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Associations between air pollution and pediatric eczema, rhinoconjunctivitis and asthma: A meta-analysis of European birth cohorts

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ABSTRACT

Background: Uncertainly continues to exist regarding the role of air pollution on pediatric asthma and allergic conditions, especially as air pollution levels have started to decrease in recent decades.
Objective: We examined associations of long-term air pollution levels at the home address with pediatric eczema, rhinoconjunctivitis and asthma prevalences in five birth cohorts (BIB, EDEN, GASPII, RHEA and INMA) from seven areas in five European countries.
Methods: Current eczema, rhinoconjunctivitis and asthma were assessed in children aged four (N = 6527) and eight years (N = 2489). A multi-morbidity outcome (≥2 conditions versus none) was also defined. Individual outdoor levels of nitrogen dioxide (NO_2), nitrogen oxides, mass of particulate matter with an aerodynamic diameter < 10 μm (PM_{10}), 10–2.5 μm (PM_{coarse}) and < 2.5 μm ($PM_{2.5}$), and $PM_{2.5}$ absorbance were assigned to the birth, four- and eight-year home addresses using highly defined spatial air pollution exposure models.

Abbreviations: BIB, Born In Bradford; EDEN, Study on the pre- and early postnatal determinants of child health and development; ESCAPE, European Study of Air Pollution Effects; GASPII, Gene and Environment: prospective study on infancy in Italy cohort; INMA, Spanish INfancia y Medio Ambiente: Environment and Childhood; LUR, Land-use regression; MeDALL, Mechanisms of the Development of Allergy; NO_2, Nitrogen dioxide; NO_x, Nitrogen oxide; PM, Particulate matter; RHEA, Mother-child Greek cohort

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Cohort-specific cross-sectional associations were assessed using logistic regression models adjusted for demographic and environmental covariates and combined in a random effects meta-analysis.
Results: The overall prevalence of pediatric eczema, rhinoconjunctivitis and asthma at four years was 15.4%, 5.9% and 12.4%. We found no increase in the prevalence of these outcomes at four or eight years with increasing air pollution exposure. For example, the meta-analysis adjusted odds ratios (95% confidence intervals) for eczema, rhinoconjunctivitis and asthma at four years were 0.94 (0.81, 1.09), 0.90 (0.75, 1.09), and 0.91 (0.74, 1.11), respectively, per 10 μg/m^3 increase in NO_2 at the birth address, and 1.00 (0.81, 1.23), 0.70 (0.49, 1.00) and 0.88 (0.54, 1.45), respectively, per 5 μg/m^3 increase in $PM_{2.5}$ at the birth address.
Discussion: In this large meta-analysis of five birth cohorts, we found no indication of adverse effects of long-term air pollution exposure on the prevalence of current pediatric eczema, rhinoconjunctivitis or asthma.

1. Introduction

Is long-term air pollution associated with the development and prevalence of asthma and related allergic conditions? Numerous studies (especially for asthma) have attempted to answer this question, and there are now six systematic reviews and meta-analyses that summarize the existing evidence. Overall, the evidence for an association between long-term air pollution exposure and asthma incidence and prevalence is frequently considered as sufficient, with most (Anderson et al., 2013; Bowatte et al., 2015; Favarato et al., 2014; Gasana et al., 2012; Khreis et al., 2017) but not all (Heinrich et al., 2016) meta-analyses reporting significant associations. Health impact assessment strategies are also suggesting that air pollution may contribute to a significant burden of childhood asthma cases (Khreis et al., 2019).

For other allergic diseases (e.g. rhinoconjunctivitis, eczema, sensitization), there are substantially fewer studies and the evidence is less strong. Most recently, one review (including studies up to March 2014) reported sufficient evidence for an association (Bowatte et al., 2015), but an extension of this effort (including studies from March 2014 to January 2016) reported the evidence as insufficient to confirm a causal association (Heinrich et al., 2016). In light of this uncertainty, further longitudinal birth cohort studies with standardized exposure assessment and outcome and confounder definitions are needed (Khreis et al., 2017), ideally from different regions in Europe and covering a wide range of exposure concentrations.

The "Mechanisms of the Development of Allergy (MeDALL)" (Benet et al., 2019; Pinart et al., 2014) and "European Study of Air Pollution Effects" (ESCAPE) collaborations have respectively yielded guidelines to define allergic outcomes (agreed upon by international consensus) and a standardized method of air pollution exposure assignment for many European cohorts. A recent longitudinal study of four cohorts which capitalized on these efforts found evidence to support an association with long-term air pollution exposure for asthma with an onset after four years of age among 14–16-year-olds, whereas no associations were found for rhinoconjunctivitis (Gehring et al., 2015). Despite the many strengths of this large longitudinal effort, the exposure models were based on air pollution measurement campaigns that coincided with the most recent follow-ups of the cohorts, which adds uncertainty in the assessment of historical exposures.

In this study, we examined whether long-term air pollution exposure is associated with the prevalence of current eczema, rhinoconjunctivitis and asthma in a large population of young children from seven areas participating in five recent population-based birth cohorts. These cohorts were selected as (1) they have outcomes defined according to MeDALL-guidelines (although deviations exist at younger ages), (2) they have available air pollution exposure models (created using ESCAPE protocols or comparable methods) and importantly, (3) these air pollution exposure models were developed using air pollution monitoring data collected at the time of birth or during the first years of life of the participants. Furthermore, although air quality limits continue to be regularly exceeded, the children participating in these cohorts were born during a time when average levels of certain pollutants were decreasing in Europe (e.g. population weighted concentrations of $PM_{2.5}$ in 1990 and 2015 were respectively 14 and 11 μg/m^3 in the United Kingdom, 16 and 13 μg/m^3 in France, 21 and 18 μg/m^3 in Italy and Greece and 12 and 10 μg/m^3 in Spain (Health Effects Insitute, 2019). The participants were thus presumably exposed to lower air pollution levels than in earlier decades, and investigations as to whether adverse associations are also detectable at these lower air pollution levels are required. Finally, we also *a priori* aimed to examine associations with having at least two health conditions (i.e. multi-morbidity), which has not yet been considered in previous work but occurs more often than expected by chance, suggesting the existence of shared causal mechanisms (Pinart et al., 2014).

