



Review

Traffic-Related Air Pollution and Childhood Asthma: Recent Advances and Remaining Gaps in the Exposure Assessment Methods

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Abstract: *Background:* Current levels of traffic-related air pollution (TRAP) are associated with the development of childhood asthma, although some inconsistencies and heterogeneity remain. An important part of the uncertainty in studies of TRAP-associated asthma originates from uncertainties in the TRAP exposure assessment and assignment methods. In this work, we aim to systematically review the exposure assessment methods used in the epidemiology of TRAP and childhood asthma, highlight recent advances, remaining research gaps and make suggestions for further research. *Methods:* We systematically reviewed epidemiological studies published up until 8 September 2016 and available in Embase, Ovid MEDLINE (R), and “Transport database”. We included studies which examined the association between children’s exposure to TRAP metrics and their risk of “asthma” incidence or lifetime prevalence, from birth to the age of 18 years old. *Results:* We found 42 studies which examined the associations between TRAP and subsequent childhood asthma incidence or lifetime prevalence, published since 1999. Land-use regression modelling was the most commonly used method and nitrogen dioxide (NO₂) was the most commonly used pollutant in the exposure assessments. Most studies estimated TRAP exposure at the residential address and only a few considered the participants’ mobility. TRAP exposure was mostly assessed at the birth year and only a few studies considered different and/or multiple exposure time windows. We recommend that further work is needed including e.g., the use of new exposure metrics such as the composition of particulate matter, oxidative potential and ultra-fine particles, improved modelling e.g., by combining different exposure assessment models, including mobility of the participants, and systematically investigating different exposure time windows. *Conclusions:* Although our previous meta-analysis found statistically significant associations for various TRAP exposures and subsequent childhood asthma, further refinement of the exposure assessment may improve the risk estimates, and shed light on critical exposure time windows, putative agents, underlying mechanisms and drivers of heterogeneity.

Keywords: asthma; childhood; traffic-related air pollution; exposure assessment; systematic review

1. Introduction

Asthma is a chronic inflammatory disease of the airway which has a large impact on quality of life and poses a great burden on health services [1]. In children, asthma is the most commonly reported chronic disease in developed countries [2]. Environmental factors, importantly including improved

hygiene, ambient air pollution exposures, and early-life exposures to microbes and aeroallergens, contribute to the development of asthma [2]. In a recent systematic review and meta-analyses, we found statistically significant associations between traffic-related air pollution (TRAP) and the incidence and lifetime prevalence of childhood asthma, although there was significant heterogeneity in some of the risk estimates [3]. These effects are biologically plausible. Britain's Committee on the Medical Effects of Air Pollutants proposed four mechanisms by which air pollution can affect asthma: (1) oxidative stress and damage; (2) inflamed pathways; (3) airway remodeling; and (4) enhancement of respiratory sensitization to allergens [4]. Oxidative stress relates to common asthmatic traits [5], and was suggested to play a role in asthma pathogenesis [6]. Further, it was previously highlighted as one chief pathway which underpins the adverse health effects of (traffic-related) air pollution on the respiratory systems [7].

TRAP is a particularly important and challenging exposure to study given its ubiquity, its dominance in present urban areas, its proximity to human receptors, and its high spatial and temporal variability [8–11]. For example, the local traffic contribution to ambient nitrogen dioxide (NO₂) can be up to 80%, and ranges between 9% and 53% for urban particulate matter less than 10 micrometres in diameter (PM₁₀), and 9%–66% for urban particulate matter less than 2.5 micrometres in diameter (PM_{2.5}) [8].

In the epidemiological studies included in the most recent meta-analyses of TRAP and the development of childhood asthma, different exposure assessment methods and indices have been used to characterise the exposure to TRAP, including distance to roads, active measurement of air pollutants, use of routinely measured air pollution data, land-use regression (LUR) modelling, air dispersion modelling and remote sensing [3]. These various methods and indices differ substantially and have advantages and disadvantages in terms of their spatial and temporal resolution, specificity to traffic, data and effort/expertise requirements, transferability and information provided on the actual pollutants. Furthermore, the different epidemiological studies focused on different pollutants and different exposure time windows [3]. The use of different exposure assessment methods in health effects or impacts studies can result in different estimates, partly due to the difference in accuracy and precision of the exposure estimates and the potential differential effects of different pollutants. Although the evidence base is very limited, research has shown differences, for example in the performance of and the results from dispersion models versus LUR [12–14] which in two studies translated into small differences in the risk estimates, but in one study translated into differences in the direction of effect estimates of NO₂ on birth weight [13]. In a previous meta-analysis on TRAP and childhood asthma, there was some suggestion of a difference between associations with NO₂ from within-community studies that used LUR models (five studies, odds ratio (OR) = 1.14, 95% confidence interval (CI) 1.06, 1.23) and those from studies that used dispersion models (five studies, OR = 1.02, 95% CI 0.97, 1.07) [15]. Further, there were differences in estimated health impacts when using different pollutant-specific exposure-response functions. For example, cases of asthma attributable to PM₁₀ and NO₂ differ substantially to cases of asthma attributable to black carbon [16].

