

Susceptibility Factors Relevant for the Association Between Long-Term Air Pollution Exposure and Incident Asthma

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Abstract In this review, we identified 15 studies in children and 10 studies in adults that assessed the association between long-term exposure to air pollution and incident asthma and that conducted stratified analyses to explore potential susceptibility factors. Overall, adult never-/former smokers seem to be at higher risk of incident asthma due to air pollution. Children without atopy and children from low socioeconomic status families also seem to be at higher risk of incident asthma due to air pollution. While interaction between air pollution and genes involved in the response to oxidative stress pathways have been explored, results are somewhat inconsistent and in need of replication. To evaluate interactions, large sample sizes are necessary, and much more research, including data pooling from existing studies, is needed to further explore susceptibility factors for asthma incidence due to long-term air pollution exposure.

Keywords Air pollution · Incident asthma · Susceptibility factors · Long-term exposure

Introduction

Ambient air pollution has been associated with several health outcomes such as cardiovascular and respiratory diseases [1], lung cancer [2] or low birth weight [3]. Some specific population groups seem to be more sensitive to air pollution effects such as children, elderly people, overweight or obese individuals [4], and subjects with chronic respiratory disease such as asthma [5] or chronic obstructive pulmonary disease [6]. Sex differences have also been found [7]. Regarding air pollution, there is no consensus on specific susceptibility factors that would be common across all health outcomes. The association between air pollution and asthma has been widely studied. Some studies evaluated acute exposure to air pollution and its relation with asthma exacerbation or hospitalization [8]; others have evaluated long-term air pollution and its relation with prevalence and incidence of asthma [9]. To our knowledge no (systematic) review has evaluated potential susceptibility factors in relation to the effects of air pollution on incident asthma. Thus, the aim of this review is to fill in this gap by summarizing results from studies that reported on air pollution and incident asthma while stratifying according to possible susceptibility factors.

Methods

This review focuses on studies that assessed the effect of long-term air pollution on asthma incidence and reported stratified analysis on possible susceptibility factors. Through PubMed research, we selected articles in peer-reviewed journals. The

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search terms included “air pollution” and “asthma or wheeze”—in the title or abstract—and “inciden*” or “onset.” The search resulted in 272 papers, for which we screened the title, abstract and full article when necessary to identify studies according to the criteria that will be described here. We also compared the list with recent reviews based on the effect of air pollution on asthma [8–10], confirming that our search did not miss any eligible papers. We included only articles in English, in adults or children (not animals), that studied long-term pollution effects on incidence asthma and that stratified according to possible susceptibility factors (a flow chart of the article selection is available in Fig. 1).

Pollution Exposure

Pollutants studied in the articles were: nitrogen oxides (NO_x), nitrogen dioxide (NO₂), particulate matter up to 10 µm (PM₁₀), particulate matter up to 2.5 µm (PM_{2.5}), ozone (O₃), sulfur dioxide (SO₂) and soot. Most of the papers included in this review used modeled [land-use regression (LUR) or dispersion models] exposure at individuals’ residential addresses [11–18, 19, 20–25, 26]; one study used modeled individual exposures at both home and school addresses [27]. Three articles used proximity to traffic/major roads as a proxy of air pollution exposure; one relied on the residential address [28], one on school and home addresses [29], and one only on the school address [30]. Two studies used community exposure to air pollution as proxies of individual exposure [31, 32], and three studies used zip code level exposures corresponding to home and work/school [33–35].

Asthma Incidence

In adults, incident asthma was the variable of interest, whereas in children incident asthma or incident wheeze was considered. Incident asthma or wheeze was assessed mostly using questionnaires, and questions used across studies vary from report of asthma symptoms to report of diagnosed asthma (parental report for children). Five studies used a physician diagnosis of incident asthma (personal visit to the physician) [17, 18, 20, 29, 35]. One study used the asthma symptom score as a proxy to identify asthma incidence [23].

Susceptibility Factors

The susceptibility factors of a priori interest were:

Age: the effect of air pollution exposure could differ according to each stage of life [4] (in particular in the prenatal period [36], early childhood and the elderly [37]). Actually, regarding age, two concepts appear: on the one hand the age of exposure and on the other the age at diagnosis. Regarding the first, it is possible that there are different windows of susceptibility. Regarding the latter, it is well known that childhood asthma is

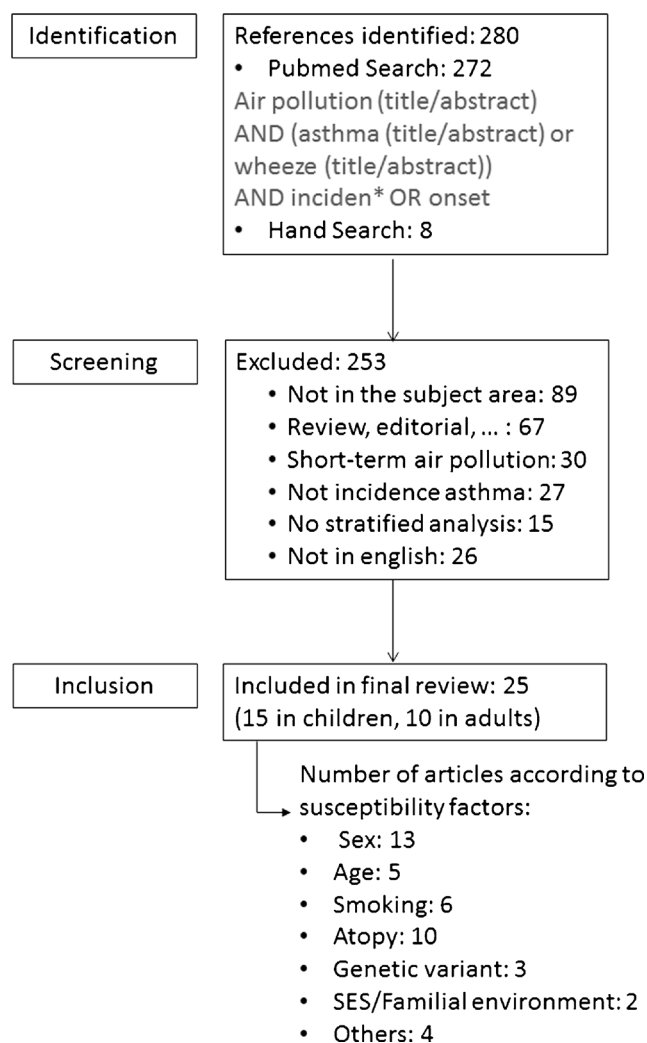


Fig. 1 Flow chart of the article selection

different from adulthood asthma, and, within adulthood asthma, teenage or elderly asthma can be also different phenotypes; thus, air pollution could have a different effect on these different phenotypes. Most of the studies stratified their analyses on age using age at inclusion or follow-up (possibly trying to integrate both concepts). However, some birth cohorts have air pollution exposure during pregnancy or early in life and therefore stratified by age of exposure.

Sex/gender: exposure to air pollution could be different according to gender (for example, women spending more time at home), or the effect of air pollution could be biologically different according to sex. Throughout the manuscript we will use the term “sex” as it is very difficult to disentangle what is related to sex—biological differences—and what is related to gender—life habit differences—regarding air pollution effects [38].

Tobacco and secondhand smoke for children: air pollution effects could be masked among smokers (or passive smokers) as smoking and air pollution share several mechanisms [24]; furthermore, recently it has been suggested that there could be an interaction between smoking and air pollution [39].

