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Exposure to Traffic-related Air Pollution and Risk of Development of Childhood Asthma: A Systematic Review and Meta-analysis

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Running title

Traffic-related air pollution and childhood asthma development.

Supplementary Materials

PRISMA Checklist, Note 1 (dealing with overlaps between studies populations and pooled analyses), CASP Checklist, Note 2 (quality assessment), Figure S2: BC fixed-effects meta-analysis, Figure S3: NO_2 fixed-effects meta-analyses, Figure S4: NO_x fixed-effects meta-analyses, Figure S5: $PM_{2.5}$ fixed-effects meta-analyses, Figure S6: PM_{10} fixed-effects meta-analyses, Figure S8: NO_2 funnel plot – fixed-effects meta-analysis, Figure S9: NO_x funnel plot – fixed-effects meta-analysis, Figure S10: $PM_{2.5}$ funnel plot – fixed-effects meta-analysis, Figure S11: PM_{10} funnel plot – fixed-effects meta-analysis, Table S1: Exposure models under TRAP surrogates and associated original risk estimates, Table S2: Exposure models under TRAP at fixed-site monitoring stations and associated original risk estimates, Table S3: Exposure models under TRAP by LUR modelling and associated original risk estimates, Table S4: Exposure models under TRAP by dispersion modelling and associated original risk estimates, Table S5: Exposure models under TRAP measured at the individual residential level and associated original risk estimates, Table S6: Exposure models under TRAP by satellite imagery and associated original risk estimates, Note 3 (sex differences), Table S7: Differences in TRAP effects on atopic and non-atopic asthma.

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Competing financial interests

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Abstract

Background and objective: The question of whether children's exposure to traffic-related air pollution (TRAP) contributes to their development of asthma is unresolved. We conducted a systematic review and performed meta-analyses to analyze the association between TRAP and asthma development in childhood.

Data sources: We systematically reviewed epidemiological studies published until 8 September 2016 and available in the Embase, Ovid MEDLINE (R), and Transport databases.

Study eligibility criteria, participants, and interventions: We included studies that examined the association between children's exposure to TRAP metrics and their risk of 'asthma' incidence or lifetime prevalence, from birth to age 18 years old.

Study appraisal and synthesis methods: We extracted key characteristics of each included study using a predefined data items template and these were tabulated. We used the Critical Appraisal Skills Programme checklists to assess the validity of each included study. Where four or more independent risk estimates were available for a continuous pollutant exposure, we conducted overall and age-specific meta-analyses, and four sensitivity analyses for each summary meta-analytic exposure-outcome association.

Results: Forty-one studies met our eligibility criteria. There was notable variability in asthma definitions, TRAP exposure assessment methods and confounder adjustment. The overall random-effects risk estimates (95% CI) were 1.08 (1.03, 1.14) per 0.5 x 10^{-5} m^{-1} black carbon (BC), 1.05 (1.02, 1.07) per 4 $\mu g/m^3$ nitrogen dioxide (NO_2), 1.48 (0.89, 2.45) per 30 $\mu g/m^3$ nitrogen oxides (NO_x), 1.03 (1.01, 1.05) per 1 $\mu g/m^3$ Particulate Matter less than 2.5 micrometers in diameter ($PM_{2.5}$), and 1.05 (1.02, 1.08) per 2 $\mu g/m^3$ Particulate Matter less than 10 micrometers in diameter (PM_{10}). Sensitivity analyses supported these findings. Across the main analysis and age-specific analysis, the least heterogeneity was seen for the BC, some heterogeneity for $PM_{2.5}$ and PM_{10} estimates and the most heterogeneity for NO_2 and NO_x.

Limitations, conclusions and implication of key findings: The overall risk estimates from the meta-analyses showed statistically significant associations for BC, NO_2, $PM_{2.5}$, PM_{10} exposures and risk of asthma development. Our findings support the hypothesis that childhood exposure to TRAP contributes to their

development of asthma. Future meta-analyses would benefit from greater standardization of study methods including exposure assessment harmonization, outcome harmonization, confounders' harmonization and the inclusion of all important confounders in individual studies.

Systematic review registration number: PROSPERO 2014: CRD42014015448

Keywords: asthma, childhood, traffic-related air pollution, meta-analysis, black carbon, transport policy

Introduction

Asthma is a complex and heterogeneous chronic inflammatory disease of the airways [1, 2]. The condition is conservatively estimated to affect 334 million people worldwide [3].Numerous studies show that the prevalence of childhood asthma has increased dramatically since the 1950s, with some suggestion of plateauing in developed regions [4-10]. The factors driving these increases are largely unknown, but coinciding changes in environmental exposures are thought to be responsible [11].

One putative environmental exposure is humans' exposure to ambient air pollution. Although there is sufficient evidence that ambient air pollution can exacerbate pre-existing asthma across a variety of outcomes [12-14], the role of air pollution exposure in the initial development of asthma is as yet contested [15-18], partly as a result of the difficulty in conducting adequate epidemiological studies required to address this question.

Earlier reviews have effectively excluded ambient air pollution as a plausible cause of the rise in asthma incidence, with one argument being that the available evidence was inconsistent [19]. Furthermore, previous studies showed that asthma prevalence did not mirror changes in ambient air pollution concentrations, and reductions in levels of sulfur dioxide (SO_2) and total suspended particles (TSP), for example, seemed to synchronize with rapid increases of the condition [15, 16, 20, 21]. However, positive associations were subsequently shown between incidence and prevalence of asthma and wheeze and exposure contrasts at the intra-urban scale, mainly dominated by traffic-related air pollution (TRAP) [22-26]. Traffic-related air pollutants are ubiquitous, are of different chemical and physical nature compared to the classical air pollution mix associated with domestic heating and power plants, and thus necessitate specific examination.

Early-life and childhood could represent critical exposure windows for asthma development due to the plasticity and susceptibility of target organs and systems during these developmental periods and the long maturation period of the respiratory, immune and detoxification systems [27-30]. Moreover, when compared to adults, infants and children exhibit higher ventilation rates [28], reduced nasal deposition efficiencies for inhaled particles [31], are more typically mouth-breathers invalidating the nasal filtering and conditioning of the inhaled air in temperature and relative humidity [30], and tend to be more active outdoors where their exposure to TRAP is generally higher [14, 30].

Objective

In this systematic review and meta-analysis, we provide an up-to-date synthesis of observational epidemiological studies that examined the association between TRAP exposures (exposure) and the subsequent development of asthma (outcome) in children from birth to 18 years of age (participants). We hypothesize that childhood exposure to TRAP increases the risk of subsequent asthma development.

Four meta-analyses were previously published on asthma and TRAP [22-24, 26]. Unlike these analyses, our review is specifically focused on TRAP exposures and childhood asthma development only. Studies of TRAP exposures and childhood wheeze, included by Gasana et al. [22], Anderson et al. [23] and their follow-up synthesis by Favarato et al. [26], were not included in our analyses as childhood wheeze is a non-specific symptom, represents different disease patterns at different ages [32-34], and can feasibly preclude making a distinction between the onset of asthma and its exacerbation [25]. Studies of TRAP exposures and childhood allergies and sensitization, included in Bowatte et al. [24] were excluded as there is emerging evidence that the importance of atopy has been overemphasized and is much less relevant in asthma pathogenesis than previously believed [35-37]. Finally, we did not limit our inclusion criteria to a single traffic-related air pollutant as done in Favarato et al. who studied nitrogen dioxide only [26], but included a wider range of traffic-related air pollutants and TRAP metrics.

This paper followed the state-of-the-art methodology adopted by the Health Effects Institute's (HEI) in 2010 that synthesized case-control and cohort studies published before October 2008 and specifically focused on TRAP exposures as a potential cause for childhood asthma development [25]. In this paper, we update the HEI's synthesis by extending the search cut-off point to September 2016; adding 34 new studies to the HEI report and 30 new studies to the latest meta-analysis published on this topic [24]. With the inclusion of these newer studies, we extend the HEI synthesis by deriving meta-analytic summaries pooling the most homogenous risk estimates, and explore the consistency of findings across the range of studies. The aims of the meta-analyses were to increase power to detect (small sized) associations, to quantify the relationship between TRAP and development of childhood asthma with increased precision and to explore the effects of different pollutants and the potential drivers of heterogeneity.

Methods

We conducted this systematic review in accordance with established guidance published by the University of York's Centre for Reviews and Dissemination [38]. We registered the protocol on PROSPERO documenting our methodological approach a priori [39]. We completed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [40],attached in the supplementary material.

Search Methods

Searches were performed on 8th September 2016 via OvidSP (http://ovidsp.ovid.com/). We searched the following databases: Embase, Ovid MEDLINE (R) and Transport Database. Relevant studies were identified using four sets of keyword combinations:

1. 'Child*' AND 'air pollution' AND 'asthma';
2. 'Child*' AND 'air quality' AND 'asthma';
3. 'Child*' AND 'vehicle emissions' AND 'asthma'; and
4. 'Child*' AND 'ultra-fine particles' AND 'asthma'.

We applied no limits on the initial publication date or language. We hand searched the reference lists of all included studies and of previous reviews on this topic [14, 16, 22-26, 41-43]. We contacted authors of unpublished studies (abstracts only) and authors of the most recurrent studies. This resulted in the inclusion of 2 extra studies [44, 45]. We searched Google for any other material related to "traffic-related air pollution and childhood asthma", and 1 further study was identified [46]. Studies were exported into an Endnote X7.4 library and duplicates automatically removed.

Inclusion Criteria

We selected studies that met all of the following criteria:

1. Were published epidemiological/observational studies including case-control, cohort and cross-sectional studies which all can offer evidence on risk factors for disease onset if designed accordingly.
2. Explicitly specified the term 'asthma' as an outcome for investigation;

3. Examined the childhood exposure from birth until 18 years old [47] to any designated TRAP metric or established traffic-related air pollutant including carbon monoxide (CO), elemental carbon (EC), nitrogen oxides (NO_x), nitric oxide (NO), nitrogen dioxide (NO_2), hydrocarbons, Particulate Matter less than 2.5 micrometers in diameter ($PM_{2.5}$), Particulate Matter less than 10 micrometers in diameter (PM_{10}), Particulate Matter between 2.5 and 10 micrometers in diameter (PM_{coarse}), Ultra-Fine Particles (UFPs) or $PM_{2.5}$ absorbance as a marker for black carbon (BC) concentrations [48, 49]; and
4. Examined and reported associations between preceding exposure to TRAP and subsequent risk of asthma reported as incidence or lifetime prevalence from birth until 18 years old.

We considered asthma development as new asthma reported between two or more follow-ups or as asthma reported over the lifetime in birth cohort studies or cross-sectional studies. The case-control studies included either looked at lifetime asthma as a measures of asthma development (i.e. similar to birth cohorts), or excluded children with a history of asthma in the control groups (i.e. similar to the cohort studies). In all instances, the exposure to TRAP had to precede the outcome to ensure the correct temporal sequence of events. For example, associations between birth year exposure and lifetime asthma prevalence in cross-sectional studies were considered as associations between TRAP exposure and asthma development. As such, studies that investigate asthma incidence and those that investigate asthma lifetime prevalence were included [25]. We ultimately excluded all non-English-language papers including a Czech, French and a Russian paper due to translation difficulties [50-52].

We included studies reporting pooled or multicenter analyses. This decision was made in line with the calls for greater standardization of cohort methods [23], and combined analyses of standardized data to obtain more accurate exposure-response estimates [53]. Furthermore, some cohort- and outcome-specific associations included in these pooled or multicenter analyses had not been previously published in individual studies [53], and hence provided new information. Cohort-specific associations were extracted from papers reporting pooled or multicenter analyses as individual studies. Specific attention was given to whether these studies should be included in the meta-analysis to avoid duplication.

We excluded studies that:

1. Were reviews, commentaries, governmental reports, letters, animal and experimental studies;

2. Only examined adulthood asthma;
3. Only examined non-traffic-related air pollutants or air pollution metrics including ozone (O_3), SO_2, indoor air pollution, proximity to point sources and woodsmoke;
4. Only examined the association between the exposure to TRAP and asthma exacerbations, severity, or other allergic or respiratory diseases and symptoms;
5. Only examined the association between the exposure to any TRAP metric in utero and risk of subsequent asthma development. Such effects may be a result of the mother's exposure rather than the fetus (e.g. epigenetic changes), and warrant distinction; and
6. Only examined associations between concurrent exposure to TRAP and risk of asthma reported as incidence or lifetime prevalence from birth until 18 years old.

Studies Selection

Titles and abstracts of all records were screened by HK. A random 20% were independently screened by CK. All potentially relevant studies were retrieved and full-papers reviewed against the inclusion criteria by HK with a random 50% independently reviewed by MN.

Data Extraction

Data was extracted by HK using a predefined data template (described in Khreis et al. (2016) [39]) . A random 20% was independently extracted (CK and JT). Data was primarily extracted from the main papers of the included studies, and where necessary information was missing from the main papers, data was extracted from the supplementary materials [17, 34, 44, 54-67], and associated publications [68-80]. Data extraction was undertaken manually.

Quality Assessment

Using the checklists and procedure provided in the Critical Appraisal Skills Programme (CASP) [81], we evaluated each study's validity across six key parameters: (1) potential for selection bias; (2) outcome measurement or classification bias; (3) exposure measurement, recall or classification bias; (4) identification of and adjustment for important confounders; (5) length and completion of follow-up and (6) any special characteristics. The CASP checklists are given in the form of 11 and 12 questions for cohort and case-control

studies, respectively, and are designed to help the assessor think about the validity of each study and are answered by a 'yes', 'no' and 'can't tell'. The cohort study checklist was used for cross-sectional studies. All included papers were independently evaluated (HK and MN).

Meta-analysis

We conducted random-effects meta-analyses to summarize the risk estimates across the range of studies, as they account for within study variance caused by chance and sampling error, but also for between studies variance caused by heterogeneity [82], a feature that is likely to be present in studies of TRAP exposures and asthma development [25]. All analyses were also performed using fixed-effect models as sensitivity analyses.

Figure 1 shows how studies were selected for inclusion in the meta- analysis. Meta- analyses were conducted by pollutant. Only studies that specifically measured or modelled the exposure to a traffic-related air pollutant and reported adjusted hazard ratios (HR), risk ratios (RR) and odds ratios (OR) for the risk of asthma per increment change in pollutant concentration were included. HH, RR and OR were all included in the same meta-analyses, following previous practice [23], and being acceptable in the present situation where the outcome is interest is common whilst the effect size is small [83]. Although no guideline exists for the minimum number of studies needed for a meta-analysis [84], we considered four risk estimates for a pollutant–outcome pair the minimum to justify running a meta-analysis and to enable running subsequent sensitivity analyses excluding the study that contributed to the largest weight (the smallest standard error) to test the robustness of findings, excluding case-control and cross-sectional studies, where the potential for selection bias is higher, and excluding studies with special characteristics that might compromise the generalizability of findings (e.g. high-risk birth cohorts).