2. Materials and methods

2.1. Study population

Of the 14 European birth cohorts that participated in the MeDALL collaboration (Benet et al., 2019), the five ongoing population-based birth cohorts that fit our inclusion criteria and agreed to participate were: the English Born In Bradford (BIB) cohort (recruited in Bradford) (Wright et al., 2013), the French mother-child EDEN cohort (recruited in Nancy and Poitiers) (Heude et al., 2016), the Gene and Environment: prospective study on infancy in Italy cohort (GASPII) (recruited in Rome) (Porta and Fantini, 2006; Porta et al., 2007), the mother-child Greek RHEA cohort (recruited in the prefecture of Heraklion) (Chatzi et al., 2009), and the Spanish INfancia y Medio Ambiente: Environment and Childhood (INMA) network of birth cohorts (recruited in Gipuzkoa, Sabadell and Valencia) (Guxens et al., 2012). For the latter INMA cohort, data from the three study areas were analyzed separately as different air pollution exposure models were developed for each area. A comparison between the time of cohort recruitment and collection of air pollution monitoring data is provided in Table 1. Approval by the local ethics committees and written consent from the participants' families were obtained by all cohorts. The cohorts are further described in the Supplemental Material, Participating cohorts section.

Table 1
Comparison of year of cohort recruitment and air pollution measurement campaign.

Cohort	Cohort recruitment	Collection of air pollution monitoring data
BIB	2007–2011	01-06-2009–15-12-2009
EDEN	2003–2006	2002–2005
GASPII	2003–2004	27-01-2010–26-01-2011
RHEA	2007–2008	18-02-2009–16-02-2010
INMA-Gipuzcoa	2006–2008	03-02-2009–15-07-2009 (NO_2 and NO_x) 2006–2007 ($PM_{2.5}$)
INMA-Sabadell	2004–2006	14-01-2009–14-01-2010
INMA-Valencia	2003–2005	17-02-2009–23-07-2009 (NO_2 and NO_x) 02-2005–06-2005 ($PM_{2.5}$)

2.2. Outcomes

The three main outcomes in this analysis were current eczema, current rhinoconjunctivitis and current asthma. All three health outcomes were available for nearly all sites at the age of four years (INMA-Sabadell had no information on eczema) whereas only five of the seven sites had outcome data at age eight years (BIB and RHEA did not have data available). Of note, participants in INMA-Sabadell were closer to age seven years. As much as possible, the health outcomes were defined following the phenotypic definitions proposed by the MeDALL consortium (Benet et al., 2019; Pinart et al., 2014). Small deviations from the proposed MeDALL definitions do exist for the GASPII and INMA cohorts at age four years only, as summarized in the Supplemental Material (Table S1).

Current eczema was defined as positive answers to both:

- Has your child had an itchy rash which was coming and going (intermittently) at any time in the past 12 months?; and
- Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes.

Current rhinoconjunctivitis was defined as positive answers to both

- In the past 12 months, has your child had problems with sneezing or a runny or blocked nose when he/she did not have a cold or flu?, and
- If yes, in the past 12 months, has this nose problem been accompanied by itchy-watery eyes?

Current asthma was defined as a positive answer to at least two of the three following questions:

- Has your child had wheezing or whistling in the chest in the past 12 months?
- Has your child ever been diagnosed by a doctor as having asthma?
- Has your child taken any medicines for asthma or breathing difficulties (wheezing, chest tightness, shortness of breath) in the last 12 months?

A secondary multi-morbidity outcome was also calculated, defined as having at least two of three conditions versus having none. This outcome was only defined for areas and ages for which information on eczema, rhinoconjunctivitis and asthma were all available (all cohorts except INMA-Sabadell at four years and BIB and RHEA at eight years).

Note that in this analysis, all outcomes required that symptoms/medications be present "in the last 12 months" and hence we modelled the prevalence of current "active" conditions and not the incidence of disease. This decision is supported by the low number of incident cases between four and eight years of age per cohort and because not all cohorts had repeated outcome and air pollution data.

2.3. Exposure assignment

For nearly all cohorts, long-term (annual average) concentrations of nitrogen dioxide (NO_2), nitrogen oxides (NO_x), mass of particulate matter with an aerodynamic diameter < 10 μm (PM_{10}), between 10 μm and 2.5 μm (PM coarse) and < 2.5 μm ($PM_{2.5}$), as well as $PM_{2.5}$ absorbance were estimated to each participant's home address at birth and at the time of outcome assessment (four and eight years) using land-use regression (LUR) models developed following ESCAPE protocols (Beelen et al., 2013; Cyrys et al., 2012; Eeftens et al., 2012a, 2012b). Briefly, as part of the ESCAPE study, three two-week air pollution monitoring campaigns were performed at chosen sites in the study areas. Site-specific annual averages were calculated using the average of these three measurement periods and were adjusted for temporal variation using data from a centrally located background reference site which operated continuously throughout the measurement year. Area-specific LUR models were developed, which relate these site-specific measured annual average concentrations to predictor variables derived from Geographic Information Systems through a supervised stepwise multivariable linear regression.

The ESCAPE exposure methodology was used to estimate NO_2 and NO_x levels in all cohorts, except in EDEN, for which NO_2 was estimated using a local dispersion model (AIRLOR, 2010; Galineau et al., 2011). For PM_{10}, $PM_{2.5}$, PM coarse and $PM_{2.5}$ absorbance, ESCAPE area-specific LUR models existed for four sites only (BIB, RHEA, GASPII and INMA-Sabadell). For EDEN, $PM_{2.5}$ levels were instead estimated using an existing European-wide LUR model (Wang et al., 2014). This European-wide LUR model was developed by combining all data collected in the 17 European areas that participated in ESCAPE and can be applied to areas that did not collect particulate matter samples and where the main source of $PM_{2.5}$ is road traffic. The study area of INMA-Gipuzkoa is characterized by low road traffic intensity but a high metal-industry pressure (Lertxundi et al, 2010), and thus, $PM_{2.5}$ levels were derived as the average measured $PM_{2.5}$ concentration from the closest monitoring site to each participant's address during the entire pregnancy period (Lertxundi et al., 2010, 2015). For INMA-Valencia, $PM_{2.5}$ levels were assigned using inverse distance weighting based on data collected from five monitoring stations during the pregnancy period of the participants. For these latter two cohorts (INMA-Gipuzkoa and INMA-Valencia), $PM_{2.5}$ levels were also available from the European-wide LUR model described above (Wang et al., 2014) and these estimates were used in a sensitivity analysis. A summary of the availability and associated methodological references of the air pollutants is provided in the Supplemental Material (Table S2).