Atopy: atopic and non-atopic asthma are possibly two different diseases with different mechanisms, and air pollution may have a different effect according to atopic status [40].

Body mass index (BMI): subjects with obesity have been found to be more susceptible to air pollution in terms of lung function (and as lung function is an asthma-related phenotype, it seems plausible that susceptibility factors related to lung function may also be interesting to study regarding asthma incidence) and asthma [41–43].

Genetic variants [4]: mainly the ones associated with oxidative stress or inflammation have been investigated so far.

During the review we also identified a posteriori socioeconomic status (SES, individual SES for adults, family SES for children) or family environment (such as parental stress or exposure to violence), race, wheeze or bronchial hyperresponsiveness at baseline and parental history as being other potential susceptibility factors that we will examine in the manuscript.

Results and Discussion

Twenty-five articles fulfilled the inclusion criteria (17 from the PubMed research and 8 from the hand research) (Fig. 1) and are presented separately for adults and children. Study characteristics and main results for each study are summarized in Table 1 for children and in Table 2 for adults.

Sex

Seven studies stratified the effects of air pollution on asthma by sex [13, 14, 17, 18, 19•, 30, 35] in children. In Canadian children at high risk for asthma [17], the association between exposure, measured at year of birth, and incident asthma at 7 years old was reported as higher among boys, but no further details were given. In a pregnancy cohort in the US [19•], the association between in-utero exposure to $PM_{2.5}$ and asthma onset at age 6 showed a sensitive exposure window between 12–26 weeks of gestation for boys but not for girls, and the authors reported a significant interaction term for sex [p -interaction=0.01, OR ($PM_{2.5}$ *boys): 1.33 (1.05–1.69)]. In the five other studies, associations were similar in boys and girls: in children aged 6–9 years from the Chiba prefecture in Japan [30], the association between air pollution, measured as school proximity to traffic and asthma incidence, was similar in boys and girls [OR (95 % CI): 3.75 (1.00–14.06) for boys and 4.06 (0.91–18.10) for girls]. The same result was found among more than 4000 children aged 8–21 years from the US and Puerto Rico [18], for NO_2 and PM ($PM_{2.5}$ and PM_{10}), considering air pollution exposures during the first year of life or first 3 years of life [first year of life: NO_2 : OR (95 % CI): 1.26 (1.05–1.52) in boys, 1.11 (0.96–1.29) in girls; PM_{10} : 1.10 (0.89–1.36) in boys, 1.15 (0.97–1.37) in girls; the p -interaction was not significant; the first 3 years of life: PM_{10} : 1.08 (0.86–1.35) in

boys, 1.19 (1.00–1.41) in girls, p -interaction NS]. In a Swedish birth cohort [13], an association between traffic NO_x and persistent wheezing was also similar whatever the sex [OR (95 % CI)=1.94 (1.07–3.50) in girls, OR: 1.55 (0.92–2.63) in boys, p -interaction=0.43]. In another birth cohort conducted in Oslo, NO_2 was not associated with asthma incidence among girls [RR (95 % CI): 1.05 (0.74–1.49)], while the effect estimate was negative among boys [RR: 0.73 (0.56–0.95), p -interaction=0.10]. Finally, in Canadian children aged between 36 and 59 months [35], associations were similar in boys and girls for both NO and NO_2 [OR (95 % CI) for NO_2 : 1.17 (1.09–1.26) for girls and 1.09 (1.03–1.16) for boys, OR for NO : 1.13 (1.06–1.20) for girls and 1.05 (1.00–1.10) for boys].

In adults, six studies stratified by sex when they assessed the associations between air pollution and asthma [22–24, 28, 33, 34]. In American non-smokers [34], for an IQR increase in the 20-year average of O_3 -8 h concentration, the association was positive in men, while there was no association in women [RR (95 % CI): 2.09 (1.03–4.16) in men, 0.86 (0.58–1.26) in women]; in the same study population, another paper [33] reached a similar conclusion when considering the 1-year O_3 -8 h average as exposure. In a European study conducted in seven countries [23], the association between NO_2 concentration and incident asthma was similar but slightly stronger among men [OR (95 % CI): 1.32 (1.12–1.56)] than among women [1.14 (0.97–1.34; p -interaction=0.13]. Among Swiss never-smokers [24], the OR per $1 \mu g \cdot m^{-3}$ increase in traffic-related PM_{10} (TPM_{10}) was also slightly higher in men, but no precise ORs were available as the results were only presented in a figure. Other studies found no significant difference between men and women in the association between air pollution and asthma [22, 26•, 28]: no difference according to sex was found in a European study conducted in seven countries [OR for NO_2 : 1.31 (0.76–2.27) in men and 1.53 (0.99–2.38) in women (p -interact=0.69)] [22] or in a Swedish cohort (OR for NO_2 : 1.32 (0.64–2.74) in men, 1.67 (0.98–2.74) in women (p -interact=0.63)] [28]. Similarly, in a European study regrouping six cohorts, no difference was found according to the sex, and no association between air pollution and incident asthma was found [OR for NO_2 : 1.06 (0.92–1.24) in men, 1.07 (0.97–1.19) in women, p -interact=0.66, PM_{10} : 1.00 (0.63–1.59) in men, 1.07 (0.91–1.26) in women, p -interact=0.80] [26•].

In both adults and children, sex was the most studied susceptibility factor. Among children, the effect of air pollution on incident asthma was similar in boys and girls. Among adults, results are discordant, with some studies showing a higher effect of air pollution exposure on incident asthma in men, whereas others reported no difference according to sex. This contradicts what Clougherty [38] pointed out in her review where she found a higher effect of air pollution among women. Overall, in both adults and children, evidence mostly supports no effect modification between air pollution measures and sex on incident asthma.

Table 1 Description of studies assessing the association between air pollution exposure and incident asthma in adults (by year of publication) and that had stratified their analyses by possible susceptibility factors