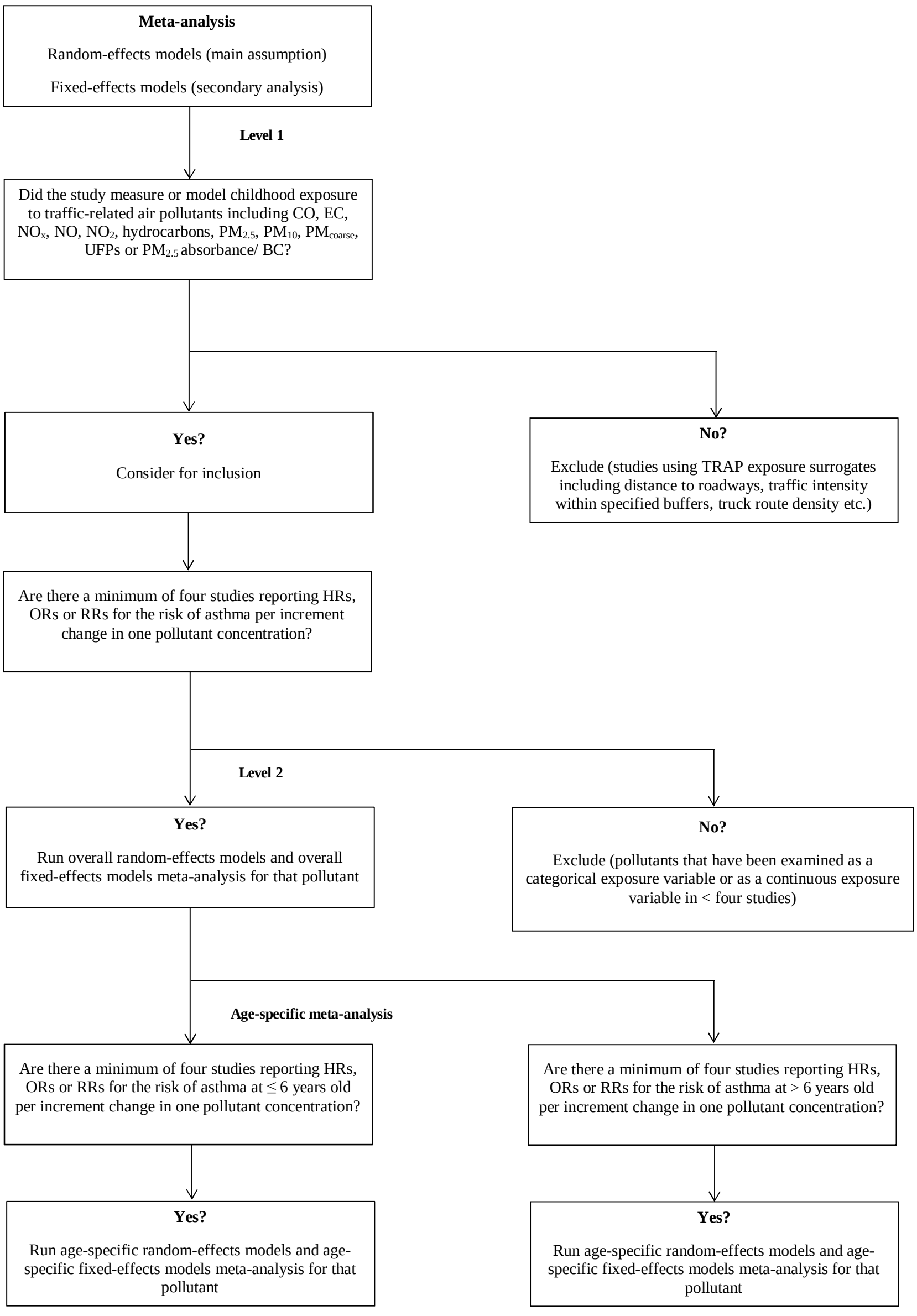


Figure 1. Study selection process for meta-analysis

Associations with five pollutants were reported in at least four studies. Adjusted risk estimates and their 95% Confidence Intervals (CI) were standardized into the following concentration increments:

- 0.5×10^{-5} m^{-1} BC;
- 4 $\mu g/m^3$ NO_2;
- 30 $\mu g/m^3$ NO_x;
- 1 $\mu g/m^3$ $PM_{2.5}$; and
- 2 $\mu g/m^3$ PM_{10}.

We selected the BC and NO_x concentration increment to approximately equal 10% of the maximum concentrations encountered in the included studies (maximum BC $\approx 6 \times 10^{-5}$ m^{-1}, maximum $NO_x \approx 300$ $\mu g/m^3$). The remaining concentration increments represent 10% increments of the World Health Organization (WHO) Air Quality Guideline values [85]. We used the WHO conversion factor between parts per billion (ppb) and $\mu g/m^3$ NO_2 to convert studies into the same metric (1 ppb = 1.88 $\mu g/m^3$ NO_2) [86].

The first series of meta-analyses ('overall meta-analysis') pooled all available risk estimates for associations between pollutants and asthma, without regard to age of onset. This approach is limited due to the broad age range at which effects estimates have been combined, but was used to maximize power to detect associations and heterogeneity. To ensure no study is double counted in the meta-analysis, a number of selection criteria applied to multiple publications using the same population, pooled analysis of multiple cohorts and publications with overlap between study populations (as explained in the supplementary material). The second series ('age-specific meta-analysis') pooled all available risk estimates for associations between pollutants and asthma split into two age groups to examine age differences: (a) asthma at ≤ 6 years old (pre-school age), and (b) asthma > 6 years old (school age). This cut-off age was used as there is general consensus that asthma is more readily diagnosed after 'school age'. Where multiple publications used the same population within the same age group [32, 73, 87-90], only the most recent publication was included [73, 87, 90].

Where more than one risk estimate per pollutant was reported in a study, we selected for inclusion the risk estimate that: (1) related to the earliest exposure window (e.g. birth address exposure vs. current/time-varying/later address exposure) [17, 49, 55, 57, 60, 62, 66, 91]; (2) was most inclusive in capturing asthma over the follow-up (e.g. incidence over 2 years vs 1 years) or that which emerged from the most recent follow-up [57,

66, 87]; (3) related to the most restrictive asthma definition [55]; (4) related to the most restrictive analysis model (e.g. including adjustment for indoor environmental factors or indirect adjustment for smoking) [18, 91]; (5) related to the total population in the wider geographical area [32, 60, 92, 93]; (6) related to the annual exposure (vs seasonal exposure) [94]; (7) was estimated using the exposure model with the higher spatial resolution [54, 55], and (8) related to the total exposure from traffic (vs separate freeway, nonfreeway, home and school exposures) [59]. We made these decisions with the aim of selecting the time period hypothesized to be most relevant for asthma development and pooling risk estimates that are most alike; conservative and reliable.

The natural logarithm of each risk estimate and its standard error (SE) were calculated and entered into RevMan version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Using the generic inverse variance method, each standardized risk estimate was weighted by the study's inverse variance in the fixed-effects models, whilst adjusting its SE to incorporate a measure of the extent of heterogeneity across studies in the random-effects models [95]. For assessing heterogeneity, the I^2 statistic [96], and the P-value from the Chi-squared test of heterogeneity were used. We considered an I^2 value $\geq 50\%$ to suggest substantial heterogeneity and a P-value ≤ 0.1 to suggest the presence of statistically significant heterogeneity [95]. We visually examined publication bias with funnel plots using SE as the measure of study size [97].

Results

Our search yielded 4,276 unique articles and from this, 94 records were identified for full-text review (Figure 2). 41 studies, published between 1999 and September 2016, met our inclusion criteria, 18 of which emerged after year 2014. Table 1 provides a summary of each study. Ages of participants ranged from 1 to 18 years old, except in Nishimura et al. 2013 [60] where 3% of the participants were 19-21 years old. We included this study as the substantial majority of participants fell within the pre-specified age range. Sample sizes ranged from 184 [98] to 1,133,938 [91]. Follow-up periods ranged from 1 to 16 years [17]. Seventeen studies were conducted in Europe, 11 in North America, 5 in Japan, 3 in China and 1 in each of Korea and Taiwan. The remaining three articles reported on pooled analysis from multiple combined cohorts, mainly conducted in Europe [17, 66, 67], and used harmonized outcome definitions, exposure assessments, and statistical methods as part of the Mechanisms of the Development of Allergy (MedALL) [99], the Traffic, Asthma and Genetics Study (TAG) [100], and the European Study of Cohorts for Air Pollution Effects (ESCAPE) [101] consortiums.

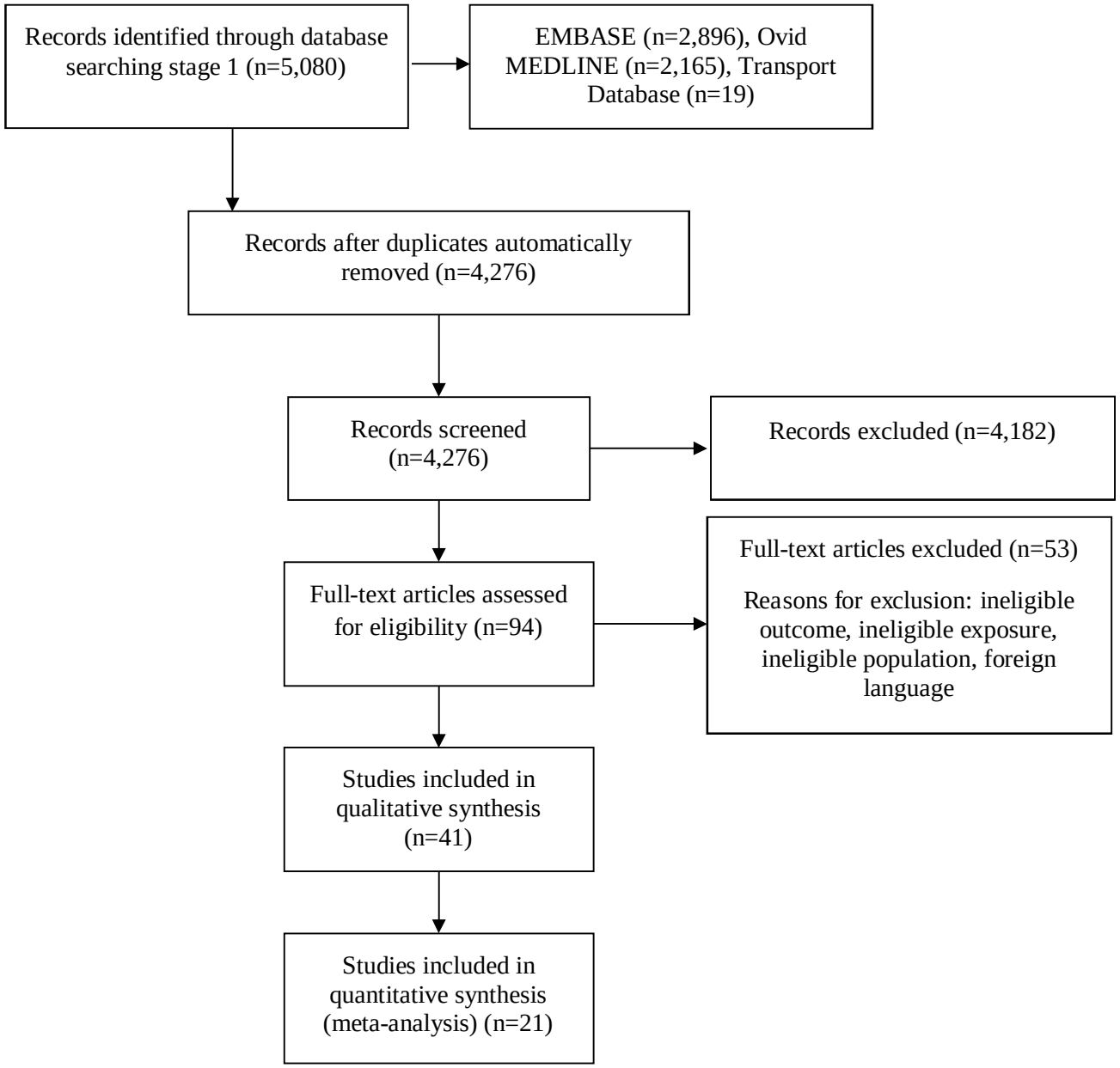


Figure 2. Flow chart of study screening process

31 studies were cohort (24 of which were birth cohorts), 6 studies were case-control (2 of which were nested in a birth cohort), and 4 studies were cross-sectional. In the 26 studies utilizing birth cohort data; we assumed that new cases of asthma were captured by study design. This assumption is in line with one (debated) biological paradigm that assumes children to be born asthma-free, and that with time, some will develop the condition because of exogenous and endogenous factors [25]. The 7 non-birth cohort studies made a distinction between incident asthma arising during follow-up and latent asthma which might have only been triggered by TRAP. As such, studies conducted within the Southern California Children's Health Study by Jerret et al. 2008 [94] and McConnell et al. 2010 [59] excluded children with a current, lifetime or missing/unknown history of asthma and wheeze at entry. Children with a current or history of asthma at the baseline survey were also excluded from the respective asthma incidence analysis in the 5 Japanese studies [46, 89, 90, 102, 103]. We included the 4 cross-sectional studies [18, 29, 45, 104] as lifetime asthma diagnosis was used as the outcome measure, in association with TRAP exposures predating the diagnosis. Finally, the 4 case-control studies which were not nested in birth cohorts were specifically designed to study incident asthma in association with TRAP exposures predating the diagnosis [55, 60, 105, 106].

Asthma Definitions

In line with our inclusion criteria, all the included studies, except Gehring et al. 2002 [32] and Morgenstern et al. 2007 and 2008 [73, 93], explicitly included the term ‘asthma’ as one outcome for their investigation. These 3 studies did not examine TRAP associations with the outcome ‘asthma’ (doctor-diagnosed asthma) as its prevalence was not sufficiently high in their young populations (< 1%). Instead, they analyzed ‘doctor-diagnosed asthmatic/spastic/obstructive bronchitis’, reflecting the more cautious diagnosis pattern found in German pediatricians who are reluctant to label a preschool-aged child as asthmatic [17, 25], and so were included. In the remaining studies, the operational definitions of ‘asthma’ varied reflecting the lack of a ‘gold standard’ for the measurement of the condition [107]. Most studies (17) exclusively relied on responses to questionnaires using parental- or self-reporting of doctor-diagnosed asthma. 21 studies used a variety of definitions of asthma as shown in Table 1; notably including more restrictive definitions e.g. combining doctor-diagnosis with symptoms and/or recent asthma medication prescriptions or use, or with symptoms and bronchial hyperreactivity or positive methacholine challenge test. Other definitions included pediatricians’ diagnosis, combining recurrent symptoms with response to β-agonist and/or anti-inflammatories, using disease codes

appearing in claim records or doctor billing records from primary care and hospital discharges, and using registry data on dispensed asthma medication. 5 studies classified asthma into its two classical phenotypes: atopic and non-atopic, using asthma diagnosis combined with blood Immunoglobulin E (IgE) levels to common aero- and food allergens [17, 56, 57, 60, 66].

