Prenatal and Postnatal Exposure to NO_2 and Child Attentional Function at 4-5 Years of Age

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Conflict of interest:

All of the authors declare that they have no conflicts of interest.

Abbreviations:

NO_2 = Nitrogen dioxide; INMA = INfancia y Medio Ambiente (Environment and Childhood); HRT(SE)= standard error of the hit reaction time; CI = Confidence Interval; PM = particulate matter; PM2.5= particulate matter of diameter less than 2.5

77 μm; ADHD= Attention deficit and hyperactivity disorder; HRT= hit reaction time;

78 IQ=intelligence quotient.

79

Abstract

Background: Prenatal and postnatal exposure to air pollution has been linked to cognitive impairment in children, but very few studies have assessed its association with attentional function.

Objectives: To evaluate the association between prenatal and postnatal exposure to nitrogen dioxide (NO_2) and attentional function in children at 4-5 years of age.

Methods: We used data from four regions of the Spanish INMA—Environment and Childhood—Project, a population-based birth cohort. Using land-use regression models (LUR), we estimated prenatal and postnatal NO_2 levels in all of these regions at the participants' residential addresses. We assessed attentional function using the Kiddie-Conners Continuous Performance Test (K-CPT). We combined the region-specific adjusted effect estimates using random-effects meta-analysis.

Results: We included 1,298 children with complete data. Prenatal exposure to NO_2 was associated with an impaired standard error of the hit reaction time (HRT(SE)) (increase of 1.12 ms [95%CI; 0.22 a 2.02] per 10μg/m³ increase in prenatal NO_2) and increased omission errors (6% [95%CI; 1.01 to 1.11] per 10μg/m³ increase in prenatal NO_2). Postnatal exposure to NO_2 resulted in a similar but borderline significant increase of omission errors (5% [95%CI;=0.99 to 1.11] per 10μg/m^3 increase in postnatal NO_2). These associations did not vary markedly between regions and were mainly observed in girls. Commission errors and lower detectability were associated with prenatal and postnatal exposure to NO_2 only in some regions.

Conclusions: This study indicates that higher exposure to ambient NO_2, mainly during pregnancy and to a lesser extend postnatally, is associated with impaired attentional function in children at 4-5 years of age.

1. Introduction

Air pollutants, and especially particulate matter (PM) and its soluble components, can become deposited in the alveolar region of the lungs, thereby causing oxidative stress and local-systemic inflammation (Block et al. 2012). They can also translocate into the systemic circulation, thereby reaching other organs, such as the brain, where they can activate microglia (Block et al. 2012). Microglia induce an inflammatory cascade, and when this activation is chronic and excessive, it can result in neurotoxicity and can initiate and/or amplify neuronal damage (Block et al. 2012). Fetal life and infancy is characterized by periods of rapid growth, cell differentiation, organogenesis, and development of the brain's neural network (Rice and Barone 2000), so this is a key window of vulnerability to the harmful effects of exposure to air pollution. Air pollution exposure during pregnancy can impair brain development through oxidative stress and systemic inflammation (Romieu et al. 2008). It can also harm the fetus' general health, resulting in smaller size for gestational age and lower birth weight (Heinonen et al. 2010), or decreased placental–fetal exchange of oxygen and nutrients by binding PM to receptors for placental growth factors (Kannan et al. 2006). Prenatal exposure to particulate matter of diameter <2.5 μm (PM2.5) has also been associated with reduced expression of two genes implicated in normal neurodevelopmental trajectories (Saenen et al. 2015), and we showed that exposure to air pollution impairs certain neuropsychological functions in both humans and animals (Guxens and Sunyer 2012; Suades-González et al. 2015).

Attention deficit and hyperactivity disorder (ADHD) is the most common mental disorder in children (CDC 2016). Children with ADHD generally have difficulty in paying attention and controlling impulsive behaviors (i.e. acting without thinking about the results of their actions), and they can be over-active (CDC 2016). Studies of the

impact of prenatal and postnatal air pollution levels on ADHD diagnoses and symptoms have had conflicting results (Abid et al. 2014; Forns et al. 2015; Gong et al. 2014; Newman et al. 2013; Perera et al. 2006, 2011, 2012, 2014; Siddique et al. 2011). However, only one study assessed prenatal air pollution levels (Chiu et al 2016), and only a few studies have examined how postnatal air pollution levels could affect attentional function (Chiu et al. 2013; Kicinski et al. 2015; Sunyer et al. 2015; van Kempen et al. 2012; Wang et al. 2009). Attentional function is a complex cognitive function that encompasses several processes, including capacity to focus on a stimulus over a period of time while ignoring other perceivable information, to absorb this stimulus, and then report it back immediately (White et al. 2009). Assessing attentional function in a more objective and precise way could hence provide a better understanding of its potential relationship with air pollution exposure.

