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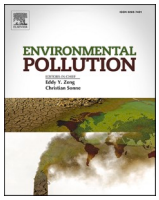

Associations of exposure to outdoor $PM_{2.5}$ and NO_2 during pregnancy with childhood asthma, rhinitis, and eczema in a predominantly rural French mother-child cohort

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ABSTRACT

Uncertainty remains regarding the effects of outdoor air pollution in rural areas on childhood asthma, rhinitis, and eczema. Although these diseases often coexist, few studies have examined the effects of air pollution on their multimorbidity. The objective of this study was to investigate the associations of pregnancy exposure to outdoor fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) with childhood asthma, rhinitis, eczema, and their multimorbidity. We included children from the 6-year (n = 1322) and 12-year (n = 1118) follow-up of the Pélagie mother-child cohort in Brittany, France where 64% of the participants lived in rural areas. Asthma, rhinitis, eczema, and a multimorbidity phenotype (concomitant presence of ≥2 diseases) were defined by validated questionnaires. $PM_{2.5}$ and NO_2 concentrations during pregnancy were modeled at residential address using land use regression. We assessed associations using logistic regressions per interquartile range ($PM_{2.5}$: 3 μg/m^3; NO_2: 10 μg/m^3). We also performed stratification by type of area (urban and rural). Asthma, rhinitis, eczema, and the multimorbidity phenotype prevalence were 12%, 20%, 22% and 12% at 6-years, and 10%, 23%, 19% and 11% at 12-years of follow-up. At 6-years, for eczema, a tendency of an association was observed with NO_2 (OR = 1.15, 95% CI = 0.97–1.36, *p-value = 0.10*), and stratification by type of area showed statistically significant associations for $PM_{2.5}$ (1.49 (1.03–2.13), $p = 0.03$) and NO_2 (1.40 (1.08–1.82), $p = 0.01$) in the urban stratum. At 12-years, main analyses showed a tendency of associations of $PM_{2.5}$ (1.38 (0.98–1.93), $p = 0.07$) and NO_2 (1.25 (0.98–1.59), $p = 0.07$) with asthma, and of NO_2 with the multimorbidity phenotype (1.23 (0.97–1.56), $p = 0.09$). While overall results were not statistically significant, associations in urban settings were stronger than in rural ones at 6-years suggesting that possible differences between the effects in urban and rural areas should be further explored.

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1. Introduction

Asthma, rhinitis, and eczema are among the most common chronic diseases in childhood. Among European children, prevalence of asthma, rhinitis, and eczema has been estimated to be around 8–11%, 9–23% and 8–35% respectively (Garcia-Aymerich et al., 2015; García-Marcos et al., 2022; The Global Asthma Report, 2022, 2022). In France, the stage 2 of the ISAAC-France survey, estimated the prevalence of diagnosed asthma, allergic rhinitis, and eczema among school-aged children to be 13%, 23%, and 25%, respectively (Sasso et al., 2019; Delmas et al., 2017). Moreover, coexistence of these three diseases is common among children (Pinart et al., 2014; Rutter et al., 2020). Prevalence rates of any combination of asthma, rhinitis, and eczema comorbidity in children have been estimated around 4–50% (Gough et al., 2015; Sigurdardottir et al., 2021).

Growing evidence suggests that an important proportion of childhood asthma and allergic diseases occurrence could be attributed to environmental factors, including exposure to outdoor air pollutants (Burbank et al., 2017; Murrison et al., 2019). For instance, up to 33% of childhood asthma incident cases in Europe may be attributable to outdoor air pollution (Khreis et al., 2019). In line with the developmental origins of health and disease (DOHaD) hypothesis, many studies have associated exposure to outdoor air pollution during pregnancy and early childhood with an increased prevalence of childhood asthma and allergic diseases, notably allergic rhinitis and eczema (Bowatte et al., 2015; Hehua et al., 2017; Yue et al., 2022; Liu et al., 2023; Deng et al., 2016; Lu et al., 2023a; Lu et al., 2023b; Lu et al., 2024). This could be due to several plausible mechanisms, including the alteration of the proinflammatory responses and sustained changes in the offspring's DNA methylation pattern (Deng et al., 2023; Rider and Carlsten, 2019).

Available systematic reviews on the exposure to air pollution during pregnancy concluded that maternal exposures to fine particulate matter ($PM_{2.5}$) and nitrogen dioxide (NO_2) were associated with an increased risk of childhood asthma (Bowatte et al., 2015; Hehua et al., 2017; Yan et al., 2020). A recent systematic review showed that exposure to traffic-related air pollution during pregnancy was significantly associated with the development of childhood allergic rhinitis (Liu et al., 2023), and another one showed that prenatal exposures to NO_2 increased the risk of childhood eczema (Yue et al., 2022). Although asthma, rhinitis, and eczema often coexist in the same individual, to our knowledge, only one study has investigated the effects of air pollution exposure on these three diseases considered together (Fuertes et al., 2020). The authors did not find significant associations between any air pollutant and the multimorbidity outcome. However, the study examined the associations with exposure to air pollution at the time of birth and not during the pregnancy period (Fuertes et al., 2020).

The majority of studies on the effects of air pollution on respiratory health and allergies have been predominantly or exclusively carried out in urban populations. Yet, air pollution differs in rural and urban areas in terms of level, sources, and composition, with urban areas generally experiencing higher levels (Sousa Santos et al., 2021; WHO global air quality guidelines, 2021). To our knowledge, only two studies have investigated the effects of air pollution during pregnancy on asthma stratifying by urban versus rural areas, showing no significant differences between these two (Madsen et al., 2017; Lavigne et al., 2018). Consequently, there is still a need for studies assessing the effects of air pollution in rural settings in order to gather more conclusive evidence. In light of these gaps, we hypothesize that exposure to outdoor air pollution during pregnancy may have a different impact on the development of childhood asthma, rhinitis, and eczema in urban areas compared to rural areas due to differences in pollutant levels.

In this study, based on a French mother-child cohort with a predominantly rural population, we investigate the associations of maternal exposure to $PM_{2.5}$ and NO_2 during pregnancy with the childhood prevalence of asthma, rhinitis, eczema, and their multimorbidity, and we examine whether the urbanization degree at the maternal place of residence during pregnancy modifies these associations.

2. Methods

2.1. Study population

The Pélagie (Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance) study, fully described in a previous publication (Warembourg et al., 2024), is a mother-child cohort that enrolled 3421 pregnant women in Brittany, France, from 2002 to 2006. Participants were recruited if they attended a consultation before 19 weeks of gestation with a midwife, gynecologist, obstetrician, or sonographer, and if they planned to give birth in the Britany region. At inclusion, the health practitioners informed pregnant women about the study objectives, obtained their written consent, provided a study kit (questionnaire and urine sampling materials), and transmitted their contact details to the research team. The women completed the questionnaire at home and mailed it, along with a 20-mL first morning urine sample, to the laboratory (Inserm U1085) (Warembourg et al., 2024). Through the inclusion questionnaire we gathered information on the parents' family and health history, diet, lifestyle, and the sociodemographic characteristics. All participants gave informed consent and the French ethics committees approved the study procedures.

At birth, 3322 liveborn singleton were eligible for subsequent follow-ups. Medical information about pregnancy, delivery, and the newborn's health was obtained from midwives, pediatricians, and hospital medical records. At 6- and 12-year follow-up, information about the family demographic characteristics and on the health, lifestyle, and immediate environment of children and their parents was gathered through self-administered questionnaires completed by the parents (mainly the mothers) that were sent and returned by mail.

For the present study we excluded 1) newborns with major congenital malformations ($n = 100$) according to the EUROCAT definition (EUROCAT Special Report, 2012), 2) extremely, very, and moderately preterm births (<34 weeks of gestation, $n = 43$) as studies have shown a higher risk of respiratory pathologies in premature children (Gutvirtz et al., 2022), 3) participants living in departments outside the Brittany region ($n = 5$).