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Shima, 2003, J Epidemiology [30]	Prospective cohort study. Recruitment in 1992, follow-up yearly until 1995. Outcome: incident asthma	1858 children from 8 communities in Chiba prefecture, Japan. (6-9 years at baseline)	School proximity to roadside: rural area, non-roadside area: ≥ 50 m from the roads, roadside area: < 50 m from the roads	Symptoms of asthma tended to increase in the order of roadside $>$ non-roadside $>$ rural areas	Sex	Sex: Ref: rural area. OR (95 % CI) for non-roadside area: 1.99 (0.79-4.99) among boys, 1.74 (0.63-4.81) among girls. OR (95 % CI) for roadside area: 3.75 (1.00-14.06) among boys, 4.06 (0.91-18.10) among girls. Significant trend among boys ($p = 0.013$), not among girls
Zmirou, 2004, JECH [29]	Case control study, conducted in 5 French metropolitan areas: VESTA, between 1998 and 2000. Outcome: incident asthma	195 pairs of matched cases and controls investigated. Aged 4-14 years	Traffic density: time-weighted average of the traffic density to road distance ratio; index of lifetime exposure to traffic exhaust. Exposure index considered in tertile. Home and school addresses	Traffic density associated with asthma when considering 3 first years of life, but not when averaging on life. OR (95 % CI) for traffic density as a quantitative predictor: 1.30 (1.04-1.62). Results in tertiles: ref= tertile 1; tertile 2: 1.48 (0.73-3.02), tertile 3: 2.28 (1.14-4.56)	Atopy (at least one positive SPT to one of nine tested allergens)	Atopy (positive SPT). Tertile 1 as reference. Atopic: tertile 2: 0.61 (0.1-3.6), tertile 3: 11.03 (1.3-100.9). Non-atopic: tertile 2: 1.23 (0.29-5.31), tertile 3: 1.47 (0.32-6.97) (p interaction = 0.20)
Pierce, 2006, Thorax [11]	Cohort study. Recruitment in 1998, follow-up in 2001. Outcome: incident wheeze, asthma symptoms	4400 children recruited in Lancaster. 1-5 years at baseline	Annual exposure to PM_{10} (dispersion mode). Year of exposure assessment: 1998 and 2001 (mean of both years). Home addresses	Exposure to PM_{10} and incidence of asthma symptoms: 1.42 (1.02-1.97) for wheeze (adjusted results)	Age, secondhand smoke	- Age: 1.43 (0.91-2.26) in children aged 1-2.99 years and 1.39 (0.86-2.25) in children aged 3-4.99 years - Secondhand smoke: (p -interact > 0.1)
Clougherty, 2007, EHP, [12]	Birth cohort, recruitment: between 1987 and 1993, follow-up in 1997. Outcome: incident asthma	413 children from Boston, recruiting pregnant women	Measured NO_2 , weekly collected. Monthly averaged, corresponding to address of participants. Year of exposure assessment: monthly from January 1987 through December 2004	Univariate OR: 1-SD increase in year of diagnosis of NO_2 showed near-significant associations with asthma: 1.17 (0.94-1.46)	Exposure to violence (ETV)	ETV: exposed above the median: 1.65 (1.16-2.34), lower than median: 0.94 (0.70-1.26). (Year of diagnosis NO_2). Multivariate: increased risk among children with above median ETV 1.63 (1.14-2.33). Above median: 2.40 (1.48-3.88)
Islam et al., 2008, AJRCCM, [31]	Prospective cohort (CHS). Recruitment between 1993 and 2004, follow-up yearly during 2-8 years. Outcome: incident asthma	1125 non-Hispanic white and 576 Hispanic white from 12 southern California communities. Age: > 7 years	Average hourly levels of O_3 , NO_2 and PM (PM_{10} and $PM_{2.5}$). For ozone: annual average of 8 h daytime average computed. Communities were classified as higher ozone communities or lower ozone communities. (1994-2003)	No general effect assessed	Genetic variants <i>MNSOD</i> Ala-9Val (rs4880), <i>CAT-262C > T</i> (rs1001179), and <i>CAT-844C < T</i> (rs769214) <i>HMOX-1</i> (GT)n repeats. Short allele (S): < 23 repeats), race	Genetic: (GT)n repeat polymorphism of <i>HMOX-1</i> : low-ozone communities: HR (95 % CI): 0.44 (0.23-0.83; high ozone communities HR = 0.88 (0.33-2.34). P for interaction = 0.003.

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Nordling, 2008, Epidemiology, [13]	Birth cohort, recruitment between 1994 and 1996, follow-up at 1, 2 and 4 years of age. Outcome: persistent wheezing and late-onset asthma	4089 infants from 4 Swedish municipalities. Age different according to the follow-up (1, 2 and 4 years old)	Dispersion model. NO _x , PM ₁₀ , SO ₂ . Home addresses. 1990: traffic NO _x and heating SO ₂ . 2000: traffic NO _x , heating SO ₂ and traffic PM ₁₀ . Outdoor levels of air pollution for the children's first year of life (1994-1997): interpolation from the data of 1999 and 2000	Persistent wheezing: Association with traffic NO _x (for a difference between the 5th and 95th percentile range in the cohort): OR: 1.60 (1.09-2.36). Similar but ns results for PM ₁₀ . No association between pollutant and late-onset asthma	Sex, atopy [atopic wheeze: allergic sensitization to pollen (specific-IgE)]	Low PM ₁₀ communities: HR: 0.94 (0.54-1.62); high PM ₁₀ communities HR = 0.62 (0.20-1.87), <i>P</i> for interaction = 0.18 - Sex: persistent wheezing: girls: OR: 1.94 (1.07-3.50), boys: OR: 1.55 (0.92-2.63) - Atopy: persistent wheezing and late onset: non-atopic wheeze: NO _x : 1.46 (1.00-2.13), atopic wheeze: NO _x : 1.11 (0.55-2.22) (<i>p</i> -interaction = 0.43)
Islam, 2009, Thorax, [32]	Prospective cohort (CHS). Recruitment between 1993 and 2004, follow-up yearly during 2-8 years. Outcome: incident asthma	1064 non-Hispanic white and 576 Hispanic white from 12 southern California communities. Age: >7 years	Average hourly levels of zone (O ₃), nitrogen dioxide (NO ₂) and particulate matter (PM ₁₀ and PM _{2.5}). For ozone: annual average of 8 h daytime average computed. Communities were classified as higher ozone communities or lower ozone communities. Years of exposure assessment: 1994-2003	None	Genetic variants <i>GSTP1</i> haplotype tagging SNPs: rs6591255, rs4147581 and Ile105Val and rs749174 <i>GSTM1</i> null genotype <i>CAT-262C>T</i> (rs1001179) and <i>HMOX1</i> (GT) ⁿ repeats. Short allele (S): <23 repeats, sport played	Genetic: risk of new onset asthma among Ile105 homozygotes in high ozone community: HR (6.15; 2.2-7.4, <i>P</i> for interaction = 0.10, limited sample size) Ile105 homozygotes in low ozone community: 1.06 (0.3-4.0) [among those who played >2 team sports, no difference among those playing less than 2 sports]
Ofstedal, 2009, EHP, [14]	Oslo Birth Cohort. Recruitment in 1992-1993, follow-up: 2001-2002 (and cross-sectional study). Outcome: incident asthma	2871 children born in Oslo	NO ₂ dispersion model. Home addresses	No positive associations between any long-term TRAP and onset of doctor-diagnosed asthma (but a negative association). Association for late asthma onset (>4 years of age) was positive but NS	Sex	Sex: RR of 0.73 (0.56-0.95) in boys and 1.05 (0.74-1.49) in girls (<i>p</i> -interaction = 0.10)
Shankardass, 2009, PNAS, [15]	Prospective cohort study (CHS). Recruitment: 2002-2003 and follow-up during 3 years. Outcome: incident asthma	2497 children from 13 southern California communities, aged 5-9 years at baseline	NO _x dispersion model. Annual concentrations. Home address. Year of exposure assessment: 1997	Risk of asthma increased with exposure to traffic-related pollution: HR (95 % CI) 1.31 (1.07-1.61), for an IQR of 21 ppb of NO _x	Parental stress, SES	- Parental stress (<i>p</i> interaction 0.05): high parental stress: HR: 1.51 (1.16-1.96). Low parental stress: 1.05 (0.74-1.49), <i>p</i> -interact for 3-way "gender--parental stress-air pollution" = 0.10; high parental stress: males: 1.60 (1.16-2.22), females: 1.36 (0.87-2.11). Low parental stress: males: 0.98 (0.61-1.59), females: 1.14 (0.68-1.90)

