegetables during pregnancy, household gas appliances during pregnancy, urbanicity and surrounding green space of living area, child's sex and age at the test, year and month of conception, and the region. Solid lines show the predicted difference in the outcomes associated with an increase of 10 $\mu g/m^3$ of NO_2. Grey colours indicate null 95 % CIs, light orange colours indicate significant positive 95 % CIs before multiple testing, and dark orange colours indicate significant positive 95 % CIs after multiple testing.

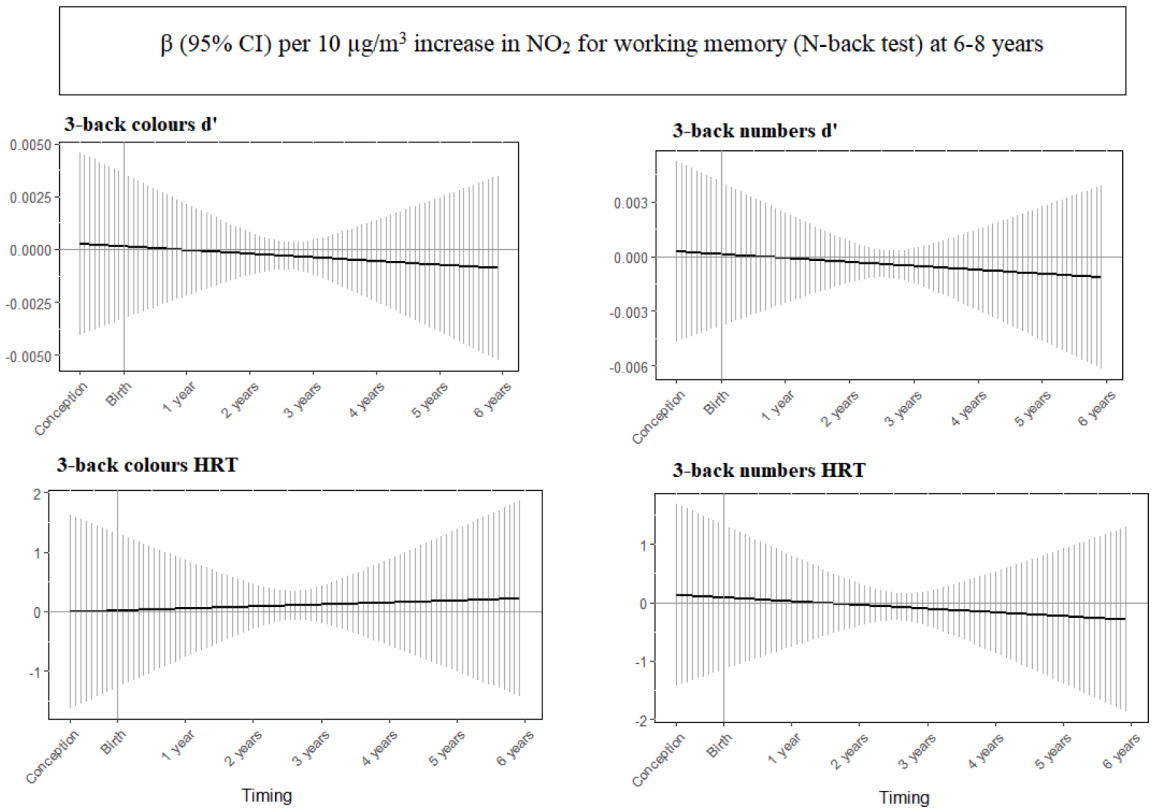

Fig. 3. *Fully-adjusted associations between 4-week NO_2 levels from conception until childhood and working memory at 6–8 years of age. Note.* β = beta coefficient. 95 % CI = 95 % confidence interval. d' = d prime. HRT = Hit reaction time (ms). NO_2 = Nitrogen dioxide. The associations are presented for n = 1213 (3-back colours) and n = 1278 participants (3-back numbers). Models were adjusted for parental education level, parental social class, parental country of birth, maternal intelligence quotient, maternal pre-pregnancy body mass index, paternal body mass index, parental age at pregnancy, maternal smoking, second-hand smoke exposure and alcohol consumption during pregnancy, maternal folic acid and Vitamin D blood levels during pregnancy, maternal consumption of fish, fruit and vegetables during pregnancy, household gas appliances during pregnancy, urbanicity and surrounding green space of living area, child's sex and age at the test, year and month of conception, and the region. Solid lines show the predicted difference in the outcomes associated with an increase of 10 μg/m^3 of NO_2. Grey colours indicate null 95 % CIs.

exposure at schools and other sites, potentially leading to an underestimation of the true association. This bias may arise from heightened traffic-related pollution near schools and increased outdoor activity during school hours, both of which can affect inhalation of pollutants and contribute to the observed underestimation. Also, since we only investigated exposure to NO_2 and NO_2 is a proxy for traffic-related air pollution, other traffic-related pollutants could confound our findings. Unfortunately, we could not adjust for other pollutants. Secondly, despite the fact that the DLNM with small time periods of 4 weeks is a more advanced methodology, there are still some methodological limitations. For example, the DLNM requires selection of tuning parameters and there is no clear guideline on how to select these, while the DLNM is sensitive to the parameters used in the analyses (Wilson et al., 2017). However, we have intended to overcome this limitation by determining the knot position on a parsimonious principle. Thirdly, residual confounding is not completely ruled out. For example, road traffic noise (van Kempen et al., 2012) is a co-exposure that can be a possible confounder, however