We performed separate analyses for participants at 6- and 12-year follow-up, therefore, we have the population of the participants who completed the 6-year follow-up (n = 1374) and those who completed the 12-year follow-up (n = 1172). Subsequently, participants for whom the address during pregnancy could not be geocoded and with missing data for outcomes and adjustment covariates at 6-year ($n = 52$) and 12-year follow-up ($n = 54$) were also excluded. A total of 1322 and 1118 mother-child pairs were respectively included for the 6- and 12-year follow-up analyses. Out of them, 853 mother-child pairs participated in both follow-ups. A flowchart depicting the selection of the analysis population is shown in Fig. 1. Geographical distribution during pregnancy of participants included in the analyses is shown in Fig. S1.

2.2. Exposure assessment

Exposures to outdoor $PM_{2.5}$ and NO_2 during pregnancy were estimated at each participant residential address i.e., where they spent the most time during pregnancy.

For our main analyses, we used Western European Land Use Regression (LUR) models developed for the ELAPSE project http://www.elapseproject.eu/. These LUR models estimated the annual means of $PM_{2.5}$ and NO_2 for 2010 based on routine monitoring data from the AirBase v8 dataset. Predictor variables entered in the LUR include satellite-derived and chemical transport air pollution estimates, and land use and road data. Models for each pollutant were applied to 100 × 100m grids across Western Europe (de Hoogh et al., 2018). Exposure estimates for $PM_{2.5}$ and NO_2 at the participants' residential addresses

were calculated using the LUR model developed as part of the ELAPSE project (de Hoogh et al., 2018). The spatial estimates generated by this model reflect the time period during which the model was developed (2009–2010). To estimate exposures during the pregnancy period of each participant in the Pélagie cohort, a temporal adjustment (back--extrapolation) was applied using NO_2 measurements from a background monitoring station (station FR19006, Rennes ENSP).

Following ESCAPE guidelines (de Hoogh et al., 2013), this back-extrapolation was performed by combining the ELAPSE LUR spatial estimates for each participant's geocoded location with a temporal adjustment factor derived from the routine monitoring data. Specifically, the adjustment factor for each day of the pregnancy period was calculated as the ratio of the daily concentration at the monitoring station to the annual average concentration from 2009 (the year of the sampling campaign) or 2010 (the year of the ELAPSE air pollution grid maps). The final adjusted concentration for a specific date was then obtained by multiplying the spatial estimate by the corresponding temporal adjustment factor. The back-extrapolated daily averages were aggregated to a 9-month average corresponding to each pregnancy.

We also had access to air pollution estimates from additional models developed for continental France. The first is a hybrid model estimating daily $PM_{2.5}$ concentrations at a 1 × 1 km spatial resolution from 2000 to 2019 using satellite aerosol optical depth data, meteorology, vegetation, and other spatiotemporal predictors (land cover, road and railway density, elevation, population, climatic region) using three base learners (mixed models, Gaussian Markov random fields, and random forests) ensembled using a generalized additive model (Hough et al., 2021). The model showed good performance with a mean absolute error of 2.72 $\mu g/m^3$ and R^2 = 0.76. The second additional model, CHIMERE, estimated daily NO_2 concentrations using a Eulerian chemistry-transport model at a 4 km spatial resolution from 2000 to 2015. This approach relying on a kriging procedure showed good performance in urban areas (bias not exceeding −3.5%) but lower performance in rural areas (overestimation by 60–80% depending on years due to a low number of monitoring stations) (Real et al., 2022).

Table S1 summarizes the main characteristics of each model.

2.3. Outcomes

Children's respiratory health and allergies at 6- and 12-year follow-up were assessed through parent-completed questionnaires adapted for the Pélagie cohort based on the French version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires (Asher et al., 1995), which have been validated for the French population and are widely used for epidemiological studies on childhood asthma and allergies (Charpin et al). Three main outcomes were considered in our study: ever asthma, ever rhinitis, and ever eczema.

We defined ever asthma based on a parent-declared doctor-diagnosis of asthma. At the 6-year follow-up, it was determined through positive answers to both of the next questions: "*Has your child ever had asthma attacks since birth?*" and *if yes:* "*Has your child's asthma been confirmed by a doctor?*". At the 12-year follow-up, it was established through a positive response to the question "*Has your child ever been diagnosed with asthma by a physician?*".

Ever rhinitis, both at 6- and 12-year follow-up, was determined through a positive answer to the next question: "*Since birth, has your child ever had sneezing, a runny nose or a blocked nose, even though they had no respiratory infection (no cold, nor rhinopharyngitis, nor flu …)?*".

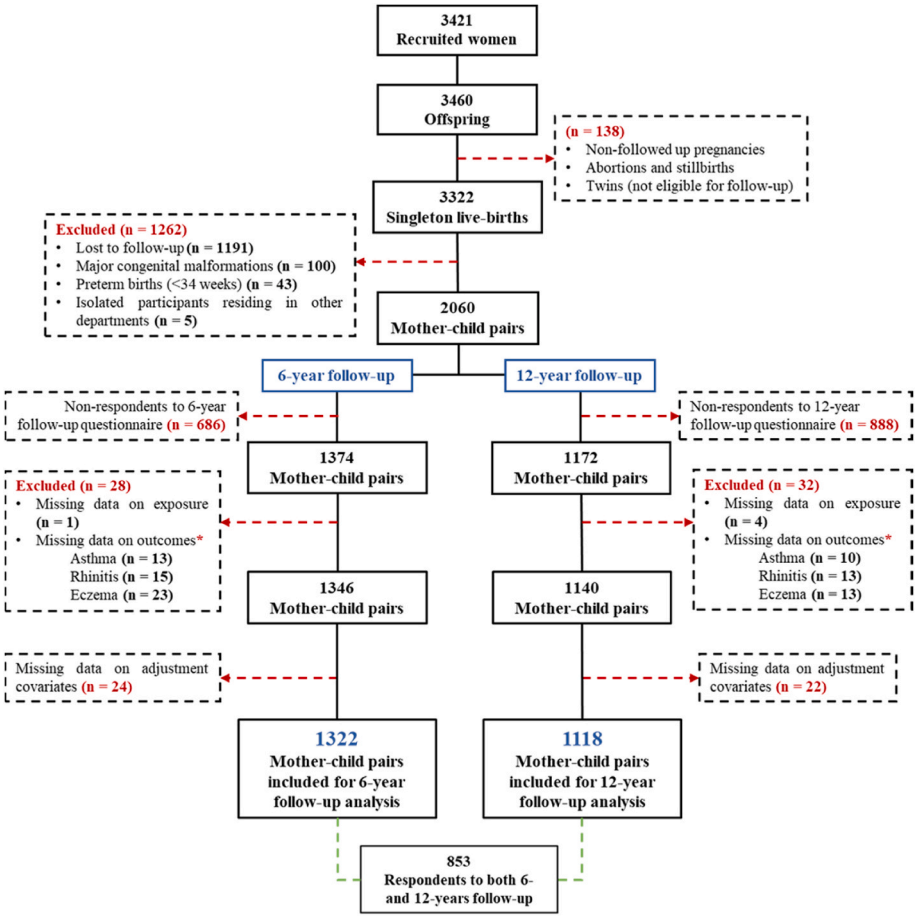

Fig. 1. Flowchart of study population.
* Some participants have missing data for more than one outcome.