The aim of the present study was, therefore, to assess whether prenatal and postnatal exposure to nitrogen dioxide (NO_2) could be associated with altered attentional function in children at 4-5 years of age.

2. Methods

2.1. Study design and participants

The INMA Project is a prospective population-based birth cohort established in seven regions of Spain following a common protocol (Guxens et al. 2012b). In the current study, we used data from the INMA regions of Valencia, Sabadell (Catalonia), Asturias, and Gipuzkoa (Basque-Country), where the cohorts were established between 2003 and 2008. Pregnant women who met the inclusion criteria (age ≥16years; intention to deliver at the reference hospital; no communication problems; singleton pregnancy; no assisted conception) were enrolled at public primary health care centers or public

hospitals during the 1st trimester of their pregnancies Ultimately, 56% of the women who were invited to participate agreed to do so, and were followed up throughout their pregnancies, until delivery. Their children were followed up from birth until 4-5 years of age. A total of 2,764 women were enrolled, and 2,157 (78%) children participated in the 4-5 years follow-up (see Figure 1). We included 1,298 children for whom data on the exposure and outcome variables were available. Most losses to follow-up were due to the late inclusion of the attentional function assessment at the 4-5 years follow-up, at which time some children had already been visited. All participants gave informed written consent, and the study was approved by the ethics committees of the hospitals in each study region.

2.2. Assessment of the exposure to NO_2

NO_2 was measured using passive samplers distributed throughout the study areas according to geographic criteria (see Supplemental Material, Table S1) (Estarlich et al. 2011). The samplers remained exposed during several 7-day sampling periods within a year. NO_2 levels were measured during pregnancy for all cohorts, and at 4 years in the Gipuzkoa and Valencia cohorts. We used land-use regression models (LUR) models to estimate NO_2 levels at each participant's residential address during pregnancy and from birth until the neuropsychological assessment using a geographic information system for each considered exposure period.

NO_2 estimates obtained from LUR models were translated to individual estimates for specific periods (prenatal and postnatal) by combining one or two maps, depending of the cohort and the period, by the mean daily levels from monitoring network stations. Measurements from different periods were combined as arithmetic

averages, thus providing the annual average concentration for each site. For all estimations and for each period, changes in home addresses were taken into account.

2.3. Children's attentional function

Attentional function was measured using the 2nd edition of the Conners Kiddie Continuous Performance Test (K-CPT) (MHS 2006). The K-CPT is a 7.5-minute computerized test that evaluates inattention, impulsivity, sustained attention, and vigilance in children aged 4-7 years. Children were individually tested in a quiet room by trained investigators.Children are instructed to push the space bar as quickly as possible when they see an image on the computer screen (the target), except if the image portrayed a ball (the non-target). The primary outcomes of interest were: the number of omission errors (i.e. the number of targets to which the test subject failed to respond); the number of commission errors (i.e. the number of times that the individual responded erroneously to a non-target); the hit reaction time (HRT, the mean response time -expressed in milliseconds- for all correct target hits during the entire test); the standard error of the hit reaction time (HRT(SE), the standard error of the reaction time for responses to target hits), and the detectability or attentiveness (d', a measure of the difference between the proportion of correct target hits out of the total number of targets and the proportion of individual failures to respond to a non-target out of the total number of non-targets) (MHS 2006). Omission errors reflect poorer orientation and a slower response. When combined with commission errors, a fast HRT reflects impulsivity; while, when combined with omissions and/or commission errors, a slow HRT is indicative of inattention. HRT(SE) indicates the consistency of the response time, such that high values indicate erraticness and inattention. Detectability reflects the