In this paper, we aim to describe and discuss the exposure assessments conducted in studies of TRAP and childhood asthma development, including the methods used in the different regions, the pollutants and exposure assignment and time windows studied. We then highlight research gaps and make suggestions for further research in this rapidly growing area. Our focus is on the exposure assessments and not the effects of TRAP on asthma development per se; which we reviewed in depth elsewhere [3]. Our results and discussion are applicable to other research on TRAP and various health outcomes, beyond childhood asthma, as the exposure assessment methods are often similar [11,17].

2. Methods

We conducted a systematic review to synthesize the literature on TRAP exposures and the subsequent risk of childhood asthma development defined as incidence or lifetime prevalence [3]. We followed established guidance published by the University of York's Centre for Reviews and

Dissemination [18]. We registered a protocol (registration number: CRD42014015448) with the international prospective register of systematic reviews (PROSPERO) documenting our methodological approach a priori [19].

We performed the searches on 8 September 2016 via the database search interface OvidSP (<http://ovidsp.ovid.com/>). We searched the following databases for relevant studies: Embase (1996 to week 36, 2016), Ovid MEDLINE (R) (1996 to August 2016), and “Transport Database” (1988 to August 2016). We identified relevant studies by entering four sets of combined keywords in the “Multi-Field Search” option in OvidSP. We searched for the selected keyword combinations in “All Fields”. The keyword combinations were:

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 and no limits on language although we eventually excluded three foreign language studies due to translation difficulties [20–22]. We conducted a hand search in the reference lists of all the included studies and of previous relevant reviews we identified [15,17,23–30]. We contacted authors of unpublished studies (abstracts only) and the authors of the most recurrent studies to ensure the inclusion of all relevant published material on the topic and this resulted in the inclusion of two additional studies [31,32]. We searched Google for any other material related to “traffic-related air pollution” AND “childhood asthma” and this resulted in the inclusion of one additional study [33]. One study was also not identified in the searches but by one of the reviewers and this was included [34]. We exported studies into an Endnote X7.4 library and removed duplicates automatically using the Endnote function “Find Duplicates”. For inclusion, we selected studies that met *all* the following criteria:

- Were published epidemiological/observational studies;
- Explicitly specified the term “asthma” as an outcome for investigation;
- Examined the childhood exposure from birth until 18 years old [35] to any designated TRAP metric or established traffic-related air pollutant including proximity to roads or traffic, carbon monoxide (CO), elemental carbon (EC), nitrogen oxides (NO_x), nitric oxide (NO), NO₂, hydrocarbons, particles of different aerodynamic diameters (PM_{2.5}, PM₁₀, PM_{coarse}, UFPs) or PM_{2.5} absorbance as a marker for black carbon (BC) concentrations [10,36]; and
- 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.

All titles and abstracts were reviewed against the inclusion criteria by one researcher (Haneen Khreis) with a random 20% independently reviewed by another researcher. All potentially relevant studies were then retrieved and the available full-papers reviewed against the inclusion criteria by one researcher (Haneen Khreis) with a random 50% independently reviewed by another researcher (Mark J. Nieuwenhuijsen). Screening was undertaken manually and differences were resolved by consensus. The following data items were extracted from each included study:

1. Study reference and setting;
2. Study design;
3. Age group;
4. Number of participants;
5. Exposure assessment method(s);
6. Pollutant(s) studied;
7. Exposure assessment place;

8. Exposure assessment time; and
9. Air pollution estimates validation, if any.

Data was primarily extracted from the main papers of the included studies. Where necessary, data items were missing from the main papers, data was extracted from the supplementary materials [31,37–52], and the associated publications [53–66]. Data extraction was undertaken manually by one researcher (Haneen Khreis). A random 50% was independently reviewed by another researcher (Mark J. Nieuwenhuijsen). A fuller detail of the screening methodology can be found in Khreis et al. (2017) [3].

3. Results

3.1. Overview

The databases searches yielded 4276 unique articles, from which 95 were selected for detailed assessment of the full text, one of which was identified by a peer reviewer. Figure 1 shows the flow of papers. A total of 42 studies met our inclusion criteria [31–34,36–48,50–52,58,67–87] (Table 1).

A summary of the included studies' key characteristics is shown in Table 1. Ages of participants ranged from 1 to 18 years old and sample sizes ranged from 184 [69] to 1,133,938 [85]. Follow-up periods ranged from 1 to 16 years [47]. Eighteen studies were conducted in Europe, 11 in North America, 5 in Japan, 3 in China and 1 in each of Korea and Taiwan. Thirty-two studies were cohort studies (25 of which were birth cohorts), 6 studies were case-control studies (2 of which were nested in a birth cohort), and 4 studies were cross-sectional.