We defined ever eczema based on a parent-declared doctor-diagnosis of eczema. At the 6-year follow-up, it was determined through positive answers to both of the next questions: "*Since birth, has your child ever suffered from eczema or atopic dermatitis?"* and *If yes: "Has your child's eczema been confirmed by a doctor?"*. At the 12-year follow-up, it was established through a positive response to the question "*Since your child was born, has a physician ever told you they had eczema?"*.

Based on these three outcomes, we also created a multimorbidity phenotype with three different categories: no disease, 1 disease, and ≥2 diseases.

2.4. Covariates

Potential confounders of the association between air pollution exposure during pregnancy and childhood asthma, rhinitis, and eczema were selected from the literature. Retained adjustment covariates were child's sex and age, mother's age and education level at inclusion, and mother's tobacco smoking habits and area-level socioeconomic status during pregnancy.

Self-declared information on mother's characteristics was obtained through the inclusion questionnaire. The mother's smoking habits during pregnancy were categorized in three classes: non-smokers and former smokers, smokers at the start of pregnancy but that quit before inclusion, and smokers at inclusion. Mother's education level at inclusion was categorized into three classes: under high school, high school diploma, and graduate education. Information on the child's sex was obtained from the maternal and pediatric chart completed at birth by the healthcare personnel. Area-level socioeconomic status was estimated using the French Deprivation Index (FDep) for the year of 2009 "FDep09". This index defines the social disadvantage as an accumulation of material and social disadvantages at the IRIS (aggregated units for statistical information) level, which divides the French territory into "neighborhoods" with a population of around 2000 (Rey et al., 2009). FDep was calculated in tertiles (1st tertile (low deprived), 2nd tertile (medium deprived), and 3rd tertile (high deprived)) for the French general population at each IRIS, and we assigned it to each participant based on the residential address where they spent the most time during pregnancy.

Urbanization degree during pregnancy was calculated using the GHSL SMOD Settlement model, which classifies 1 km^2 grid cells according to three main spatial entities: Urban Centre, Urban Cluster, and Rural Grid Cells (Florczyk et al., 2019). For our analysis, we created a binary variable to partition study participants into rural (Rural Grid Cells) and urban areas (Urban Centre and Urban Cluster Grid Cells).

2.5. Statistical analyses

The number of missing data was low, less than 2% for each variable, accounting for less than 3% for all variables at each follow-up. We decided to carry out complete case analyses, therefore, only participants without missing data for outcome variables, air pollution exposure and adjustment covariates were included.

Characteristics of the population and their exposure to air pollutants were summarized using frequencies, percentages, means, standard deviations, quartiles, and interquartile ranges (IQR). Differences between participants with and without asthma, rhinitis or eczema were assessed with Chi-square tests for categorical variables, Wilcoxon Rank Sum tests for air pollution exposure data, which did not meet normality assumptions, and Student tests for all other continuous variables. Differences of participants among categories of the multimorbidity phenotype were compared to those of the reference category (no disease), using One-Way ANOVA for continuous variables and Chi-square tests for categorical variables.

We performed models with restricted cubic splines (df = 4) and compared them with our main models using a likelihood ratio test of nested models to assess the linearity of the relationship between each air pollutant and each health outcome. The associations of $PM_{2.5}$ and NO_2 with each of the three main outcomes taken into account separately were examined using binary logistic regression models. Multinomial logistic regression models were used to assess the associations of each air pollutant with the multimorbidity phenotype categories (no disease (as reference), 1 disease, and ≥2 diseases). Associations were presented as odds ratio (OR) with 95% confidence interval (95% CI) expressed for an increase of one IQR in the concentration of each air pollutant. All models were performed with an increasing order of adjustment: univariate analyses, *model 1:* adjusted by child's sex and age, mother's age at inclusion, and mother's smoking habits during pregnancy, *model 2:* adjustment model 1 + mother's education level at inclusion, and *model 3:* adjustment model 2 + area-level socioeconomic status.

We also performed interaction tests and stratified analyses by participants' urbanization degree during pregnancy to assess the effect modification. Likewise, we performed interaction tests and stratified analyses according to children's sex.

Additional analyses with air pollutants estimates categorized into quartiles were carried out to further assess linearity of the associations between the exposure to $PM_{2.5}$ and NO_2 during pregnancy and childhood asthma, rhinitis, and eczema.

Lastly, to confirm the robustness of the findings, we performed sensitivity analyses using the air pollution estimates from the French models. Furthermore, as the prevalence of our studied outcomes is high and thus logistic regression models could overestimate the relative risks, we performed additional analyses using Poisson regression models with robust error variance, and log-binomial regression models to verify the robustness of our main findings (Callas et al., 1998).

All statistical analyses were performed using SAS Enterprise Guide version 8.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Demographic characteristics of the participants

Participants included for the 6- or 12-year follow-up analyses were, at inclusion, generally older mothers and less likely to smoke (Table S2). In addition, participants included for the 12-year follow-up analyses were more educated, more likely to be from levels of lower socioeconomic deprivation, and slightly more exposed to air pollutants than the non-respondents.

Among the 1322 children included at the 6-year follow-up, 50.1% were boys, and the mean age was 6.2 years (Table 1). Mother's mean age at inclusion was 30.5 years, 77.1% of mothers did not smoke during the pregnancy, 68.9% of them had a graduate education, 50% had low socio-economic deprivation and 64.2% of them lived in a rural setting during pregnancy. The 1118 mother-child pairs included at the 12-year follow-up presented very similar characteristics (Table 1).

Prevalence of asthma, rhinitis, and eczema at the 6-year follow-up were 11.9%, 19.6% and 22.3% respectively, and 11.7% of children had at least two diseases. At the 12-year follow-up, prevalence of asthma, rhinitis, and eczema were of 10%, 23.2% and 19% respectively, and 11.3% of children had at least two diseases. Both at 6- and 12-year follow-ups, prevalence of asthma, rhinitis, eczema, and the multimorbidity (≥2 diseases) were very similar among children of mothers from urban and rural areas, except for asthma at 12-years where the prevalence was higher in urban areas (*p-value = 0.04*) (Table S3).

Baseline characteristics of participants according to their status of asthma, rhinitis, and eczema at 6- and 12-year follow-ups are respectively presented in Table S4 and Table S5. At 6 years old, participants with asthma or eczema compared to participants without the disease were more likely to be boys (58.6% vs 48.9% and 56.6% vs 48.2%, respectively). Furthermore, the mean age of mothers of children with asthma or rhinitis was significantly lower compared to mothers of children without the disease (29.9 vs 30.6 years and 29.8 vs 30.7 years, respectively). No other significant differences according to children's

Table 1
Characteristics of participants included for 6-year and 12-year follow-up analyses.

	6-year follow-up (n = 1322)	12-year follow-up (n = 1118)
Sex, *n (%)*		
Boys	662 (50.1)	561 (50.2)
Girls	660 (49.9)	557 (49.8)
Child's age in years, *mean (SD)*	6.2 (0.2)	12.6 (0.3)
Mother's age in years at inclusion, *mean (SD)*	30.5 (4.0)	30.7 (4.0)
Mother tobacco smoking during pregnancy, *n (%)*		
Non-smoker or former smoker	1019 (77.1)	881 (78.8)
Smoker at the start of pregnancy who has quit	171 (12.9)	141 (12.6)
Smoker at inclusion	132 (10.0)	96 (8.6)
Mother's education level at inclusion, *n (%)*		
Under high school	188 (14.2)	122 (10.9)
High school diploma	223 (16.9)	186 (16.6)
Graduate education	991 (68.9)	810 (72.5)
French Deprivation Index (FDep) during pregnancy, *n (%)*		
1st tertile (low deprived)	667 (50.4)	589 (52.7)
2nd tertile (medium deprived)	412 (31.2)	343 (30.7)
3rd tertile (high deprived)	243 (18.4)	186 (16.6)
Urbanization degree during pregnancy, *n (%)*		
Urban	473 (35.8)	411 (36.8)
Rural	849 (64.2)	707 (63.2)
Air pollutants concentration (μg/m^3) during pregnancy, *median (IQR)*		
$PM_{2.5}$	15.14 (3.3)	15.28 (3.5)
NO_2	17.51 (9.6)	17.76 (9.9)
Outcomes' prevalence		
Ever asthma, *n (%)*	157 (11.9)	112 (10.0)
Ever rhinitis, *n (%)*	259 (19.6)	259 (23.2)
Ever eczema, *n (%)*	295 (22.3)	212 (19.0)
Multimorbidity phenotype		
No disease, *n (%)*	811 (61.4)	701 (62.7)
1 disease, *n (%)*	357 (27.0)	291 (26.0)
≥2 diseases, *n (%)*	154 (11.7)	126 (11.3)
Ever asthma + ever rhinitis, *n (%)*	33 (2.5)	32 (2.9)
Ever asthma + ever eczema, *n (%)*	24 (1.8)	10 (0.9)
Ever rhinitis + ever eczema, *n (%)*	51 (3.9)	44 (3.9)
Ever asthma + ever rhinitis + ever eczema, *n (%)*	46 (3.5)	40 (3.6)

$PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2: nitrogen dioxide; SD: standard deviation; IQR: interquartile range.

disease status were observed among the rest of covariates.

At the 12-year follow-up, participants with asthma or rhinitis compared to participants without the disease were more likely to be boys (64.3% vs 48.6% and 60.6% vs 47%, respectively). Mothers of children without asthma had higher education and were more likely to reside in rural areas during pregnancy compared to mothers of children with asthma (72.7% vs 70.5% and 64.2% vs 54.5%, respectively). Otherwise, no other significant differences among covariates according to children's disease status were observed.

Similar trends were observed for the baseline characteristics of participants according to each multimorbidity profile (Table S6). Furthermore, we observed that the coexistence of rhinitis and eczema was the most common combination both at 6- and 12-year follow-up (Table 1).

3.2. Ambient air pollution estimates

The median concentration from the main exposure model for the whole pregnancy was 15 μg/m^3 (IQR = 3) for $PM_{2.5}$ and 18 μg/m^3 (IQR = 10) for NO_2 (Table 1). NO_2 and $PM_{2.5}$ were moderately correlated (r^2 = 0.53 $p<0.0001$) (Fig. S2). $PM_{2.5}$ and NO_2 exposure levels during pregnancy were significantly lower for women in rural areas compared to their counterparts in urban areas ($p<0.0001$), both among participants included for 6- and 12-year follow-up analyses (Table S3).

Estimates from the main model were considerably higher than those from the French models, especially for $PM_{2.5}$ (mean value: 15 μg/m^3 vs 10 μg/m^3, respectively) (Table S7). For $PM_{2.5}$, the correlation was weak between the main model and the hybrid model (r^2 = 0.26, $p<0.0001$); for NO_2, the correlation between the main model and the CHIMERE model was moderate (r^2 = 0.56, $p<0.0001$) (Fig. S2).

3.3. Association of pregnancy exposure to $PM_{2.5}$ and NO_2 with childhood asthma, rhinitis, and eczema

Fully-adjusted analyses carried out with participants from the 6-year follow-up did not show evidence of associations between exposure to $PM_{2.5}$ with asthma (OR = 1.01, 95% CI = 0.77–1.32, $p = 0.94$), rhinitis (1.11 (0.90–1.38), $p = 0.33$), nor with eczema (0.99 (0.80–1.22), $p = 0.93$) (Table 2). Similarly, we found no associations between exposure to NO_2 with asthma (1.03 (0.83–1.28), $p = 0.81$) or rhinitis (1.01 (0.85–1.21), $p = 0.89$). We observed a tendency for an association between NO_2 and eczema (1.15 (0.97–1.36), $p = 0.10$).

Fully-adjusted analyses performed with participants in the 12-year follow-up did not show evidence of associations between exposure to $PM_{2.5}$ and rhinitis (0.91 (0.72–1.15), $p = 0.43$), or eczema (1.03, (0.80–1.33), $p = 0.83$) (Table 2). However, we observed a tendency for an association with asthma (1.38 (0.98–1.93), $p = 0.07$). Likewise, we did not observe associations of exposure to NO_2 with rhinitis (0.98 (0.81–1.18), $p = 0.80$), nor with eczema (1.03 (0.85–1.25), $p = 0.79$), but we observed a tendency with asthma (1.25 (0.98–1.59), $p = 0.07$).

We did not find any associations between exposure to $PM_{2.5}$ nor NO_2 and any category of the multimorbidity phenotype at the 6- or 12-year follow-up, except for the category of only one disease at the 6-year follow-up that was associated with exposure to NO_2 (1.20 (1.02–1.41), $p = 0.03$) (Table 2). At 12 years-follow-up we observe a tendency of a higher risk of having ≥2 diseases in association with exposure to $PM_{2.5}$ and NO_2 during pregnancy, notably for NO_2 (1.23 (0.97–1.56), $p = 0.09$).

Results of other levels of adjustment were similar to those from the fully adjusted models (Tables S8 and S9).

Table 2
Adjusted associations of pregnancy exposure to $PM_{2.5}$ and NO_2 with ever asthma, ever rhinitis, ever eczema, and the multimorbidity phenotype among children at 6- and 12-years of follow-up.

Disease	$PM_{2.5}$			NO_2		
	OR	95% CI	p-value	OR	95% CI	p-value
6-year follow-up						
Ever asthma	1.01	[0.77–1.32]	0.94	1.03	[0.83–1.28]	0.81
Ever rhinitis	1.11	[0.90–1.38]	0.33	1.01	[0.85–1.21]	0.89
Ever eczema	0.99	[0.80–1.22]	0.93	1.15	[0.97–1.36]	0.10
Multimorbidity phenotype						
No disease	Ref.			Ref.		
1 disease	1.14	[0.93–1.38]	0.21	1.20	[1.02–1.41]	**0.03**
≥2 diseases	1.03	[0.79–1.36]	0.82	1.08	[0.86–1.35]	0.52
12-year follow-up						
Ever asthma	1.38	[0.98–1.93]	0.07	1.25	[0.98–1.59]	0.07
Ever rhinitis	0.91	[0.72–1.15]	0.43	0.98	[0.81–1.18]	0.80
Ever eczema	1.03	[0.80–1.33]	0.83	1.03	[0.85–1.25]	0.79
Multimorbidity phenotype						
No disease	Ref.			Ref.		
1 disease	0.87	[0.69–1.10]	0.25	0.88	[0.73–1.07]	0.19
≥2 diseases	1.26	[0.90–1.74]	0.17	1.23	[0.97–1.56]	0.09

$PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2: nitrogen dioxide; OR: Odds Ratio; CI: confidence interval.
OR (95% CI) were calculated for an increase of an interquartile range (3.32 μg/m^3 for $PM_{2.5}$, and 9.56 μg/m^3 for NO_2 for participants at 6-year follow-up, and 3.53 μg/m^3 for $PM_{2.5}$, and 9.92 μg/m^3 for NO_2 for participants at 12-year follow-up). All models were adjusted for child's sex and age, mother's age and education level at birth, mother's tobacco smoking habits during pregnancy and area-level socioeconomic status during pregnancy (French Deprivation Index).