202 subject's perceptual sensitivity to targets, or how well they discriminate between targets
203 and non-targets.
204
205 **2.4. Potential confounding variables**
206 To decide which potential cofounding variables should be included in our models, we
207 drew a direct acyclic graph (DAG) (Hernán et al. 2002) based on up-to-date published
208 evidence (Supplemental Material, Figure S1). Questionnaires were administered during
209 pregnancy to obtain information on: maternal and paternal educational level; maternal
210 and paternal age; parents' social class defined by their occupation during the pregnancy
211 according to the Spanish adaptation of ISCO88; maternal and paternal countries of
212 birth; maternal height and pre-pregnancy weight; paternal body mass index; maternal
213 smoking and exposure to second hand smoke; maternal alcohol use; maternal
214 consumption of fish, fruit, vegetables, vitamin D, and folic acid; maternal noise
215 annoyance; and household gas appliances (cooking stove and heating. Maternal
216 circulating blood levels of vitamin D (25-hydroxyvitamin D3 [25 (OH) D]) were
217 measured during the first trimester. The child's sex was recorded according to the
218 clinical records. When the children were 4-5 year old, a questionnaire was administered
219 to collect information on the number of siblings; maternal mental health (assessed using
220 the Symptom Checklist-90-R questionnaire, with higher scores indicating poorer mental
221 health status); and maternal verbal intelligence quotient (IQ) (using the Wechsler Adult
222 Intelligence Scale, third edition, with higher scores indicating higher verbal IQ). All
223 questionnaires were administered in person by trained interviewers. The child's age at
224 the time of the attentional function test was recorded in days. Lastly, we recorded
225 urbanicity at the place of residence during pregnancy and during the postnatal period
226 (e.g. urban versus rural).

227

228 **2.5. Statistical analyses**

229 In children for whom we had data on exposure and outcome variables (n=1,298), we
230 performed multiple imputation of missing values for the potential confounding variables
231 using chained equations: we generated 25 complete datasets and analysed them using
232 standard combination rules for multiple imputation (Spratt et al. 2010; Sterne et al.
233 2009). The distributions of the imputed data were similar to those of the directly
234 collected data (data not shown).

235 Of the children recruited initially, those with available exposure and outcome
236 data (n=1,298) were more likely to have mothers from a higher socioeconomic position
237 than those without available exposure and outcome data (n=1,466) (see Supplemental
238 Material, Table S2). We used inverse probability weighting to correct for loss to follow-
239 up, i.e. to account for potential selection bias that results from using participants with
240 data in the last visit as opposed to the full cohort with data during pregnancy
241 (Weisskopf et al. 2015; Weuve et al. 2012). Briefly, we used information for all
242 participants at recruitment to predict the probability of participating in the study, and
243 used the inverse of these probabilities to weight the analysis so that results would be
244 representative of the initial cohort.

245 We used linear regression models to test for association between prenatal and
246 postnatal NO_2 exposure and HRT, HRT(SE), and detectability, and binomial negative
247 regression models to test for association between prenatal and postnatal NO_2 exposure
248 and omission and commission errors. We could not include both prenatal and postnatal
249 NO_2 levels in the models since they were highly correlated (0.86 in Valencia, 0.71 in
250 Sabadell, 0.92 in Asturias, and 0.58 in Gipuzkoa). First, the models were adjusted for
251 the child's sex and age at the time of the attentional function test (minimally adjusted

252 models). Second, the models were further adjusted for all potential confounding
253 variables described above (fully-adjusted models). We used generalized additive models
254 to assess the linearity of the relationship between prenatal and postnatal NO_2 levels and
255 each attentional function outcome, using fully-adjusted models by graphical
256 examination and deviance comparison.

257 We used a two-stage approach: i) we analyzed associations separately for each
258 region and ii) we used random-effects meta-analysis to combine region-specific effect
259 estimates from regression models. We assessed heterogeneity in the estimates using the
260 Q test and the I^2statistic.

261 We performed additional meta-analyses stratified by the sex of the child.
262 Statistical hypothesis tests were two-tailed, with significance set at 0.05. All analyses
263 were performed using STATA (version 13; Stata Corporation, College Station, TX,
264 USA).

265

266 ## 3. Results

267 Table 1 shows the characteristics of the mothers recruited in each region. Women
268 exposed to higher levels of NO_2 during pregnancy were more likely to be younger, less
269 well-educated, to consume more alcohol during the pregnancy, and to live in urban
270 areas, compared to women exposed to lower levels of NO_2 (Supplemental Material,
271 Table S3).