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Clark, 2010, EHP, [35]	Nested case control in a cohort study, all 1999 and 2000 births in British Columbia (Canada). Outcome: incident asthma	3482 cases and 17,410 controls, among 37,401 children. 36-59 months at the end of the follow-up	LUR modeling/DW. High resolution (10 m) TRAP: NO ₂ , PM _{2.5} and black carbon. Exposure levels assigned at the zip code level. Average exposure calculated for duration of pregnancy and first year of life	Increased risk of asthma diagnosis with increased early life exposure (in utero and 1st year of life; greater results for 1st year of life). OR for 1st year of life: 1.08 (1.04-1.12) for a 10 mg.m ⁻³ increase of NO ₂ , 1.12 (1.07-1.17) for a 10 mg.m ⁻³ increase of NO ₂ , 1.10 (1.06-1.13) for a 100 mg.m ⁻³ increase of CO, 1.07 (1.03-1.12) for an increase of 1 mg.m ⁻³ in PM ₁₀	Sex NO: 1.13 (1.06-1.20) for girls and 1.05 (1.00-1.10) for boys. NO ₂ : 1.17 (1.09-1.26) for girls and 1.09 (1.03-1.16) for boys	-SES: (<i>p</i> interaction 0.25): high SES: 1.20 (0.93-1.55). Low SES: 1.55 (1.09-2.19) Sex:
Gehring, 2010, AJRCCM, [16]	Prospective birth cohort (PIAMA). Recruitment in 1996-1997 of pregnant women, follow-up yearly during 8 years. Outcome: incident asthma	3863 Netherlands children	LUR. NO ₂ , PM _{2.5} , soot: four times 2-week measurement in a year and then adjustment on temporal trend to calculate long-term average concentrations. Birth address	Association between PM _{2.5} concentration and incidence of asthma: 1.28 (1.10-1.49) (same results for NO ₂ and soot)	Atopy (specific IgE to 6 allergens), age	Non-adjusted models (due to small sample size) - Atopy: Non-atopic: NO ₂ , PM _{2.5} and soot: 1.85 (0.92-3.73), 2.98 (1.21-7.37) and 2.06 (0.99-4.3). Atopic: NO ₂ , PM _{2.5} and soot: 0.95 (0.64-1.40), 1.00 (0.63-1.58) and 0.97 (0.64-1.46). - Age: effect of air pollution on incidence of asthma was stronger at ages 6-8 years (OR ≈ 1.6, significant at 8, NS at 7 and borderline at 6 compared to OR ≈ 1.2 NS for younger age. Results available in a figure)
Carlsten, 2011, OEM, [17]	Intervention prenatal study. Recruitment during pregnancy in 1995, follow-up until 7 years of age. Outcome: incident asthma	184 children from Vancouver, at high risk for asthma	LUR. NO, NO ₂ , black carbon and PM _{2.5} . Year of exposure assessment: 2003, exposure of birth year estimated. Residential address	Elevation in exposure to some traffic-related air pollution during the year of birth is associated with new-onset asthma at 7. Results by quartile. Significant for last quartile only for PM _{2.5} . No significant results for the others pollutants, despite the increase	Sex, race	Suggestion of increase in males (data not shown) Suggestion of increase in Caucasians (data not shown)
Gruzdeva, 2013, BAMSE.	Swedish birth cohort Recruitment	4089 children	Gaussian dispersion model and wind model used to assess the concentration of PM ₁₀ and	Incidence of wheeze symptoms seems to be highest during the first 2 years of life.	Sex, allergic/non-allergic asthma (atopy assessed by specific IgE to 8 allergens), age	- Sex: no significant interaction <i>p</i> = 0.21 - Allergic/non-allergic asthma

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Epidemiology, [27]	between 1994 and 1996, follow-up during 12 years. Outcome: incident wheeze, incident asthma		NO _x . Years of exposure assessment: 1994 to 1998. Interpolation of concentrations for some years for NO _x . Residential, daycare and school addresses	Associations between exposure to NO _x or PM ₁₀ and incident asthma over the first 12 years of life: OR: 1.21 (0.79–1.84) for NO _x , OR: 1.34 (0.80–2.23) for PM ₁₀ . Results significant only at age 12		4 years: non-allergic asthma: OR (95 % CI) 1.6 (0.5–5.3) for PM ₁₀ and 2.4 (1.0–5.6) for NO _x . Allergic asthma: 1.4 (0.3–6.8) for PM ₁₀ and 1.5 (0.4–5.1) for NO _x 8 years: non-allergic asthma: 3.8 (0.9–16.2) for PM ₁₀ and 2.6 (0.9–8.1) for NO _x . Allergic asthma: 1.1 (0.3–3.8) for PM ₁₀ and 0.8 (0.2–2.4) for NO _x . (ref of OR: no asthma/no sensitization) - Age: in children aged 8 to 12 years: 2.0 (1.1–3.5) Incident asthma ORs: 1 years: 0.85 (0.44–1.62) for NO _x and 0.79 (0.39–1.62) for PM ₁₀ 2 years: 0.96 (0.51–1.80) for NO _x and 1.14 (0.57–2.25) for PM ₁₀ 4 years: 1.48 (0.85–2.57) for NO _x and 1.59 (0.83–3.05) for PM ₁₀ 8 years: 1.07 (0.53–2.14) for NO _x and 1.30 (0.61–2.74) for PM ₁₀ 12 years: 1.87 (1.01–3.44) for NO _x and 2.39 (1.18–4.86) for PM ₁₀
Nishimura, 2013, AJRCCM, [18]	GALA II (case control) and SAGE II. Recruitment between 2006 and 2011. Outcome: incident asthma	Latinos from urban regions in the USA and Puerto Rico and African Americans from SF bay, 3343 Latinos and 977 African Americans, with no history of other lung or chronic illness. 8–21 years	O ₃ , NO ₂ , SO ₂ , PM ₁₀ , PM _{2.5} . Inverse distance-squared weighted average. Residence address. Exposure over the first 3 years of life.	A 5-ppb increase in NO ₂ during the first year of life associated with incident asthma: OR (95 % CI) for the first year of life: OR ₁ : 1.17 (1.04–1.31). OR (95 % CI) for first 3 years of life: OR ₃ : 1.26 (1.07–1.48). NS for PM and O ₃	Sex, Total-IgE	-Sex: NO ₂ : OR ₁ : 1.26 (1.05–1.52) in boys, 1.11 (0.96–1.29) in girls; OR ₃ : 1.47 (1.05–1.52) in boys, 1.24 (1.02–1.50) in girls. PM ₁₀ : OR ₁ : 1.10 (0.89–1.36) in boys, 1.15 (0.97–1.37) in girls; OR ₃ : 1.08 (0.86–1.35) in boys, 1.19 (1.00–1.41) in girls. PM _{2.5} : OR ₁ : 0.92 (0.73–1.16) in boys, 1.13 (0.98–1.30) in girls; OR ₃ : 0.91 (0.77–1.06) in boys, 1.15 (1.02–1.30) in girls All <i>p</i> for interaction NS - Total IgE

Table 1 (continued)

First author, year, journal, reference	Design, study, outcome	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effect
Hsu, 2015, AJRCCM, [19•]	Pregnancy cohort. Recruitment between 2002 and 2009, follow-up to age 6 years. Outcome: incident asthma	736 full-term birth children, from Brigham and Boston	PM _{2.5} . Novel spatio-temporal model incorporating moderate resolution imaging spectroradiometer (MODIS) satellite-derived aerosol optical depth (AOD) measurements at a 10*10 km spatial resolution. Residence over pregnancy	Significant sensitive window of PM _{2.5} exposure around mid-pregnancy on asthma onset by age 6, specifically during 16-25-week gestation. OR: 1.09 (0.98-1.21)	Sex	NO₂: OR₁: 1.12 (0.93-1.36) in IgE <200, 1.20 (0.91-1.58) in IgE ≥200; OR₃: 1.19 (0.97-1.46) in IgE <200, 1.38 (0.90-2.12) in IgE ≥200 PM₁₀: OR₁: 1.12 (1.00-1.25) in IgE <200, 1.22 (0.97-1.55) in IgE ≥200; OR₃: 1.04 (0.83-1.29) in IgE <200, 1.35 (0.98-1.85) in IgE ≥200. PM_{2.5}: OR₁: 1.06 (0.93-1.21) in IgE <200, 1.00(0.85-1.17) in IgE ≥200; OR₃: 0.93 (0.72-1.21) in IgE <200, 1.10 (0.96-1.25) in IgE ≥200. All <i>p</i> for interaction NS Sex: Sensitive exposure window between 12-26-week gestations: boys: OR ≈ 1.2, significant, girls: OR ≈ 1.03, NS. Difference in log odds between boys and girls: significant in 14-20. Significant interaction between PM_{2.5} and sex (<i>p</i> = 0.01). OR (PM_{2.5}*boy) : 1.33 (1.05-1.69)