3.4. Supplementary analyses

At 6-years of follow-up, an interaction between the urbanization degree and $PM_{2.5}$ and NO_2 was found for eczema ($p = 0.05$ and $p = 0.10$ respectively, Table S10). Increased odds of eczema were associated with pregnancy exposure to $PM_{2.5}$ (1.49 (1.03–2.14), $p = 0.03$) and NO_2 (1.40 (1.08–1.82), $p = 0.01$) in urban areas, and decreased odds of eczema were associated with exposure to $PM_{2.5}$ in rural areas (0.72 (0.55–0.95), $p = 0.02$) (Table 3). No interactions with urbanization degree were found for asthma, rhinitis, and the multimorbidity phenotype (all $p \geq 0.39$, Table S10). However, the category of children suffering one disease alone showed associations with exposure to $PM_{2.5}$ (1.69 (1.18–2.42), $p = 0.005$) and NO_2 (1.55 (1.19–2.02), $p = 0.001$) during pregnancy in urban areas, but not in rural areas (Table 3). At 12-years of follow-up, no interactions between the urbanization degree and any of the air pollutants were found for any outcome (all $p \geq 0.23$).

In sex-stratified analyses at 6- and 12-year follow-up, we observed no differences between boys and girls for asthma, rhinitis, or eczema (Table S11) and all interaction p-values were ≥0.15 (Table S10). For the multimorbidity phenotype, only the category of children suffering one disease alone showed associations with exposure to NO_2 (1.28 (1.03–1.60), $p = 0.03$) among boys at 6-year follow-up.

Despite we observed no significant differences between our main models and models with restricted cubic splines, except for NO_2 and eczema at the 6-year follow-up ($p = 0.02$) (Figs. S3–S6), we further explored the possible non-linear effects by categorizing the air pollutants into quartiles. These analyses did not show associations of exposure to $PM_{2.5}$ nor NO_2 with any of the three diseases at either follow-up (Table S12) and all of the p-for-trend values were ≥0.10 (Table S10). The single exception was an increase in the odds of asthma at 12-years for children in the third quartile of exposure to $PM_{2.5}$ (1.95 (1.05–3.62), $p = 0.04$).

Sensitivity analyses using air pollution estimates from the French models (Table S13), showed consistent results with those from the main analyses. Similarly, analyses using Poisson regression models with robust error variance, and log-binomial regression models yielded results consistent with those from the main analyses using logistic regression models (Tables S14 and S15).

4. Discussion

Despite the lack of statistically significant associations between $PM_{2.5}$ and NO_2 and our outcomes, tendencies for asthma, eczema, and the multimorbidity phenotype were observed. The associations were stronger in urban settings.

Regarding asthma, our analysis at 12-years follow-up showed increased ORs at the limit of statistical significance in association with exposure to $PM_{2.5}$ and NO_2 during pregnancy, which is in line with the literature (Hehua et al., 2017; Yan et al., 2020). Indeed, a recent meta-analysis including 9 studies concluded that exposure to NO_2 during pregnancy is associated with an increased risk of childhood asthma (OR = 1.12, 95% CI = 1.04–1.19; I^2 = 84%) (Hehua et al., 2017). Another meta-analysis concluded that $PM_{2.5}$ is associated with an increased risk of childhood asthma and wheezing (OR = 1.06, 95% CI = 1.02–1.11; I^2 = 83%) (Yan et al., 2020). Although our study did not find statistically significant effects of pregnancy exposure to $PM_{2.5}$ on asthma, these results are not entirely inconsistent with the broader literature. The substantial heterogeneity among studies, as reflected by high I^2 values in meta-analyses, suggests that the effects of air pollution on asthma vary widely. This variability in the literature can be partly explained by differences in the studied populations and their level of exposure to air pollution. In contrast to other studies in the literature, our population is predominantly rural and exposed to relatively lower levels of exposure which may partly explain some of the non-significant results.

We did not find any associations with exposure to $PM_{2.5}$ or NO_2 and rhinitis, which is not completely in line with the literature. Indeed, the only systematic review assessing air pollution exposure during pregnancy concluded that exposure to traffic-related air pollution tended to be associated with a higher risk of childhood allergic rhinitis (Liu et al., 2023). The difference between those results and ours could be due to the fact that the review only included allergic rhinitis, whereas we considered allergic and non-allergic rhinitis together.

Regarding eczema, at 6-year follow-up, we observed a tendency of association with exposure to NO_2 in the non-stratified analyses and statistically significant associations with both $PM_{2.5}$ and NO_2 among children of mothers from urban areas. This is in line with the literature where one published meta-analysis concluded that exposure to NO_2 during pregnancy increase the odds for childhood eczema, but no

Table 3
Adjusted associations of pregnancy exposure to $PM_{2.5}$ and NO_2 in urban versus rural areas with ever asthma, ever rhinitis, ever eczema, and the multimorbidity phenotype at 6- and 12-years of follow-up.

Disease	$PM_{2.5}$						NO_2					
	Urban area			Rural area			Urban area			Rural area		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
6-year follow-up												
Ever asthma	1.09	[0.68–1.74]	0.73	0.93	[0.66–1.32]	0.69	1.07	[0.76–1.51]	0.69	0.88	[0.56–1.37]	0.56
Ever rhinitis	1.37	[0.91–2.06]	0.14	1.05	[0.80–1.38]	0.73	1.05	[0.78–1.42]	0.74	1.11	[0.78–1.58]	0.55
Ever eczema	1.49	[1.03–2.14]	**0.03**	0.72	[0.55–0.95]	**0.02**	1.40	[1.08–1.82]	**0.01**	0.75	[0.52–1.07]	0.12
Multimorbidity phenotype												
No disease	Ref.			Ref.			Ref.			Ref.		
1 disease	1.69	[1.18–2.42]	**0.005**	0.91	[0.70–1.18]	0.49	1.55	[1.19–2.02]	**0.001**	1.02	[0.74–1.42]	0.90
≥2 diseases	1.39	[0.84–2.29]	0.20	0.84	[0.59–1.20]	0.33	1.16	[0.80–1.68]	0.44	0.86	[0.54–1.37]	0.53
12-year follow-up												
Ever asthma	1.23	[0.71–2.13]	0.46	1.36	[0.86–2.15]	0.20	1.12	[0.78–1.60]	0.54	1.41	[0.80–2.51]	0.24
Ever rhinitis	0.86	[0.56–1.30]	0.47	0.95	[0.70–1.28]	0.72	0.98	[0.73–1.31]	0.88	1.00	[0.68–1.47]	0.99
Ever eczema	1.20	[0.76–1.91]	0.43	0.99	[0.71–1.36]	0.94	1.17	[0.87–1.59]	0.30	1.01	[0.67–1.53]	0.96
Multimorbidity phenotype												
No disease	Ref.			Ref.			Ref.			Ref.		
1 disease	0.78	[0.51–1.20]	0.26	0.95	[0.71–1.27]	0.74	0.87	[0.64–1.18]	0.36	0.98	[0.67–1.42]	0.90
≥2 diseases	1.38	[0.79–2.44]	0.26	1.17	[0.76–1.79]	0.48	1.28	[0.89–1.84]	0.18	1.34	[0.78–2.29]	0.29

$PM_{2.5}$ particulate matter with an aerodynamic diameter less than 2.5 μm; NO_2: nitrogen dioxide; OR: Odds Ratio; CI: confidence interval.
OR (95% CI) were calculated for an increase of an interquartile range (3.32 μg/m^3 for $PM_{2.5}$, and 9.56 μg/m^3 for NO_2 for participants at 6-year follow-up, and 3.53 μg/m^3 for $PM_{2.5}$, and 9.92 μg/m^3 for NO_2 for participants at 12-year follow-up). All models were adjusted for child's sex and age, mother's age and education level at birth, mother's tobacco smoking habits during pregnancy and area-level socioeconomic status during pregnancy (French Deprivation Index).

significant results were found for $PM_{2.5}$ (Yue et al., 2022).