TRAP Exposure Assessment Methods and Pollutants Studies

The exposure to TRAP was assessed using various models but most studies (22) used land-use regression (LUR) models. One study employed satellite imagery as a new technique for estimating particles exposure [91]. An in-depth review of these models' quality and performance can be found elsewhere [25, 108]. To explore whether consistency of results across the range of studies was based on the methodological quality of the exposure assessment [109], we categorized the TRAP exposure assessment into 4 methods. This was to group the available risk estimates under similar exposure models to give an indication whether part of the differences in findings is attributable to differences in exposure assessment.

1. TRAP surrogates (e.g. proximity to roadways): 16 studies (Table S1);
2. Traffic-related air pollutant concentrations measured at fixed-site monitoring stations: 11 studies (Table S2);
3. Traffic-related air pollutant concentrations estimated by LUR modelling: 22 studies (Table S3) and by dispersion modelling: 7 studies (Table S4);
4. Traffic-related air pollutant concentrations measured at the individual residential level: 1 study.

In studies using measured or modelled pollutant concentrations in main analyses to represent TRAP exposures: NO_2 was the pollutant most studied (31 studies), followed by $PM_{2.5}$ (18 studies), $BC/PM_{2.5\ absorbance}$ (15 studies), and PM_{10} (14 studies). Less frequently studied pollutants were NO_x (6 studies), EC (4 studies), CO (3 studies), PM_{coarse} (3 studies), NO (2 studies), and several particulate matter composition elements including copper (Cu), iron (Fe), zinc (Zn), nickel (Ni), sulfur (S), and vanadium (V); each of which investigated in two studies [63, 110]. No study was found to examine UFPs effects on onset asthma, yet one study investigated associations with Oxidative potential (OP), a measure of the inherent capacity of fine particulate matter to oxidize target molecules [44]. In studies employing LUR modelling to estimate TRAP, we found evidence that the models'

validity differs across pollutants. LUR models captured the variability in mean BC and NO_2 concentrations best and were less adequate in estimating $PM_{2.5}$ (Table S3).

TRAP exposures were almost exclusively assigned based on the participants' residential addresses, with a few exceptions where routine measurements from fixed-site stations near schools [89, 90], and children's nurseries [18, 29] were used to represent exposures. Only 8 studies, 5 of which published after 2014, considered children's mobility at older ages and assigned time-weighted TRAP exposures at daycare-centers and schools [46, 57, 59, 65, 103, 106] and other locations where the child spends significant time [34, 111], alongside residence.

Quality Assessment

Results from the CASP assessment are attached in the supplementary material. Overall, we considered that the selected studies are of a good quality to make an appropriate evaluation of the relationship between TRAP and asthma development, as mainly reported by questionnaires. Some of the limitations identified relate to non-representative samples, evaluating asthma by questionnaires and not adjusting for important confounders.

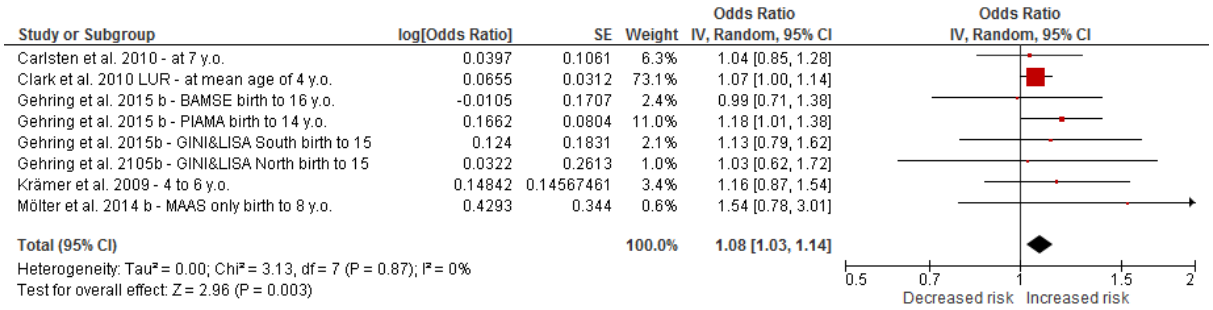
Meta-analytic Summary Risks Estimates

Results from the random-effects meta-analysis are shown in Figures 3-7. Results from the fixed-effects meta-analysis are shown in Figures S2-S6. Both random- and fixed-effects meta-analyses results are numerically presented in Table 2, alongside the heterogeneity parameters and the number of studies included in each analysis. Results from the sensitivity analyses are also given in Table 2. The funnel plots are shown in Figures S7-S11. Overall results for each pollutant are described next.

Risks in Association with BC Exposures

In the overall meta-analysis for BC, the random-effects overall risk estimate for asthma development was statistically significantly increased (for 0.5×10^{-5} m^{-1} BC, overall risk estimate = 1.08, 95% CI 1.03, 1.14), with 0% estimated heterogeneity (Figure 3). Results from the fixed-effects model were comparable (Figure S2). The overall risk estimate remained increased and statistically significant, with no estimated heterogeneity, in all sensitivity analyses. In the age-specific meta-analysis, the random-effects overall risk estimate was also statistically significantly increased for both age groups, but heterogeneity increased in the ≤ 6 years' old. The

363 overall risk estimate was generally robust in sensitivity analyses, although the PIAMA cohort was driving the
364 associations in the older age group (Table 2).



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366 Figure 3. BC random-effects meta-analysis. Individual and summary random-effects estimates for associations between BC per 0.5 x 10^{-5} m^{-1}
367 and asthma at any age.

368 **Risks in Associations with NO_2 Exposures**

369 In the overall meta-analysis for NO_2, the random-effects overall risk estimate for asthma development was
370 statistically significantly increased (for 4 µg/m^3 NO_2, overall risk estimate = 1.05, 95% CI 1.02, 1.07). There
371 was substantial and statistically significant heterogeneity (Figure 4). Results from the fixed-effects model were
372 comparable (Figure S3). Random-effects overall risk estimate remained statistically significantly increased in all
373 sensitivity analyses. In the age-specific meta-analysis, the random-effects overall risk estimate was increased
374 and statistically significant for both age groups. Heterogeneity remained high in both analyses (Table 2).

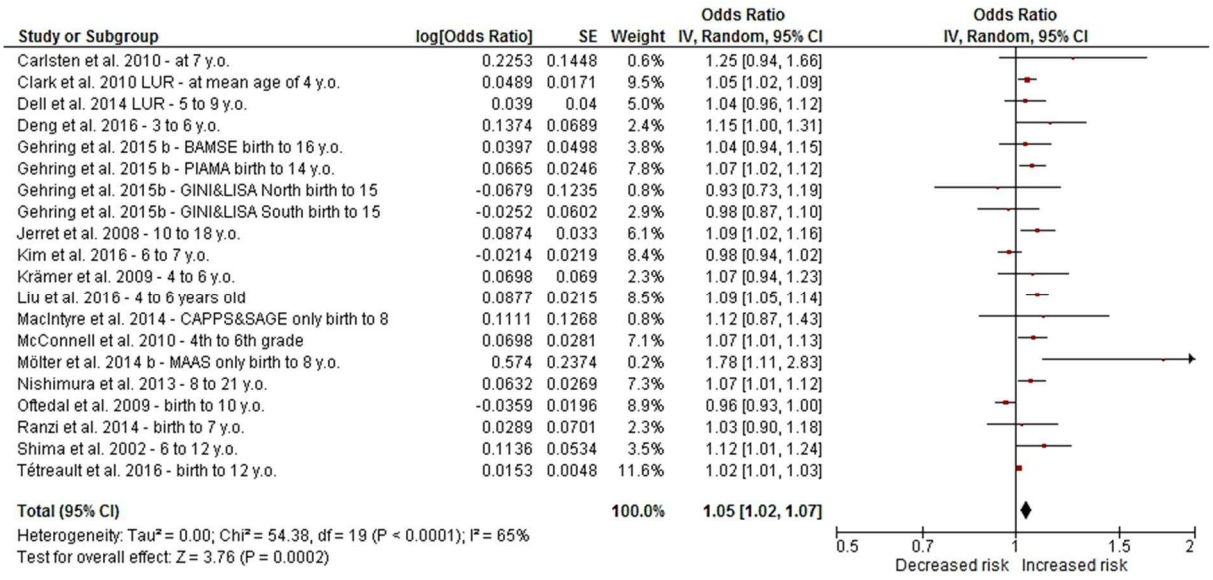

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Figure 4. NO_2 random-effects meta-analyses. Individual and summary random-effects estimates for associations between NO_2 per 4 µg/m³ and asthma at any age.

Risks in Association with NO_x Exposures

In the overall meta-analysis for NO_x, the random-effects overall risk estimate for asthma development was increased, but was not statistically significant (for 30 µg/m³ NO_x, overall risk estimate = 1.48, 95% CI 0.89, 2.45). There was substantial and statistically significant heterogeneity which was the highest detected across all analyses (Figure 5). Results from the fixed-effects model, however, showed a statistically significantly increased risk, with substantial and statistically significant heterogeneity (Figure S4). In the age-specific meta-analyses, the random-effects overall risk estimates were increased in children diagnosed > 6 years old only but similarly to the overall analysis, these were statistically insignificant.

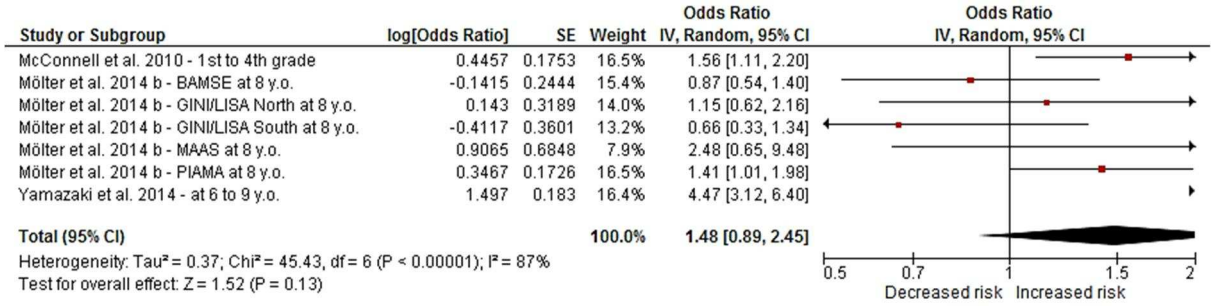

Figure 5. NO_x random-effects meta-analyses. Individual and summary random-effects estimates for associations between NO_x per 30 µg/m³ and asthma at any age.

Risk in Association with $PM_{2.5}$ Exposures

In the overall meta-analysis for $PM_{2.5}$, the random-effects overall risk estimate for asthma development was statistically significantly increased (for 1 µg/m³ $PM_{2.5}$, overall risk estimate = 1.03, 95% CI 1.01, 1.05), with some heterogeneity (Figure 6). Results from all sensitivity analysis showed a statistically significantly increased risk of asthma with the exposure, as did the fixed-effects model (Figure S5). Of note was the significant reduction in heterogeneity in sensitivity analysis excluding the high risk birth cohort [98]. In the age-specific meta-analyses of children ≤ 6 years old age results were positive but statistically insignificant, whilst results from older children supported a statistically significantly increased risk, with reduced heterogeneity (Table 2).

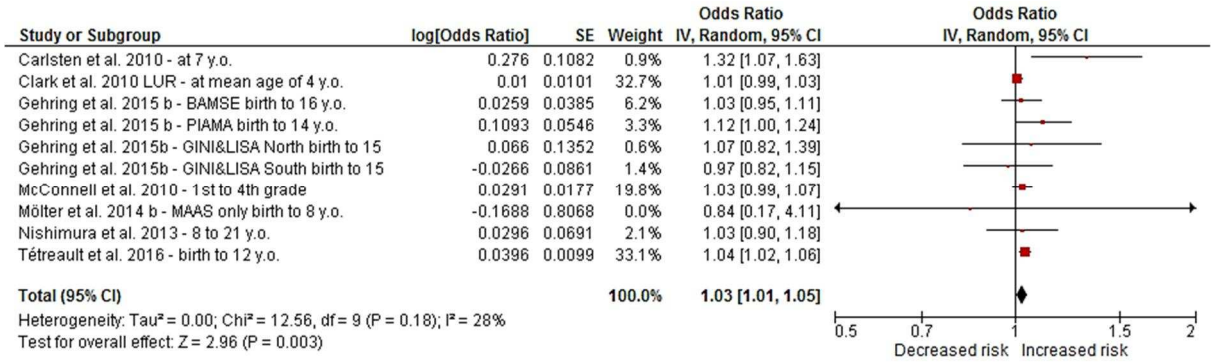

Figure 6. $PM_{2.5}$ random-effects meta-analyses. Individual and summary random-effects estimates for associations between $PM_{2.5}$ per 1 µg/m^3 and asthma at any age.

Risks in Association with PM_{10} Exposures

In the overall meta-analysis for PM_{10}, the random-effects overall risk estimates for asthma development was statistically significantly increased (for 2 µg/m^3 PM_{10}, overall risk estimate = 1.05, 95% CI 1.02, 1.08), with some heterogeneity (Figure 7). Results from the fixed-effects model were comparable (Figure S6), and sensitivity analyses supported these findings. The age specific analysis showed increased risks in both age groups (Table 2). Sensitivity analysis supported these findings in the younger age group only.