For nearly all cohorts, the home address at the time of birth was used to assign exposures early in life (birth exposures). However, for EDEN, the address given at the third trimester was used, and for INMA-Valencia, the address that the mother reported spending the most time at during her pregnancy was used. To assign the air pollution exposure levels later in life (current exposures), we used the home addresses given at the four-year and eight-year follow-ups (see Supplemental Material, Table S2).

2.4. Statistical analysis

Logistic regression models were used to analyze cross-sectional associations of air pollution exposure with the prevalence of each outcome at each age. We conducted separate analyses for air pollution estimated to the birth address (birth exposure) and to the address at each time of follow-up (current exposure). We analyzed cohort-specific associations and subsequently combined them in a random-effects meta-analysis to allow for potential heterogeneity between study areas (Basagaña et al., 2018), using the "meta" package in the statistical software R (Schwarzer, 2007). Following recommendations, we conducted a meta-analysis when a minimum of two cohorts were available (Valentine et al., 2010). The percentage variability between the studies that is present beyond what would be expected by chance is described using the I^2 statistic (Higgins and Thompson, 2002). A test for heterogeneity of effect estimates between cohorts was conducted. Prediction intervals (95%), which represent the range of true effects that can be expected for 95% of similar future settings (Borenstein et al., 2017; IntHout et al., 2016), are also reported for meta-analyses using data from at least three cohorts.

Air pollution exposures were entered as continuous variables without transformation. Odds ratios (ORs) and their 95% confidence intervals are presented per 10 $\mu g/m^3$ NO_2, 20 $\mu g/m^3$ NO_x, 10 $\mu g/m^3$ PM_{10}, 5 $\mu g/m^3$ $PM_{2.5}$ and PM coarse and 1 $10^{-5}/m$ $PM_{2.5}$ absorbance.

Models were adjusted for the following covariates selected *a priori* to match those in recent ESCAPE and MeDALL studies (Gehring et al., 2015; Mölter et al., 2014): maternal and paternal asthma and hay fever,

Table 2
Characteristics of study population.

		BIB (N = 2594)		EDEN (N = 1141)		GASPII (N = 581)		RHEA (N = 897)		INMA-Guipuzcoa (N = 451)		INMA-Sabadell (N = 590)		INMA-Valencia (N = 602)	
		N	n (%)/mean ± SD	N	n (%)/mean ± SD	N	n (%)/mean ± SD	N	n (%)/mean ± SD	N	n (%)/mean ± SD	N	n (%)/mean ± SD	N	n (%)/mean ± SD
Health outcomes															
Eczema	4 yrs	2514	422 (16.8)	1041	138 (13.3)	511	68 (13.3)	859	87 (10.1)	394	96 (24.4)	na	na	492	88 (17.3)
	8 yrs	na	na	744	117 (15.7)	468	22 (4.7)	na	na	394	75 (19.0)	501	74 (14.8)	470	77 (16.4)
Rhinoconjunctivitis	4 yrs	2352	197 (8.4)	1140	72 (6.3)	568	33 (5.8)	891	43 (4.8)	398	13 (3.3)	583	11 (1.9)	591	19 (3.2)
	8 yrs	na	na	812	79 (9.7)	480	26 (5.4)	na	na	392	28 (7.1)	541	22 (4.1)	469	38 (8.1)
Asthma	4 yrs	2592	407 (15.7)	1110	84 (7.6)	478	18 (3.8)	894	103 (11.5)	400	31 (7.8)	581	91 (15.7)	586	87 (14.8)
	8 yrs	na	na	806	68 (8.4)	486	26 (5.3)	na	na	395	31 (7.8)	543	57 (10.5)	470	41 (8.7)
Multi-morbidity[a]	4 yrs	1745	164 (9.4)	845	49 (5.8)	373	12 (3.2)	693	30 (4.3)	278	12 (4.3)	na	na	358	21 (5.9)
	8 yrs	na	na	559	42 (7.5)	414	9 (2.2)	na	na	304	22 (7.2)	401	19 (4.7)	377	29 (7.7)
Demographics															
Age (years)	4 yrs	4.5 ± 0.4		4.0 ± 0.1		4.1 ± 0.2		4.2 ± 0.2		4.5 ± 0.1		4.4 ± 0.2		4.3 ± 0.1	
	8 yrs	na	na	8.1 ± 0.2		7.8 ± 0.2		na	na	7.9 ± 0.1		6.7 ± 0.5		7.6 ± 0.2	
Male		2594	1301 (50.2)	1141	609 (53.4)	581	280 (48.2)	897	463 (51.6)	451	218 (48.3)	590	301 (51.0)	602	317 (52.7)
Birth weight (grams)		3196 ± 579		3285 ± 521		3346 ± 496		3179 ± 474		3299 ± 446		3275 ± 418		3234 ± 507	
Older sibling		2519	1620 (64.3)	1140	590 (51.8)	581	245 (42.2)	897	476 (53.1)	451	196 (43.5)	585	236 (40.3)	597	263 (44.1)
Breastfeeding (≥12 weeks)[b]		2593	1821 (70.2)	1141	527 (46.2)	581	427 (73.5)	840	413 (49.2)	408	205 (50.2)	589	290 (49.2)	602	267 (44.4)
Premature (< 37 weeks gestational age)		2566	169 (6.6)	1141	69 (6.0)	580	26 (4.5)	869	113 (13.0)	451	15 (3.3)	590	13 (2.2)	602	32 (5.3)
Maternal asthma or hayfever		2587	814 (31.5)	1140	246 (21.6)	578	148 (25.6)	787	133 (16.9)	451	73 (16.2)	588	102 (17.3)	601	95 (15.8)
Paternal asthma or hayfever		2503	692 (27.6)	1140	197 (17.3)	573	160 (27.9)	782	110 (14.1)	451	71 (15.7)	512	100 (19.5)	601	89 (14.8)
High maternal education[c]		2594	722 (27.8)	1141	406 (35.6)	581	215 (37.0)	897	277 (30.9)	451	240 (53.2)	590	181 (30.7)	602	164 (27.2)
High paternal education[c]		2594	703 (27.1)	1141	314 (27.5)	581	183 (31.5)	897	205 (22.9)	451	131 (29.0)	590	132 (22.4)	602	98 (16.3)
Daycare during 1st year of life[d]		na	na	1141	126 (11.0)	576	160 (27.8)	888	52 (5.9)	426	189 (44.4)	567	100 (17.6)	602	113 (18.8)
Maternal smoking during pregnancy		2589	252 (9.7)	1141	257 (22.5)	578	65 (11.2)	845	181 (21.4)	439	98 (22.3)	580	160 (27.6)	602	234 (38.9)
Smoking in the home during early-life		2594	308 (11.9)	1141	410 (35.9)	581	118 (20.3)	838	76 (9.1)	439	57 (13.0)	506	167 (33.0)	599	275 (45.9)
Gas for heating/cooking during early-life[e]		2594	2392 (92.2)	1141	760 (66.6)	581	578 (99.5)	na	na	439	58 (13.2)	508	311 (61.2)	602	387 (64.3)
Mould/dampness in home during early-life[f]		2594	595 (22.9)	1141	177 (15.5)	581	59 (10.2)	795	226 (28.4)	427	29 (6.8)	571	46 (8.1)	602	65 (10.8)
Pets in the home during early-life[g]		na	na	1141	91 (8.0)	581	155 (26.7)	755	89 (11.8)	440	65 (14.8)	508	179 (35.2)	602	278 (46.2)
Changed address between birth and 4 yrs		2594	1141 (44.0)	1133	662 (58.4)	568	107 (18.8)	799	620 (77.6)	409	49 (12.0)	501	186 (37.1)	594	145 (24.4)
Changed address between birth and 8 yrs		na	na	na	na	491	151 (30.8)	na	na	366	69 (18.9)	488	215 (44.1)	527	168 (31.9)