Abbreviations: OR: odds ratio, RR: risk ratio, HR: hazard ratio, CI: confidence interval, PM: particulate matter, NO₂: nitrogen dioxide, NOx: nitrogen oxide, O₃: ozone, IgE: immunoglobulin E, SPT: skin prick test, BHR: bronchial hyperactivity, NS: not significant, TRAP: traffic-related air pollution

Table 2 Description of studies assessing the association between air pollution exposure and incident asthma or wheeze in children (by year of publication) and that had stratified their analyses by possible susceptibility factors

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
Greer, 1993, JOM, [33]	Prospective cohort (California), AHSMOG. Recruitment in 1977, follow-up in 1987	3577 non-smokers Seventh-day Adventist. Mean age: 27-87 years	Monthly interpolations of O ₃ from fixed-site monitoring stations applied to residential addresses and work site. Year of exposure assessment: 1987	Borderline association of increased risk of asthma associated with increased ambient concentrations of ozone exposure (RR = 1.31, CI: 0.96-1.78)	Sex	Sex: increase in ambient concentrations of ozone exposure (mean ozone concentration exposure through 1987). RR: 3.12, CI: 1.61-5.85 in males, RR: 0.94 "not significant at 0.05 level" in females)
McDonnell, 1999, Environmental Research, [34]	Prospective cohort (California), AHSMOG. Recruitment in 1977, follow-up in 1987	3091 non-smokers Seventh-day Adventist (101 cases). Mean age: 27-87 years	O ₃ , PM ₁₀ , SO ₄ , NO ₂ , SO ₂ . Exposure concentrations interpolated to zip code according to home and work location, cumulated and averaged over time. For ozone and PM ₁₀ : alternative indices: 8-h average ozone concentration (work hours) Years of exposure assessment: 1973-1992	20 years O ₃ -8-h average associated with report of doctor diagnosis of asthma: RR 2.09 (1.03-4.16)	Sex, smoking status	- Sex: Males: RR: 2.09 (1.03-4.16), females: 0.86 (0.58-1.26) -Smoking: similar association for ex-smoking and never-smoking
Modig, 2006, ERJ, [20]	Case-control study. Recruitment between 1995 and 1999	203 cases/203 sex and age-matched controls from Lulea, Sweden. 20-60 years	Home outdoor NO ₂ measurements for 1 week, standardized and adjusted to represent annual average (for the year of recruitment). Traffic intensity at home address. Years of exposure assessment: 1999-2000	No association between NO ₂ level and asthma incidence [OR: 1.1(0.9-1.2)]. Living close to high traffic was non-significantly associated with asthma incidence	Atopy (defined as positive SPT : no more details)	Atopy: [Among those who live >2 years in the present home]: OR for an increase of 1 mg.m ⁻³ of NO ₂ : >0 SPT: 1.2 (1.0-1.3); <0 SPT: 1.0 (0.9-1.1)
Castro-Giner, 2009, EHP, [21]	Prospective cohort, in 13 cities from European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	2250 subjects. 20-44 years	NO ₂ dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Significant association between NO ₂ levels and new-onset asthma for the 120 subjects who developed asthma during the follow-up period (OR = 1.52; 95 % CI, 1.09-2.16)	Genetic variants <i>GSTM1</i> and <i>GSTT1</i> deletion <i>GSTP1</i> Ile105Val, <i>NQO1</i> (rs1800566, rs2917666) <i>TLR4</i> (5 SNPs) <i>TNFA</i> (3 SNPs) <i>ADRB2</i> (4 SNPs)	Genetic: homozygous for the <i>NQO1</i> rs291766 C allele: OR = 2.02 (1.16-3.73); subjects with CG/GG genotypes: OR = 1.26 (0.83-1.99). (<i>p</i> -value for interaction = 0.04)
Jacquemin, 2009, ERJ, [23]	Prospective cohort, in 17 cities from European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	4185 subjects. Analysis on 387 participants: having no asthma and no symptoms at baseline; 20-44 years	NO ₂ dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Outcome: score of symptoms of asthma, used as a tool to identify incidence of asthma. Ratio of the RMS after excluding participants with asthma and symptoms at baseline: 1.25 (1.05-1.51) for an increase of 10 mg.m ⁻³	Sex, smoking status, atopy (specific IgE to 4 allergens)	- Sex: males: 1.32 (1.12-1.56), females: 1.14 (0.97-1.34) (<i>p</i> -interact: 0.13) - Smoking status: never/ex-smokers: 1.30 (1.11-1.52). Current smokers: 1.07 (0.92-1.26) (<i>p</i> -interact = 0.005)

Table 2 (continued)

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
Jacquemin, 2009, Epidemiology, [22]	Prospective cohort, in 17 cities from 7 European countries (ECRHS). Recruitment in 1990-1994, follow-up: 1999-2001	4185 subjects, 20-44 years	NO ₂ dispersion model (1 × 1 km) for 2001 (APMoSPHERE model). Extrapolated to place of residence	Positive association between NO ₂ and asthma incidence [1.43 (1.02-2.01) per 10 mg.m ⁻³]. When known age of asthma onset between the 2 surveys: 1.72 (0.99-3.00)	Sex, atopy (specific IgE to 4 allergens)	- Atopy: without atopy: 1.20 (1.02-1.41). With atopy: 1.37 (1.14-1.65) (<i>p</i> -interact = 0.63) - Sex: OR per 10 mg.m ⁻³ increase of NO ₂ : Males: 1.31 (0.76-2.27). Females: 1.53 (0.99-2.38) (<i>p</i> -interact = 0.69) - Atopy: OR: 1.31 (0.84-2.04) per 10 mg.m ⁻³ increase of NO ₂ . No atopy: 1.57 (0.92-2.67) (<i>p</i> -interact = 0.77)
Künzli, 2009, Thorax, [24]	Prospective cohort in 8 Swiss areas (SAPALDIA). Recruitment in 1990-91 and follow-up in 2002	2725 never-smokers, without asthma or COPD. 18-60 years	Traffic-related PM ₁₀ (particulate matter up to 10 mg.m ⁻³ , TPM ₁₀) change, from 1990 and 2000 using the dispersion model. Exposure interpolated at participants' place	Incidence of asthma was associated with a change in PM ₁₀ in never-smokers. HR: 1.30 (1.05-1.61) per 1 mg.m ⁻³ change in PM ₁₀	Sex, atopy (SPT to 8 allergens), age, parental asthma, parental allergy, BHR, smoking status	Results in a figure (HR) - Sex: males OR ≈ 1.4, borderline, females: OR ≈ 1.25 NS (<i>p</i> interaction > 0.1) - Atopy: atopic: OR ≈ 1.35, significant, non-atopic: OR ≈ 1.2 NS (<i>p</i> interaction > 0.1). - Age: >40: OR ≈ 1.65, significant, ≤40 years: OR ≈ 1.3 NS. (<i>p</i> interaction > 0.1) - Parental allergy: OR ≈ 1.7 significant, no parental allergy: OR ≈ 1.3 NS (<i>p</i> -interact = 0.088) - Smoking status: ever-smoker: HR: 0.99 (0.64-1.53)
Modig, 2009, ERJ, [28]	Prospective cohort, 3 Swedish cities (RHINE). Recruitment in 1990, follow-up in 1999	3609 participants, 18-45 years	NO ₂ dispersion models (50 × 50 m), distance to major road <50 m. Both estimates at home address. Year of exposure assessment: 1990	Association between per 10 mg.m ⁻³ increase in NO ₂ and incident asthma [1.54(1.00-2.36)] Risk of developing asthma related to living close to a major road: 3.88 (1.93-7.82)	Sex, atopy (hay fever as proxy)	- Sex: OR for NO ₂ per 10 mg.m ⁻³ : Females: 1.67 (0.98-2.74), males: 1.32 (0.64-2.74) (<i>p</i> -interact = 0.63) - Hay fever status: OR for NO ₂ per 10 mg.m ⁻³ : subject with hay fever: 1.15 (0.59-2.24) Subject without hay fever: 1.79 (1.04-3.05) a (<i>p</i> -interact = 0.30)
Young, 2014, AJRCCM, [25]	Sister study, cohort. Recruitment: 2003-2009, follow-up 2008-2012	50884 US sisters of women with breast cancer, mean age: 55	PM _{2.5} and NO ₂ . National landuse/Kriging model incorporating roadway information. Addresses of the participants geocoded.	OR of incident asthma for an IQR increase of PM _{2.5} : 1.20 (0.99-1.46) and NO ₂ : OR: 1.12 (0.96-1.30). OR of incident wheeze for an IQR increase of PM _{2.5} : 1.14	Smoking status	Smoking status: Never/ex-smoker: 1.14 (1.04-1.24). Current smoker: 0.89 (0.74-1.06) (<i>p</i> interaction = 0.012)

