Air pollution exposure during pregnancy and symptoms of attention deficit and hyperactivity disorder in children in Europe

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Availability of data and code for replication: The data used for this study is owned by each of the individual cohorts. ISGlobal had access to the data for the specific research purpose, but is not allowed to share the data publicly. Researchers who wish to access the data should submit a request directly to each cohort. The computing code can be available upon request to the corresponding author.

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Abstract

Background: Exposure to air pollution during pregnancy may increase attention-deficit/ hyperactivity disorder (ADHD) symptoms in children, but findings have been inconsistent. We aimed to study this association in a collaborative study of eight European population-based birth/child cohorts, including 29,127 mother–child pairs.

Methods: Air pollution concentrations [nitrogen dioxide (NO_2) and particulate matter (PM)] were estimated at the birth address by land-use regression models based on monitoring campaigns performed between 2008 and 2011. We extrapolated concentrations back in time to exact pregnancy periods. Teachers or parents assessed ADHD symptoms at 3-10 years of age. We classified children as having ADHD symptoms within the borderline/clinical range and within the clinical range using validated cut-offs. We combined all adjusted area-specific effect estimates using random-effects meta-analysis and multiple imputation and applied inverse probability weighting methods to correct for loss to follow-up.

Results: We classified a total of 2,801 children as having ADHD symptoms within the borderline/clinical range, and 1,590 within the clinical range. Exposure to air pollution during pregnancy was not associated with a higher odds of ADHD symptoms within the borderline/clinical range (e.g., adjusted odds ratio (OR) for ADHD symptoms of 0.95, 95% confidence interval (CI) 0.89-1.01 per $10\mu g/m^3$ increase in NO_2 and 0.98, 95%CI 0.80-1.19 per $5\mu g/m^3$ increase in $PM_{2.5}$). We observed similar associations for ADHD within the clinical range.

Conclusions: There was no evidence for an increase in risk of ADHD symptoms with increasing prenatal air pollution levels in children aged 3 to 10 years.

Keywords: Nitrogen Oxides, Particulate Matter, Environmental Pollution; Attention Deficit Disorder with Hyperactivity, Child Development; Longitudinal studies, Prospective Studies, Meta-Analysis

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common psychiatric disorders during childhood with a worldwide prevalence of 5.2%[1]. ADHD is characterized by a spectrum of inattention and/or hyperactive/impulsive symptomatology affecting daily functioning in multiple settings, and entails substantial social and economic burden[2]. The heritability of ADHD is high (around 75%), with male predominance, and higher prevalence among children of lower parental socioeconomic strata and younger parents[3,4]. Environmental factors and potential gene–environment interactions may play a role in the manifestation and exacerbation of the ADHD symptoms[5–8].

Air pollution has recently raised a suspicion of neurotoxicity for the developing brain[9], but the evidence on the effects of air pollution on ADHD symptoms is limited. There are some indications that air pollution exposure prenatally or during the first years of life –especially exposure to indoor nitrogen dioxide (NO_2) and gas cooking at home, polycyclic aromatic hydrocarbons (PAHs), particulate matter with aerodynamic diameters >10μm (PM_{10}), and elemental carbon– are associated with ADHD symptoms in children[10–16], but these results were not replicated in other studies[17–20]. Due to the widespread nature of the air pollution exposure and the impact of ADHD on society and children's quality of life, larger studies including data from different countries are needed to confirm this potential association. Therefore, the aim of the current study was to assess whether air pollution exposure during pregnancy including NO_2 and PM is associated with an increased risk of ADHD symptoms in 29,127 children between 3 and 10 years old from eight European population-based birth/child cohort studies.