na: not available.

[a] Having at least two of three conditions versus having none.

[b] For all INMA centers (Guipuzcoa, Sabadell and Valencia), considered "yes" if breastfeeding was at least 16 weeks as data for 12 weeks were not available. For BIB, defined as "yes" versus "no" reported breastfeeding as data on length of time of breastfeeding was missing for a large percentage of the cohort (58%).

[c] For BIB, coded as a four-level variable (high, medium, low and other/unknown) to capture the large percentage of missing data for this cohort.

[d] For GASPII, this was asked for 15 months instead of 12 months. For BIB, this information was only collected for a subset of the cohort and is thus not included.

[e] Information not collected in RHEA.

[f] For EDEN, only includes information on mould as there was no data on dampness.

[g] For all INMA centers (Guipuzcoa, Sabadell and Valencia), pet information was collected at month 8. For BIB, this information was only collected for a subset of the cohort and is thus not included.

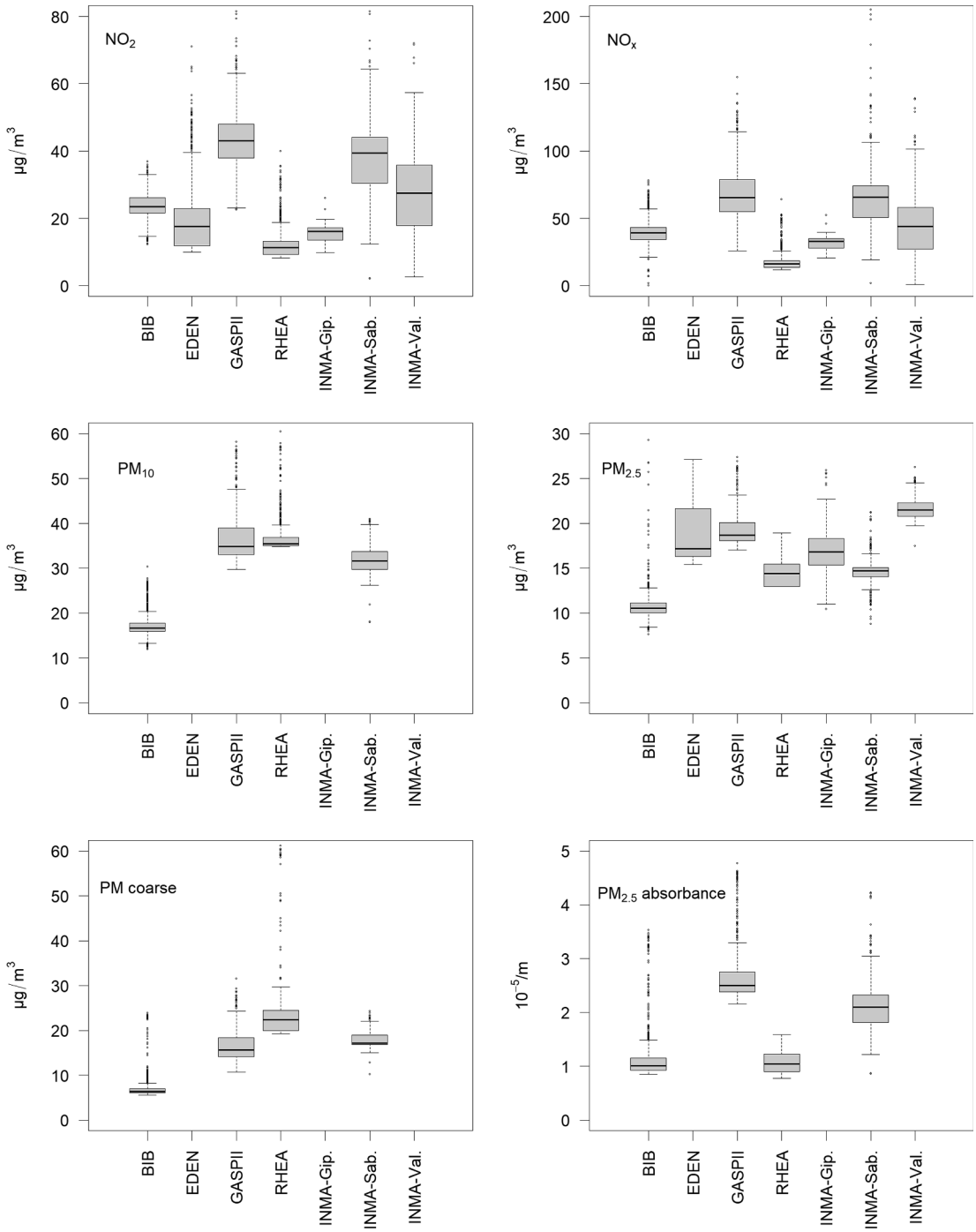


Fig. 1. Distribution of pollutants per cohort at the birth address. The horizontal dark line represents the median. The ends of the grey box show the upper and lower quartiles.

maternal and paternal education, breastfeeding, older siblings, daycare attendance during first year of life, maternal smoking during pregnancy, parental smoking at home during early-life, mould or dampness at home during early-life, furry pets in the home during early-life and use of gas for cooking during early-life. Use of gas for cooking was not included in the models in RHEA (data not collected) and GASPII (99.5% prevalence of use of gas for cooking), nor was daycare attendance and furry pet ownership included in the models in BIB (data not collected for a large proportion of this cohort). Native nationality was not included as a covariate due to large differences in the way these data were collected across cohorts.