Table 2 (continued)

First author, year, journal, reference	Design, study, follow-up	Population; age	Exposure assessment	Main association	Susceptibility factors	Modifying effects
Jacquemin, 2015, EHP, [26•]	6 prospective cohorts (ECRHS, EGEA, SAPALDIA, E3N, NHSD, SALIA).	23704 adults. Mean age: 60 years	Year of exposure assessment: 2006 ESCAPE project. NO ₂ , NOx, PM ₁₀ , PM _{2.5} , PM _{2.5} substance, PM _{course} . LUR model. Exposure estimated at participant's addresses. Back-extrapolated concentrations of NO ₂ and PM ₁₀ when necessary according to the year of the follow-up. Years of exposure assessment: 2010 or 2011	(1.04-1.26) and NO ₂ : 1.08 (1.00-1.17) Asthma incidence positively, but NS, associated with all exposure metrics, except for PM _{course} . OR: NO ₂ : 1.10 (0.99-1.21) per 10 mg.m ⁻³ , NOx: 1.04 (0.99-1.08) per 20 mg.m ⁻³ , PM ₁₀ : 1.04 (0.88-1.23) per 10 mg.m ⁻³ , PM _{2.5} : 1.04 (0.88-1.23) per 5 mg.m ⁻³ , PM _{2.5} substance: 1.06 (0.95-1.19) per 10-5/m. Traffic load: 1.10 (0.93-1.30). Traffic intensity: 1.10 (0.93-1.30). PM _{course} : 0.98 (0.87-1.14)	Sex, smoking status, age	- Sex: NO ₂ : Males: 1.06 (0.92-1.24). Females: 1.07 (0.97-1.19) (<i>p</i> -interact = 0.66). PM ₁₀ : Males: 1.00 (0.63-1.59) Females: 1.07 (0.91-1.26) (<i>p</i> -interact = 0.80) - Smoking status: NO ₂ : Ever-smokers: 1.13 (0.99-1.29). Never-smokers: 1.01 (0.88-1.16). (<i>P</i> -interaction = 0.35). PM ₁₀ : Ever-smokers: 1.17 (0.79-1.74). Never-smokers: 1.10 (0.87-1.39), <i>p</i> -interact = 0.69 - Age: NO ₂ : <50: 1.08 (0.96-1.21), >50: 1.02 (0.94-1.12). (<i>p</i> -interact = 0.88). PM ₁₀ : <50: 1.07 (0.86-1.32) and >50: 1.05 (0.78-1.42) (<i>p</i> -interact = 0.99)

Abbreviations: OR: odds ratio, RR: risk ratio, HR: hazard ratio, CI: confidence interval, PM: particulate matter, NO₂: nitrogen dioxide, NOx: nitrogen oxide, O₃: ozone, IgE: immunoglobulin E, SPT: skin prick test, BHR: bronchial hyperactivity, NS: not significant, TRAP: traffic-related air pollution

Age

In children, three studies stratified their analysis according to age, [11, 16, 27]. In children from Lancester aged 1-5 years at baseline [11], no evidence for a modifier effect of age (1-2.9 years vs. 3-4.9 years) was found. In a Netherlands birth cohort [16], a slightly higher association of air pollution and onset asthma at 6-8 years vs. younger (age at follow-up, no exact OR available, only OR showed in a figure) was found. Among children followed-up at 1, 2, 4 and 12 years of age in a Swedish birth cohort [27], an association between air pollution during the first year of life and asthma risk increased with age [OR (95 % CI)=1.48 (0.85-2.57) for NO_x and 1.59 (0.83-3.05) for PM₁₀ at 4 years of age at follow-up and 1.87 (1.01-3.44) for NO_x and 2.39 (1.18-4.86) for PM₁₀ at 12 years at follow-up].

In adults, we found only two studies stratifying the analysis of the association between air pollution and incident asthma according to age at baseline [24, 26•]. Among Swiss non-smokers [24], the association between traffic-related PM₁₀ and incident asthma was slightly higher among participants aged >40 years at baseline (OR ≈ 1.65 significant in >40 years, OR ≈ 1.3 NS in ≤40 years, no exact OR available, *p*-interact>0.1). In a meta-analysis of six European studies [26•], no difference was found in the association between NO₂ and incident asthma in participants with more or less than 50 years old at baseline.

In children as in adults, only few studies stratified according to age—whatever age at baseline or at follow-up—and no particular patterns were found, except perhaps stronger estimated effects among children between 6 to 12 years at diagnosis. As epidemiological studies are either conducted among adults or among children, and often focus on a specific age range, few studies stratify the results according to age. However it is of special interest that one study reported a higher incidence of asthma in children (even if only boys) who were more exposed in utero during 12-26 weeks of gestation, pointing out to a possible prenatal susceptibility window [19•]. This result is concordant with a study that found that prenatal exposure to air pollution was associated with long-term lung function deficits at preschool age [44].

Smoking

In children, we found no study that stratified according to passive smoking or maternal smoking. A study in children from Lancester, however, stated that the “effect of PM₁₀ on health outcomes did not depend on whether children were exposed to secondhand tobacco smoke (*p*-interaction>0.1)” [11]. Generally, this factor was taken into account in the adjusted models.