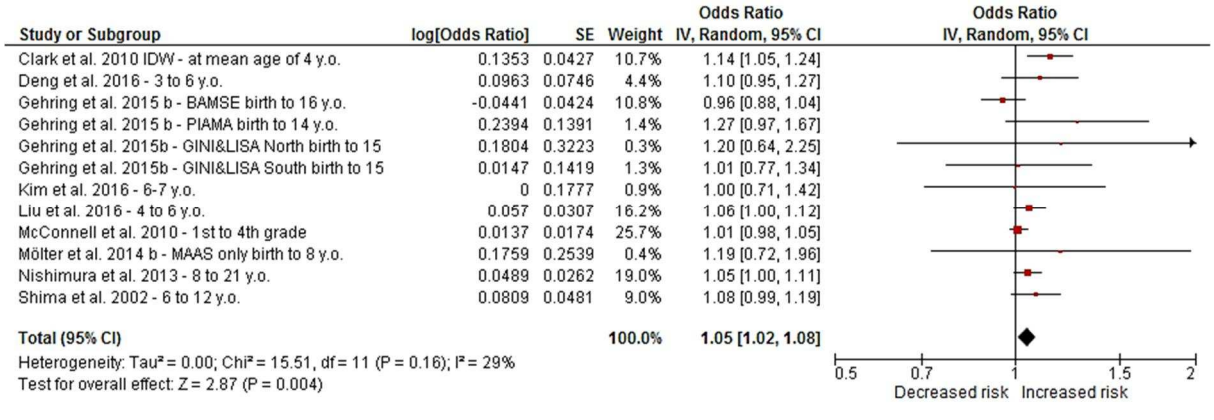

Figure 7. PM_{10} random-effects meta-analyses. Individual and summary random-effects estimates for associations between PM_{10} per 2 µg/m^3 and asthma at any age.

Publication Bias

The funnel plots are shown in Figures S7-S11. In general, there are not enough studies to comprehensively examine publication bias. However, it seems that there is not much concern for publication bias except for the NO_x analysis where the funnel plot is clearly asymmetrical.

Differences between Sexes and Atopic and Non-Atopic Asthma

There was suggestion that effects may be different by sex, although this was inconsistent (see supplementary material). In the five studies which phenotyped asthma as atopic and non-atopic, ORs were only increased [17, 56, 66] or were higher in magnitude [57, 60] for the non-atopic asthma phenotype (Table S7).

Discussion

Overview, Strengths and Limitations

In this systematic review and meta-analysis, we synthesized 41 studies, published between 1999 and September 2016, investigating the association between exposure to TRAP and subsequent development of childhood asthma. We conducted overall and age-specific meta-analyses and estimated statistically significant random-effects risk estimates with BC, NO_2, $PM_{2.5}$, and PM_{10} exposures. Multiple sensitivity analyses supported our finding and conclusions. Across the overall meta-analysis and the age-specific analysis, the least heterogeneity was seen for the BC estimates, some heterogeneity for $PM_{2.5}$ and PM_{10} estimates and the most heterogeneity for the NO_2 and NO_x estimates. Overall, we noted significant variability in asthma definitions, TRAP exposure assessment methods and confounder adjustment.

To our knowledge, this is the largest and most up-to-date review and analysis of current evidence of the etiology of childhood asthma and TRAP. Our systematic review and meta-analysis provide evidence for a positive association between TRAP exposures and subsequent childhood asthma development. Our results are concordant with most previous individual studies (Tables S1-S6). There is also considerable support from other syntheses for the hypothesis that childhood exposure to TRAP contributes to the development of asthma [23-25]. Discordant findings were reported by a small number of studies, but we highlighted some of these at high risk of selection bias [46, 58], and the negative associations reported by Gehring et al. (2002) [32] and Mölter et al. (2014) [66] were not confirmed in their follow-up studies [17, 73]. The key strengths of our synthesis is its

large coverage alongside its in-depth, transparent and reproducible evaluation of the evidence from studies focused on TRAP exposures as a potential cause of childhood asthma. It is a timely contribution to a rapidly evolving field which could inform the focus and design of future research, to improve its utility.

We, however, report some limitations. We solely relied on results from continuous exposure analyses in our meta-analysis. Continuous exposure analysis is based on the notion of a natural log linear relationship between the exposure and the outcome, which may not be the case in TRAP-asthma association, although we assumed this. Studies reporting high versus low analysis were on the other hand very few and of limited power restricting their usability. All the studies included in our review have specifically investigated "traffic-related" metrics and established traffic-related air pollutants, yet only a few used air pollution dispersion models, and hence we cannot completely distinguish effects of traffic sources from others with confidence. An assumption underlying our review is that childhood and early-life in particular represent the most critical exposure windows. As such, precedence in the meta-analysis was given to the risk estimates that related to the earliest exposure Window (e.g. we selected birth address exposure instead of current/later address exposure). Yet, it can be that exposures in later life also contribute to the development of asthma. We also excluded estimates/studies pertaining to prenatal exposures [18, 54, 104, 112], and although this can be an artificial distinction as birth year exposure may well be correlated to prenatal exposures, our conceptual framework required the child's own exposure for inclusion. In the age-specific meta-analyses, we used 'school-age' (i.e. 6 years old) as the cut-off age. This approach did not allow us to explore potential differences in the effects of TRAP on asthma between pre-pubescent and pubescent children as the range > 6 years old includes both. In the underlying data contributing to the meta-analysis, there was some of lack of equivalence among the exposure measures, populations and 'asthma' definitions. Yet, we considered the steadily increasing number of studies in this area, much of which are conducted using LUR models and in the same populations at different follow-ups, alongside the recent availability of new studies using harmonized methods [17, 66], to justify a meta-analysis approach. We further conducted a number of hypothesis driven sensitivity analyses, retaining studies that are most alike, and these supported our main findings. We consider the ability to explore the association with the different pollutants, the drivers of heterogeneity, and age-specific effects as an important function of our meta-analyses. Due to the variability across studies, these findings need to be explored in future analyses when more studies are available. Future synthesis would benefit from greater standardization of study methods, although some differences are inevitable, especially considering the current indistinct definition of asthma.

Studied Pollutants and Meta-Analysis Interpretation

The focus on studying NO_2 effects was related to the wide availability of this pollutant measure and its relative specificity to TRAP [26]. There is also a focus on NO_2 in air quality guidelines, plans and mitigation strategies, whilst less attention is generally given to the other pollutants. In recent years, there appears to be a move from studying standard air pollutants to studying other agents including black and elemental carbon, particulate matter composition elements and other properties such as oxidative potential. We only conducted meta-analyses for BC, NO_2, NO_x, $PM_{2.5}$ and PM_{10}. There was variability in the numbers of studies contributing to the meta-analyses for different pollutants (Table 2). The results showed that the meta-analyses for NO_2, which had the highest number of studies, produced the highest heterogeneity and a relatively small effect size, which may indicate that NO_2 may not be the putative agent in the TRAP mixture, but may act as a surrogate for example BC or $PM_{2.5}$ which showed less heterogeneity. Results from the $PM_{2.5}$ meta-analyses, where 10 studies were available, were also relatively low in magnitude but had less heterogeneity. In particular, when excluding the high risk birth cohort by Carlsten et al. (2010) [98], where $PM_{2.5}$ could act as an adjuvant for transporting allergens deep in the lungs of predisposed children, the random-effects model estimated no heterogeneity. The results of the meta-analyses for BC and $PM_{10,}$ where there were 8 and 12 studies, respectively, produced higher effect sizes and minimal heterogeneity, and these findings were robust in sensitivity analyses, especially for BC. Finally, only 7 studies were available for NO_x, and although the overall risk estimate was high in magnitude, it did not reach statistical significance and there was suggestion for publication bias. Given the smaller number of studies available for pollutants other than NO_2, the power to detect heterogeneity and associations is likely limited and further analysis is needed to support our findings and assertions.

As there is evidence that the accuracy of asthma diagnosis might differ according to the child's age and that younger children might outgrow their asthma symptoms at older ages [113], we attempted to explore this by conducting age-specific meta-analyses with a cut-off age of 6 years when asthma is diagnosed more readily. This reduced the number of applicable studies and with such small numbers interpretation should be cautious. In the age-specific meta-analysis, the overall risk estimate of $PM_{2.5}$ in the younger age group lost its statistical significance, which could be attributable to the reduction of power, but all other risk estimates remained significantly increased. Generally, the effects seemed to be higher in the younger age group. The heterogeneity in both the $PM_{(2.5,10)}$ analyses and BC analysis was reduced in the older children as compared to the overall and

492 the younger children analyses; a trend that was previously suggested to imply differences in susceptibility
493 between children at a younger age, which attenuated over time [17]. Future meta-analyses, when more studies
494 become available, could explore effects and heterogeneity at different age cut-off points. The design of our
495 review (cut-off age at 18 years old) and the current evidence base did not allow for further exploration regarding
496 whether or not the detected associations persist in adolescents at older ages. Furthermore, in following the HEI
497 methods our paper largely uses the practice of defining asthma as physician diagnosed asthma rather than
498 relying on wheeze outcomes. Although wheeze if often used as part of asthma definitions in practice, we believe
499 that wheeze on its own is a non-specific symptom and clearly precludes making a distinction between onset of
500 asthma and its exacerbations [25]. Further meta-analyses could look at TRAP and wheeze but this was outside
501 the scope of our paper.

502 Although our overall meta-analysis showed positive and statistically significant associations with four pollutants
503 examined, these pollutants are highly correlated in traffic exhaust and the overall risk estimates cannot be
504 conclusively interpreted as a certain pollutant's effect. In fact, as mentioned above, the high heterogeneity levels
505 found in the NO_2 and NO_x analyses, in line with other studies [66] may suggest these pollutants are surrogate for
506 another pollutant or mixture responsible for the observed effects such as BC or $PM_{2.5}$. However, the number and
507 quality of studies differ which makes it difficult to draw definitive conclusions. Pollutants like BC and PM_{10} are
508 considered to act as tracers of older diesel, particularly heavy-duty traffic emissions which are typically not
509 equipped with engine control and exhaust after-treatment systems such as diesel particle filters, so their
510 emissions of larger, heavier particulate matter are high. The morphology of these larger particulates can include
511 unburnt hydrocarbons held hydroscopically between carbon/BC. BC has been shown to be highly correlated
512 with EC too [114]; but importantly with other species known for their toxicological potency [115, 116] like
513 polycyclic aromatic hydrocarbons, benzene and volatile organic compounds [117, 118].

514 **Studies Quality and Heterogeneity**

515 A number of other possible factors can explain heterogeneity identified between the studies. Firstly, there were
516 differences in methods used to identify asthma cases, with the most commonly employed method being
517 parental-reporting of doctor-diagnoses. Some of the heterogeneity we detected therefore might be due to
518 regional differences in doctors' practices. Other methods employed to assess asthma varied across the remaining
519 studies making their estimates more difficult to compare. As for the quality of these estimates, recall bias

remains a concern in parental-reporting of doctor-diagnoses. Further, the extent by which asthma estimates were captured by these different methods was not discussed much in this literature, but there are examples of the poor overlap and significantly different estimates one obtains utilizing different approaches. For instance, a Danish study of > 50,000 children showed that asthma prevalence from parental-reporting of doctor-diagnoses, diagnoses from hospitalization registries and medication data from prescription registries, varied substantially with poor agreement [107]. Further assessment of the nature of disease misclassification due to the above factors and its effect on exposure-response associations is needed.

Secondly, the different levels of exposure, and constituents of air pollutants in the different areas may explain differences between studies. The different models used to assess TRAP exposures could also result in further heterogeneity. Most studies using LUR models showed consistently increased risk of TRAP-associated asthma. Although we consider that exposure indices from LUR models are relatively robust in capturing the small-area variation of TRAP in comparison to the other models, we note that LUR may introduce an exposure misclassification by pollutant. Whilst NO_2 and BC can be truly considered as traffic-related and primarily exhaust pollutants [49], $PM_{2.5}$ is primarily a non-exhaust pollutant and has other important local (traffic and non-traffic), regional sources and secondary particle formation mechanisms which are not encompassed in the geographic variables founding typical LUR models. The fact that the encountered LUR models were not as accurate in capturing $PM_{2.5}$ concentrations is therefore essential in this debate and potential for more downward bias due to the less robust regression models in the case of $PM_{2.5}$ is expected [119]. Studies using monitoring stations data were consistent in demonstrating increased risks. However, given that most network monitors are usually located to measure urban or regional background air pollution [103], these studies are less specific to traffic, fail to account for TRAP spatial variability, and by definition, introduce an inevitable mismatch between the stations' and subjects' locations [120]. This affects our confidence in the PM_{10} meta-analyses results where 7 out of the 12 studies included used fixed-site monitoring stations. Finally, results from studies using dispersion models were inconsistent. Studies have suggested that dispersion models systematically underestimate TRAP concentrations at the roadside and in congested areas, a problem attributable to inputting these models with unrealistically low vehicle emission factors, especially for NO_x and NO_2 [121, 122]. Furthermore, the unusually high exposure estimates that occur in canyonised streets [48, 123] were only captured in one study using a street canyon module [57]. Unfortunately, due to the limited number of studies, we could not formally assess whether

the type of exposure model explains part of the heterogeneity between studies, but had to rely on qualitative synthesis.

Finally, as there is wide interindividual variability in responses to air pollution [124], genetic variations could explain some of the observed heterogeneity. This was only investigated Kerkhof et al. (2010) and MacIntyre et al. (2013) who found that toll-like receptor genes responsible for activating the innate immune system, and variant GSTP1 genotypes which code for an enzyme that metabolizes reactive oxygen species; influence the susceptibility to effects of TRAP on asthma [67, 110].

Conclusions and Recommendations

Based on this updated evidence base, we believe there is now sufficient evidence to support an association between the exposure to TRAP and the development of childhood asthma. The high degree of consistency in findings and conclusions of the individual studies, the results of the meta-analysis, and considerable support from the existing literature reinforce the hypothesis that childhood exposure to TRAP contributes to their development of asthma. The evidence for BC was less heterogeneous than for $PM_{2.5}$ and PM_{10} and in particularly NO_2, which may give further indication of any putative agent. The question of whether the increase in asthma incidence and/or lifetime prevalence we estimated represents added cases or merely an acceleration of the development of asthma or increased severity making the disease sufficiently apparent for clinical diagnosis is unresolved and cannot be answered based on current evidence.

Future meta-analyses would benefit from greater standardization of study methods including exposure assessment harmonization, outcome harmonization, confounders' harmonization and the inclusion of all important confounders in the individual analyses (e.g. socioeconomic status, environmental tobacco smoke exposure, heredity). Future synthesis could also explore different exposure windows comparing effects of early life to later childhood exposures and possibly prenatal exposures. Other specific recommendations that would help improve the utility of new research in this field are as below:

- Systematically reporting categorical exposure analysis, alongside continuous exposure analysis.
- Systematically investigating associations with multiple windows of exposure.