Sensitivity analyses included (1) using a pooled analysis approach with a fixed adjustment for center, (2) adjusting for birth weight, which may lie in the causal pathway, (3) excluding those born prematurely (< 37 weeks gestational age, $N = 437$) who may be at increased risk, (4) removing the adjustment for parental allergy which may represent an over-adjustment, (5) excluding cohorts/air pollutants that were estimated using methods not strictly adhering to ESCAPE protocols, (6) replicating the meta-analysis for $PM_{2.5}$ mass using estimates from the European-wide LUR model (Wang et al., 2014) for INMA-Gipuzkoa and INMA-Valencia and testing for effect modification by (7) sex and (8) whether or not the child had moved since birth using interaction terms and stratification analyses. The models stratified by sex and moving status, as well as those run on the multi-morbidity secondary outcome,

were only adjusted for maternal and paternal asthma and hay fever, smoking during pregnancy and parental smoking at home during early-life because of problems with model singularities when additional covariates were included, attributable to the small number of cases in certain strata. Finally, we also analyzed the three components of the asthma outcome definition separately (wheezing, medication and asthma doctor diagnosis) as the practice of providing a clinical diagnosis of asthma at young ages may vary by country.

3. Results

After restricting the data to those with available health and air pollution data at any time point, 6856 participants were available for analysis (6527 and 2489 at age four and eight years, respectively). The characteristics of this study population are presented in Table 2. The mean age at the four-year follow-up was narrowly around four years for all cohorts, whereas that at the eight-year follow-up was more varied (mean age was 6.7 years in INMA-Sabadell and 8.1 years in EDEN). Eczema prevalences ranged from 4.7% at eight years in GASPII to 24.4% at four years in INMA-Gipuzkoa. Rhinoconjunctivitis prevalences ranged from 1.9% at four years in INMA-Sabadell to 9.7% at eight years in EDEN. Asthma prevalences ranged from 3.8% at four years in GASPII to 15.7% at four years in both BIB and INMA-Sabadell. Multi-morbidity prevalences were lowest in GASPII (2.2% at eight years) and highest in BIB (9.4% at four years).

The distribution of the air pollutants estimated to the birth (Fig. 1), four- (Supplemental Material, Fig. S1) and eight-year (Supplemental Material, Fig. S2) home addresses are presented per cohort. For NO_2 and NO_x (only available for 6/7 cohorts), the levels and range of pollutants estimated to the birth address were highest in GASPII, INMA-Sabadell and INMA-Valencia. For $PM_{2.5}$ estimated to the birth address, concentrations were highest in GASPII and INMA-Valencia.

Pollutants estimated to the same addresses tended to be moderately to highly correlated in most cases (Table S3). However, lower correlations were observed between $PM_{2.5}$ with NO_2 and NO_x in INMA-Gipuzkoa and INMA-Valencia. Among those who moved during the study, there was no consistent pattern in the correlations between the air pollutants estimated to the birth address and those estimated to the four- and eight-year addresses (Table S4).

The meta-analytic adjusted associations for the air pollutants estimated to the birth and current addresses are presented in Tables 3 and 4, respectively (forests plots are presented in the Supplemental Material, Figs. S3–S14). Overall, there was no indication of an increase in prevalence of any of the outcomes in association with higher levels of any of the pollutants. Only for the associations between asthma at age eight years and the pollutants estimated to the current (eight year) addresses were the ORs consistently greater than one, although no association reached statistical significance. When considering each of the three components of the asthma outcome definition separately (wheezing, medication and asthma doctor diagnosis, presented in Table S5 and Table S6 for ages four and eight years, respectively), ORs were only greater than one for ever having a doctor diagnosis of asthma by age eight years (Table S6).

In the adjusted models for asthma at four years, there was moderate (I^2 between 30 and 50%) heterogeneity between the cohort-specific effect estimates for NO_2 estimated to the birth and current addresses and the heterogeneity was more marked ($I^2 > 50\%$) for $PM_{2.5}$ estimated to the birth and current addresses. Heterogeneity was also observed for both rhinoconjunctivitis and asthma at eight years for nearly all pollutants estimated to the birth address and for rhinoconjunctivitis at eight years when pollutants were estimated to the current address.

No association was found between any air pollutant and the secondary multi-morbidity outcome (Table S7). Throughout all sensitivity analyses, we found no evidence to indicate the existence of an association between any of the air pollutants and the outcomes (Tables S8 and S9 for the health outcomes at ages four and eight, respectively, for sensitivity analyses (1) to (4)). Excluding cohorts/air pollutants that were estimated using methods not strictly adhering to ESCAPE protocols and replicating the meta-analysis for $PM_{2.5}$ mass using estimates from the European-wide LUR model for INMA-Gipuzkoa and INMA-Valencia also did not change the findings.

All interaction terms between sex and the air pollutants as well as moving status and the air pollutants were non-significant ($p > 0.05$). Associations stratified by sex are presented in the Supplemental Material (Table S10) as are analyses restricted to never-movers for the air pollutants estimated to the birth address (to decrease exposure misclassification) and movers for the air pollutants estimated to the current address (Table S11).

4. Discussion

Using all available data from five birth cohorts covering seven areas in Europe, we found no evidence to support the hypothesis that long-term air pollution levels estimated to the home address are associated with an increased prevalence of current pediatric eczema, rhinoconjunctivitis or asthma. Results remained null throughout all sensitivity analyses conducted, including stratification by sex and moving behaviour.