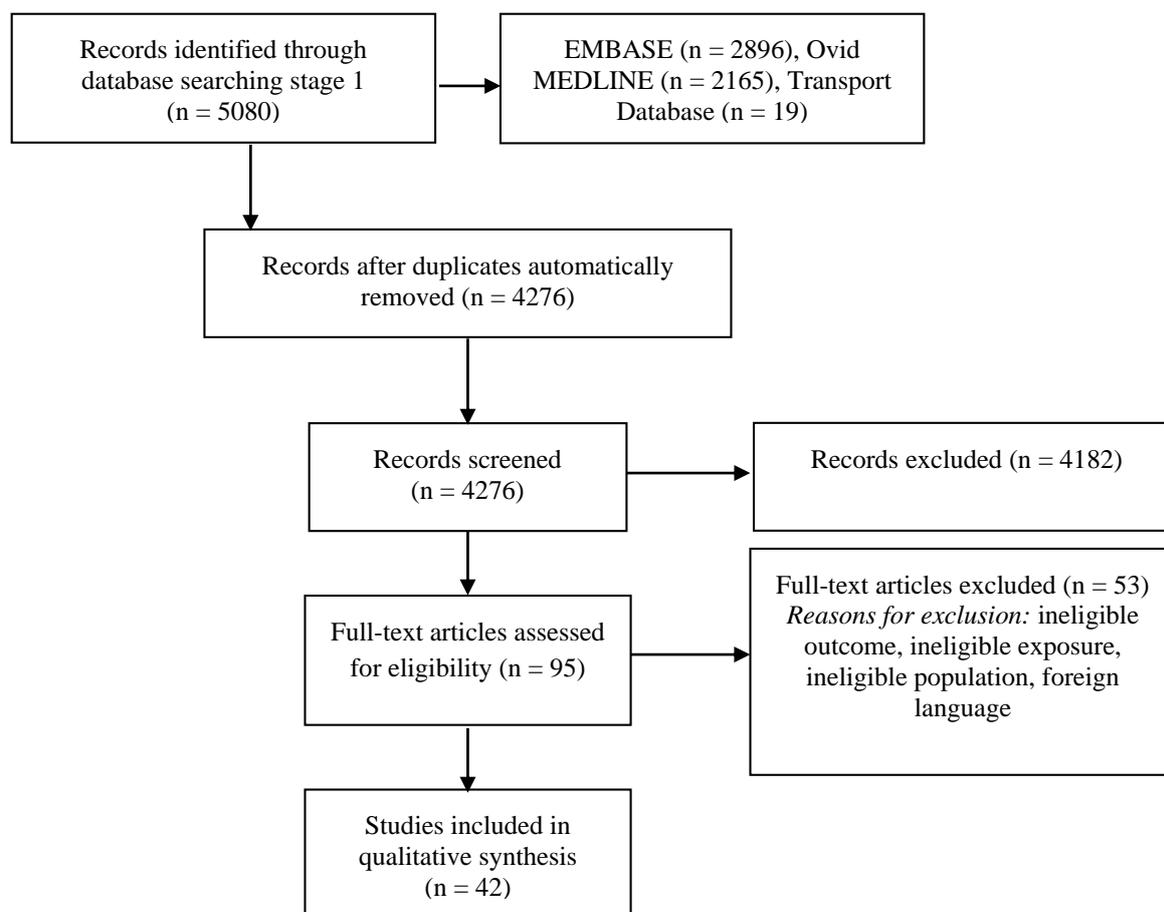


Figure 1. Study screening process.

Table 1. Main characteristics of the included studies.

Study Reference	Setting	Study Design	Age Group (Years)	Participants Included in the Analysis	Exposure Assessment	Pollutant(s)
Brauer, Hoek, Van Vliet, Meliefste, Fischer, Wijga, Koopman, Neijens, Gerritsen and Kerkhof [68]	The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth–2	2989	LUR modelling	BC, NO ₂ , PM _{2.5}
Brauer, Hoek, Smit, De Jongste, Gerritsen, Postma, Kerkhof and Brunekreef [67]	The Netherlands, north, west and center communities	Follow-up on Brauer et al. (2002)	Birth–4	2826	LUR modelling	BC, NO ₂ , PM _{2.5}
Brunst, Ryan, Brokamp, Bernstein, Reponen, Lockey, Khurana Hershey, Levin, Grinshpun and LeMasters [46]	USA, Cincinnati	Birth cohort (CCAAPS)	Birth–7	589	LUR modelling	EC
Carlsten, Dybuncio, Becker, Chan-Yeung and Brauer [69]	Canada, Vancouver	Birth cohort (CAAPS)	Birth–7	184	LUR modelling	BC, NO, NO ₂ , PM _{2.5}
Clark, Demers, Karr, Koehoorn, Lencar, Tamburic and Brauer [37]	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}
Fuertes, Standl, Cyrys, Berdel, von Berg, Bauer, Krämer, Sugiri, Lehmann and Koletzko [72]	Germany	2 birth cohorts (GINIplus and LISAplus)	3–10	4585	LUR modelling	BC, NO ₂ , PM _{2.5}
Gehring, Cyrys, Sedlmeir, Brunekreef, Bellander, Fischer, Bauer, Reinhardt, Wichmann and Heinrich [73]	Germany, Munich	2 birth cohorts (GINI and LISA)	Birth–2	1756	LUR modelling	BC, NO ₂ , PM _{2.5}
Gehring, Wijga, Brauer, Fischer, de Jongste, Kerkhof, Oldenwening, Smit and Brunekreef [39]	The Netherlands, north, west and center communities	Follow-up on Brauer et al. (2007)	Birth–8	3143	LUR modelling	BC, NO ₂ , PM _{2.5}
Gehring, Beelen, Eeftens, Hoek, de Hoogh, de Jongste, Keuken, Koppelman, Meliefste and Oldenwening [48]	The Netherlands, north, west and center communities	Follow-up on Gehring et al. (2010)	Birth–12	3702	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)
Gehring, Wijga, Hoek, Bellander, Berdel, Brüske, Fuertes, Gruzieva, Heinrich and Hoffmann [47]	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}
Gruzieva, Bergström, Hulchiy, Kull, Lind, Melén, Moskalenko, Pershagen and Bellander [40]	Sweden, Stockholm	Birth cohort (BAMSE)	Birth–12	3633	Dispersion modelling (Airviro, street canyon contribution for 160 houses)	NO _x , PM ₁₀
Jerrett, Shankardass, Berhane, Gauderman, Künzli, Avol, Gilliland, Lurmann, Molitor and Molitor [74]	USA, 11 southern Californian communities	Cohort (CHS)	10–18	209	NO ₂ Palmes tubes monitoring for 2 weeks in 2 seasons at the child's residence	NO ₂
Kerkhof, Postma, Brunekreef, Reijmerink, Wijga, De Jongste, Gehring and Koppelman [75]	The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth–8	916	LUR modelling	BC, NO ₂ , PM _{2.5}
Krämer, Sugiri, Ranft, Krutmann, von Berg, Berdel, Behrendt, Kuhlbusch, Hochadel and Wichmann [36]	Germany, Wesel	2 birth cohorts (GINIplus and LISAplus)	4–6	2059	LUR modelling, distance to next major road traversed by more than 10,000 cars/day	BC, NO ₂
LeMasters, Levin, Bernstein, Lockey, Lockey, Burkle, Khurana Hershey, Brunst and Ryan [76]	USA, Cincinnati	Birth cohort (CCAAPS)	Birth–7	575	LUR modelling	EC
Lindgren, Strohm, Björk and Jakobsson [41]	Sweden, Scania	Birth cohort	Birth–6	6007	Dispersion modelling (AERMOD), traffic intensity on road with heaviest traffic within 100 m around residence	NO _x