Regarding the multimorbidity phenotype, we found a statistically significant association between NO_2 exposure and only one disease category at 6-year follow-up, and a tendency of an association between NO_2 and ≥2 diseases category at 12 years-follow-up. Few previous studies have investigated the role of air pollution exposure on the occurrence of multimorbidity phenotypes encompassing childhood asthma, rhinitis, and eczema. A meta-analysis from five recent European birth cohorts, investigated the effects of air pollution exposure at the home addresses on children's multimorbidity (≥2 conditions versus none among pediatric eczema, rhinoconjunctivitis, and asthma) and found no associations between any air pollutant and the multimorbidity (Fuertes et al., 2020). However, the authors considered current eczema, rhinoconjunctivitis, and asthma at 4 and 8 years of age instead of ever asthma, ever rhinitis, and ever eczema, which may explain the difference with our results. Our results also show that it could be interesting to study the specific category of participants who have only one of the diseases and not the others, as this could be a category of people more susceptible to the effects of air pollution.

Exposure among Pélagie participants in Brittany remain lower compared to populations from other regions in France and other European countries like Belgium or The Netherlands (Khreis et al., 2019; Bilan de la qualité de, 2014; Bilan de la qualité de, 2023), however, they still exceed the recommended values from the 2021 update of the WHO air quality guidelines (WHO global air quality guidelines, 2021). While these guidelines recommend that annual mean concentrations should not exceed 5 $\mu g/m^3$ for $PM_{2.5}$, and 10 $\mu g/m^3$ for NO_2, the mean values of exposure for our population are 15 $\mu g/m^3$ for $PM_{2.5}$, and 19 $\mu g/m^3$ for NO_2 respectively. Moreover, evidence indicates that even low levels of air pollution can have effects on childhood asthma, rhinitis, and eczema. The ELAPSE (Effects of Low-Level Air Pollution: A Study in Europe) project which specifically investigated the health effects of long-term exposure to air pollutants at low concentrations, found that chronic exposure to low concentrations of these pollutants is associated with an increased risk of developing asthma in children (Gehring et al., 2013), suggesting a non-threshold effect of air pollution.

One of the original features of our study is that the population of analysis was mostly rural, whereas the majority of published studies on the effects of air pollution are conducted in city areas. Differences in air pollution levels and composition exist between urban and rural areas. NO_2 displays higher concentrations in more densely populated urban areas, mainly from transportation sources. $PM_{2.5}$ shows more homogeneous patterns regionally due to its longer atmospheric lifetime and diversity of sources, varying between urban (mainly traffic and industry) and rural settings (mainly agriculture and natural sources) (Sousa Santos et al., 2021; WHO global air quality guidelines, 2021). This is also the case in our study as participants from urban areas were exposed to higher concentrations of air pollutants compared to rural areas. Thus, we also performed stratified analyses according to urban and rural areas. At 6-year follow-up no significant interactions were observed between the urban and rural stratum for asthma, rhinitis, or the multimorbidity phenotype, with results showing confidence intervals overlap between both strata. However, eczema and the category of children suffering one disease alone, showed statistically significant higher ORs in urban compared to rural areas in association with $PM_{2.5}$ and NO_2. Moreover, we observed a negative association of $PM_{2.5}$ exposure in rural areas with eczema at 6-years follow-up (0.72 (0.55–0.95), $p = 0.02$). This counterintuitive finding should be interpreted cautiously, and we cannot rule out the possibility that this result is due to chance, given the multiple tests conducted in our analyses. This hypothesis is further supported by the inconsistency of this result across our analyses and by the absence of similar findings in the literature. Results for 12-year follow-up were heterogeneous when comparing participants from urban and rural areas. Among the published literature, we identified only two studies assessing the effect modification of the type of area (urban versus rural) on the associations of air pollution exposure during pregnancy with childhood asthma, however, none of them found statistically significant differences in the effects between urban and rural areas (Madsen et al., 2017; Lavigne et al., 2018). To our knowledge, our study is the first to have investigated the effect modification of the urbanization degree on the associations between air pollution exposure during pregnancy and childhood rhinitis, eczema, or an allergic multimorbidity phenotype. This highlights the need for further research taking rural populations more prominently into account.

Regarding the effect modification by the children's sex, we did not observe differences in associations between girls and boys. However, the majority of studies on effect modification by child's sex and air pollutants have showed that associations are stronger among boys, especially for asthma and rhinitis (Fuertes et al., 2020; Leon Hsu et al., 2015; Rancière et al., 2017; Hao et al., 2021). Yet, most of these studies have focused on exposure during childhood and some reported contrasting results.

Exposure to $PM_{2.5}$ and NO_2 during pregnancy may determine the children's susceptibility to asthma, rhinitis, and eczema through a range of complex and interconnected mechanisms. NO_2 can penetrate the placenta and affect fetal development triggering oxidative stress and inflammation, potentially disrupting the immune responses and the maturation of the respiratory system (Murrison et al., 2019). This disruption may result in long-term consequences, increasing the odds of childhood asthma (Murrison et al., 2019; Deng et al., 2023). Similarly, $PM_{2.5}$ can traverse the placental barrier affecting fetal organs and impairing the immune system development. $PM_{2.5}$-induced oxidative stress and inflammation during pregnancy may contribute to asthma onset by influencing lung development and function (Murrison et al., 2019; Johnson et al., 2021). Moreover, prenatal exposure to $PM_{2.5}$ and NO_2 has been associated with alterations in DNA methylation (Deng et al., 2023; Abraham et al., 2018), particularly in genes related to the immune system development as shown in a recent study including the Pélagie cohort (Broséus et al., 2024).

Our study has several strengths. We used a well characterized and homogeneous population from a mother-child cohort that allowed us to examine the associations between air pollution exposure during pregnancy and the prevalence of childhood asthma, rhinitis, eczema, and their multimorbidity. Since pulmonary function measures and biomarkers were not available for our study population, the three health outcomes were defined based on parents' responses to the French validated version of the ISAAC questionnaire, which is considered one of the main tools for assessing the prevalence of asthma and allergies in childhood, and has been widely used for epidemiology studies worldwide (García-Marcos et al., 2022; Gough et al., 2015). Additionally, examining the effects of prenatal exposure to air pollutants across multiple follow-ups can help us understand their impacts on children's health at different stages of development. As some effects of air pollution exposure during pregnancy may appear early in life, and others could emerge or intensify later, comparing results across follow-ups allows us to determine whether these effects persist, diminish, or increase over time. Moreover, the estimation of exposure at each participant's residential address enabled the assessment of individual-level exposure. Lastly, having data from three models that estimated the air pollution exposure through different methods, allowed us to confirm the robustness of our main analyses.

Despite these strengths, we also acknowledge several limitations. First, high statistical power is required to demonstrate significant effects of air pollution, and with a population of around 1100 to 1300 participants, statistical power may be somewhat limited, especially as air pollution levels are relatively low and contrasts in exposure are not very high among the Pélagie participants. Statistical power is even more limited in our stratified analyses, which could partly explain the observed null associations. Additionally, as described in a previous publication (Warembourg et al., 2024), a selection of the Pélagie cohort has been observed at baseline towards more highly-educated women with higher socioeconomic level than the general French population,

which was slightly accentuated in subsequent follow-ups, as also shown in our analysis population, thus, our results must be generalized with caution. We also acknowledge the possibility of chance findings due to the multiplicity of tests in our study. Yet, observed patterns of effects sizes were consistent across comparisons.

In our study, asthma and eczema definitions are based on the parent-declared doctor-diagnosis, this could introduce potential outcome misclassification, which can occur if participants inaccurately report their diagnosis, either due to recall bias or misunderstanding of their condition. Among our population, this misclassification would likely be non-differential, meaning it is not related to the exposure status, which could bias our results towards the null. Moreover, it is difficult to establish a clear diagnosis of asthma in children under 6 years of age (Yang et al., 2019; Global Strategy for Asthma Management, 2023), potentially leading to a misestimation of asthma cases at 6-year follow-up, which could explain why we have less ever asthma at the 12-year than at the 6-year follow-up, and the difference in our observed results.