4.1. Comparisons with the literature

Previous studies conducted using individual-level data in Western countries have yielded inconsistent evidence for a role of air pollution on eczema and rhinoconjunctivitis. For eczema, some studies report adverse associations for specific exposure-outcome combinations (Brunekreef et al., 2009; Krämer et al., 2009; Morgenstern et al., 2008; Pénard-Morand et al., 2010), whereas others report overall null findings (Aguilera et al., 2013; Gehring et al., 2010), such as a recent large pooled analysis of 5685 children (aged up to eight years) from six birth cohorts (Hüls et al., 2018). For rhinoconjunctivitis, differences across ages (Fuertes et al., 2013; Morgenstern et al., 2008) have been noted or associations appear restricted to population subgroups (e.g. those living in urban areas in Germany (Krämer et al., 2000) or non-movers in the Dutch PIAMA cohort (Gehring et al., 2010)). The largest most recent analysis on rhinoconjunctivitis (on 14,126 participants aged 14–16 years-old from four birth cohorts) found no indication of an adverse effect of air pollution (Gehring et al., 2015). In contrast, a recent meta-analysis of five cohort studies (all based in Asia) which explicitly used the term “allergic rhinitis” concluded an adverse effect of air pollution (Zou et al., 2018). However, given the small number of studies considered, the results of this latter work are unlikely to be generalizable. In general, the lack of associations observed in the current study for eczema and rhinoconjunctivitis are in line with the overall body of scientific literature, which does not suggest a strong, robust impact of air pollution on these outcomes.

It is more difficult to reconcile the observed null findings for asthma with the existing literature, as most (Bowatte et al., 2015; Khreis et al., 2017) but not all (Heinrich et al., 2016) recent efforts summarizing published studies support an adverse role of air pollution in asthma. It is nonetheless interesting that our overall null findings are in line with the large cross-sectional meta-analysis of five birth cohorts (MAAS, BAMSE, PIAMA, GINIplus and LISAplus, N = 17,041) conducted as part of the ESCAPE collaboration, in which asthma at age four and eight years was analyzed (Mölter et al., 2014). Only when four (of these five) cohorts were re-analyzed longitudinally (including data up to 14–16 years of age, N = 14,126) were adverse associations apparent, and primarily for asthma with an onset after four years of age (Gehring et al., 2015, e.g. meta-analyzed OR for the association between NO_2 and incident asthma up to 14–16 years was 1.13 (1.02, 1.25) per 10 $\mu g/m^3$). Gehring et al., 2015 suggest that asthma may be more easily diagnosed at older ages, which would reduce outcome misclassification and the (likely) resulting non-differential bias. When present, this bias would drive

Table 3
Random effects meta-analyses of adjusted associations (odds ratios and 95% confidence intervals) between the health outcomes (at two ages, modelled separately) and the air pollution exposures estimated to the home address at birth.

Health outcome	Air pollution	Age 4 years				Age 8 years			
		OR (95% CI)	I^2 (p_{het})	Number cohorts	Number observations	OR (95% CI)	I^2 (p_{het})	Number cohorts	Number observations
Eczema	NO_2	0.94 (0.81, 1.09)	0.26 (0.241)	6	5085	0.83 (0.72, 0.95)	0.00 (0.563)	5	2213
	NO_x	0.86 (0.74, 1.00)	0.00 (0.801)	5	4265	0.82 (0.67, 0.99)	0.18 (0.299)	4	1654
	PM_{10}	0.84 (0.59, 1.19)	0.07 (0.340)	3	3443	0.80 (0.44, 1.45)	0.00 (0.771)	2	861
	$PM_{2.5}$	1.00 (0.81, 1.23)	0.00 (0.423)	6	4911	0.91 (0.66, 1.26)	0.00 (0.566)	5	2043
	PM coarse	0.95 (0.79, 1.15)	0.00 (0.545)	3	3443	0.92 (0.58, 1.45)	0.00 (0.757)	2	861
	$PM_{2.5}$ absorbance	0.96 (0.90, 1.02)	0.00 (0.725)	3	3443	0.92 (0.80, 1.06)	0.00 (0.674)	2	861
Rhinoconjunctivitis	NO_2	0.90 (0.75, 1.09)	0.00 (0.884)	7	5669	0.87 (0.62, 1.22)	0.62 (0.033)	5	2308
	NO_x	0.93 (0.74, 1.15)	0.00 (0.882)	6	4754	0.87 (0.50, 1.50)	0.73 (0.012)	4	1699
	PM_{10}	0.83 (0.52, 1.34)	0.04 (0.373)	4	3829	0.28 (0.02, 3.57)	0.83 (0.014)	2	909
	$PM_{2.5}$	0.70 (0.49, 1.00)	0.00 (0.733)	7	5465	0.76 (0.49, 1.16)	0.00 (0.494)	5	2138
	PM coarse	0.85 (0.64, 1.13)	0.00 (0.559)	4	3829	0.66 (0.21, 2.05)	0.44 (0.181)	2	909
	$PM_{2.5}$ absorbance	0.88 (0.79, 0.98)	0.00 (0.961)	4	3829	0.90 (0.75, 1.08)	0.00 (0.380)	2	909
Asthma	NO_2	0.91 (0.74, 1.11)	0.49 (0.067)	7	5803	0.94 (0.65, 1.35)	0.69 (0.013)	5	2320
	NO_x	1.00 (0.84, 1.20)	0.28 (0.222)	6	4890	1.16 (0.87, 1.54)	0.49 (0.120)	4	1710
	PM_{10}	0.82 (0.56, 1.19)	0.00 (0.471)	4	3967	1.18 (0.66, 2.11)	0.00 (0.350)	2	916
	$PM_{2.5}$	0.88 (0.54, 1.45)	0.68 (0.005)	7	5600	0.65 (0.35, 1.21)	0.39 (0.162)	5	2150
	PM coarse	0.89 (0.69, 1.15)	0.24 (0.270)	4	3967	1.01 (0.46, 2.26)	0.50 (0.158)	2	916
	$PM_{2.5}$ absorbance	1.02 (0.97, 1.07)	0.00 (0.672)	4	3967	0.93 (0.70, 1.24)	0.71 (0.063)	2	916

Odds ratios and their 95% confidence intervals, I^2 values and p-value of test for heterogeneity (p_{het}) of effect estimates between cohorts are presented for the following increments in exposure: per 10 μg/m^3 NO_2, per 20 μg/m^3 NO_x, per 10 μg/m^3 PM_{10}, per 5 μg/m^3 $PM_{2.5}$ and PM coarse and per 1 10^{-5}/m $PM_{2.5}$ absorbance. Models are adjusted for sex, exact age at follow-up, maternal and paternal asthma and hay fever, maternal and paternal education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home during early-life, mould or dampness at home during early-life, furry pets in the home during early-life, use of gas for cooking. Exceptions include: gas for cooking not included in models for GASPII and RHEA; daycare and pets not included in models for BIB; father education not considered in GASPII for models for eczema at age eight years; maternal education not considered in INMA-Gipuzkoa for models for rhinitis at age four years with $PM_{2.5}$ mass.