272 Table 2 shows the results for NO_2 exposure and attention function in each
273 region. The mean prenatal NO_2 level was 31.1 $\mu g/m^3$ (ranging from 18.4 to 37.9 $\mu g/m^3$
274 between regions), while the mean postnatal NO_2 level was 25.6 $\mu g/m^3$ (ranging from
275 19.5 to 35.2 $\mu g/m^3$ between regions). Children from the Valencia region were older and
276 had lower HRT and HRT(SE), and fewer omission errors (Table 2). Impaired

attentional function, revealed mainly by HRT(SE), was associated with lower socioeconomic status (data not shown).

In the fully adjusted models, higher exposure to prenatal levels of NO_2 was associated with a 1.12 ms increase in HRT(SE) (95% confidence interval [CI] =0.22 to 2.02) and a 6% increase in the number of omission errors (95%CI=1.01 to 1.11) per 10μg/m^3 increase in prenatal NO_2 (Table 3). For postnatal NO_2 levels, we found a similar but borderline significant association with the number of omission errors (5% more omission errors (95%CI=0.99 to 1.11) per 10μg/m^3 increase in postnatal NO_2 levels). These associations did not vary markedly between regions (Figure 2). In contrast, we only found an association between pre- and postnatal NO_2 levels and a higher number of commission errors in the regions of Gipuzkoa and Asturias regions; and lower detectability in the Gipuzkoa region (p for interaction = 0.02) (Figure 2).

Stratifying the analysis by sex, the observed association between higher exposure to pre- and postnatal NO_2 levels and a higher number of omission errors only persisted in girls (6% (95%CI=0.99 to 1.14) and 8% (95%CI=1.00 to 1.17) per 10μg/m3 increase in prenatal and postnatal NO_2 levels, respectively) (Table 3). The minimally-adjusted analysis showed similar associations overall (Table S4 and Supplementary Figure S2).

4. Discussion

In this study we assessed the association between prenatal and postnatal exposure to residential NO_2 air pollution and attentional function in children at 4-5 years of age. We found that prenatal NO_2 levels impair two attentional function outcomes, namely HRT(SE) and omission errors, which are both indicative of inattentiveness (Egeland and Kovalik-Gran 2010). We found a similar association between postnatal NO_2 levels and omission errors, and that these associations between pre- and postnatal NO_2

exposure and omission errors were predominantly observed in girls. In two regions, Gipuzkoa and Asturias, higher pre- and postnatal NO_2 levels were also associated with impairment of two further attentional function outcomes, detectability and commission errors.

The majors strengths of this study are the use of standardized air pollution assessment in all regions; the prospective design; and exposure assessment during two crucial periods, namely pregnancy and early life. Additional strengths are the assessment of attentional function using a computerized test, which provides an objective measure that allows us to detect small changes in vigilance/attention control and inhibition responses in young children. Another strength is the fact that we adjusted for many socioeconomic and lifestyle variables that are known to confound the association between prenatal and postnatal air pollution exposure and attentional function in children.

A limitation of our study is that we had no data on air pollution exposure at the children's daycare centers and schools, which could have an important influence on the children's neuropsychological development given that they spend a lot of time at these sites on weekdays (Sunyer et al. 2015). Another limitation of the study was that we only had data on self-reported noise annoyance during pregnancy, as a proxy for exposure to noise pollution. Air and noise pollution mainly come from motor vehicle traffic, and some studies have reported an association between road traffic noise and cognition in children (Clark and Stansfeld 2007). We adjusted for noise annoyance in our study, but we cannot fully rule out a possible residual confounding by noise exposure.

To our knowledge only one previous study has assessed the association of prenatal exposure to air pollution, assessed during each week of pregnancy, and attentional function in children aged 6-7 years (Chiu et al. 2016a). They found that

higher PM2.5 levels at the end of pregnancy was associated with poorer attentional function in boys and poorer memory in girls (Chiu et al. 2016). In contrast, we observed in the current study that NO_2 was associated with poorer attentional function predominantly in girls, although we assessed this association in younger children. The stronger effect in girls may be due to some biological mechanism, such as sex hormones, which could modulate visual temporal attention in girls (Kranczioch et al. 2016) or module their response to pro-inflammatory exposures such as air pollution (Melcangi et al. 2008). Moreover, female foetuses have been reported to be more vulnerable to certain suboptimal intrauterine environments, and to be particularly susceptible to attention difficulties in childhood (Murray et al. 2015). Further studies with larger samples are needed to better understand the sex-differences in the association between air pollution exposure and child neuropsychological development. This is especially important given the marked differences between girls and boys in terms of attention, brain development, and the effects of air pollution (Chiu 2016).