Table 1. Cont.

Study Reference	Setting	Study Design	Age Group (Years)	Participants Included in the Analysis	Exposure Assessment	Pollutant(s)
MacIntyre, Brauer, Melén, Bauer, Bauer, Berdel, Bergström, Brunekreef, Chan-Yeung, Klümper, Fuertes, Gehring, Gref, Heinrich, Herbarth, Kerkhof, Koppelman, Kozyrskiy, Pershagen, Postma, Thiering, Tiesler, Carlsten and Group [52]	Sweden, Canada, Germany, The Netherlands	Pooled data from 6 birth cohorts: BAMSE; CAPP; GINI; LISA; PIAMA; SAGE	Birth–8	5115	LUR modelling, dispersion modelling for BAMSE only	NO ₂ (sensitivity analyses for BC and PM _{2.5})
McConnell, Islam, Shankardass, Jerrett, Lurmann, Gilliland and Gauderman [42]	USA, 13 southern Californian communities	Cohort (CHS)	Kindergarten/first grade–fourth grade	2497	Dispersion modelling for NO _x (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 150 m around residence and school	NO _x , NO ₂ , PM _{2.5} , PM ₁₀
Mölder, Agius, de Vocht, Lindley, Gerrard, Custovic and Simpson [50]	England, Greater Manchester	Birth cohort (MAAS)	Birth–11	1108	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
Mölder, Simpson, Berdel, Brunekreef, Custovic, Cyrys, de Jongste, de Vocht, Fuertes and Gehring [51]	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 100-m radius	BC, NO ₂ , NO _x , PM _{2.5} , PM ₁₀ , PM _{coarse}
Morgenstern, Zutavern, Cyrys, Brockow, Gehring, Koletzko, Bauer, Reinhardt, Wichmann and Heinrich [58]	Germany, Munich Metropolitan area	2 birth cohorts (GINI and LISA)—extension on Gehring et al. (2002)	Birth–2	3577	LUR modelling, living close to major road	BC, NO ₂ , PM _{2.5}
Morgenstern, Zutavern, Cyrys, Brockow, Koletzko, Kramer, Behrendt, Herbarth, von Berg and Bauer [77]	Germany, Munich	2 birth cohorts (GINI and LISA)	4–6	2436	LUR modelling, minimum distance to next motorway, federal or state road	BC, NO ₂ , PM _{2.5}
Oftedal, Nystad, Brunekreef and Nafstad [78]	Norway, Oslo	Oslo birth cohort and sample from simultaneous cross-sectional study	Birth–10	2329	Dispersion modelling (EPISODE), distance to main transport routes with any form of motor transport	NO ₂
Patel, Quinn, Jung, Hoepner, Diaz, Perzanowski, Rundle, Kinney, Perera and Miller [44]	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
Rancière [34]	Paris, France	Birth cohort (PARIS)	Birth–4	2015	Dispersion modelling	NO _x
Ranzi, Porta, Badaloni, Cesaroni, Lauriola, Davoli and Forastiere [45]	Italy, Rome	Birth cohort (GASPII)	Birth–7	672	LUR modelling, proximity to high traffic roads	NO ₂
Shima and Adachi [79]	Japan, 7 Chiba Prefecture communities	Cohort	9/10–12/13	842	Monitoring data	NO ₂
Shima, Nitta, Ando and Adachi [81]	Japan, 8 Chiba Prefecture communities	Cohort	6–12	1910	Monitoring data	NO ₂ , PM ₁₀
Shima, Nitta and Adachi [80]	Japan, 8 Chiba Prefecture communities	Cohort	6/9–10/13	1858	Distance to trunk roads	NA

Table 1. Cont.