Table 4
Random effects meta-analyses of adjusted associations (odds ratios and 95% confidence intervals) between the health outcomes (at two ages, modelled separately) and the air pollution exposures estimated to the home address at the time of outcome assessment.

Health outcome	Air pollution	Age 4 years				Age 8 years			
		OR (95% CI)	I^2 (p_{het})	Number cohorts	Number observations	OR (95% CI)	I^2 (p_{het})	Number cohorts	Number observations
Eczema	NO_2	0.95 (0.84, 1.08)	0.00 (0.880)	6	5046	0.89 (0.77, 1.03)	0.00 (0.401)	4	1634
	NO_x	0.92 (0.80, 1.07)	0.00 (0.970)	5	4230	0.88 (0.74, 1.04)	0.13 (0.329)	4	1634
	PM_{10}	0.85 (0.61, 1.20)	0.00 (0.713)	3	3408	0.99 (0.56, 1.76)	0.00 (0.349)	2	841
	$PM_{2.5}$	0.96 (0.77, 1.19)	0.00 (0.886)	4	4224	0.79 (0.40, 1.56)	0.00 (0.851)	2	841
	PM coarse	0.99 (0.83, 1.19)	0.00 (0.729)	3	3408	1.07 (0.69, 1.66)	0.00 (0.391)	2	841
	$PM_{2.5}$ absorbance	0.98 (0.93, 1.04)	0.00 (0.899)	3	3408	0.96 (0.82, 1.14)	na	1[a]	407
Rhinoconjunctivitis	NO_2	0.91 (0.75, 1.10)	0.00 (0.488)	7	5626	0.87 (0.62, 1.22)	0.49 (0.120)	4	1678
	NO_x	0.96 (0.77, 1.19)	0.00 (0.738)	6	4715	0.98 (0.63, 1.52)	0.64 (0.039)	4	1678
	PM_{10}	0.85 (0.54, 1.34)	0.00 (0.494)	4	3790	0.59 (0.25, 1.41)	0.24 (0.250)	2	888
	$PM_{2.5}$	0.69 (0.49, 0.97)	0.00 (0.765)	5	4701	0.55 (0.21, 1.40)	0.00 (0.420)	2	888
	PM coarse	0.89 (0.69, 1.14)	0.00 (0.596)	4	3790	0.83 (0.48, 1.42)	0.00 (0.579)	2	888
	$PM_{2.5}$ absorbance	0.91 (0.83, 1.00)	0.00 (0.670)	4	3790	0.79 (0.57, 1.10)	na	1[a]	443
Asthma	NO_2	0.95 (0.78, 1.15)	0.47 (0.076)	7	5763	1.09 (0.91, 1.30)	0.00 (0.391)	4	1688
	NO_x	0.98 (0.86, 1.11)	0.00 (0.607)	6	4854	1.14 (0.93, 1.41)	0.22 (0.281)	4	1688
	PM_{10}	0.92 (0.66, 1.30)	0.00 (0.659)	4	3931	1.25 (0.70, 2.21)	0.00 (0.656)	2	894
	$PM_{2.5}$	1.06 (0.56, 2.01)	0.80 (0.001)	5	4840	1.07 (0.53, 2.13)	0.00 (0.583)	2	894
	PM coarse	0.96 (0.79, 1.18)	0.13 (0.329)	4	3931	1.20 (0.77, 1.87)	0.00 (0.376)	2	894
	$PM_{2.5}$ absorbance	1.03 (0.99, 1.08)	0.00 (0.457)	4	3931	0.98 (0.80, 1.18)	na	1[a]	444

Odds ratios and their 95% confidence intervals, I^2 values and p-value of test for heterogeneity (p_{het}) of effect estimates between cohorts are presented for the following increments in exposure: per 10 μg/m^3 NO_2, per 20 μg/m^3 NO_x, per 10 μg/m^3 PM_{10}, per 5 μg/m^3 $PM_{2.5}$ and PM coarse and per 1 10^{-5}/m $PM_{2.5}$ absorbance. Models are adjusted for sex, exact age at follow-up, maternal and paternal asthma and hay fever, maternal and paternal education, breastfeeding, older siblings, daycare attendance, maternal smoking during pregnancy, parental smoking at home during early-life, mould or dampness at home during early-life, furry pets in the home during early-life, use of gas for cooking. Exceptions include: gas for cooking not included in models for GASPII and RHEA; daycare and pets not included in models for BIB; father education not considered in GASPII for models for eczema at age eight years only.

[a] No meta-analysis was conducted as data were available for only one cohort. Association reported is calculated within one cohort.

associations towards the null. A similar observation was made in the Swedish BAMSE birth cohort, in which associations between NO_x and PM_{10} during the first year of life were only apparent for prevalent asthma at 12 years (1.66 (1.01, 2.72) per 46.8 μg/m^3 increase and 1.96 (1.08, 3.53) per 7.2 μg/m^3 increase, respectively, N = 4089) but not at younger ages (Gruzieva et al., 2013).

It is indeed intriguing that in the current study, the ORs were most consistently greater than one for associations with asthma at age eight years using both the MeDALL-based outcome definition (Table 4) and the single question on ever doctor diagnosis (Supplemental Material, Table S6). However, given the number of tests conducted and the more limited number of cohorts contributing data to these models, these results should be interpreted with caution.

It should be noted that although a high percentage of European urban populations continue to be exposed to levels that exceed European Union and World Health Organization reference levels, air pollution levels in general have decreased in Europe during the last decades (Colette et al., 2017; Guerreiro et al., 2014). Hence the children included in the current analysis, who are participating in more recently established birth cohorts, would likely have been exposed to lower average levels of air pollution than in earlier decades. Ultimately, we can only speculate regarding the reasons behind the lack of consistent associations with asthma, but it is possible that a future re-analysis of the participating cohorts, in which repeated and longitudinal data are available on asthma at older ages, could yield different results.