- Using air pollution dispersion models or equivalent methods (e.g. source apportionment models) to distinguish effects of TRAP from other sources with more confidence.
- Expanding the focus on NO_2 to other traffic-related pollutants including BC, NO_x, PM, UFPs, and particles constituents.
- Exploring effects and heterogeneity at different age cut-off points, distinguishing between pre-pubescent and pubescent children and undertaking follow-up studies in the same populations.
- Expanding the methods of asthma assessment beyond reporting of doctor-diagnosis (e.g. using prescribed medication from prescription registry or diagnosis codes).
- Assessing the nature of disease misclassification due to different asthma definition methods and its effect on exposure-response associations.
- Systematically reporting bias concerns and performing adjustments where necessary.
- Formally assessing whether the type of exposure model explains part of the heterogeneity in effects (e.g. by meta-regression or meta-analyses specific to the exposure models).
- Systematically investigating differences in the associations between sexes.
- Systematically investigating differences in the associations between different phenotypes and distinguishing between family history of asthma and family history of allergies.

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Tables

Table 1: Main Characteristics of Studies Included in the Systematic Review with studies previously included in HEI synthesis highlighted in gray

Study reference and setting	Study design	Age group (years)	Participants included in the analysis	Exposure assessment	Pollutant(s)	Traffic-related exposures distribution	Asthma assessment and phenotypic characterization	Follow-up	Adjustment variables	CASP notes
Brauer et al. 2002 [88], The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth-2	2,989	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: range (0.77-3.68); mean (1.72) $10^{-5}m^{-1}$ NO_2: range (12.6-58.4); mean (25.6) $\mu g/m^3$ $PM_{2.5}$: range (13.5-25.2); mean (16.9) $\mu g/m^3$	Parental reporting of doctor-diagnosed asthma	@ 3 months, 1 and 2 y.o.	Mother smoking during pregnancy, smoking in home, study arm/mattress cover, mother education, father education, sex, gas stove, unvented gas water heater, siblings, ethnicity, breastfeeding at 3 months, any home mold, any home pets, allergies in mother, allergies in father, age of mother at child birth, region (in sensitivity analysis only)	Very young age for accurate diagnosis, follow-up duration is short, potential for recall bias in defining the outcome
Brauer et al. 2007 [87], The Netherlands, north, west and center communities	Follow-up on Brauer et al. (2002)	Birth-4	2,826	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: range (0.77-3.68); mean (1.71) $10^{-5}m^{-1}$ NO_2: range (12.6-58.4); mean (25.2) $\mu g/m^3$ $PM_{2.5}$: range (13.5-25.2); mean (16.9) $\mu g/m^3$	Parental reporting of doctor-diagnosed asthma	@ 3 months, 1, 2, 3 and 4 y.o.	As in Brauer et al. (2002)	Young age for accurate diagnosis, follow-up duration is short, potential for recall bias in defining the outcome
Brunst et al. 2015 [34], USA, Cincinnati	Birth cohort (CCAAPS)	Birth-7	589	LUR modelling	EC	EC: 75th percentile (0.45) $\mu g/m^3$ at birth; 75th percentile (0.39) $\mu g/m^3$ at age 7 y.o.	Asthma defined based on (1) asthma symptoms and bronchial hyperreactivity (>12% increase in FEV1 after bronchodilation) or a positive methacholine challenge test (>20% fall in baseline FEV1 at an inhaled methacholine concentration of <4 mg/ml) (2) parental reporting of doctor-diagnosis by a physician not associated with CCAAPS and, if so, at what age	@ 1, 2, 3, 4, and 7 y.o. and age of doctor diagnosis where applicable	Maternal education, parental history of asthma, daycare attendance, presence of a cat and/or dog in the home (race, sex, breastfeeding (< or >4 months), secondhand smoke exposure in 1st year of life, daily number of cigarettes smoked by household member > 0 were considered but not included in the final models)	High risk birth cohort[b], potential for recall bias in defining the outcome and selection bias, small (non-representative) sample size
Carlsten et al. 2010 [98], Canada, Vancouver	Birth cohort (CAPPS)	Birth-7	184	LUR modelling	BC, NO, NO_2, $PM_{2.5}$	BC: mean (1.6) $10^{-5}m^{-1}$ NO: mean (35.7) $\mu g/m^3$ NO_2: mean (32.6) $\mu g/m^3$ $PM_{2.5}$: mean (5.6) $\mu g/m^3$	A single blinded pediatric allergist diagnosed asthma defined as ≥ 2 distinct episodes of 2+ weeks of cough, ≥ 2 distinct episodes of 1+ week of wheeze and one of the following: 1 weekly non-cold nocturnal cough, or hyperpnoea-induced cough/wheeze, or response to treatment with β-agonist and/or anti-inflammatories	@ 7 y.o.	Maternal post-secondary education, mother/father/sibling asthma history, atopic status at 1 year, ethnicity, sex, intervention status	High risk birth cohort[b], no adjustment for smoking, small (non-representative) sample size
Clark et al. 2010 [54], Canada, southwestern British Columbia	Case-control nested in British Columbia birth cohort	Birth-4	37,401	LUR modelling, monitoring data at closest three monitors weighted by inverse distance to child's residence, proximity to highways/ major roads	BC, CO, NO, NO_2, PM_{10}, $PM_{2.5}$	BC (LUR): mean (0.66 controls; 0.68 asthma cases) $10^{-5}m^{-1}$ CO: mean (605.0 controls; 617.5 asthma cases) $\mu g/m^3$	Asthma diagnosis identified from doctor billing records for primary care and hospital discharge records. Asthma defined as ≥ 2 primary care doctor diagnoses in a rolling 12-month period or ≥ 1 hospital admission for asthma using ICD-9 code 493	Mean age at end of follow-up: 4 years±7 months	Multiple births, age, sex, native status, breastfeeding, income quintile, education quartile, birth weight, gestational length (maternal age, maternal smoking and native status were considered but not included in the final models)	Young age for accurate diagnosis, excluding low birth weight /premature birth children may bias results towards the null, socioeconomic status variables assigned at the Census dissemination level, no adjustment for heredity

						NO (LUR): mean (30.42 controls; 30.83 asthma cases) µg/m^3 NO_2 (LUR): mean (29.50 controls; 29.82 asthma cases) µg/m^3 PM_{10} (IDW): mean (12.37 controls; 12.42 asthma cases) µg/m^3 $PM_{2.5}$ (LUR): mean (4.50 controls; 4.59 asthma cases) µg/m^3				
Fuertes et al. 2013 [92], Germany	2 birth cohorts (GINIplus and LISAplus)	3-10	4,585	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: range (1.0-3.6); mean (1.5) $10^{-5}m^{-1}$ NO_2: range (11.5-62.8); mean (22.4) µg/m^3 $PM_{2.5}$: range (0.4-21.5); mean (15.3) µg/m^3	Parental reporting of doctor-diagnosed asthma	GINIplus @ birth, 1, 2, 3, 4, 6 and 10 y.o., LISAplus @ birth, 0.5, 1, 1.5, 2, 4, 6 and 10 y.o.	Sex, age, older siblings, parental history of atopy, parental education, maternal smoking during pregnancy, smoke exposure in home, contact with furry pets during 1st year of life, use of gas stove during 1st year of life, home dampness/indoor molds during 1st year of life, intervention participation, cohort and geographical area. Only children born at full-term and normal weight were recruited.	Participants differed from initial cohort, excluding children from the LISA with low birth weight /premature birth may bias results towards the null, potential for recall bias in defining the outcome
Gehring et al. 2002 [32], Germany, Munich	2 birth cohorts (GINI and LISA)	Birth-2	1,756	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: range (1.38-4.39); mean (1.77) $10^{-5}m^{-1}$ NO_2: range (19.5-66.9); mean (27.8) µg/m^3 $PM_{2.5}$: range (11.9-21.9); mean (13.4) µg/m^3	Parental reporting of doctor-diagnosed asthmoid/ spastic/obstructive bronchitis	GINI @ birth, 1, and 2 y.o., LISA @ birth, 0.5, 1, 1.5, and 2 y.o.	Sex, parental atopy, tobacco smoke at home, maternal education, siblings, use of gas for cooking, home dampness, indoor mould, pets keeping and study arm	Very young age for accurate diagnosis, follow-up duration is short, excluding children from the LISA with low birth weight /premature birth may bias results towards the null, potential for recall bias in defining the outcome
Gehring et al. 2010 [56], The Netherlands, north, west and center communities	Follow-up on Brauer et al. (2007)	Birth-8	3,143	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: range (0.77-3.68); mean (1.72) $10^{-5}m^{-1}$ NO_2: range (12.6-58.4); mean (25.2) µg/m^3 $PM_{2.5}$: range (13.5-25.2); mean (16.9) µg/m^3	Parental reporting of doctor-diagnosed asthma. Asthma categorized in 1,499 children at 8 years of age to atopic and non-atopic based on blood IgE concentrations to inhalant or food allergens	@ birth, 1, 2, 3, 4, 5, 6, 7 and 8 y.o.	As in Brauer et al. (2007) plus daycare attendance	Potential for recall bias in defining the outcome
Gehring et al. 2015 a [63], The Netherlands, north, west and center communities	Follow-up on Gehring et al. (2010)	Birth-12	3,702	LUR modelling	BC, NO_2, $PM_{2.5}$, PM_{10}, PM_{coarse} and PM composition elements: copper (Cu), iron (Fe), zinc (Zn), nickel (Ni), sulfur (S), vanadium (V)	BC: range (0.8-3.0); mean (1.2) $10^{-5}m^{-1}$ NO_2: range (9.2-59.6); mean (23.1) µg/m^3 $PM_{2.5}$: range (15.3-21.1); mean (16.4) µg/m^3	Parental reporting of doctor-diagnosed asthma	@ birth, 1, 2, 3, 4, 5, 6, 7, 8 and 11-12 y.o.	As in Gehring et al. (2010) plus birth weight in sensitivity analysis	Participants more likely to have highly educated parents and live in non-smoking homes

						PM_{10}: range (23.7-33.2); mean (24.9) µg/m^3 PM_{coarse}: range (7.6-14.0); mean (8.4) µg/m^3 For PM elemental composition elements; seeable 2 in original paper				
Gehring et al. 2015 b [17], Sweden, Germany, The Netherlands	Pooled data from four birth cohorts: BAMSE; GINIplus; LISAplus and PIAMA	Birth-16	14,126	LUR modelling	BC, NO_2, $PM_{2.5}$, PM_{10}, PM_{coarse}	BC at birth: BAMSE - range (0.4-1.3); mean (0.7) $10^{-5}m^{-1}$ GINI/LISA North - range (1.0-3.1); mean (1.2) $10^{-5}m^{-1}$ GINI/LISA South - range (1.3-3.6); mean (1.7) $10^{-5}m^{-1}$ PIAMA - range (0.8-1.2); mean (1.2) $10^{-5}m^{-1}$ NO_2 at birth: BAMSE - range (6.0-33.0); mean (14.1) µg/m^3 GINI/LISA North - range (19.7-62.8); mean (23.8) µg/m^3 GINI/LISA South - range (11.5-61.1); mean (21.8) µg/m^3 PIAMA - range (8.7-59.6); mean (23.2) µg/m^3 $PM_{2.5}$ at birth: BAMSE - range (4.2-11.4); mean (7.8) µg/m^3 GINI/LISA North - range (15.8-21.5); mean (17.4) µg/m^3 GINI/LISA South - range (10.6-18.3); mean (13.4) µg/m^3 PIAMA - range (15.3-21.1); mean (16.4) µg/m^3 PM_{10} at birth: BAMSE - range (6.0-30.9); mean (15.7) µg/m^3 GINI/LISA North - range (23.9-33.9); mean (25.5) µg/m^3 GINI/LISA South - range (14.8-34.4); mean (20.4) µg/m^3	Asthma defined as a positive answer to at least two of the three questions: (1) “has a doctor ever diagnosed asthma in your child?” (2) “has your child had wheezing or whistling in the chest in the last 12 months?”, and (3) “has your child been prescribed asthma medication during the last 12 months?” Asthma categorized to allergic and non-allergic based on blood IgE concentrations against common aeroallergens	@ 1, 2, 4, 6–8, 10–12 and 14–16 y.o.	Sex, parental socioeconomic status, parental education, native nationality, maternal and paternal asthma or hay fever, older siblings, breastfeeding for at least 3 months, maternal smoking during pregnancy, parental smoking at home, mould or dampness, and furry pets in the child’s home, use of natural gas for cooking, attendance at day-care centers, municipality (BAMSE only)	Does not account for long-term trends in TRAP levels, potential for selection bias as children of atopic and highly educated parents were over-represented, potential for recall bias in defining the outcome

						GINI/LISA South - range (23.7- 33.2); mean (25.0) µg/m^3 PM_{coarse} at birth: BAMSE - range (0.7- 20.2); mean (7.9) µg/m^{3}GINI/LISA North - range (1.9-13.9); mean (8·5) µg/m^3 GINI/LISA South - range (4.1- 16.0); mean (6.8) µg/m^3 PIAMA - range (7.6-14.0); mean (8.4) µg/m^3				
Gruzieva et al. 2013 [57], Sweden, Stockholm	Birth cohort (BAMSE)	Birth-12	3,633	Dispersion modelling (Airviro, street canyon contribution for 160 houses) NO_x, PM_{10}	NO_x, PM_{10}	NO_x: mean (21.4) µg/m^3 - above regional background (= 3 µg/m^3) PM_{10}: mean (4.2) µg/m^3 - above regional background (= 10 µg/m^3)	At 1 and 2 y.o., asthma defined as ≥ 3 episodes of wheeze and treatment with inhaled corticosteroids or signs of bronchial hyperreactivity without concomitant respiratory infection. At 4, 8 and 12 y.o., asthma defined as ≥ 4 episodes of wheeze in last year, ≥ 1 episode and prescription of inhaled corticosteroids. Asthma was categorized at 4 or 8 y.o. to atopic and non-atopic based on blood IgE concentrations to inhalant allergens	@ 1, 2, 4, 8 and 12 y.o.	Municipality, socioeconomic status, heredity, year the house was built	No adjustment for smoking, PM_{10} model calculations were performed only for year 2004 and assumed constant for all years during the study period (1994 to 2008), potential for recall bias in defining the outcome
Jerret et al. 2008 [94], USA, 11 southern Californian communities	Cohort (CHS)	10-18	209	NO_2 Palmes tubes monitoring for 2 weeks in 2 seasons at child's residence	NO_2	NO_2: annual mean in the 11 communities ranging from 9.6 ppb (at Lompoc) to 51.3 ppb (at San Dimas)	Parental and self-reporting of doctor-diagnosed asthma	@ 10, 11, 12, 13, 14, 15, 16, 17 and 18 y.o.	Age, sex, relative humidity, ethnicity, enrolment group, medical insurance coverage, enrollment group (body mass index, wheeze and symptoms of hay fever, medical care and socioeconomic status, parental education, mildew in home, carpet in bedroom, plants and pets in home, gas stove in home, current daily smoker in home, maternal smoking during pregnancy, parental history of asthma considered but not included in the final models)	Small sample size, potential for recall bias in defining the outcome
Kerkhof et al. 2010 [110], The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth-8	916	LUR modelling	BC, NO_2, $PM_{2.5}$	BC: median (1.77); interquartile range (1.30-1.91) $10^{-5}m^{-1}$ NO_2: median (25.8); interquartile range (17.4-28.6) µg/m^3 $PM_{2.5}$: median (17.2); interquartile range (14.7-18.1) µg/m^3	Two definitions: (1) parental reporting of doctor-diagnosed asthma (2) at least one attack of wheeze or dyspnoea and/or the prescription of inhaled corticosteroids in the last 12 months from age 2 up to age 8	@ birth, 1, 2, 3, 4, 5, 6, 7 and 8 y.o.	Sex, type of intervention (mite-impermeable mattress covers, placebo covers or no intervention), allergies of mother and father, parental education (low, intermediate or high), maternal smoking during pregnancy, exposure to smoke at home in the first year of life, duration of breastfeeding (never, 1e12 weeks, >12 weeks), presence of a gas stove, presence of older siblings, daycare attendance, signs of dampness in the house, presence of cats and/or dogs, type of home (single family dwelling ,apartment/flat) and presence of fitted carpeting	Small sample size, potential for selection bias, potential for recall bias in defining the outcome
Krämer et al. 2009 [49], Germany, Wesel	2 birth cohorts (GINIplus and LISAplus)	4-6	2,059	LUR modelling, distance to next major road traversed by more than 10,000 cars/ day	BC, NO_2	BC: range (0.8-2.3); mean (1.6) $10^{-5}m^{-1}$	Parental reporting of doctor-diagnosed asthma	GINI @ birth, 1, 2, 3, 4 and 6 y.o.,	Study arm, sex, years of parental schooling, maternal smoking in pregnancy, tobacco smoke, use of gas for cooking, contact with dog,	Study in rural and small town areas, participants differed than non-participants, potential for