Study Reference	Setting	Study Design	Age Group (Years)	Participants Included in the Analysis	Exposure Assessment	Pollutant(s)
Tétreault, Doucet, Gamache, Fournier, Brand, Kosatsky and Smargiassi [85]	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}
Wang, Tung, Tang and Zhao [82]	Taiwan, 11 communities in Taipei	Cohort (CEAS)	Birth–kindergarten (average age 5.5 ± 1.1)	2661	Monitoring data	CO, NO ₂ , PM _{2.5} , PM ₁₀
Yamazaki, Shima, Nakadate, Ohara, Omori, Ono, Sato and Nitta [83]	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
Yang, Janssen, Brunekreef, Cassee, Hoek and Gehring [31]	The Netherlands, north, west and center communities	Birth cohort (PIAMA)	Birth–14	3701	LUR modelling	Oxidative Potential, BC, NO ₂ , PM _{2.5} , copper (Cu), iron (Fe), zinc (Zn), nickel (Ni), sulfur (S), vanadium (V)
Dell, Jerrett, Beckerman, Brook, Foty, Gilbert, Marshall, Miller, To and Walter [38]	Canada, Toronto	Case-control	5–9	1497	LUR modelling, monitoring data weighted by inverse distance to child's residence, distance to highways/major roadways	NO ₂
English, Neutra, Scaif, Sullivan, Waller and Zhu [71]	USA, San Diego	Case-control	≤14	8280	Average daily traffic on streets within a 168-m buffer around residence	NA
Hasunuma, Sato, Iwata, Kohno, Nitta, Odajima, Ohara, Omori, Ono and Yamazaki [33]	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
[43]	USA, Chicago, Bronx, Houston, San Francisco, Puerto Rico	2 case-controls (GALA II and SAGE II)	8–21	3015	Monitoring data at closest four monitors weighted by inverse distance squared to child's residence	NO ₂ , PM _{2.5} , PM ₁₀
Zmirou, Gauvin, Pin, Momas, Sahraoui, Just, Le Moulllec, Bremont, Cassadou and Reungoat [84]	France, Paris, Nice, Toulouse, Clermont-Ferrand, Grenoble	Case-control (VESTA)	4–14	390	Traffic density within 300 m to road distance ratio	NA
Deng, Lu, Norbäck, Bornehag, Zhang, Liu, Yuan and Sundell [70]	China, Changsha	Cross-sectional (CCHH)	3–6	2490	Monitoring data weighted by inverse distance to child's kindergarten	NO ₂ , PM ₁₀ (as a mixture surrogate)
Deng, Lu, Ou, Chen and Yuan [86]	China, Changsha	Cross-sectional (CCHH)	3–6	2598	Monitoring data weighted by inverse distance to child's kindergarten	NO ₂ , PM ₁₀ (as a mixture surrogate)
[32]	Korea, 45 elementary schools	Cross-sectional	6–7	1828	Monitoring data	CO, NO ₂ , PM ₁₀
Liu, Huang, Hu, Fu, Zou, Sun, Shen, Wang, Cai and Pan [87]	China, Shanghai	Cross-sectional (CCHH)	4–6	3358	Monitoring data	NO ₂ , PM ₁₀

Abbreviations: BAMSE, Barn (children), Allergy, Milieu, Stockholm, an Epidemiology project; BC: black carbon; CAPPs, The Canadian Asthma Primary Prevention Study; CCAAPS, The Cincinnati Childhood Allergy and Air Pollution Study; 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; LISApplus, 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; PM: particulate matter; SAGE II, The Study of African Americans, Asthma, Genes and Environments; 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.

3.2. Exposure Assessment Methods

The exposure to TRAP was assessed using different methods, sometimes in isolation and other times in combination with each other (Table 1). Most studies ($N = 22$) used LUR models, 16 studies used TRAP surrogates (e.g., proximity to roadways), 11 studies used traffic-related air pollutant concentrations measured at fixed-site monitoring stations, 8 studies used air dispersion modelling, 1 study used remote sensing and 1 study used diffusion tubes at the residence to measure NO_2 . These methods vary substantially in terms of their spatial and temporal resolution, specificity to traffic, data and effort/expertise required, transferability and information provided on the actual pollutants (Table 2). These are key criteria important in studies of TRAP and asthma (and other health effects).

Table 2. Pros and cons of exposure assessment methods used in the systematic review literature. TRAP: traffic-related air pollution.