4.2. Strengths and limitations

This analysis included all available data from several large prospective well characterized birth cohorts, which allowed adjustments for many early-life and current known risk factors for asthma and allergic diseases. We chose to adjust the models for the same covariates as used in a previous similar analysis (Gehring et al., 2015) to increase the compatibility of our results. Unfortunately, because of the lack of existing data in most cohorts, we were unable to adjust for area-level socioeconomic variables (although maternal and paternal education were included as markers of individual-level socioeconomic status), consider gene-environment interactions (for which the epidemiological evidence is strongest for asthma (e.g. (MacIntyre et al., 2014)), or stratify the associations by atopic status (for which there is growing evidence that air pollution may be more strongly associated with non-allergic asthma compared to allergic asthma (Khreis et al., 2017)). Participation bias, a near universal concern for cohorts with long follow-ups, and the fact that each cohort has its own respective characteristics may affect the generalizability of the results (e.g. BIB is composed of a deprived multi-ethnic population (Wright et al., 2013), 13% of the RHEA cohort was born prematurely, attrition in the INMA and GASPII cohorts appears linked to lower socioeconomic markers (Guxens et al., 2012; Porta et al., 2007)). However, it is notable that no consistent association for any air pollutant - health outcome combination was observed in any cohort (forest plots provided in the Supplemental Material, Figs. S3–S14). This confirms that the overall null meta-analytic results are not driven by the results from a single cohort.

Despite using all available data, we chose to model disease prevalence instead of incidence due to an insufficient number of incident cases between four and eight years of age per cohort (e.g. range of 11–38 new asthma cases in GASPII and EDEN, respectively) and because our outcome definitions required symptoms/medications “in the last 12 months”, which is indicative of prevalent “active” disease. Similarly, as not all cohorts had repeated outcome and air pollution data, we pursued cross-sectional analyses instead of longitudinal analyses to maximize the use of all available data. As such, the analyses presented here suggest there may be no associations between air pollution exposure and childhood asthma, rhinoconjunctivitis or eczema prevalence, but are unable to inform on the role of air pollution on the development of these conditions.

As much as possible, we used the outcome definitions proposed by the MeDALL collaboration. However, because much of the health data at four years were collected prior to MeDALL, there are differences in how the outcomes were defined at age four years only (summarized in Table S1), which may affect the comparison of outcome prevalences across cohorts and ages. Furthermore, even when the same wording was used, there are likely differences in country-specific practices related to providing a clinical asthma diagnosis, especially at four years. Wide differences in the prevalence of asthma, rhinoconjunctivitis and eczema have been documented in children in large global studies using identical questionnaires (Aït-Khaled et al., 2009; Lai et al., 2009; Odhiambo et al., 2009). Given the null findings we observed for air pollution, the main determinants of this variability in disease prevalence remain undefined but are likely related to local environmental or ecologic factors, and probably reflect differences in language, socioeconomic development, lifestyle, culture, education, medical practice and health concepts (Mallol et al., 2013). Finally, the extensive available health data allowed us to examine associations with multi-morbidity, which has not yet been reported in relation to air pollution using large cohort studies.

Most air pollutants were estimated to the home addresses using area-specific LUR models developed following ESCAPE protocols. An exception to this was that $PM_{2.5}$ was assigned using a single European-wide LUR model in EDEN (Wang et al., 2014). Previous work has found the application of this European-wide LUR model to areas not used in its development to be a reasonable approach, although the precision of the effect estimates may be reduced (Wang et al., 2014). Furthermore, $PM_{2.5}$ was assigned using average measurements from the nearest monitor in INMA-Gipuzkoa and distance inverse weighting methods in INMA-Valencia. These differences in exposure methodology may be one reason why the correlations between $PM_{2.5}$ with NO_2 and NO_x were quite low in these two study areas. However, the results did not change when excluding EDEN, INMA-Gipuzkoa and INMA-Valencia from the meta-analysis for $PM_{2.5}$ mass, using the European-wide LUR model $PM_{2.5}$ mass estimates (Wang et al., 2014) for INMA-Gipuzkoa and INMA-Valencia, or excluding EDEN from the analyses with NO_2, which was the only area which did not use the ESCAPE LUR models to assign NO_2 exposure levels.

Despite these differences in exposure assessment, this study is notable in that the monitoring data used to inform the development of the air pollution exposure models were collected at (four areas) or near (within four to seven years, three areas) the time of birth of the participants. As such, the years in which monitoring data were collected differs by cohort. This likely reduced some exposure misclassification for the air pollutants estimated to the home address at birth, as there is no need to assume that the spatial distribution of the air pollution sources (large roads, land use patterns, industrial areas) and their associated pollutants has not changed between the birth of a participant and the time the monitoring data were collected. However, it is still necessary to make this assumption for the air pollutants estimated to the four and eight-year home addresses and thus the potential for exposure misclassification is likely greater at these later time points. Associations with these latter air pollution exposures are also more likely to be at risk of reverse causation (i.e. families of asthmatic children being more likely to move to areas of low air pollution), although we did not find that those with asthma or allergic diseases were more likely to move throughout the follow-up.

Additional sources of potential exposure misclassification include that we did not consider exposures that occurred away from the home (at daycares/schools, during commuting), although previous studies have found exposures at the home address to be good approximations of those at schools (Gruzieva et al., 2012; Reungoat et al., 2005). We also did not consider all potential outdoor pollutants that may influence health, such as ozone levels (Sousa et al., 2013). The effects of NO_2 and ozone have been shown to be underestimated in single-pollutant analyses when these pollutants are highly negatively correlated (Janssen et al., 2017). We were also unable to consider indoor air pollution

exposures (and those with asthma or other respiratory disorders may exhibit different indoor and outdoor time-activity patterns), the composition of particulate matter (which can vary significantly over geographical areas (Götschi et al., 2005) and may be as or more important for health than particulate matter concentrations (Traversi et al., 2009)), and many other unknown and unmeasured factors within an individual's exposome that may be related to asthma and allergic diseases (Cecchi et al., 2018). Finally, we chose not to pursue multi-pollutant models as we found no evidence of associations in any of the single pollutant models.

In conclusion, using observational data from seven areas participating in five European birth cohorts, we found no evidence to suggest that long-term air pollution levels are associated with the prevalence of current pediatric eczema, rhinoconjunctivitis or asthma up to age eight years. Future follow-ups of these cohorts using large-scale cross-cohort analyses are needed to determine whether adverse associations may become apparent at older ages, particularly for asthma. Despite the observed null findings, policies and actions promoting a reduction in air pollution should continue given the relatively strong evidence for adverse effects of air pollution on numerous other health outcomes.

CRediT authorship contribution statement

Elaine Fuertes: Conceptualization, Formal analysis, Funding acquisition, Methodology, Writing - original draft, Visualization. **Bénédicte Jacquemin:** Conceptualization, Funding acquisition, Methodology, Project administration, Writing - original draft, Supervision. **Jordi Sunyer:** Conceptualization, Funding acquisition, Project administration. **All other authors:** Data curation, Investigation, Writing - review & editing.

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Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105474.

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