Exposure assessment during participants' pregnancy, which occurred from 2002 to 2006, was based on back-extrapolated daily estimates using the higher resolution 2010 LUR annual mean surface and daily measurements from a single background station, which could lead to non-differential measurement errors and reduce associations to the null hypothesis. Nevertheless, this model has shown good long-term spatiotemporal stability (de Hoogh et al., 2018). Furthermore, the sensitivity analyses using the air pollution estimates from the French models, which had a better temporal resolution, yielded similar results. Lastly, given that logistic regression may overestimate relative risks when outcomes are not rare (Callas et al., 1998), as in our case, we conducted sensitivity analyses using Poisson regression models with robust error variance, as well as log-binomial regression models to assess the robustness of our estimates. These additional analyses yielded results consistent with those from the main analyses using logistic regression models, allowing us to validate the robustness of our findings.

5. Conclusions

While we did not find statistically significant associations between exposure to $PM_{2.5}$ and NO_2 and the prevalence of asthma, rhinitis, eczema, and the multimorbidity phenotype, we observed a tendency of some associations for $PM_{2.5}$ and NO_2 exposure with asthma and the multimorbidity phenotype ($\geq$2 diseases) at 12-years old. Furthermore, results suggest that some of these associations may be stronger among participants from urban settings, notably for eczema. This shows the importance of considering urbanity/rurality when assessing the effects of air pollution on health, and points out the need for further studies including rural populations in order to gather conclusive evidence.

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CRediT authorship contribution statement

Alan R. Patlán-Hernández: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Marine Savouré:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Etienne Audureau:** Writing – review & editing, Funding acquisition. **Christine Monfort:** Writing – review & editing, Investigation, Data curation. **Montserrat de Castro:** Writing – review & editing, Data curation. **Ralph Epaud:** Writing – review & editing, Funding acquisition. **Kees de Hoogh:** Writing – review & editing, Investigation, Data curation. **Ian Hough:** Writing – review & editing, Investigation, Data curation. **Itai Kloog:** Writing – review & editing, Investigation, Data curation. **Sophie Lanone:** Writing – review & editing, Funding acquisition. **Johanna Lepeule:** Writing – review & editing, Investigation, Data curation. **Mark Nieuwenhuijsen:** Writing – review & editing, Investigation, Data curation. **Danielle Vienneau:** Writing – review & editing, Investigation, Data curation. **Charline Warembourg:** Writing – review & editing, Investigation, Data curation. **Cécile Chevrier:** Writing – review & editing, Investigation. **Bénédicte Jacquemin:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.125206.

Data availability

The authors do not have permission to share data.

References

Abraham, E., Rousseaux, S., Agier, L., Giorgis-Allemand, L., Tost, J., Galineau, J., et al., 2018. Pregnancy exposure to atmospheric pollution and meteorological conditions and placental DNA methylation. Environ. Int. 118, 334–347.

Asher, M., Keil, U., Anderson, H., Beasley, R., Crane, J., Martinez, F., et al., 1995. International study of asthma and allergies in childhood (ISAAC): rationale and methods. Eur. Respir. J. 8 (3), 483–491.

Bilan de la qualité de l'air en France en 2013 [Internet]. France: Commissariat général au développement durable (CGDD). http://www.statistiques.developpement-durable.gouv.fr, 2014.

Bilan de la qualité de l'air extérieur en France en 2022 [Internet]. France: Commissariat général au développement durable (CGDD). Available from: http://www.statistiques.developpement-durable.gouv.fr.

Bowatte, G., Lodge, C., Lowe, A.J., Erbas, B., Perret, J., Abramson, M.J., et al., 2015. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. Allergy 70 (3), 245–256.

Broséus, L., Guilbert, A., Hough, I., Kloog, I., Chauvaud, A., Seyve, E., et al., 2024. Placental DNA methylation signatures of prenatal air pollution exposure and potential effects on birth outcomes: an analysis of three prospective cohorts. Lancet Planet. Health 8 (5), e297–e308.

Burbank, A.J., Sood, A.K., Kesic, M.J., Peden, D.B., Hernandez, M.L., 2017. Environmental determinants of allergy and asthma in early life. J. Allergy Clin. Immunol. 140 (1), 1–12.

Callas, P.W., Pastides, H., Hosmer, D.W., 1998. Empirical comparisons of proportional hazards, Poisson, and logistic regression modeling of occupational cohort data. Am. J. Ind. Med. 33 (1), 33–47.

Charpin D, Kubler MCK, Oryszczyn MP, Ray P, Raherison C, Taytard A, et al. Présentation générale de l'étude ISAAC.

de Hoogh, K., Wang, M., Adam, M., Badaloni, C., Beelen, R., Birk, M., et al., 2013. Development of land use regression models for particle composition in twenty study areas in Europe. Environ. Sci. Technol. 47 (11), 5778–5786.

de Hoogh, K., Chen, J., Gulliver, J., Hoffmann, B., Hertel, O., Ketzel, M., et al., 2018. Spatial PM2.5, NO2, O3 and BC models for western Europe – evaluation of spatiotemporal stability. Environ. Int. 120, 81–92.

Delmas, M.C., Guignon, N., Leynaert, B., Moisy, M., Marguet, C., Fuhrman, C., 2017. Augmentation de la prévalence de l'asthme chez le jeune enfant en France. Rev. Mal. Respir. 34 (5), 525–534.