In adults, five studies stratified their analysis on smoking status, but classification of smoking was not homogeneous

across studies. An American study of women and a European study grouped never- and ex-smokers together. In both studies, they found a higher association between NO₂ and asthma or wheeze incidence among ex-/never-smokers: American study: OR (95 % CI)=1.14 (1.04-1.24) in never-/ex-smokers and 0.89 (0.74-1.06) in current smokers, *p*-interaction=0.01 [25]; European study: 1.30 (1.11-1.52) in never-/ex-smokers and 1.07 (0.92-1.26) in current smokers, *p*-interaction=0.005 [23]. The interactions were significant in both studies, but the first one only stratified according to smoking status for incident wheeze because of a lack of power for incident asthma, and this population was restricted to women. Another study conducted in seven European countries [26•] considered ex-smokers and current smokers together, and associations were slightly stronger for NO₂ among ever-smokers [OR (95 % CI): 1.13 (0.99-1.29)] than never-smokers [OR = 1.01 (0.88-1.16; *p*-interact=0.35)], and no difference was found for PM₁₀ in ever-smokers [1.17 (0.79-1.74)] versus never-smokers [OR = 1.10 (0.87-1.39)]. Among American non-smokers [34], the association between ozone and incident asthma was similar among ex-smokers and never-smokers, but stratification was only done for men. In another study, for non-smokers only [24], there was an association between traffic-related PM₁₀ and incident asthma among never-smokers [HR (95 % CI) =1.30 (1.05-1.61)] but no association among ex-smokers [HR =0.99 (0.64-1.53)]. They also reported no association between air pollution and asthma in smokers.

Overall, the association between air pollution and incident asthma according to smoking status was studied only in adults, and while the results were not always consistent, the effects of air pollutants on incident asthma seemed to be stronger among never-/ex-smokers. This susceptibility might be explained by the fact that any air pollution effect may be masked among smokers, who may already have a higher risk of asthma [45].

Atopic Status

Five studies stratified their analyses according to atopy status in children. Atopy status was defined according to the level of specific immunoglobulin E (IgE >35 kU/l) [13, 16, 27], positive skin-prick test (SPT) [29] or levels of total IgE (total IgE ≥200) [18]. Two birth cohorts [13, 16, 27] reported a stronger association between air pollution and incident asthma in non-atopic children: a Swedish birth cohort [13] reported an association between NO_x exposure and incident asthma in non-atopic children and no association in atopic children at age 4 [OR (95 % CI): 1.46 (1.00-2.13) in non-atopic, 1.11 (0.55-2.22) in atopic, *p*-interaction NS]. Another study conducted in the same birth cohort [27] reached similar results for exposure to PM₁₀ and NO_x and incident asthma at age 8 [OR (95 % CI) for NO_x: 2.6 (0.9-8.1) in non-atopic, 0.8 (0.2-2.4 in atopic)].

In a Dutch birth cohort [16], the association between NO₂, PM_{2.5} and soot and incident asthma was higher among non-atopic children at age 8, but in this study it was not possible to adjust for any type of confounding because of the small sample size [OR (95 % CI) for NO₂: 1.85 (0.92–3.73) in non-atopic, 0.95 (0.64–1.40) in atopic]. Contrary to all of these results, a French case-control study examined traffic density—expressed in tertiles—before age 3 [29], and associations between traffic density and incident asthma were stronger among atopic children, but with wide confidence intervals, and the results were probably mainly driven by the way they categorized exposure [tertile 1 as reference, OR (95 % CI): tertile 2: 0.61 (0.1–3.6) and tertile 3: 11.03 (1.3–100.9) and in non-atopic tertile 2: 1.23 (0.29–5.31) and tertile 3: 1.47 (0.32–6.97), *p*-interact=0.20]. Finally, in a study in children from the US and Puerto Rico [18], there was no differences in estimated effects according to low or high total IgE levels.

In adults, five studies stratified the analyses according to allergic sensitization. Atopy status was defined by a positive SPT [20, 24], high levels of specific IgE [22, 23] or using the report of hay fever as a proxy of allergic sensitization [28]. No difference according to atopic status was found in a European study, regardless of how asthma incident cases were defined: OR for NO₂: (95 % CI): 1.20 (1.02–1.41) in non-atopic, 1.37 (1.14–1.65) in atopic, *p*-interaction=0.63], using asthma symptom reports [23], and 1.31 (0.84–2.04) in atopic, 1.57 (0.92–2.67) in non-atopic, *p*-interaction=0.77, using asthma symptom scores [22]. On the one hand, a study in Swiss non-smokers [24] reported an association between TPM₁₀ concentration and asthma incidence among atopic but no association among non-atopic participants (OR ≈ 1.35 in atopic, CI higher than 1, OR ≈ 1.2, CI including 1 in non-atopic; OR available in a figure). In a Swedish case-control study [20], association only reached significance in atopic subjects [OR for NO₂ (95 % CI): 1.2 (1.0–1.3) in those with ≥1 SPT, 1.0 (0.9–1.1) in those with no SPT]; however, no significant associations were found for the whole population. On the other hand, in a prospective Swedish cohort [28], the association between NO₂ and asthma incidence was higher in participants without hay fever [OR (95 % CI): 1.15 (0.59–2.24) in those with hay fever, 1.79 (1.04–3.05) in those without, *p*-interaction=0.30].

Stratification according to atopy status was one of the most commonly assessed susceptibility factors, particularly in children. Estimated effects of air pollution on incident asthma seem to be stronger in non-atopic children' possibly because air pollution effects may be masked among atopic participants, a sensitive population who already is at higher risk of asthma. In adults, the results were too discordant to come to a conclusion. Allergic and non-allergic asthma could be two distinct diseases, and it can be hypothesized that the biological response to air pollution differs according to allergic sensitization. Furthermore, studying the effect of air pollution with and

without atopy may help to better understand the mechanism that air pollution exhibits on asthma.

Genetic Factors

Only two papers—both conducted in the same study—investigated interactions between genetic variants and air pollution on asthma incidence during childhood and adolescence [31, 32]. Among children from 12 Southern Californian communities, non-Hispanic white children carrying at least one “short” allele (<23 repeats) in the HMOX-1 gene and residing in low ozone communities had a twofold lower risk of new-onset asthma than those residing in high ozone communities: HR (95 % CI): 0.44 (0.23–0.83) for low-ozone communities, 0.88 (0.33–2.34) for high ozone communities, *p*-interaction=0.003 [31]. Associations did not vary according to children's participation in sports or time spent outside [31]. No interaction was found with PM₁₀ [31]. Among children from the same cohort, those homozygous for Ile105 in the *GSTP1* gene and playing more than two team sports had an increased risk of asthma, and the risk was highest in those living in high ozone communities: HR (95 % CI): 1.06 (0.3–4.0) in low-ozone communities, 6.15 (2.2–7.4) in high-ozone communities, *p*-interaction=0.10 [32].

In adults, only one study investigated interactions between genetic variants and NO₂ concentration on asthma incidence [21]: in a European prospective cohort, subjects homozygous for the *NQO1* rs291766 C allele were at greater risk for developing asthma due to air pollution compared with those with CG/GG genotypes [OR (95 % CI): 2.02 (1.16–3.73)] in those homozygous for the *NQO1* rs291766 C allele compared with those with CG/GG genotypes: OR (95 % CI): 1.26 (0.83–1.99), *p*-interaction=0.04.

Polymorphisms in few genes involved in xenobiotic metabolism or in the NRF2-mediated oxidative stress response modified associations between ozone and asthma incidence in children and adolescents and between NO₂ and adult onset asthma. No association was observed with PM, suggesting a different chemical mechanism of action between pollutants. Overall, results confirm the complex interplay among pollutants, ethnicity, exercise and antioxidant defenses on the development of asthma.