Regarding postnatal exposure to air pollution, exposure to traffic pollution have been shown to affect sustained attention in adolescents aged 14-16 years (Kicinski et al. 2015), and balck carbon to impair attentional function in 7- to 14-year-old boys (Chiu et al. 2013). A study in 8- to 10-year-old children also found that exposure to higher levels of NO_2 was associated with impaired attentional function (Wang et al. 2009). We recently reported similar findings, namely that exposure to traffic-related air pollutants at school (i.e. elemental carbon, NO_2, and ultrafine particles) is associated with inattentiveness in 7- to 10-year-olds (Sunyer et al. 2015). In contrast, a previous study found no association between NO_2 levels at school and attentional function in 9- to 11-year-olds (van Kempen et al. 2012).

In general, we interpret NO_2 as a marker of traffic, rather than as just a toxicant. Note that attentional function at this age is crucial for achieving proper neuropsychological development (Garon et al. 2008). In relation to prenatal exposure, our results, and those of Chiu et al. (2016a), show that the association with prenatal exposure is stronger and more homogeneous than for postnatal exposure, so prenatal exposure to air pollution appears to be the main driver of impaired attentional function. However, we cannot completely dissociate prenatal and postnatal air pollution exposures because they are strongly correlated. Future improvements in our air pollution models, combining land use variables and satellite remote sensing data, will allow us to better estimate the differencial effects of shorter time windows of exposure (Chiu et al. 2016b). There may be various biological mechanisms through which prenatal, as opposed to postnatal, exposure to air pollution impairs brain development in children. Prenatal brain development may be impaired by damage to the organ itself as a result of oxidative stress and systemic inflammation (Romieu et al. 2008), or by inhibited fetal growth, among other mechanisms (Heinonen et al. 2010). Regarding postnatal exposure, in addition to systemic inflammation (Romieu et al. 2008), pollutants may reach the brain directly through the nose and olfactory bulb (Minn et al. 2002), thereby directly damaging the prefrontal cortex.

We found that NO_2 levels were associated with a higher number of commission errors and impaired detectability, specifically in the Gipuzkoa and Asturias regions. These regions are situated on the Atlantic coast, while the other two regions, Valencia and Sabadell, are situated on the Mediterranean coast. Precipitation maps show much higher rainfall on the Atlantic coast than the Mediterranean coast, which may explain the regional variation in NO_2 levels observed in our study, given the known effects of rainfall on air pollution parameters (Guo et al. 2016). Also, rainfall can regulate

nitrification inhibitors used in agriculture, leading to lower NO_2 emissions under semiarid Mediterranean conditions (Abalos et al. 2017). Despite this, we observed lower NO_2 levels in the Atlantic areas than in the Mediterranean areas, probably because of lower traffic congestion in the former. In a previous study of the same regions (Guxens et al. 2012a), we also observed that the association between prenatal exposure to residential air pollution and mental development at a younger age was only observed in the Atlantic regions.

In this study, we assessed attentional function using a standardized, computerized neuropsychological test. In contrast, other studies have assessed the relationship between air pollution exposure and ADHD symptoms or diagnosis using information reported mainly by the parents, and have yielded inconsistent results (Abid et al. 2014; Forns et al. 2015; Gong et al. 2014; Newman et al. 2013; Perera et al. 2006, 2011, 2012, 2014; Siddique et al. 2011). The late age-onset of the inattentive subtype of ADHD in children (Applegate et al. 1997) could partly explain these contrasting results for ADHD, while it has been reported that the performance of the computerized test used in our study improves during childhood (Mani et al. 2005). A remaining question is whether exposure to air pollution is simply related with impaired attentional function, as we observed in our study (with all the negative consequences that this can entail), or whether it may also drive the development of inattention and hyperactivity symptoms, or the appearance of ADHD.