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Methods

Population and study design

This study was part of the European Study of Cohorts for Air Pollution Effects (ESCAPE) Project(www.escapeproject.eu). We included eight European population-based birth cohorts: DNBC (Denmark)[21], ABCD (The Netherlands)[22], GENERATION R (The Netherlands)[23], GINIplus/LISAplus (Germany, consisting of two sub-cohorts)[24,25], EDEN (France, including 2 sub-cohorts)[26], GASPII (Italy)[27], and INMA (Spain, consisting of four sub-cohorts)[28] and a European longitudinal child and adolescent twin study, CATSS (Sweden)[29] (Table 1). Mother–child pairs were recruited from 1992 to 2008. A total of 29,127 children with available exposure and outcome data (52.4% of the children recruited at baseline) were included. Ethical approval was obtained from the local authorized Institutional Review Boards.

Air pollution exposure

Air pollution concentrations at each participant's home address at birth were estimated for the whole pregnancy period by land-use regression models following a standardized procedure described elsewhere[30,31] (eAppendix 1; http://links.lww.com/EDE/B363). Briefly, air pollution monitoring campaigns were performed in the study areas between October 2008 and January 2011. In all areas, three 2-week measurements of NO_2 and nitrogen oxides (NO_x) were performed within 1 year[32,33]. In all cohorts, except in the Spanish cohorts of Valencia, Gipuzkoa, and Granada and the French cohort, simultaneous measurements of PM_{10}, $PM_{2.5}$, PM with aerodynamic diameters between 2.5-10µm (PM_{coarse}), and $PM_{2.5}$ absorbance (determined as the absorbance of the $PM_{2.5}$ filters) were performed (Table 1). Land-use regression models were developed for each pollutant metric using all measurement sites to estimate annual average air pollution concentration at each participants' home address at birth. We used a back-extrapolation procedure to estimate pregnancy-average concentrations

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from annual average concentrations using routine data from background sites of air quality monitoring networks in the study areas[34]. Traffic intensity on the nearest road and total traffic load (intensity*length) on all major roads within a 100m buffer were available, except for the Spanish cohorts for which traffic intensity on the nearest road was not obtained and for the Spanish cohort of Gipuzkoa for which traffic load was not obtained.

ADHD symptoms assessment

ADHD symptoms were assessed using four different questionnaires: the Autism-tics, Attention Deficit and Hyperactivity Disorders, and Other Comorbidities (A-TAC)[6], the Attention Deficit and Hyperactivity problems subscale of the Child Behavior Checklist for Toddlers (CBCL1½-5)[35], the Hyperactivity/Inattention problems subscale of the Strengths and Difficulties Questionnaire (SDQ)[36], and the ADHD Criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (ADHD-DSM-IV) list[2]. The A-TAC was used in the Swedish cohort at age 10 years, the SDQ was used in the Danish cohort at age 7 years, the Dutch cohort of Amsterdam at age 5 years, the German cohorts at age 10 years, and the French cohort at age 3 years, the CBCL1½-5 was used in the Dutch cohort of Rotterdam at age 6 years and the Italian cohort at age 4 years, and the ADHD-DSM-IV list was used in the Spanish cohorts at age 4-5 years (Table 1, eAppendix 2; http://links.lww.com/EDE/B363). All questionnaires were completed by the parents, except for the ADHD-DSM-IV list which was completed by the teacher. For all questionnaires, higher scores indicated more ADHD symptoms. We also used questionnaire-specific validated cut-offs to yield proxies for ADHD symptoms within the borderline/clinical (borderline or clinical) range and within the clinical range only[36–38] (eAppendix 2; http://links.lww.com/EDE/B363).

Other variables

We defined potential confounding variables a priori as similarly as possible across cohorts given available information. Maternal characteristics including age at delivery, educational

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level (cohort-specific categories were standardized (eTable 1;

http://links.lww.com/EDE/B363)), country of birth, prenatal smoking, and parity were

collected by questionnaires during pregnancy or at birth. Maternal height and pre-pregnancy

weight were measured or self-reported during the 1st trimester of pregnancy or at birth and

used to calculate pre-pregnancy body mass index (kg/m^2). Child's sex and season of birth

were obtained from hospital or national registries or questionnaires. Child's age at ADHD

assessment and evaluator (parents or teachers) of the ADHD symptoms were also collected.