						NO_2: range (13.6-41.4); mean (24.0) µg/m^3		LISA @ birth, 0.5, 1, 1.5, 2, 4 and 6 y.o.	cat, other furry pets, home mold and dampness, biological siblings, participant of intervention, intervention formulas, living on a farm, parental asthma, hay fever or eczema	recall bias in defining the outcome
LeMasters et al. 2015 [111], USA, Cincinnati	Birth cohort (CCAAPS)	Birth-7	575	LUR modelling	EC	EC: 75th percentile (0.42) µg/m^3 26.4% of normal BMI children and 27.5% of high BMI children were at ≥ 0.42 µg/m^3 73.7% of normal BMI children and 72.5% of high BMI children were at < 0.42 µg/m^3	Children were doctor diagnosed as asthmatic with symptoms of asthma and evidence of bronchial hyper-reactivity or a positive methacholine challenge test	@ 1, 2, 3, 4 and 7 y.o.	Sex, smoking in home, ethnicity, mother's education, breastfeeding, dog and/or cat in home during 1st year of life, attendance at day care during 1st year of life, stratification by BMI	High risk birth cohort[b], potential for recall bias of residential history and household smoking history
Lindgren et al. 2013 [58], Sweden, Scania	Birth cohort	Birth-6	6,007	Dispersion modelling (AERMOD), traffic intensity on road with heaviest traffic within 100m around residence	NO_x	NO_x: range (6.1-45.9); mean (17.0) µg/m^3 73.8% living at ≤ 100 m from 0–8640 cars/day and 26.6% living at ≤ 100 m from ≥ 8640 cars/day	Asthma onset defined as incidence of 1st ever and 3rd year dispensed inhaled β2-agonist and corticosteroid	Children followed from birth (2005-2010) until 2011 (maximum= 6 y.o.)	Sex, tobacco smoke, breastfeeding, parental allergy, parental origin, parental education, birth year (birth weight, smoking during pregnancy, home mold, furred pets at home, problems to pay bills, type of housing considered but not included in the final models)	Potential for selection bias, crude traffic intensity categorization
MacIntyre et al. 2014 [67], Sweden, Canada, Germany, The Netherlands	Pooled data from 6 birth cohorts: BAMSE; CAPPS; GINI; LISA; PIAMA; SAGE	Birth-8	5,115	LUR modelling, dispersion modelling for BAMSE only	NO_2 (sensitivity analyses for BC and $PM_{2.5}$)	NO_2: pooled data - range (2.2-66.8); mean (22.7) µg/m^3	Parental reporting of doctor-diagnosed asthma. CAPPS and SAGE children were also evaluated by a pediatric allergist to confirm asthma	Children followed at different time points depending on the cohort	Study, city, sex, birth weight, parental history of allergy, maternal age at birth, maternal smoking reported anytime during pregnancy, environmental tobacco smoke reported in the home, and intervention, stratification by genotype	No adjustment for socioeconomic status, potential for selection bias, potential for recall bias in defining the outcome
McConnell et al. 2010 [59], USA, 13 southern Californian communities	Cohort (CHS)	Kindergarten/1st grade - 4th grade	2,497	Dispersion modelling for NOx (CALINE 4), monitoring data for NO_2, $PM_{2.5}$, PM_{10}, distance to nearest freeway or other highways or arterial roads, traffic density within 150m around residence and school	NO_x, NO_2, $PM_{2.5}$, PM_{10}	NO_x: total at residence - range (0.23-144.1); mean (18.4) ppb NO_2: range (8.7-32.3); mean (20.4) ppb $PM_{2.5}$: range (6.3-23.7); mean (13.9) µg/m^3 PM_{10}: range (17.6-61.5); mean (35.5) µg/m^3 Traffic density: at residence - range (<0.0001-1,029); mean (48.3) Distance to freeway: at residence - range (24-18,210); mean (1,912) m	Self-reporting of doctor-diagnosed asthma	Annual questionnaires during 3 years' follow-up	Age, sex, ethnicity (history of allergy, play team sport, parental history of asthma, maternal smoking during pregnancy, secondhand smoke, mildew, pets in home, indoor NO_2 sources, wildfire exposure, health insurance, household income and parental education were considered but not included in the final models)	Potential for recall bias in defining the outcome, potential for selection bias

						Distance to major road: at residence - range (0.02- 7,516); mean (433) m				
Mölter et al. 2014 a [65], England, Greater Manchester	Birth cohort (MAAS)	Birth-11	1,108	Microenvironmental exposure model (LUR modelling for outdoor and INDAIR for indoor environments, indoor to outdoor ratios: journey to school and school)	NO_2, PM_{10}	NO_2: birth year - mean (21.7) µg/m^3 PM_{10}: birth year - mean (12.8) µg/m^3	Asthma defined as at least two positive answers to the following three questions: (1) doctor-diagnosis of asthma ever; (2) child having wheezed during the previous 12 months and (3) child having received asthma medication during the previous 12 months	@ 3, 5, 8, and 11 y.o.	Age, sex, body mass index, paternal income at birth, sensitization, family history of asthma, hospitalization during the first 2 years of life, smoking within the child's home during the first year of life, and Tanner stage (age 11 only) (ethnicity, older siblings, parental atopy, day care attendance, presence of a gas cooker in the home, visible signs of dampness or mould in the home, presence of a dog or a cat in the home, birth weight, gestational age, maternal age at birth, and duration of breastfeeding were considered but not included in the final models)	Limited number of children with a full set of exposure estimates available for follow-up, more restrictive asthma definition, potential for recall bias as review of microenvironments only done at age 11, potential for recall bias in defining the outcome
Mölter et al. 2014 b [66], ESCAPE multi-center analysis, England, Sweden, Germany, The Netherlands	Pooled data from 5 birth cohorts: MAAS, BAMSE, PIAMA, GINI, LISA (South and North)	Birth-10	10,377	LUR modelling, traffic intensity on the nearest street, traffic intensity on major roads within a 100m radius	BC, NO_2, NO_x, $PM_{2.5}$, PM_{10}, PM_{coarse}	BC at birth: MAAS - range (0.7-2.0); mean (1.2) $10^{-5}m^{-1}$ BAMSE - range (0.4-1.3); mean (0.7) $10^{-5}m^{-1}$ PIAMA - range (0.9-3.0); mean (1.2) $10^{-5}m^{-1}$ GINI/LISA South - range (1.3-3.6); mean (1.7) $10^{-5}m^{-1}$ GINI/LISA North - range (0.9-3.1); mean (1.2) $10^{-5}m^{-1}$ NO_2 at birth: MAAS - range (16.0-30.4); mean (22.9) µg/m^3 BAMSE - range (6.0-33.0); mean (14.0) µg/m^3 PIAMA - range (9.2-55.3); mean (23.2) µg/m^3 GINI/LISA South - range (11.5-61.1); mean (22.0) µg/m^3 GINI/LISA North - range (19.6-62.8); mean (23.9) µg/m^3 $PM_{2.5}$ at birth: MAAS - range (9.4-11.0); mean (9.4) µg/m^3 BAMSE - range (4.2-11.4); mean (7.8) µg/m^3 PIAMA - range (15.3-20.9); mean (16.4) µg/m^3	Asthma defined as at least two positive answers to the following three questions: (1) doctor-diagnosis of asthma ever; (2) child having wheezed or whistled during the previous 12 months and (3) child having received asthma medication during the previous 12 months	@ 4 (age 5 in MAAS), and 8 y.o. (age 10 in GINI/LISA)	Age, sex, older siblings, gas cooking, dampness or mould, maternal smoking during pregnancy, any smoker living in the home, >12 weeks of breastfeeding, day-care attendance, parental atopy, personal socioeconomic status, maternal age at birth, presence of a dog in the home, presence of a cat in the home, region, area-level socioeconomic status, birth weight, moving status (sensitivity analysis)	Potential for misclassification of personal exposure, more restrictive asthma definitions, potential for recall bias in defining the outcome

						GINI/LISA South - range (10.6-18.3); mean (13.4) µg/m^3 GINI/LISA North - range (15.8-21.5); mean (17.4) µg/m^3 PM_{10} at birth: MAAS - range (12.6-22.7); mean (17.2) µg/m^3 BAMSE - range (6.0-30.9); mean (15.7) µg/m^3 PIAMA - range (23.7-32.7); mean (25.0) µg/m^3 GINI/LISA South - range (14.8-34.3); mean (20.4) µg/m^3 GINI/LISA North - range (23.9-33.5); mean (25.5) µg/m^3 PM_{coarse} at birth: MAAS - range (5.0-11.5); mean (7.0) µg/m^3 BAMSE - range (0.7-20.2); mean (7.9) µg/m^3 PIAMA - range (7.6-11.1); mean (8.4) µg/m^3 GINI/LISA South - range (4.1-16.0); mean (6.8) µg/m^3 GINI/LISA North - range (2.0-13.8); mean (8.5) µg/m^3				
Morgenstern et al. 2007 [73], Germany, Munich Metropolitan area	2 birth cohorts (GINI and LISA) – extension on Gehring et al. (2002)	Birth-2	3,577	LUR modelling, living close to major road	BC, NO_2, $PM_{2.5}$	BC: range (1.3-3.2); mean (1.7) $10^{-5}m^{-1}$ NO_2: range (19.4-71.7); mean (35.3) µg/m^3 $PM_{2.5}$: range (6.8-15.3); mean (12.8) µg/m^3	Parental reporting of doctor-diagnosed asthmoid/ spastic/obstructive bronchitis	GINI @ birth, 1, and 2 y.o., LISA @ birth, 0.5, 1, 1.5, and 2 y.o.	Sex, age, parental atopy, tobacco smoke at home, maternal education, siblings, use of gas for cooking, home dampness, indoor mould, dogs and cats keeping	Very young age for accurate diagnosis, follow-up duration is short, potential for recall bias in defining the outcome
Morgenstern et al. 2008 [93], Germany, Munich	2 birth cohorts (GINI and LISA)	4-6	2,436	LUR modelling, minimum distance to next motorway, federal or state road	BC, NO_2, $PM_{2.5}$	BC at 2/3 y.o.: range (1.1-3.3); mean (1.7) $10^{-5}m^{-1}$ NO_2 at 2/3 y.o.: range (8.0-58.4); mean (34.7) µg/m^3 $PM_{2.5}$ at 2/3 y.o.: range (1.3-15.0); mean (11.1) µg/m^3	Parental reporting of doctor-diagnosis of asthmatic/spastic/obstructive bronchitis or asthma	GINI @ birth, 1, 2, 3, 4 and 6 y.o., LISA @ birth, 0.5, 1, 1.5, 2, 4 and 6 y.o.	Sex, age, parental atopy, maternal education, siblings, tobacco smoke at home, use of gas for cooking, home dampness, indoor molds, dogs and cats keeping	Potential for recall bias in defining the outcome
Oftedal et al. 2009 [125], Norway, Oslo	Oslo birth cohort and sample from	Birth-10	2,329	Dispersion modelling (EPISODE), distance to main transport routes with	NO_2	NO_2 at birth year: range (1.5-84.0); mean (39.3) µg/m^3	Parental reporting of doctor-diagnosed asthma	Questionnaires completed at baseline and at 10	Sex, parental atopy, maternal smoking in pregnancy, paternal education, maternal marital status at	Potential for selection bias and recall bias in defining the outcome and diagnosis age, no

	simultaneous cross-sectional study			any form of motor transport				y.o. with a question about age of first diagnosis	the child's birth, contextual neighborhood level socioeconomic factors cohort indicator, keeping furry pets now, dampness problems now, parental ethnicity (age, birth weight, furry pets in early life, wall to wall carpeting in early life, dampness problems in early life, parental ethnicity and maternal education considered but not included in the final model)	adjustment for secondhand smoking
Patel et al. 2011 [61], USA, New York	Birth cohort (CCCEH)	Birth-5	593	Proximity to roadways, roadway density, truck route density, four-way street intersection density, number of bus stops, percentage of building area designated for commercial use	NA	At prenatal address (following addresses only reported as change in reference to prenatal address) Proximity to roadways: range (0.01-3.8); median (0.44) km Roadway density: range (10.9-45.5); median (19.4) km roadways/km^2 land Truck route density: range (0-12.6); median (2.5) km truck routes/km^2 land Four-way street intersection density: range (0-107); median (45.9) (# intersections/km^2 land Number of bus stops: range (0-17); median (6) stops Percentage of commercial building area: range (0.55-56.8); median (6.2)	Parental reporting of doctor-diagnosed asthma	Questionnaires completed every 3 months between birth and 2 y.o. and every 6 months from 2 y.o. to 5 y.o.	Sex, age, ethnicity, presence of smokers in the home, annual household income, concentrations of German cockroach and mouse allergen in dust samples	Study of Dominicans and African Americans, subjects included in analysis had lower asthma proportions than fully enrolled cohort, no adjustment for heredity, potential for recall bias in defining the outcome
Ranzi et al. 2014 [62], Italy, Rome	Birth cohort (GASPII)	Birth-7	672	LUR modelling, proximity to high traffic roads	NO_2	NO_2 at birth year: range (15.2-59.58); mean (37.17) µg/m^3 Proximity to high traffic roads at baseline: range (1.00- 10054.78); mean (395.12) m	Maternal reporting of doctor-diagnosed asthma	@ 6, 15 months, 4 and 7 y.o.	Sex, age, breastfeeding at 3 months, day care attendance, presence of pets in home, siblings, maternal and paternal smoking, maternal smoking during pregnancy, maternal and paternal education, presence of mold or dampness at home, familial asthma/allergies	Potential for selection bias and recall bias in defining the outcome
Shima and Adachi 2000 [89], Japan, 7 Chiba Prefecture communities	Cohort	9/10-12/13	842	Monitoring data	NO_2	NO_2: annual mean in the 7 communities ranging from 7.0 ppb (at Tateyama) to 31.3 ppb (at Ichikawa)	Parental reporting of asthma defined as ≥ 2 episodes of wheezing accompanied by dyspnoea that had ever been given the diagnosis of asthma by a doctor and occurrence of attacks or need for medication in past 2 years	Annual questionnaires during 3 years' follow-up	Sex, history of allergic disease, early-life respiratory diseases, breastfeeding in infancy, parental history of allergic disease, parental smoking habits, indoor NO_2, use of unvented heater in winter	Non-participants higher in urban districts, no adjustment for socioeconomic status, potential for recall bias in defining the outcome