Exposure Model	Resolution		Specificity to Traffic	Pros	Cons
	Spatial	Temporal			
TRAP surrogates main e.g., proximity to “major roads” or “freeways”	-	-	+	Intuitive, simple and cost effective, more insightful when complemented with vehicle counts and composition, low need for updated data.	Assumes a road of a certain type or size corresponds to a certain amount of traffic, sometime uses self-reported traffic intensity (collected via questionnaires) which can be subjective, assumes all pollutants disperse similarly (limited directional dependence), cannot consider street canyon effects, generally does not consider compounded effects of proximity to multiple roads, disregards exposure variability due to mobility/individual activity.
Air pollutants measurements from fixed-site monitoring stations	-	++	-	High and continuous temporal resolution, actual measurements rather than predictions, cost-effective, can provide large sample sizes, medium need for updated data.	Not present at all locations, locations usually based on regulatory (not scientific) purposes, cannot consider street canyon effects (unless located in a street canyon), conceals persons’ differences because of a mismatch between data used to estimate exposure and actual subjects’ locations, potential for significant amounts of missing data in practice, quality of the data depends on quality of data ratification and verification, disregards exposure variability due to mobility/individual activity.
Air pollutant measurements from residential (stationary) samplers	++	-	-	Provides individualized data, captures spatial variability in exposure between study subjects, actual measurements rather than predictions, cost effective for select pollutants (e.g., NO_2), medium need for updated data.	Only practical/feasible in small timeframes and populations, logistic and costs concerns, not available or cost prohibitive (e.g., ultra-fine particles) for all pollutants of concern, disregards exposure variability due to mobility/individual activity.
Remote sensing	+	-	-	Can provide estimate for large areas, can provide estimate areas where measurements or models are not available (e.g., low income countries), relatively standardized method across regions, medium need for updated data.	Availability depends on satellite presence (i.e., time resolution is limited), crude spatial resolution (10×10 km), only available for select pollutants, challenging to assess errors in estimates, cannot consider street canyon effects, disregards exposure variability due to mobility/individual activity.
Land-use regression models	+	-	+	Assume independence between sampled locations, good agreement between measured and predicted averages of NO_2 , less with PM, modelling based on measurements and information around measurement points, relatively easy to collate input data, practical, low costs, medium need for updated data.	Only reflect the predictors used in the model, subject to varying uncertainties amongst different pollutants, the true contribution of traffic to the regression is not always known or reported, difficult to take into account street canyon effects; meteorology and atmospheric chemistry, the quality of the data representing “meaningful” predictors may be an issue and will affect the overall accuracy of the model, the model’s outputs are sensitive to the locations and density of the sampling sites, generally disregards exposure variability due to mobility/individual activity.
Air dispersion models	++	++	++	Continuous exposure metric, traffic-specific i.e., based on traffic flows and flow mix, traffic emissions, meteorology and atmospheric chemistry, covers relatively large areas, can assess episodic short-term and long-term exposures, can consider street canyon effects through optional built-in street canyon model, considers compounded effects of proximity to multiple roads, medium need for updated data.	Severe data demands, resource intensive, at the mercy of the emission factors inputted in the model (subject to high uncertainty), meteorology at the exposure scale is influenced by complex physical features including traffic turbulence which is difficult to consider, overestimates pollution levels during periods of calm wind, generally disregards exposure variability due to mobility/individual activity.

Ratings: +: good; ++: very good; -: potentially inadequate; --: highly inadequate.

In the literature, it was also apparent that the use of the different exposure assessment methods varied by region (Table 1). For example, 8 out of the 11 studies using pollutant measurements at fixed-site monitoring stations *only* used this exposure method (i.e., not in combination with other methods or metrics), 7 of which were from Japan, Taiwan, Korea and China. Also, 12 out of the 22 studies using LUR model used this exposure method *only*, 9 of which were from Europe (predominantly from the PIAMA cohort in The Netherlands), while the remaining 3 were from Canada and the USA. The remaining USA studies showed the most variability in the exposure assessment methods choice and used residential diffusion tube monitoring, dispersion modelling, fixed-site monitoring stations, proximity measures and multiple novel TRAP surrogates (see Patel et al. 2011 who used some new surrogates, including “four-way street intersection density” and “number of New York City transit bus stops”).

3.3. Pollutants Studied

NO₂ was the pollutant most studied (31 studies), followed by PM_{2.5} (18 studies), BC or PM_{2.5} absorbance (15 studies), and PM₁₀ (14 studies). Other pollutants including NO_x (7 studies), EC (4 studies), CO (3 studies), PM_{coarse} (3 studies), NO (2 studies) were less frequently studied. Only two studies assessed particulate matter composition elements, considered as non-exhaust road traffic emissions, including copper (Cu), iron (Fe), zinc (Zn), nickel (Ni), sulfur (S), and vanadium (V). These studies exclusively originated from the Dutch PIAMA cohort [48,75]. One study assessed oxidative potential, which is a measure of the inherent capacity of particulate matter to oxidise target molecules, [31], and no studies assessed ultra-fine particles.

3.4. Exposure Assessment Place and Time (Windows)

Table S1 in the supplementary material is a summary of where and when the exposure to TRAP was assessed in each included study and whether any validation was undertaken. The assignment of TRAP exposures was almost exclusively based on the residential address of the participating children. Only a few studies considered the impact of moving residence on TRAP exposure levels and undertook additional or sensitivity analyses for movers/non-movers or assigned the exposure at multiple addresses based on the residential history. There were a few studies which assigned the exposure based on school locations instead of residence. Shima and Adachi [79] and Shima et al. [81] used routine measurements from fixed-site stations near school addresses to represent TRAP exposures in Japan, whilst Deng, Lu, Norbäck, Bornehag, Zhang, Liu, Yuan and Sundell [70] and Deng, Lu, Ou, Chen and Yuan [86] used routine measurements from fixed-site stations near children’s kindergartens to represent TRAP exposures in China.