We classified participants as living in an urban area when they lived in municipalities with

>40 inhabitants/hectare in the Swedish cohort, within the administrative borders of the city of

Munich and Wesel in the German cohorts, in municipalities with >2,000 inhabitants in the

Danish, Dutch, Italian, and Spanish cohorts, and in the metropolitan areas around the cities of

Poitiers and Nancy in the French cohorts, and as living in a rural area otherwise. Mothers

reported on changes in residence (since birth until ADHD symptoms assessment) through

questionnaires.

Statistical analyses

Dealing with missing data and attrition

We applied multiple imputation of missing values using chained equations to impute missing

values for potential confounding variables among all participants with available exposure and

outcome data. We obtained 25 completed datasets, which we analyzed using standard

procedures for multiple imputation[39,40]. Children with available exposure and outcome data

(n=29,127) were more likely to have mothers from a higher socioeconomic position compared

to those recruited at baseline, but without available exposure or outcome data (n=94,913)

(eTable 2; http://links.lww.com/EDE/B363). We used inverse probability weighting to correct

for loss to follow-up, i.e. to account for selection bias that potentially arises when only

population with available exposure and outcome data, and here thus with relatively higher

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socioeconomic position, is included as compare to the full cohort recruited at baseline[41,42].

Briefly, we used the available information of all participants at baseline to predict the

probability of participation in the study and used the inverse of those probabilities as weights

in the analysis so that results would be representative for the initial population of the cohort.

The variables used to create the weights and the area under the receiver operating

characteristic curve of the models, a measure of goodness-of-fit, are described in eTable 3;

http://links.lww.com/EDE/B363.

Main analyses

We used logistic regression models to assess the association between air pollution exposure

and ADHD symptoms within the borderline/clinical and within the clinical range. For both

analyses we considered children with scores below the borderline cut-off as controls. Models

for the Swedish cohort included a random intercept to account for clustering of children

within twin pairs. First, models were adjusted for child's age and sex (minimally adjusted

models). Secondly, models were additionally adjusted for all covariates described above

(fully-adjusted models). We used generalized additive models to assess the linearity of the

relationship between each air pollutant and ADHD symptoms scores by graphical

examination and deviance comparison. Linear coding of exposure provided a good fit in all

cases. We explored spatial clustering of observations by adding random area-level intercepts

(Swedish cohort: small administrative units; Danish cohort: municipality; Dutch cohorts:

neighborhood; German cohort: zip-code; French cohort: commune; Italian and Spanish

cohorts: census area) to fully adjusted models without the air pollution data. The inclusion of

the spatial clustering component had a negligible impact on the Akaike Information Criterion.

We therefore conducted all analysis without including the spatial clustering component. We

used a two-stage approach to assess the effect of air pollution exposure on ADHD symptoms.

First, associations were analyzed separately for each cohort. Secondly, cohort-specific effect

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estimates from the logistic regression models were combined using random-effects meta-analysis. We assessed heterogeneity in the estimates using the Q test and the I^2 statistic.

Sensitivity analyses

We performed several meta-analyses as sensitivity analyses: i) without applying inverse probability weighting; ii) leaving out one cohort at time to determine the influence of a particular cohort; iii) including only cohorts with information on both NO_2 and PM (94.0% of the children); iv) stratifying by the type of evaluator (teachers, parents); v) using the 90th percentile of each ADHD symptoms scale as cut-off for children at risk; vi) stratifying by children with and without a stable residence from birth until the ADHD symptoms assessment, vii) stratifying by child's sex, viii) stratifying by degree of urbanization at the birth address, ix) stratifying by maternal educational level; and x) restricting to children in scholar age ($\geq$6 years) because questionnaires used to assess ADHD in our study might present low validity in preschoolers[43].