Shima et al. 2002 [90], Japan, 8 Chiba Prefecture communities	Cohort	6-12	1,910	Monitoring data	NO_2, PM_{10}	NO_2: annual mean in the 8 communities ranging from 7.3 ppb (at Tateyama) to 31.4 ppb (at Ichikawa) PM_{10}: annual mean in the 8 communities ranging from 27.9 µg/m^3 (at Tateyama) to 53.7 µg/m^3 (at Chiba)	As in Shima and Adachi (2000)	Annual questionnaires during 6 years' follow-up	City, sex, history of allergic disease, early-life respiratory diseases, parental history of allergic diseases, maternal smoking habits, use of unvented heater in winter, house of steel/reinforced concrete	Non-participants higher in urban districts, no adjustment for socioeconomic status, potential for recall bias in defining the outcome
Shima et al. 2003 [102], Japan, 8 Chiba Prefecture communities	Cohort	6/9-10/13	1,858	Distance to trunk roads	NA	Traffic density range (33,775-83,097) vehicles/12 hours	As in Shima and Adachi (2000)	Annual questionnaires during 4 years' follow-up	Sex, school grade, history of allergic diseases, early-life respiratory diseases, breastfeeding in infancy, parental history of allergic diseases, maternal smoking, house of steel/reinforced concrete, use of unvented heater in winter	Non-participants higher in urban districts, no adjustment for socioeconomic status, potential for recall bias in defining the outcome
Tétreault et al. 2016 [91], Canada, Québec	Birth cohort	Birth-12	1,133,938	LUR modelling for NO_2, satellite imagery for $PM_{2.5}$	NO_2, $PM_{2.5}$	NO_2 at birth: range (4.47, 35.90); mean (15.51) ppb $PM_{2.5}$ at birth: range (2.32, 14.85); mean (9.86) µg/m^3	Any hospital discharge showing a diagnosis of asthma (in any diagnostic field) or two physician claims for asthma (visits to the emergency room or physician's office) occurring within a 2-year period (indexing occurred on the second visit)	NA	Sex, quintiles of the Pampalon deprivation index, year of birth in the cohort, secondhand smoke, region	Socioeconomic status was not available on individual base and was assessed using an area wide variable, adjustment for secondhand smoke was indirect, $PM_{2.5}$ calculations were performed at a large scale and only for years 2001 to 2006 and assumed constant for all years during the study period (1996 to 2011), no adjustment for heredity
Wang et al. 2016 [126], Taiwan, 11 communities in Taipei	Cohort (CEAS)	Birth-kindergarten (average age 5.5 ± 1.1)	2,661	Monitoring data	CO, NO_2, $PM_{2.5}$, PM_{10}	CO: range (0.39, 0.82); mean (0.63) ppb NO_2: range (16.48, 26.03); mean (23.04) ppb $PM_{2.5}$: range (17.55, 30.45); mean (28.81) µg/m^3 PM_{10}: range (27.75, 52.77); mean (48.14) µg/m^3	Doctor-diagnosed asthma and the presence of nocturnal cough or exercise wheeze in the past 12 months	At average age 5.5 ± 1.1	Sex, age, body mass index, environmental tobacco smoke, maternal history of atopy, maternal education and nationality, duration of breastfeeding, duration of sleep, number of siblings, temperature, relative humidity, and distance from home to the monitoring station (family income, dampness in the house, fungus on the house walls considered but not included in the final models)	Excluding premature birth children may bias results towards the null, potential for selection bias, potential for exposure misclassification (children's residences within 10 km from the air monitoring stations), potential for recall bias in defining the outcome
Yamazaki et al. 2014 [103], Japan, 57 elementary schools	Cohort (SORA)	6-9	10,069	Dispersion modelling for outdoor and indoor concentrations, living near heavily trafficked roads	EC, NO_x	EC: 814 children at highest EC level (≤ 2.2 µg/m^3) and 892 children at lowest EC level (≥ 3.3 µg/m^3) NO_x: 997 children at highest NO_x level (≤ 38.9 ppb) and 978 children at lowest NO_x level (≥ 57.4 ppb) Living near heavily trafficked roads: 794 children at < 50 m	Asthma defined based on "yes" answers to all of the following five questions: "has your child ever had an attack of wheezing or whistling that has caused him/her to be short of breath?", "has he/she ever had 2 or more such episodes?", "has a doctor ever said that he/she had asthma, asthmatic bronchitis, or child asthma?", "on that occasion, did his/her chest sound wheezy or produce a whistling sound?", and "at that time, did he/she have difficulty in breathing, accompanied by wheezing or whistling?"	Follow-up surveys were conducted annually for 4 years after baseline survey	Sex, grade as a surrogate variable of age, body mass index, respiratory symptoms, presence of allergic disease, feeding during the lactation period, past history of diseases or surgery, smoker in the household, siblings and first-born child, parents' past history of respiratory illnesses, housing materials, cookware used at home, heating system installed, humidifier/dehumidifier use, presence of mold in house, flooring materials used, presence of pets, use of air cleaners, use of clothes dryers, background concentrations of air pollution, and area	Restrictive asthma definition, decreasing concentration of air pollutants over the study period could have caused the ORs to be overestimated, potential for recall bias in defining the outcome, no adjustment for socioeconomic status

						zone; 7726 children at ≥ 50 m zone; 1549 children at reference area				
Yang et al. 2016 [44], The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth-14	3,701	LUR modelling	Oxidative Potential, BC, NO_2, $PM_{2.5}$, copper (Cu), iron (Fe), zinc (Zn), nickel (Ni), sulfur (S), vanadium (V)	BC at birth: range (0.8-3); mean (1.2) $10^{-5}m^{-1}$ NO_2 at birth: range (8.7-59.6); mean (23.1) $\mu g/m^3$ $PM_{2.5}$ at birth: range (15.3-21.1); mean (16.4) $\mu g/m^3$ For oxidative potential; see figure 1 in original paper	Parental reporting of doctor-diagnosed asthma	@ birth, 1, 2, 3, 4, 5, 6, 7, 8, 11-12 and 14 y.o.	Sex, maternal education, parental allergies, breastfeeding, maternal smoking during pregnancy, smoking in the child's home, use of gas for cooking, mould/ dampness in the child's home, pets at home, daycare attendance during first year of life and neighborhood percentage of low income household	Using LUR models to model oxidative potential, potential for recall bias in defining the outcome
Dell et al. 2014 [55], Canada, Toronto	Case-control	5-9	1,497	LUR modelling, monitoring data weighted by inverse distance to child's residence, distance to highways/ major roadways	NO_2	NO_2 (LUR): range (17.9-47.7); mean (28.3) ppb at birth < 50 m of a major roadway (birth) (13.5% of children)	Parental reporting of doctor-diagnosed asthma	NA	Adjustment variables selected from potential clustering by school, age, sex, parental asthma, prematurity, breastfeeding, low birthweight, crowding, lifetime daycare attendance, income adequacy, respondent's education level and home exposures to tobacco smoke, gas stoves, pets, cockroaches, damp spots and mold. These differ by model	Study participants differed in number of characteristics to non-participants, potential for recall bias in defining the outcome
English et al. 1999 [105], USA, San Diego	Case-control	≤ 14	8,280	Average daily traffic on streets within 168m buffer around residence	NA	Traffic volume at all streets within 550 ft. (cars/day): mean (41,497 controls; 42,880 asthma cases)	Asthma diagnosis based on data from Medi-Cal paid claims database which includes diagnosis based on ICD-9 code 493	NA	Sex, ethnicity, urban status (census block characteristics representing socioeconomic considered but not included in final models)	No adjustment for smoking and heredity, low income population
Hasunuma et al. 2016 [46], Japan, 9 cities and wards	Case-control (nested in SORA)	1.5-3	416	Dispersion modelling including indoor concentration assuming an infiltration rate from outdoor concentration, distance from heavily trafficked roads	EC, NO_x	EC: 6.5% of controls and 5.6% of cases at highest EC level (3.6-7.5 $\mu g/m^3$) 18.1% of controls and 17.8% of cases at lowest EC level (1.3-2.4 $\mu g/m^3$) NO_x: 6.0% of controls and 4.8% of cases at highest NO_x level (50.9-136.8 ppb) 25.3% of controls and 25.8% of cases at lowest NO_x level (13.9-32.5 ppb) Distance from traffic: 4.0% of controls and 3.4% of cases at <50 m from a main road 91.7% of controls and 92.3% of cases at ≥ 100 m from a main road	Asthma defined as a history of two or more attacks of dyspnoea accompanied by wheezing	@ 1.5 and 3 y.o.	Sex, districts, birth season, years of residence, feeding method during the first 3 months of life, familial smoking habits, house structure, heating system, history of pneumonia/bronchitis, empyema and allergic diseases, parental history of asthma, atopic dermatitis and pollinosis, and background air pollution concentrations	Potential for selection bias and follow-up rate low, case-control matching done by geographical region/ area, incidence of asthma identified only between 1.5 and 3 y.o. which is not sufficiently long for effects to reveal themselves, very young age for accurate diagnosis, no adjustment for socioeconomic status, potential for recall bias in defining the outcome

Nishimura et al. 2013 [60][c], USA, Chicago, Bronx, Houston, San Francisco, Puerto Rico	2 case-controls (GALA II and SAGE II)	8-21	3,015	Monitoring data at closest four monitors weighted by inverse distance squared to child's residence	NO_2, $PM_{2.5}$, PM_{10}	NO_2 at median birth year: all communities 25th and 75th percentiles (12.7, 24.0); mean (19.3) ppb $PM_{2.5}$ at median birth year: all communities 25th and 75th percentiles (8.5, 14.5); mean (11.8) µg/m^3 PM_{10} at median birth year: all communities 25th and 75th percentiles (23.6, 31.4); mean (27.8) µg/m^3	Reporting of doctor-diagnosed asthma plus ≥ 2 symptoms of coughing, wheezing or shortness of breath in 2 years before recruitment. Cases reporting asthma diagnosis in the first three years of life were excluded. Subgroup analysis undertaken stratified by high/low IgE as a proxy for risk of atopic/nonatopic asthma	NA	Sex, age, geographic region, ethnicity, composite socioeconomic status, familial asthma (in stratified analysis), maternal in utero smoking, environmental tobacco smoke in the household between 0 and 2 years old, and maternal language of preference in sensitivity analysis	Study of Latino Americans and African Americans, case-control matching done by geographical region/ area
Zmirou et al. 2004 [106], France, Paris, Nice, Toulouse, Clermont-Ferrand, Grenoble	Case-control (VESTA)	4-14	390	Traffic density within 300m to road distance ratio	NA	See figure 1 and 2 in original paper	Doctor-diagnosis of asthma by a network of private pediatricians or general practitioners. Cases had not to report doctor-diagnosis of asthma from ≥ 2 years before inclusion	NA	Age, sex, city, smoking during pregnancy, number of months of exposure to maternal smoking at home, day care attendance, parents' social category, number of months of gas usage for cooking, number of months with pets and traces of humidity at home (siblings considered but not included in the final model)	Crude traffic intensity categorization, potential for selection bias, case-control matching done by geographical region/ area, parents of control children had more often a university level education
Deng et al. 2015 [29], China, Changsha	Cross-sectional (CCHH)	3-6	2,490	Monitoring data weighted by inverse distance to child's kindergarten	NO_2, PM_{10} (as a mixture surrogate)	NO_2: range (31-62); mean (48) µg/m^3 PM_{10}: range (85-138); mean (103) µg/m^3	Parental reporting of doctor-diagnosed asthma	NA	Sex, age, breastfeeding, living area (downtown, suburban), parental atopy (birth weight, diagnosis of asthma or other allergic diseases) (parental smoking during pregnancy, maternal age, socioeconomic status (house size and mother occupation) and gestational age were considered but not included in the final models)	Excluding low birth weight /premature birth children may bias results towards the null, potential for selection bias by excluding kindergartens with low response rates and others with missing data, potential for recall bias in defining the outcome, higher likelihood that exposures include other sources of emissions, exposure at kindergarten location is not necessarily the same at home location
Deng et al. 2016 [18], China, Changsha	Cross-sectional (CCHH)	3-6	2.598	Monitoring data weighted by inverse distance to child's kindergarten	NO_2, PM_{10} (as a mixture surrogate)	NO_2: mean (49) µg/m^3 PM_{10}: mean (93) µg/m^3	Parental reporting of doctor-diagnosed asthma	NA	Sex, age, breastfeeding, environmental tobacco smoke at home, furry pets, parental atopy, indoor mold and dampness, indoor renovation	Excluding low birth weight /premature birth children may bias results towards the null, no adjustment for socioeconomic status, potential for selection bias by excluding kindergartens with low response rates and others with missing data, potential for recall bias due to the retrospective questionnaire study, higher likelihood that exposures include industrial emissions, exposure at kindergarten location is not necessarily the same at home location
Kim et al. 2016 [45], Korea, 45 elementary schools	Cross-sectional	6-7	1,828	Monitoring data	CO, NO_2, PM_{10}	CO: 25th and 75th percentiles (570, 740); mean (650) ppb	Parental reporting of doctor-diagnosed asthma	NA	Sex, allergic diseases of the parents, education levels of the parents, passive smoking, and family income	Potential for recall bias in defining the outcome, higher likelihood that exposures include other sources of emissions