5. Conslusions

In conclusion, this study shows that higher exposure to NO_2 during pregnancy is associated with impaired attentional function, especially increased inattentiveness, in children aged 4-5 years. Our data suggest that postnatal exposure to NO_2 is also

401 associated increased inattentiveness, although we could not completely dissociated the
402 effects of pre- and postnatal exposure because they are highly correlated. These
403 associations were more pronounced in girls. In this sample, for each 1-month increase in
404 the children's age, we observe a general decrease in HRT(SE) of 0.76 ms,
405 corresponding to their improving attentional function. In comparison, we observed a
406 1.12 ms increase in HRT(SE) for each 10μg/m³ increase in prenatal NO_2 exposure,
407 which represents an almost 2-month delay in the development of attentional function.
408 The clinical impact of this increase in HRT(SE) is unknown, but it could have
409 implications for the whole population, especially because of the ubiquity of the
410 exposure. Reduced attentional function in the population could lead to poorer
411 educational indicators, thus affecting the population's productivity at subsequent stages
412 (Das et al. 2012; Plamondon and Martinussen 2015).

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Appendix A. Supplemental Material

Supplemental Material to this article can be found online.

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Figure Legend

Figure 1. Flowchart illustrating the main stages of the study

Figure 2. Forest plots of fully adjusted association between NO_2 exposure during pregnancy and attentional function outcomes. Region-specific and summary risk estimates from random effects analysis (coefficient/IRR and 95% CI) for: HRT (A), HRT(SE) (B), Detectability (C), Omission errors (D), and Commission errors (E) for each 10 µg/m³ increase in NO_2 level

P-value from Heterogeneity test (p-heter)/I^2 index to quantify the degree of heterogeneity in a meta-analysis (I^2(%)) for prenatal NO_2 exposure (overall) to HRT=0.92/0, HRT(SE)=0.92/0, Detectability=0.02/69.5, Omissions=0.65/0, Commissions=0.02/69.7. Models were adjusted for several cofounding variables (see fully adjusted model in methods section).

Table 1. Maternal characteristics of the study population by region.

	Valencia (n=524)	Sabadell (n=274)	Asturias (n=241)	Gipuzkoa (n=259)
Educational level during pregnancy				
University	28.4	36.2	38.6	50.6
Secondary	43.9	38.8	45.2	38.6
Primary	27.7	25.0	16.2	10.8
Social Class during pregnancy				
I/II managers/technicians	19.1	23.2	24.1	32.0
III skilled manual/non-manual	26.7	31.9	23.2	28.6
IV/V semiskilled/unskilled	54.2	44.9	52.7	39.4
Country of birth (Spain vs. elsewhere)	92.2	90.9	97.9	97.3
Residence urbanicity during prengancy (Rural vs. urban)	15.3	0.0	7.0	47.9
Age at child's birth (years)	30.5 (4.1)	30.5 (4.2)	31.9 (4.1)	31.3 (3.3)
Pre-pregnancy body mass index				
Normal weight/underweight	71.0	78.3	70.1	79.9
Overweight	19.8	15.2	23.2	15.4
Obese	9.2	6.5	6.6	4.6
Smoking during pregnancy (yes vs. no)	38.2	27.4	27.0	20.5
Alcohol consumption during pregnancy				
No consumption	73.8	74.3	90.9	81.1
Below the median[a]	15.3	14.1	2.1	12.0
Above the median[b]	10.9	11.6	7.0	6.9

Values are percentages for categorical variables and mean ± SD for continuous variables

[a]0.01/0.938 servings/week

[b]>0.939/maximum servings/week

Table 2. Distribution of NO_2 levels and attentional function scores by region.

	Valencia (n=524)	Sabadell (n=274)	Asturias (n=241)	Gipuzkoa (n=259)
NO_2 levels ($\mu g/m^3$)				
Prenatal	37.9 ± 11.8	37.7 ± 10.3	22.7 ± 7.5	18.4 ± 6.2
Postnatal	31.0 ± 9.9	35.2 ± 8.0	21.0 ± 6.6	19.5 ± 5.7
Attentional Function Scores				
Hit reaction time (milliseconds)	676.3 ± 103.9	734.3 ± 121.7	775.2 ± 161.1	763.2 ± 145.4
Hit reaction time standard error (milliseconds)	24.9 ± 12.5	35.5 ± 13.3	34.5 ± 15.6	33.9 ± 15.8
Detectability (no units)	0.6 ± 0.4	0.6 ± 0.4	0.7 ± 0.5	0.6 ± 0.5
Omission errors (number)	15 (13, 82)	27 (17, 15)	27 (20.81)	34 (22, 12)
Commission errors (number)	22 (9, 51)	23 (10, 98)	20 (13, 32)	19 (10, 63)
Age at attentional function assessment (years)	5.77 ± 0.16	4.53 ± 0.17	4.43 ± 0.23	4.47 ± 0.10

Values are mean ± SD for normally distributed continuous variables and median (interquartile range) for non-normally distributed continuous variables.