Quantitative bias analysis

We performed a quantitative bias analysis for the association between exposure to NO_2 (above vs. below median) and ADHD symptoms within the borderline/clinical range to assess how much the estimates were affected by the lack of validity of the questionnaires used to assess ADHD[44,45]. Sensitivity and specificity estimates for A-TAC, CBCL1½-5, SDQ, and ADHD-DSM-IV[38,46–48] from previous validation studies were applied to the entire population to obtain the unadjusted corrected ORs.

Statistical analyses were conducted using STATA (version 12.1; StataCorporation, College Station, TX, USA).

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Results

Description of cases

A total of 2,801 children were classified as having ADHD symptoms within the

borderline/clinical range, and 1,590 within the clinical range (eTable 4;

http://links.lww.com/EDE/B363). Distributions of child and maternal characteristics per

cohort are shown in Table 1. Children with ADHD symptoms within the borderline/clinical

range were more often boys, more likely to have mothers with low/medium educational level,

younger, and who smoked during pregnancy compared to children without ADHD symptoms

(eTable 5; http://links.lww.com/EDE/B363).

Distribution of the exposure across cohorts

Cohort-specific median air pollution levels ranged from $14.1\mu g/m^3$ (the French cohort of

Poitiers) to $43.4\mu g/m^3$ (the Spanish cohort of Sabadell) for NO_2 and from $8.4\mu g/m^3$ (the

Swedish cohort) to $22.4\mu g/m^3$ (the Italian cohort) for $PM_{2.5}$ (eFigure 1;

http://links.lww.com/EDE/B363). We found low to high correlation (between 0.29 and 0.99)

between the different air pollutants and low to moderate correlations (between 0.10 and 0.62)

between air pollutants and traffic variables in the different participating cohorts (eTable 6;

http://links.lww.com/EDE/B363). In most of the cohorts highly educated mothers had slightly

higher levels of NO_2. This trend was not observed for $PM_{2.5}$ (eTable 7-8;

http://links.lww.com/EDE/B363).

Main analyses

Overall, exposure to air pollution during pregnancy was not associated with higher odds of

having ADHD symptoms in the borderline/clinical range in the fully-adjusted models (e.g.

OR for ADHD symptoms was 0.95, 95%CI 0.89-1.01 per $10\mu g/m^3$ increase in NO_2 and 0.98,

95%CI 0.80-1.19 per $5\mu g/m^3$ increase in $PM_{2.5}$) (Table 2, eFigure 2;

http://links.lww.com/EDE/B363). Associations were similar in the minimally-adjusted models

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(eTable 9; http://links.lww.com/EDE/B363). Although ORs varied somewhat between cohorts, associations did not systematically differ by the age of the children, the questionnaire used, or the evaluator assessing ADHD symptoms (eFigure 2; http://links.lww.com/EDE/B363). Similar associations were observed between air pollution during pregnancy and ADHD symptoms within the clinical range (Table 2, eFigure 3; http://links.lww.com/EDE/B363).

Sensitivity analyses

ORs of the analysis without applying inverse probability weighting moved slightly away from the null compared to the main analyses (eTable 10; http://links.lww.com/EDE/B363). Results remained consistent when cohorts were excluded one by one (eTable 11; http://links.lww.com/EDE/B363), when meta-analyses were restricted to cohorts with information on both NO_2 and PM (eTable 12; http://links.lww.com/EDE/B363), when we stratified the meta-analyses by the type of evaluator (eTable 13; http://links.lww.com/EDE/B363), when we used the 90th percentile of each ADHD symptoms scale to define children at risk (eTable 14; http://links.lww.com/EDE/B363), or when meta-analyses were performed separately for children with and without stable residence from birth until the ADHD symptoms assessment (eTable 15; http://links.lww.com/EDE/B363). We observed consistent ORs equal to or exceeding unity in females when we repeated the meta-analyses stratifying by sex (eTable 16; http://links.lww.com/EDE/B363), in children from rural areas when we repeated the meta-analyses stratifying by urbanicity (eTable 17; http://links.lww.com/EDE/B363), and in children from highly educated mothers when we repeated the meta-analyses stratifying by maternal educational level (eTable 18; http://links.lww.com/EDE/B363). Results did not change when we restricted the meta-analysis to children in scholar age (eTable 19; http://links.lww.com/EDE/B363).