The exposure assignment was generally static; i.e., not taking children’s mobility into account. In many cases, this could be argued as reasonable as participants were in their infancy or early life (birth–3 years old), and residential exposure is then thought to be most relevant. Only 10 studies, mostly recent, considered children’s mobility in the exposure assessment and assigned time-weighted exposures at day cares and/or schools [33,34,38,40,42,50,83,84], and other locations where the child spends significant time [46,76], alongside residence. These studies were conducted at ages when exposure at the residential address becomes less relevant due to children’s increased mobility.

In terms of the exposure time window investigated, studies differed, but birth year was the most explored time window (Table S1). Very few studies investigated alternative exposure windows such as different years of life, longer duration, cumulative or life-time exposure.

3.5. Exposure Assessment Validation

Studies using LUR or dispersion modelling validated their modelled exposure estimates against measured concentration using different methods including leave-one-out cross validation procedure (mainly for LUR models) and independent cross validation against fixed-site monitoring stations measurements (mainly for dispersion models). Generally, the validation of the LUR model

estimates were not conducted using a separate test validation dataset which significantly limits the comprehensiveness of the validation. No study reported validation against personal exposures.

3.6. Risk Estimates by Exposure Assessment Model

Studies using different TRAP surrogates were the least consistent to show an increased asthma risk associated with TRAP. Studies using dispersion model were more consistent in showing associations. For example, out of 8 studies using dispersion models, 5 showed positive and statistically significant risk estimates. Studies using traffic-related air pollutants concentrations at fixed-site monitoring stations, and studies using LUR modelling generally showed an increased asthma risk associated with TRAP. For example, out of 22 studies using LUR models, 17 showed positive and statistically significant risk estimates. The one study that measured NO₂ exposure at the individual residential level also showed statistically significant associations between the exposure and asthma [74]; so did the one study that used remote sensing [85]. Some of the same studies which found no association between roadway proximity and asthma, found increased risks when employing more refined exposure models such as LUR model estimates [36–38,42,45,78].

4. Discussion

We found 42 studies that examined the association between TRAP and the subsequent onset of childhood asthma defined as incidence or lifetime prevalence. Exposures metrics differed in terms of their spatial and temporal resolution and their specificity to traffic. LUR modelling was the most commonly used exposure assessment method and NO₂ was the most commonly studied pollutant. Most studies estimated TRAP exposures at the residential address and only a few considered the mobility of the children and/or their residential address changes. Most studies estimated the TRAP exposures at the first year of life (birth year) and only a few studies assessed the effects of cumulative exposures and/or exposures at different time-windows. Validation was undertaken for LUR and dispersion models estimates only and no study has validated exposure estimates against personal monitored exposures. Although our previous meta-analysis found positive and statistically significant associations for various TRAP exposures (black carbon, NO₂, PM_{2.5}, PM₁₀) with the onset asthma [3], further refinement of the exposure assessments may improve the exposure-response functions and shed light on associations with other under-investigated pollutants.

4.1. Putative Agents

The prominent focus on NO₂ in the literature is probably related to the wide availability of this pollutant measure, the ease and relatively low cost to measure it and its relative specificity to road traffic [30]. The focus on NO₂ in air quality guidelines, plans and mitigation strategies in the EU, and beyond, is perhaps reinforcing the study of this pollutant. Fewer studies measured or modelled PM_{2.5} or particulate components, even though it is more widely implicated in the health effects of air pollution [88]. The cost of measuring and/or modelling PM tends to be higher. The literature, however, suggests that there has been a recent move from studying standard air pollutants to studying other agents, most notably including black and elemental carbon, two agents that are considered as TRAP signatures, but also PM composition elements and other properties such as oxidative potential [31,48,75]. As it stands, there were no studies investigating the impacts of long-term exposure to ultra-fine particles on asthma but there are studies under way to measure ultra-fine particles [89]. The work on PM composition is particularly relevant with the expected wide-spread introduction of electric vehicles and the associated likely reductions of exhaust emissions and increase in non-exhaust emissions [90]. PM composition research could potentially lead to further insight on the putative agents and source of pollutants. For example, Gehring, Beelen, Eeftens, Hoek, de Hoogh, de Jongste, Keuken, Koppelman, Meliefste and Oldenwening [48] suggested that iron, copper, and zinc in PM, reflecting poorly regulated non-exhaust traffic emissions, may increase the risk of asthma and allergy in Dutch schoolchildren. A birth cohort study using oxidative potential measures, particularly

using the dithiothreitol assay, found that asthma and other respiratory health outcomes were more strongly related to oxidative potential when compared to $PM_{2.5}$, suggesting that this exposure metric may be closer to the underlying mechanisms [31]. These different measures are rarely studied and should be further explored in future research, principally in locations where ratios between oxidative potential and other TRAP markers such as NO_2 differ; to determine with more confidence which metric predicts respiratory health better.