Deng, Q., Lu, C., Li, Y., Sundell, J., Norbäck, Dan, 2016. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. Environ. Res. 150, 119–127.
Deng, Q., Liu, L., Cheng, X., Xue, Y., Li, M., Liu, X., et al., 2023. The role of air pollution in fetal origins of childhood allergy: challenges and opportunities. Curr Opin Environ Sci Health 33, 100474.
EUROCAT Special Report, 2012. Congenital Anomalies are a major group of mainly rare diseases [internet]. Newtownabbey, northern Ireland: EUROCAT central registry. Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/eurocat-pub-docs/Special-Report-Major-Group-of-Mainly-Rare-Diseases.pdf.
Florczyk, A.J., Corbane, C., Ehrlich, D., Freire, S., Kemper, T., Maffenini, L., et al., 2019. GHSL Data Package 2019: Public Release GHS P2019. Publications Office of the European Union, Luxembourg.
Fuertes, E., Sunyer, J., Gehring, U., Porta, D., Forastiere, F., Cesaroni, G., et al., 2020. Associations between air pollution and pediatric eczema, rhinoconjunctivitis and asthma: a meta-analysis of European birth cohorts. Environ. Int. 136, 105474.
Garcia-Aymerich, J., Benet, M., Saeys, Y., Pinart, M., Basagaña, X., Smit, H.A., et al., 2015. Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. Allergy 70 (8), 973–984.
García-Marcos, Luis, Innes Asher, M., Pearce, Neil, Ellwood, Eamon, Bissell, Karen, Chiang, Chen-Yuan, et al., 2022. The burden of asthma, hay fever and eczema in children in 25 countries: GAN Phase I study. Eur. Respir. J. 60 (3), 2102866.
Gehring, U., Gruzieva, O., Agius, R.M., Beelen, R., Custovic, A., Cyrys, J., et al., 2013. Air pollution exposure and lung function in children: the ESCAPE project. Environ. Health Perspect. 121 (11–12), 1357–1364.
[Internet] Global Strategy for Asthma Management and Prevention, 2023. Global Initiative for Asthma. Available from: www.ginasthma.org.
Gough, H., Grabenhenrich, L., Reich, A., Eckers, N., Nitsche, O., Schramm, D., et al., 2015. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. Pediatr. Allergy Immunol. 26 (5), 431–437.
Gutvirtz, G., Wainstock, T., Sheiner, E., Pariente, G., 2022. Prematurity and long-term respiratory morbidity—what is the critical gestational age threshold? J. Clin. Med. 11 (3), 751.
Hao, S., Yuan, F., Pang, P., Yang, B., Jiang, X., Yan, A., 2021. Early childhood traffic-related air pollution and risk of allergic rhinitis at 2–4 years of age modification by family stress and male gender: a case-control study in Shenyang, China. Environ. Health Prev. Med. 26 (1), 48.
Hehua, Z., Qing, C., Shanyan, G., Qijun, W., Yuhong, Z., 2017. The impact of prenatal exposure to air pollution on childhood wheezing and asthma: a systematic review. Environ. Res. 159, 519–530.
Hough, I., Sarafian, R., Shtein, A., Zhou, B., Lepeule, J., Kloog, I., 2021. Gaussian Markov random fields improve ensemble predictions of daily 1 km PM2.5 and PM10 across France. Atmos. Environ. 264, 118693.
Johnson, N.M., Hoffmann, A.R., Behlen, J.C., Lau, C., Pendleton, D., Harvey, N., et al., 2021. Air pollution and children's health—a review of adverse effects associated with prenatal exposure from fine to ultrafine particulate matter. Environ. Health Prev. Med. 26 (1), 72.
Khreis, H., Cirach, M., Mueller, N., de Hoogh, K., Hoek, G., Nieuwenhuijsen, M.J., et al., 2019. Outdoor air pollution and the burden of childhood asthma across Europe. Eur Respir J [Internet] 54 (4). Available from: https://www.embase.com/search/results?subaction=viewrecord&id=L2013846982&from=export.
Lavigne, É., Bélair, M.A., Rodriguez Duque, D., Do, M.T., Stieb, D.M., Hystad, P., et al., 2018. Effect modification of perinatal exposure to air pollution and childhood asthma incidence. Eur. Respir. J. 51 (3), 1701884.
Leon Hsu, H.H., Mathilda, Chiu YH., Coull, B.A., Kloog, I., Schwartz, J., Lee, A., et al., 2015. Prenatal particulate air pollution and asthma onset in urban children. Identifying sensitive windows and sex differences. Am. J. Respir. Crit. Care Med. 192 (9), 1052–1059.
Liu, L., Ma, J., Peng, S., Xie, L., 2023. Prenatal and early-life exposure to traffic-related air pollution and allergic rhinitis in children: a systematic literature review. In: Yon, D.K. (Ed.), PLoS One 18 (4), e0284625.
Lu, C., Wang, L., Liao, H., Li, B., Liu, Q., Li, Q., et al., 2023a. Impacts of intrauterine and postnatal exposure to air pollution on preschool children's asthma: a key role in cumulative exposure. Build. Environ. 245, 110874.
Lu, C., Wang, F., Liu, Z., Li, B., Yang, W., Liao, H., 2023b. Intrauterine and early postnatal exposure to air pollution associated with childhood allergic rhinitis. Chemosphere 336, 139296.
Lu, C., Li, Q., Qiao, Z., Li, B., Liu, Q., Wang, F., 2024. Early and late onset childhood eczema: role of preconceptional, pre-natal and post-natal environmental exposures. Build. Environ. 258, 111626.
Madsen, C., Haberg, S.E., Magnus, M.C., Aamodt, G., Stigum, H., London, S.J., et al., 2017. Pregnancy exposure to air pollution and early childhood respiratory health in the Norwegian Mother and Child Cohort Study (MoBa). BMJ Open 7 (12) [Internet]. https://www.embase.com/search/results?subaction=viewrecord&id=L623794045&from=export.
Murrison, L.B., Brandt, E.B., Myers, J.B., Hershey, G.K.K., 2019. Environmental exposures and mechanisms in allergy and asthma development. J. Clin. Invest. 129 (4), 1504–1515.
Pinart, M., Benet, M., Annesi-Maesano, I., von Berg, A., Berdel, D., Carlsen, K.C.L., et al., 2014. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. Lancet Respir. Med. 2 (2), 131–140.
Rancière, F., Bougas, N., Viola, M., Momas, I., 2017. Early exposure to traffic-related air pollution, respiratory symptoms at 4 Years of age, and potential effect modification by parental allergy, stressful family events, and sex: a prospective follow-up study of the PARIS birth cohort. Environ. Health Perspect. 125 (4), 737–745.
Real, E., Couvidat, F., Ung, A., Malherbe, L., Raux, B., Gressent, A., et al., 2022. Historical reconstruction of background air pollution over France for 2000–2015. Earth Syst. Sci. Data 14 (5), 2419–2443.
Rey, G., Jougla, E., Fouillet, A., Hémon, D., 2009. Ecological association between a deprivation index and mortality in France over the period 1997 – 2001: variations with spatial scale, degree of urbanicity, age, gender and cause of death. BMC Publ. Health 9 (1), 33.
Rider, C.F., Carlsten, C., 2019. Air pollution and DNA methylation: effects of exposure in humans. Clin Epigenetics 11 (1), 131.
Rutter, C.E., Silverwood, R.J., Asher, M.I., Ellwood, P., Pearce, N., Garcia-Marcos, L., et al., 2020. Comparison of individual-level and population-level risk factors for rhinoconjunctivitis, asthma, and eczema in the international study of asthma and allergies in childhood (ISAAC) phase three. World Allergy Organ J 13 (6), 100123.
Sasso, F., Izard, M., Beneteau, T., Rakotozandry, T., Ramadour, M., Annesi-Maesano, I., et al., 2019. 18-year evolution of asthma and allergic diseases in French urban schoolchildren in relation to indoor air pollutant levels. Respir. Med. 148, 31–36.
Sigurdardottir, S.T., Jonasson, K., Clausen, M., Lilja Bjornsdottir, K., Sigurdardottir, S.E., Roberts, G., et al., 2021. Prevalence and early-life risk factors of school-age allergic multimorbidity: the EuroPrevall-iFAAM birth cohort. Allergy 76 (9), 2855–2865.
Sousa Santos, G., Clemetsen, T., Weydahl, T., Guerreiro, C., 2021. Air Quality Plans and Measures. Analysis of Data Submitted from 2014 to 2020. European Topic Centre on Air Pollution, Transport, Noise and Industrial Pollution.
The Global Asthma Report 2022, 2022. Int J Tuberc Lung Dis 26 (1), 1–104.
Warembourg, C., Monfort, C., Costet, N., Rouget, F., Pelé, F., Garlantézec, R., et al., 2024. Cohort Profile: the PELAGIE mother-child cohort. Int. J. Epidemiol. 53 (3), dyae064.
WHO global air quality guidelines, 2021. Particulate Matter (PM2.5 and PM10), Ozone, Nitrogen Dioxide, Sulfur Dioxide and Carbon Monoxide. World Health Organization, Geneva.
Yan, W., Wang, X., Dong, T., Sun, M., Zhang, M., Fang, K., et al., 2020. The impact of prenatal exposure to PM2.5 on childhood asthma and wheezing: a meta-analysis of observational studies. Environ. Sci. Pollut. Res. 27 (23), 29280–29290.
Yang, C.L., Gaffin, J.M., Radhakrishnan, D., 2019. Question 3: can we diagnose asthma in children under the age of 5 years? Paediatr. Respir. Rev. 29, 25–30.
Yue, D., Shen, T., Mao, J., Su, Q., Mao, Y., Ye, X., et al., 2022. Prenatal exposure to air pollution and the risk of eczema in childhood: a systematic review and meta-analysis. Environ. Sci. Pollut. Res. 29 (32), 48233–48249.