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Quantitative bias analysis

After applying a quantitative bias analysis, the unadjusted corrected ORs of the association of

NO$_2$ exposure and ADHD symptoms within the borderline/clinical range showed some

variations. Some ORs were above 1, and some other ORs were below 1, although no clear

pattern of misclassification of the outcome was detected (eTable 20;

http://links.lww.com/EDE/B363).

Discussion

The present study assessed the association between prenatal air pollution exposure and

ADHD symptoms in 29,127 participants of eight European population-based birth/child

cohorts aged 3 to 10 years. Overall, there was no evidence for an adverse association between

air pollution exposure during pregnancy and ADHD symptoms in children. Effect estimates

varied slightly across cohorts without a clear pattern in relation to the age of the children, the

questionnaire, or the evaluator used to assess ADHD symptoms. The results were consistent

for different cut-offs of ADHD symptoms and after adjusting for several socioeconomic status

and life-style variables and degree of urbanization.

Strengths and limitations

The strengths of our study are the large sample size together with the prospective and

longitudinal study design, the use of a standardized and validated air pollution assessment for

all cohorts, the assessment of exposure to a large number of air pollutants including NO$_2$ and

PM at the individual level, the assessment of ADHD symptoms in childhood using validated

questionnaires, and the statistical analysis following a consensus protocol for all cohorts. We

adjusted for many socioeconomic and lifestyle variables known to be associated with air

pollution exposure during pregnancy and ADHD symptoms in children. We also used

advanced statistical methods including multiple imputation combined with inverse probability

weighting to reduce possible selection bias[41,42]. However, although the models used to predict

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the loss to follow-up had an overall moderate goodness-of-fit, effect estimates only moved slightly towards the null. We could have been missed variables related to this potential selection bias that would have a stronger effect in the results.

The main limitation of our study is that we did not have medical registries of ADHD diagnoses. Instead, four different questionnaires were used in the different cohorts to assess ADHD symptoms: A-TAC, SDQ, CBCL, and ADHD-DSM-IV. These questionnaires include different numbers of items and assign different weight to the two main groups of ADHD symptoms: inattention and hyperactivity/impulsivity. The use of these different questionnaires with uncertain positive predictive validity may have increased the risk of outcome misclassification, and then, assuming that the misclassification was non-differential, biased the association between air pollution and ADHD symptoms towards the null. Results of the quantitative bias analysis testing the impact of outcome misclassification did not shed light on this issue. The unadjusted corrected ORs flipped from null to either protective or increased risk side without showing any clear trend. The quantitative bias analysis reports unadjusted ORs, but as there is confounding demonstrated in the association between air pollution and ADHD symptoms, it was difficult to interpret the results of the quantitative bias analysis that does not account for this confounding. Also, due to the distribution of cases and controls under the sensibility and specificity values obtained from the literature the unadjusted corrected ORs could be non-valid in some cohorts since they were mathematically impossible to calculate. As expected, we observed a consistently higher prevalence of ADHD symptoms within the borderline/clinical range in boys than in girls across the different questionnaires. In addition, the prevalence of children with ADHD symptoms within the clinical range ranged from 3% to 7% in almost all the participating cohorts, which is close to the estimated worldwide prevalence of ADHD of 5.2%[1]. There are also differences in child's age at the time of the ADHD symptoms assessment between the participating cohorts. The age ranged from 3