						NO_2: 25th and 75th percentiles (22.6, 36.5); mean (29.7) ppb PM_{10}: 25th and 75th percentiles (51.5, 66.8); mean (58.8) µg/m^3				
Liu et al. 2016 [104], China, Shanghai	Cross-sectional (CCHH)	4-6	3,358	Monitoring data	NO_2, PM_{10}	NO_2: birth year - range (36.0, 67.1); mean (55.4) µg/m^3 PM_{10}: birth year - range (69.2, 96.6); mean (82.9) µg/m^3	Parental reporting of doctor-diagnosed asthma	NA	Age, sex, family history of atopy, ownership of the current residence, breastfeeding, home dampness, distance of residence from the nearest main traffic road, use of heating during winter, renovating the residence or buying new furniture during early lifetime, and household environmental tobacco smoke	Potential for recall and reporting bias due to the retrospective questionnaire study, higher likelihood that exposures include other sources of emissions

Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; BMI, Body Mass Index; CAPPS, The Canadian Asthma Primary Prevention Study; CCAAPS, The Cincinnati Childhood Allergy and Air Pollution Study; CASP, Critical Appraisal Skills Programme; CCCEH, Columbia Center for Children's Environmental Health birth cohort study; CCHH, China-Children-Homes-Health study; CEAS, Childhood Environment and Allergic Diseases Study; CHS, The Children's Health Study; EC, Elemental Carbon; ESCAPE, The European Study of Cohorts for Air Pollution Effects; GALA II, The Genes–environments and Admixture in Latino Americans; GASPII, The Gene and Environment Prospective Study in Italy; GINIplus, German Infant study on the influence of Nutrition Intervention plus air pollution and genetics on allergy development; ICD, International Classification of Diseases; IgE, Immunoglobulin E, LISAplus, Life style Immune System Allergy plus air pollution and genetics; LUR, Land-use Regression; MAAS, The Manchester Asthma and Allergy Study; Medi-Cal, California Medical Assistance Program; NA, Not Applicable; NO, Nitrogen Oxide; ORs, Odds Ratios; ppb, parts per billion; SAGE II, The Study of African Americans, Asthma, Genes and Environments; SES, socioeconomic status; SAGE, The Study of Asthma, Genes and the Environment; SORA, Study on Respiratory Disease and Automobile Exhaust; VESTA, Five (V) Epidemiological Studies on Transport and Asthma; y.o., years old. [a] CCAAPS children were born to at least one atopic parent, [b] defined as having, according to parental report, at least one first-degree relative with asthma or two first-degree relatives with other immunoglobulin E-mediated allergic disease including atopic dermatitis, seasonal or perennial allergic rhinitis or food allergy.

938 Table 2: Overall and age-specific meta-analyses results

	Exposure	Overall random-effects OR (95% CI)	Overall fixed-effects OR (95% CI)	Number included studies	Sensitivity analysis 1: excluding study/ studies contributing to largest weight in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 2: excluding case-control studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 3: excluding cross-sectional studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 4: excluding studies with special characteristics in random-effects meta-analysis OR (95% CI)
Overall meta-analysis	BC	**1.08 (1.03, 1.14)**, I^2 = 0%, P = 0.87	**1.08 (1.03, 1.14)**, I^2 = 0%, P = 0.87	8	Study: Clark et al. 2010 (Weight = 73.1%) **1.12 (1.01, 1.24)**, I^2 = 0%, P = 0.88	Study: Clark et al. 2010 **1.12 (1.01, 1.24)**, I^2 = 0%, P = 0.88	None included	Study: Carlsten et al. 2010 (reason: high risk birth cohort) **1.09 (1.03, 1.15)**, I^2 = 0%, P = 0.81
	NO_2	**1.05 (1.02, 1.07)**, I^2 = 65%, P = 0.0001	**1.02 (1.01, 1.03)**, I^2 = 65%, P = 0.0001	20	Study: Tétreault et al. 2016 (Weight = 11.6%) **1.05 (1.02, 1.08)**, I^2 = 61%, P = 0.0003	Studies: Clark et al. 2010, Dell et al. 2014, Nishimura et al. 2013 **1.04 (1.02, 1.07)**, I^2 = 67%, P = 0.0001	Studies: Deng et al. 2015, Kim et al. 2016, Liu et al. 2016 **1.04 (1.02, 1.07),** I^2 = 58%, P = 0.001	Study: Carlsten et al. 2010 (reason: high risk birth cohort) **1.04 (1.02, 1.07)**, I^2 = 66%, P = 0.0001
	NO_x	1.48 (0.89, 2.45), I^2 = 87%, P = 0.00001	**1.68 (1.42, 1.9**9), I^2 = 87%, P = 0.00001	7	Study: Mölter et al. 2014 b – PIAMA component (Weight = 16.5%) 1.49 (0.79, 2.82), I^2 = 89%, P = 0.00001	None included	None included	None included
	$PM_{2.5}$	**1.03 (1.01, 1.05)**, I^2 = 28%, P = 0.18	**1.03 (1.02, 1.04),** I^2 = 28%, P = 0.81	10	Study: Tétreault et al. 2016 (Weight = 33.1%) **1.03 (1.00, 1.05)**, I^2 = 20%, P = 0.26	Studies: Clark et al. 2010, Nishimura et al. 2013 **1.04 (1.02, 1.06)**, I^2 = 8%, P = 0.37	None included	Study: Carlsten et al. 2010 (reason: high risk birth cohort) **1.03 (1.01, 1.04)**, I^2 = 0%, P = 0.51
	PM_{10}	**1.05 (1.02, 1.08)**, I^2 = 29%, P = 0.16	**1.04 (1.02, 1.06),** I^2 = 29%, P = 0.16	12	Study: McConnell et al. 2010 (Weight = 25.7%) **1.06 (1.02, 1.10)**, I^2 = 16%, P = 0.29	Studies: Clark et al. 2010, Nishimura et al. 2013 **1.03 (1.00, 1.06)**, I^2 = 4%, P = 0.40	Study: Deng et al. 2015, Kim et al. 2016, Liu et al. 2016 **1.05 (1.00, 1.10)**, I^2 = 44%, P = 0.07	None included
Age-specific meta-analysis ≤ 6 years' old	Exposure	Age-specific ≤ 6 years old random-effects meta-analysis OR (95% CI)	Age-specific ≤ 6 years old fixed-effects meta-analysis OR (95% CI)	Number included studies	Sensitivity analysis 1: excluding study/ studies contributing to largest weight in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 2: excluding case-control studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 3: excluding cross-sectional studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 3: excluding studies with special characteristics in random-effects meta-analysis OR (95% CI)
	BC	**1.17 (1.01, 1.36)**, I^2 = 45%, P = 0.12	**1.09 (1.03, 1.16)**, I^2 = 45%, P = 0.12	5	Study: Clark et al. 2010 (Weight = 47.4%) **1.27 (1.05, 1.54)**, I^2 = 42%, P = 0.18	Study: Clark et al. 2010 **1.27 (1.05, 1.54)**, I^2 = 02%, P = 0.29	None included	None included
	NO_2	**1.08 (1.04, 1.12)**, I^2 = 26%, P = 0.23	**1.07 (1.05, 1.10)**, I^2 = 26%, P = 0.23	7	Study: Clark et al. 2010 (Weight = 38.6%) **1.10 (1.06, 1.13)**, I^2 = 0%, P = 0.42	Study: Clark et al. 2010 **1.10 (1.06, 1.213)**, I^2 = 0%, P = 0.42	Study: Deng et al. 2015, Liu et al. 2016 **1.07 (1.02, 1.36)**, I^2 = 32%, P = 0.21	None included
	NO_x	1.02 (0.69, 1.49), I^2 = 69%, P = 0.007	1.02 (0.85, 1.24), I^2 = 69%, P = 0.007	6	Study: Mölter et al. 2014 b – PIAMA component (Weight = 22.9%) 0.97 (0.59, 1.58), I^2 = 70%, P = 0.010	Study: Hasunuma et al. 2016 1.15 (0.80, 1.66), I^2 = 52%, P = 0.08	None included	None included
	$PM_{2.5}$	1.04 (0.99, 1.11), I^2 = 41%, P = 0.16	**1.02 (1.00, 1.04)**, I^2 = 41%, P = 0.16	4	Study: Clark et al. 2010 (Weight = 58.8%) **1.09 (1.02, 1.17)**, I^2 = 0%, P = 0.94	Study: Clark et al. 2010 (Weight = 58.8%) **1.09 (1.02, 1.17)**, I^2 = 0%, P = 0.94	None included	None included
	PM_{10}	**1.09 (1.04, 1.15)**, I^2 = 12%, P = 0.34	**1.09 (1.04, 1.14)**, **I^2 = 12%, P = 0.34**	5	Study: Liu et al. 2016 (Weight = 49.2%) **1.09 (1.02, 1.17)**, I^2 = 34%, P = 0.21	Study: Clark et al. 2010 **1.07 (1.01, 1.12)**, I^2 = 0%, P = 0.46	Study: Deng et al. 2015, Liu et al. 2016 **1.12 (1.00, 1.25)**, I^2 = 24%, P = 0.27	None included
Age-specific meta-analysis > 6 years' old	Exposure	Age-specific > 6 years old random-effects meta-analysis OR (95% CI)	Age-specific > 6 years old fixed-effects meta-analysis OR (95% CI)	Number included studies	Sensitivity analysis 1: excluding study/ studies contributing to largest weight in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 2: excluding case-control studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 3: excluding cross-sectional studies in random-effects meta-analysis OR (95% CI)	Sensitivity analysis 3: excluding studies with special characteristics in random-effects meta-analysis OR (95% CI)
	BC	**1.12 (1.00, 1.24)**, I^2 = 0%, P = 0.79	**1.12 (1.00, 1.24),** I^2 = 0%, P = 0.79	6	Study: Gehring et al. 2015 b – PIAMA component (Weight = 46.8%) 1.06 (0.92, 1.23), I^2 = 0%, P = 0.83	None included	None included	Carlsten et al. 2010 (reason: high risk birth cohort) **1.15 (1.01, 1.30)**, I^2 = 0%, P = 0.78
	NO_2	**1.03 (1.00, 1.06)**, I^2 = 62%, P = 0.001	**1.02 (1.01, 1.03)**, I^2 = 62%, P = 0.001	14	Study: Tétreault et al. 2016 (Weight = 17.6%) **1.04 (1.00, 1.08)**, **I^2 = 65%**, **P = 0.02**	Study: Nishimura et al. 2013 **1.03 (1.00, 1.06)**, I^2 = 62%, P = 0.002	Study: Kim et al. 2016 **1.04 (1.01, 1.07)**, **I^2 = 62%**, **P = 0.002**	Carlsten et al. 2010 (reason: high risk birth cohort) **1.03 (1.00, 1.06)**, I^2 = 63%, P = 0.001
	NO_x	1.46 (0.77, 2.78), I^2 = 89%, P = 0.00001	**1.72 (1.41, 2.09), I^2 = 89%, P = 0.00001**	6	Study: Mölter et al. 2014 b – PIAMA component (Weight = 19.1%) 1.47 (0.62, 3.52), I^2 = 91%, P = 0.00001	None included	None included	None included
	$PM_{2.5}$	**1.04 (1.02, 1.07)**, I^2 = 3%, P = 0.41	**1.04 (1.02, 1.06),** I^2 = 13%, P = 0.41	8	Study: Tétreault et al. 2016 (Weight = 80.3%) **1.06 (1.00, 1.12)**, I^2 = 12%, P = 0.34	Study: Nishimura et al. 2013 **1.05 (1.01, 1.09)**, I^2 = 16%, P = 0.31	None included	Carlsten et al. 2010 (reason: high risk birth cohort) **1.04 (1.02, 1.06)**, I^2 = 0%, P = 0.78
	PM_{10}	**1.04 (1.00, 1.08)**, I^2 = 5%, P = 0.39	**1.04 (1.00, 1.08),** I^2 = 5%, P = 0.39	8	Study: Nishimura et al. 2013 (Weight = 51.0%) 1.03 (0.96, 1.11), I^2 = 14%, P = 0.32	Study: Nishimura et al. 2013 1.03 (0.96, 1.11), I^2 = 14%, P = 0.32	Study: Kim et al. 2016 1.04 (0.99, 1.09), I^2 = 18%, P = 0.29	None included

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Figures legends

Figure 1. Study selection process for meta-analysis.

Figure 2. Flow chart of study screening process.

Figure 3. BC random-effects meta-analysis. Individual and summary random-effects estimates for associations between BC per 0.5 x 10^{-5} m^{-1} and asthma at any age. Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; GINI, German Infant study on the influence of Nutrition Intervention on allergy development; LISA, Life style Immune System Allergy; MAAS, The Manchester Asthma and Allergy Study; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy.

Figure 4. NO_2 random-effects meta-analyses. Individual and summary random-effects estimates for associations between NO_2 per 4 µg/m^3 and asthma at any age. Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; CAPPS, The Canadian Asthma Primary Prevention Study; GINI, German Infant study on the influence of Nutrition Intervention on allergy development; LISA, Life style Immune System Allergy; MAAS, The Manchester Asthma and Allergy Study; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy; SAGE, The Study of Asthma, Genes and the Environment.

Figure 5. NO_x random-effects meta-analyses. Individual and summary random-effects estimates for associations between NO_x per 30 µg/m^3 and asthma at any age. Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; GINI, German Infant study on the influence of Nutrition Intervention on allergy development; LISA, Life style Immune System Allergy; MAAS, The Manchester Asthma and Allergy Study; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy; SAGE, The Study of Asthma, Genes and the Environment.

Figure 6. $PM_{2.5}$ random-effects meta-analyses. Individual and summary random-effects estimates for associations between $PM_{2.5}$ per 1 µg/m^3 and asthma at any age. Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; GINI, German Infant study on the influence of Nutrition Intervention on

963 allergy development; LISA, Life style Immune System Allergy; MAAS, The Manchester Asthma and Allergy
964 Study; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy; SAGE, The Study of Asthma, Genes
965 and the Environment.

966 Figure 7. PM_{10} random-effects meta-analyses. Individual and summary random-effects estimates for associations
967 between PM_{10} per 2 $\mu g/m^3$ and asthma at any age. Abbreviations: BAMSE, Barn (children), Allergy, Milieu,
968 Stockholm, an Epidemiology project; GINI, German Infant study on the influence of Nutrition Intervention on
969 allergy development; LISA, Life style Immune System Allergy; MAAS, The Manchester Asthma and Allergy
970 Study; PIAMA, The Prevention and Incidence of Asthma and Mite Allergy; SAGE, The Study of Asthma, Genes
971 and the Environment.

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