it was not available for most of the participants. Furthermore, by excluding extremely preterm births from the DLNM analyses, a potential risk of selection bias could persist. Lastly, comparing results from tests conducted at two different ages for attentional function using distinct testing methodologies requires caution, as potential developmental variations and differences in test characteristics could lead to misleading interpretations or inaccurate conclusions.

The levels of NO_2 across the entire time period in all regions reported in this study were above the 2021 World Health Organisation guidelines (10 μg/m^3), however, the mean air pollution exposure was below the standards of the European Union (40 μg/m^3) in every studied region, suggesting that air pollution can affect brain function at levels lower than current air quality standards (European Environment Agency (EEA)., 2022). Even a small effect at the individual level of relatively low exposure levels, as in Spain, can have major consequences at the population level, especially with a large number of people exposed to even higher NO_2 levels. This makes it important to lower these emissions with extra focus on the most affected regions.

5. Conclusion

In conclusion, this study shows that higher exposure to NO_2 was associated with worse attentional function in 4- to 6-year-olds with a heightened susceptibility observed during the second year of life. This association remained at an age of 6 to 8 years old only in boys, with a slightly larger susceptible period from birth until age 2. Furthermore, no association was found between higher NO_2 exposure and working memory in children aged 6 to 8 years. These findings underscore the potential impact of increased traffic-related air pollution on the delay in attentional function development, highlighting the importance of continued research in exploring long-term effects of air pollution in older age groups.

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CRediT authorship contribution statement

Kellie L.H.A. Crooijmans: Writing – original draft, Investigation, Formal analysis. **Carmen Iñiguez:** Writing – review & editing, Resources, Methodology. **Kristina W. Withworth:** Writing – review & editing. **Marisa Estarlich:** Writing – review & editing, Resources. **Aitana Lertxundi:** Writing – review & editing, Resources. **Ana Fernández-Somoano:** Writing – review & editing, Resources. **Adonina Tardón:** Writing – review & editing, Resources, Funding acquisition. **Jesús Ibarluzea:** Writing – review & editing, Resources, Funding acquisition. **Jordi Sunyer:** Writing – review & editing, Resources, Funding acquisition. **Mònica Guxens:** Writing – review & editing, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Anne-Claire Binter:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108604.

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