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to 10 years. Although ADHD is normally clinically diagnosed at school age, ADHD symptoms, especially attention problems, could already appear during the preschool period[49–52]. Despite the differences in assessment of ADHD symptoms across cohorts, associations between prenatal air pollution exposure and ADHD symptoms were not influenced by the type of evaluator, the type of questionnaire, or the age at assessment. The diagnostic stability of ADHD which is low in community samples (around 50% in children <7 years)[53] may be another source of measurement error that biases our point estimates towards the null. However, in the present study we used three different questionnaires (SDQ, CBCL, and ADHD-DSM-IV) for which previous studies identified associations of air pollution exposure with ADHD[10,54,55], and another study using A-TAC where they did not find associations of air pollution exposure[19].

Another limitation of our study is related to the exposure assessment. Air pollution exposure models were developed based on monitoring campaigns performed between 2008 and 2011 and used to estimate exposures of pregnant women between 1992 and 2008. Previous research, however, suggests that the spatial distribution of air pollution concentrations and its predictors are stable over time[56,57]. Moreover, air pollution concentrations were back-extrapolated to the pregnancy period using long-term routine monitoring data, which could have led to non-differential exposure measurement error in cases of missing information about monitoring data (particularly PMs, for which we used background monitoring sites of other pollutants). We restricted our analyses to pregnancy average exposures and did not assess associations with trimester-specific exposures as correlations between pregnancy average and trimester-specific air pollution concentrations were high[34] and consequently associations with trimester-specific exposures would not be expected to be different from associations with pregnancy average exposures. Moreover, since air pollution levels during the postnatal period were not available, we performed separate analysis for children with and

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without stable residence from birth until the ADHD symptoms assessment and found very similar results. Finally, although exposure measurement error in the measurement may have influenced our findings, other papers using a similar methodology than the one used in the present study have found associations between air pollution and other outcomes, such as psychomotor development[58], low birth weight[34], lung cancer incidence[59], mortality[60] and incidence of acute coronary events[61].

Possible mechanisms

Of note, although all estimates of the association between air pollution during pregnancy and ADHD symptoms were close to unity, some were below one. Given the results of the previous studies[58,62], and the absence of any postulated mechanism for a potential protective association, this is unlikely to represent a true protective association of exposure to air pollutants during pregnancy on ADHD symptoms. NO_2 as well as some components of PM such as trace elements and PAHs have been suggested to be suspected neurotoxic, producing developmental neurotoxicity in the developing brain[9]. Some animal studies and human autopsies have pointed out that air pollution might affect brain maturation through oxidative stress and neuroinflammation implicating microglial activation, disruption of the blood–brain barrier, inflammatory cell trafficking, and accumulation of ultrafine particles in the respiratory nasal epithelium and olfactory bulb neurons[63–66]. These alterations caused by air pollution exposure may be involved in the development of ADHD. However, it has also been postulated that some constituents of air pollution could reduce the risk of ADHD (i.e. cadmium) while others could increase its risk (e.g. manganese)[67]. The effect of joint exposure to multiple metals, in particular when the mixtures include lead, have limited epidemiologic evidence and should be further investigated.

Discussion of the main results

Possible explanations of these counterintuitive results could be residual negative confounding, information bias, or selection bias. Residual negative confounding would have occurred in

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case of failing to adjust for factors related to both low air pollution exposure and high ADHD symptoms or vice versa. Maternal mental health could be one of these factors under the assumption that mothers with existing ADHD symptoms whose children are more likely to have ADHD symptoms would have moved to more quiet areas with less air pollution exposure. We did not have information on maternal ADHD symptoms for most of the cohorts but we had information on degree of urbanization for the birth address. When results were stratified for degree of urbanization, children in rural areas showed a tendency of increase in risk of ADHD symptoms related to higher air pollution exposure which might be in line with the hypothesis of lack of adjustment by maternal ADHD symptoms.