Familial Environment and SES

Among Californian children age 5–9 years at baseline [15], those exposed to a higher level of parental stress were more susceptible to the association between NO_x and incident asthma [HR (95 % CI): 1.51 (1.16–1.96) in high parental stress, 1.05 (0.74–1.49) in low parental stress, *p*-interaction=0.05], and this association was greater in boys. A stronger association was also found among children with low SES: 1.20 (0.93–1.55) in high SES, 1.55 (1.09–2.19) in low SES, *p*-

interaction = 0.25. In a US birth cohort [12], susceptibility due to exposure to violence was reported: associations between NO₂ concentration and incident asthma were stronger among children most exposed to violence [OR (95 % CI): 1.63 (1.14–2.33) lower than median exposure, 2.40 (1.48–3.88) above median].

In adults, we found no study that stratified according to SES.

Two studies included in our review reported that children with low SES or exposed to a harmful familial environment were at a higher risk of asthma due to air pollution, concordant with results related to short-term air pollution [46] or mortality [47] and with the fact that low SES has been traditionally associated with higher air pollution exposure even if recent studies found that this is not always the case [48]. The association between air pollution and SES still needs to be better understood to explore more effectively whether SES could be a susceptibility factor in the association between asthma and air pollution.

Some studies assessed others potential susceptibility factors. In Canadian children at high risk for asthma [17], the association between air pollution and incident asthma seemed stronger among Caucasian participants. In adults, two studies had looked at the association between air pollution and incident asthma according to baseline characteristic associated with asthma: wheeze [28] and BHR [23]. In a Swedish cohort, the association was positive among those with wheezing at baseline, but not in those without wheeze at baseline [28]. In the same way, in a European study, the association was positive and significant among those with BHR at baseline, whereas those without BHR at baseline had a nonsignificant association [23]. In a Swiss non-smokers population, the association between incident asthma and PM₁₀ level was higher among those with a parental history of allergy [24]. These results may suggest that participants who are already predisposed to develop asthma or at higher risk of developing asthma may be more susceptible to air pollution.

Overall Discussion and Conclusion

In this review, we identified 15 studies in children and 10 in adults with stratified analyses on potential susceptibility factors assessing associations between long-term exposure to air pollution and incident asthma. Overall, never-/former smoker adults seem to be more susceptible to air pollution in relation to incident asthma. Children without atopy seem to have a higher risk of incident asthma due to air pollution, as well as children with low SES. Some early studies also suggest a role for gene involvement in the response to oxidative stress.

We focused on incident asthma, but incident asthma is strongly associated with prevalent asthma, and as they share commons features, we could expect to find similar

susceptibility factors for both outcomes. Papers that had specifically studied susceptibility factors of the association between air pollution and prevalence of asthma found discordant results about sex [49, 50], parental asthma or allergic symptoms [50, 51]. As for incident asthma, it seems difficult to draw a firm conclusion on who could be more susceptible to the effects of air pollution. It also seems plausible that susceptibility factors involved in the association between air pollution and lung function have a role in the association between air pollution and asthma onset as lung function is an asthma-related phenotype. More previous studies investigated possible susceptibility factors in regard to air pollution and lung function. Downs et al. [52] showed that lung function in adults declined less in areas where air pollution improved more, but they did not find any interaction with sex, atopy or smoking status. Another study [53] reported that the association between NO₂ concentration and lung function decline was stronger among girls and older children, and stronger but not significantly so among children of high SES and in those exposed to parental smoking. However, the association was not modified by asthma status.

Surprisingly, very few studies have assessed the potential role of SES as a susceptibility factor in the association between air pollution and asthma incident, although asthma is known to be socially patterned [54] and SES is very probably associated with air pollution exposure [55]. We found no study with stratified analysis on BMI or dietary factors despite of the known association between BMI and asthma [43]. Several papers suggested that obesity can play a role in susceptibility to pollutants effects [41, 42] in lung function, and in a randomized trial [56] antioxidant intake was associated with a moderate impact of ozone exposure on lung function in children with moderate to severe asthma. Whereas susceptibility of older adults to the health effects of air pollution is well recognized, and particularly concerning lung function [57] where frailty was associated with a higher decline of forced vital capacity due to air pollution, we did not find a study stratifying according to these factors. Other potential susceptibility factors such as low birth weight, second-hand tobacco smoke or ethnicity have also been proposed in a recent review as risk modifiers of the association between air pollution and asthma in general [58•], but none of these were taken into account in the articles included in this review.

One of the limitations of this review is that most of the studies used different methodologies to assess air pollution exposure and also different definitions for some susceptibility factors. Some studies assessed the association between several pollutants and incident asthma, and correlations between pollutants were not always taken into account or reported. Some studies did not report the year of exposure assessment and did not clearly define the window of exposure. Whether in children or adults, half of the studies had considered the problem of participants having moved during the window of exposure

to air pollutants. Among those assessing this problem, several had conducted sensitivity analyses, and basically the results among non-movers were only either stronger or similar to those among all participants. Another limitation of this review is that several studies did not assess the interaction term related to the susceptibility factor, and for those who presented it, only a few reported a significant *p*-value. Among the 25 articles identified, a majority assessed air pollution exposure to NO₂ and few assessed PM or other pollutants, making it difficult to identify which pollutants could be more important for which susceptibility factor and not allowing the conducting of any meta-analyses. The definition of the susceptibility factors also differed according to the study; for example, for atopy some studies used IgEs, others SPT and others total IgE or concomitant allergic disease. In children, all studies that found stronger associations among non-atopic participants used specific IgEs to define atopy, while studies using other definitions did not find interactions between atopy and air pollution. Therefore, the question arises whether the results depend on the way atopy is defined. Differences in exposure or phenotypic characterization may explain, at least in part, the heterogeneity of results across studies.

Regarding genetic factors, it is now well established that asthma is due to a complex interplay of environmental and genetic factors. There have been considerable efforts to characterize the genetic determinants of asthma; however, the identified genetic factors explain only a small part of its genetic component. One of the reasons is that many genetic factors are likely to be involved in the development of asthma through complex mechanisms that involve interactions with environmental factors and with other genes through pathways or networks. Furthermore, the effect of such genetic factors may be missed if genes are considered alone, regardless of the biological functions they share or the pathways they are involved in [59]. Studies of candidate genes and long-term air pollution in relation to incident asthma are scarce, have only been conducted on genes involved in the response to oxidative/nitrosative stress and have explored a limited number of genes. Future studies should investigate a greater number of candidate genes selected from a pathway-based approach [60]. The gene selection process may need to integrate information on the biological processes shared by genes, the pathways to which genes belong and the biological knowledge related to the environmental exposure under study.

Overall, so far no clear susceptibility factors concerning the relation between outdoor air pollution and incident asthma have been established. Discordant results could be due to misclassification of exposure, such as not taking into account time-activity patterns, as is usually the case in epidemiological air pollution studies. Among the papers included, no study was explicitly designed to assess susceptibility factors concerning the association between air pollution and incident asthma. Few studies had enough power to stratify or find

significant interaction terms. A major challenge in the future would be to have studies specifically designed, or pooling data from existing studies, to address the role of susceptibility factors in the association between air pollution and asthma and also to explore which pollutant is the most relevant for which susceptibility factors. For this purpose, we would need both a detailed characterization of the disease together with a precise modeled individual exposure to air pollution and a better definition of some susceptibility factors such as atopy or smoking.

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Compliance with Ethical Standards

Conflict of Interest Emilie Burte, Rachel Nadif and Bénédicte Jacquemin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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