Table 3. Fully-adjusted combined association between prenatal and postnatal NO_2 (overall and by sex) and attentional function[a].

		HRT		HRT(SE)		Detectability		Omissions		Commissions	
Prenatal NO_2 (per Δ 10 µg/m³)	**N**	**β**	**(95% CI)**	**β**	**(95% CI)**	**β**	**(95% CI)**	**IRR**	**(95% CI)**	**IRR**	**(95% CI)**
Overall	1,298	-1.12	(-9.00; 6.75)	1.12	(0.22; 2.02)	-0.03	(-0.09; 0.03)	1.06	(1.01; 1.11)	1.04	(0.97; 1.12)
By sex											
Girls	648	2.07	(-9.63; 13.77)	0.47	(-0.51; 1.45)	-0.02	(-0.08; 0.04)	1.06	(0.99; 1.14)	1.00	(0.96; 1.05)
Boys	650	-0.85	(-12.06; 10.37)	1.23	(-0.22; 2.68)	-0.00	(-0.07; 0.07)	0.99	(0.89; 1.11)	1.01	(0.93; 1.10)
Postnatal NO_2 (per Δ 10 µg/m³)											
Overall	1,298	-4.70	(-13.80; 4.39)	0.81	(-0.82; 2.43)	-0.03	(-0.09; 0.03)	1.05	(0.99; 1.11)	1.04	(0.96; 1.13)
By sex											
Girls	648	1.97	(-11.53; 15.46)	0.34	(-0.80; 1.49)	0.01	(-0.03; 0.05)	1.08	(1.00; 1.17)	0.99	(0.94; 1.04)
Boys	650	-7.82	(-21.01; 5.38)	0.09	(-2.38; 2.55)	-0.01	(-0.08; 0.05)	0.96	(0.85; 1.10)	1.03	(0.94; 1.14)

β = beta coefficient. 95% CI= 95% confidence interval. IRR= Incidence-rate ratio. HRT = Hit reaction time (ms). HRT(SE) = Hit reaction time standard error (ms). Omissions = Omission errors (n). Commissions = Commission errors (n). NO_2 = Nitrogen dioxide. Δ = per each increase of 10 µg/m³.

P-value from Heterogeneity test (p-heter)/ I^2 index to quantify the degree of heterogeneity in a meta-analysis (I^2(%)) for prenatal NO_2 exposure (overall) to HRT =0.92/0, HRT(SE) =0.92/0, Detectability= 0.02/69.5, Omissions =0.65/0, Commissions = 0.02/69.7.

p-heter/I^2(%) for prenatal NO_2 exposure in girls to HRT =0.62/0, HRT(SE) =0.82/0, Detectability= 0.22/30.6, Omissions =0.81/0, Commissions = 0.44/0.

p-heter/I^2(%) for prenatal NO_2 exposure in boys to HRT =0.71/0, HRT(SE) =0.72/0, Detectability= 0.09/53.49, Omissions =0.12/49.03, Commissions = 0.03/66.9.

p-heter/I^2(%) for postnatal NO_2 exposure (overall) to HRT =0.54/0, HRT(SE) = 0.15/43.8, Detectability=0.05/62.8, Omissions =0.78/0, Commissions = 0.01/71.1.

p-heter/I^2(%) for postnatal NO_2 exposure in girls to HRT =0.43/0, HRT(SE) =0.95/0, Detectability= 0.43/0, Omissions =0.76/0, Commissions = 0.45/0.

p-heter/I^2(%) for postnatal NO_2 exposure in boys to HRT =0.69/0, HRT(SE) =0.17/39.6, Detectability= 0.22/32.3, Omissions =0.11/49.6, Commissions = 0.05/61.2.

[a]Estimated associations by random-effects meta-analysis by region. Models were adjusted for several cofounding variables (see fully adjusted model in methods section).