Other unmeasured family or home environment characteristics that could differ between low and high air pollution areas and could be inversely related to the prevalence of ADHD symptoms in children could also confound our results. Information bias could also play a role if we think that mothers from high and low polluted areas would have different contextual or personal characteristics leading to a differential reporting of ADHD symptoms which could be related to a different awareness of the problems of their children or a different accessibility to the health care system. Although we adjusted for many socioeconomic and lifestyle variables known to be associated with air pollution exposure during pregnancy and ADHD symptoms in children, we could have failed to properly adjust for other relevant contextual or family characteristics related to this possible information bias.

Finally, we cannot rule out the possibility that selection bias has influenced our results since not all mother–child pairs initially recruited were included in the analysis sample and loss to follow-up was related to lower socioeconomic position. The finding of increased risk of ADHD symptoms among the highly educated mother stratum emphasize this possibility. In a previous study[11], the authors also reported higher ADHD risk in association with air pollution only in the highly educated mothers. One of the most plausible hypothesis to explain these

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results is that children from low socioeconomic position have other risk factors strongly associated with ADHD than air pollution, such as parental history of ADHD, less actively engaged parents, or less stimulating family environment.

Based on previous literature, it was unclear whether exposure to air pollution during pregnancy or during childhood is related to an increase risk of ADHD. Some studies reported an increased odds of ADHD symptoms with increasing air pollution exposure during pregnancy[13,14] or during childhood[10,11,15,16], while other studies did not find an association[17–20]. Moreover, in a recent review of the evidence on the associations between air pollution and neuropsychological development, the authors concluded that there is inadequate or insufficient evidence for an association between air pollution and ADHD due to the limited number of studies, deficient quality, or low consistency of the results between studies[62]. We also observed a tendency of increased risk of ADHD symptoms in females compared to males in relationship to air pollution exposure during pregnancy, although we do not have a reliable hypothesis to explain this finding. In view of the results of our study and the inconsistencies of the literature, we hypothesize that exposure to air pollution might not increase the risk of ADHD in children in the general population. However, it has been suggested that air pollution exposure could have harmful effects on neuropsychological development especially in children that are genetically susceptible[10]. It has been shown that ADHD is the result of complex interactions between genetic background (estimated heritability of about 75%[5]), environmental factors (of which air pollution could be one), and social determinants[68].

Conclusion

In conclusion, our results do not suggest that air pollution exposure during pregnancy is associated with a higher risk of ADHD symptoms in children aged 3 to 10 years.

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Table 1. Distribution of the child and maternal characteristics

	N	Child's sex % female	Maternal educational level % low	% medium	%high	Maternal country of birth % foreign	Maternal age at delivery (years) mean (SD)	Maternal pre-pregnancy body mass index (kg/m^2) mean (SD)	Maternal height (cm) mean (SD)	Prenatal maternal smoking % smokers	Parity % nulliparous
All population											
CATTS, Sweden	3363	49	10	48	42	15	32 (4.6)	24 (3.7)	168 (6.3)	14	23
DNBC, Denmark	10382	49	38	18	44	NA	31 (4.2)	23 (3.7)	169 (6.1)	25	49
ABCD, The Netherlands	4276	50	15	36	49	26	33 (4.7)	23 (3.9)	169 (7.1)	8.7	57
GENERATION R, The Netherlands	4532	50	6.2	38	54	38	32 (4.6)	24 (4.1)	169 (7.3)	13	59
GINI/LISA, Germany-Wesel	1695	49	18	49	33	0.0	32 (0.8)	NA	169 (6.1)	14	45
GINI/LISA, Germany-Munich	2229	49	8.9	30	61	0.0	32 (0.8)	NA	168 (6.1)	12	57
EDEN, France-Nancy	413	52	16	13	70	4.6	30 (4.5)	23 (4.4)	165 (5.9)	17	47
EDEN, France-Poitiers	440	43	25	21	54	4.3	30 (4.9)	23 (4.5)	163 (6.1)	26	54
GASPII, Italy	527	50	11	51	38	4.2	33 (4.2)	22 (3.4)	165 (5.8)	11	57
INMA, Spain-Gipuzkoa	295	50	11	38	51	2.7	33 (3.5)	23 (3.4)	164 (5.8)	19	53
INMA, Spain-Sabadell	411	48	25	41	34	9.3	32 (4.0)	24 (4.8)	162 (5.9)	27	58
INMA, Spain-Valencia	410	48	26	45	29	5.9	32 (4.0)	24 (4.5)	162 (6.3)	39	58
INMA, Spain-Granada	154	0.0	19	68	13	0.0	31 (4.3)	24 (4.1)	162 (5.9)	21	46

NA, Not Available.

Table 2. Fully adjusted combined associations[a] between prenatal exposure to each air pollutant[b] and ADHD symptoms within the borderline/clinical range and within the clinical range

	ADHD traits within the borderline or clinical range					ADHD traits within the clinical range only				
	N[c]	OR	(95% CI)	p-heter	I^2	N[c]	OR	(95% CI)	p-heter	I^2
NO_2 (per $\Delta 10$ μg/m^3)	13	0.95	(0.89 - 1.01)	0.527	0.0	12	0.95	(0.87 - 1.04)	0.405	4.0
NO_X (per $\Delta 20$ μg/m^3)	11	0.97	(0.92 - 1.01)	0.475	0.0	10	0.95	(0.89 - 1.02)	0.578	0.0
PM_{10} (per $\Delta 10$ μg/m^3)	8	0.97	(0.79 - 1.19)	0.105	41	8	0.91	(0.73 - 1.13)	0.303	16
$PM_{2.5}$ (per $\Delta 5$ μg/m^3)	8	0.98	(0.80 - 1.19)	0.203	28	8	0.94	(0.74 - 1.19)	0.290	18
PM_{coarse} (per $\Delta 5$ μg/m^3)	8	0.98	(0.84 - 1.13)	0.082	45	8	0.92	(0.79 - 1.09)	0.244	23
$PM_{2.5}$absorbance (per $\Delta 10^{-5}$m^{-1})	8	0.89	(0.75 - 1.07)	0.180	31	8	0.85	(0.70 - 1.02)	0.835	0.0
Traffic density on nearest street (per $\Delta 5000$ mv/day)	9	1.03	(0.98 - 1.07)	0.216	26	9	1.03	(0.98 - 1.09)	0.282	18
Traffic load on major road in 100m buffer (per $\Delta 4000000$ mv/day*m)	11	1.04	(0.96 - 1.13)	0.321	13	11	1.02	(0.93 - 1.11)	0.567	0.0

95% CI, 95% Confidence Interval; OR, Odds Ratio; I^2 =Percentage of the total variability due to between-areas heterogeneity; NO_2, nitrogen dioxide; NO_x, nitrogen oxides; p-heter, P value of heterogeneity using the Cochran's Q test; PM_{10}, particle matter less than 10μm; $PM_{2.5}$, particle matter less than 2.5μm; PM_{coarse}, particle matter between 2.5 and 10μm; $PM_{2.5}$absorbance, reflectance of $PM_{2.5}$ filters; ADHD attention deficit hyperactivity disorder.
[a] Odds Ratio and 95% confidence interval estimated by random-effects meta-analysis by area. Models were adjusted for maternal characteristics (education or socioeconomic level, country of birth, age at delivery, pre-pregnancy body mass index, height, prenatal smoking, parity), child's sex, season at child's birth, type of zone at child's birth address, child's age at assessment, and type of evaluator of the test. Models of traffic variables were additionally adjusted for non-back-extrapolated background levels of NO_2

[b] Air pollution levels were temporally adjusted to the exact pregnancy period except for traffic variables
[c] Number of (sub-) cohorts included in the meta-analysis. (Sub-) Cohorts with less than 10 children with ADHD traits within the clinical range were not included.

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