4.2. Exposure Assessment Methods

Many studies have used LUR modelling to estimate TRAP exposures, partly because of its relatively low costs, ease of implementation and possibility to consider traffic determinants of exposure such as the road network and traffic density. LUR models also tend to provide a good spatial coverage and resolution for TRAP exposure. The LUR method is an empirical method and uses least squares regression to combine measured data with geographic information system (GIS)-based predictor data reflecting pollutant sources, to build a prediction model applicable to non-measured locations, e.g., residential addresses of cohort members. An advantage of LUR models is that they are stable over time [91–93]. However, their validation, most commonly undertaken using leave-one-out cross validation procedure, is incomplete. Relatively few studies used air dispersion models which are based on more detailed knowledge of the physical, chemical, and fluid dynamical processes in the atmosphere. Air dispersion models use information on emissions, source characteristics, chemical and physical properties of the pollutants, topography, and meteorology to model the transport and transformation of gaseous or particulate pollutants through the atmosphere to predict air pollutant concentrations. They allow for a finer temporal and spatial resolution of TRAP exposure and specific source apportionment (beyond TRAP) which is valuable when recommending specific policy interventions targeted at specific sources. Yet, their main drawback is related to the quality of the input data; especially the vehicle emission factors which are highly uncertain [94]. Amongst the encountered exposure methods, these two methods are favorable in terms of their spatial and temporal resolution and their specificity to traffic (Table 2). The preferred method for exposure assessment is not so obvious and depends on available resources, the quality of the input data, expertise, place of study and transferability considerations. For example, de Hoogh, et al. [95] found that the median Pearson R (range) correlation coefficients between LUR and air dispersion model estimates for the annual average concentrations of NO_2 , PM_{10} and $PM_{2.5}$ were 0.75 (0.19–0.89), 0.39 (0.23–0.66) and 0.29 (0.22–0.81) for 112,971 (13 study areas), 69,591 (7) and 28,519 (4) addresses respectively, suggesting a much better agreement for NO_2 than for PM, probably because the main source for NO_2 is traffic and PM has other sources. The median Pearson R correlation coefficients (range) between air dispersion model estimates and measurements were 0.74 (0.09–0.86) for NO_2 ; 0.58 (0.36–0.88) for PM_{10} and 0.58 (0.39–0.66) for $PM_{2.5}$. Wang et al. [96] compared both methods in a study of children's lung function and found that exposure estimates from LUR and dispersion models correlated very well for $PM_{2.5}$, NO_2 , and black carbon, but not for PM_{10} . Health effect estimates did not depend on the type of model used in their population of Dutch children. Yet, with a very limited number of comparison studies, the extent to which estimates of air pollution effects are affected by the choice of exposure model remains unclear. A combination of the LUR and dispersion models may further improve the exposure assessment estimates, possibly accounting for some of the imperfections in the emission databases [97].

Compared to estimates from routine monitoring stations LUR and air dispersion model have the advantage that they provide a better spatial resolution, but also require more effort and are costlier. The better spatial resolution may be quite important when the study area is small and clear exposure differences can be observed by detailed exposure assessment. At least, all three methods provide some level of pollutants which may be important for policy reasons, while surrogate measures like distance from roads do not. A relatively new method, remote sensing [85] has the advantage that air pollution estimates can be obtained where there are no or fewer monitors or less resources and expertise is

available i.e., medium- and low-income countries, but still needs some further refinement in terms of spatial resolution and the number of pollutants for which good estimation methods are available.

We attempted to evaluate the effects of the exposure assessment method on the health risk estimates observed in the included studies, for example with meta-regression, but the number of studies available are still too small to conduct such analyses. Even for NO₂ exposure, there were only 20 studies entering the meta-analysis, 12 of which used LUR models and 1 used dispersion modelling. The meta-analyses though suggested considerable heterogeneity, especially in the case of NO₂ where most studies were available, and part of this heterogeneity could be caused by different exposure assessment methods. Given the rapid increase in the number of studies in this field, it may become possible to conduct such analysis in the near future.

4.3. Exposure Assessment Places and Time Windows

Only a small number of studies considered children's mobility at ages when exposure at the residential address becomes less relevant and assigned time-weighted TRAP exposures at day care centres and schools and other locations where the child spends significant time alongside residence. Children may spend only around 50%–60% of their time at home, and the rest elsewhere e.g., at school [98]. TRAP exposure levels such as black carbon can be considerably higher when commuting compared to being at home [98], and therefore residential estimates may underestimate the true exposure and bias the exposure-response functions. New tracking technology and portable sensors have now made it possible obtain information on TRAP exposure levels over the day, even though it requires considerable effort and may only be feasible for smaller samples [98]. New approaches such as indicating the home and school address and commuting route in geographical information system packages and overlaying this with time adjusted air pollution maps may provide estimates for larger study samples and can be an area of further inquiry. Considering the significant amount of time spent indoors, it may also be beneficial to investigate indoor air pollution exposures and the impact of specifically incorporating these on the exposure-response functions. Currently, all available exposure models, except personal monitors (which have not been used in any of the included studies), estimate outdoor air pollution only and use this as a surrogate for the indoor levels without taking into account indoor-outdoor penetration factors. However, outdoor and indoor TRAP are correlated as there is considerable penetration of outdoor sources to indoor environments. These correlations may be one rapid and practical method to assign indoor exposures. One study which characterized the indoor-outdoor relationship of PM_{2.5} in Beijing found that there is a strong correlation between indoor and outdoor PM_{2.5} mass concentrations, and that the ambient data explained $\geq 84\%$ variance of the indoor data [99]. Another study similarly showed that PM_{2.5} levels in an Australian primary school were mainly affected by the outdoor PM_{2.5} ($r = 0.68, p < 0.01$) [100]. Another study in Germany found that over 75% of the daily indoor PM_{2.5} and black smoke variation could be explained by daily outdoor variation for those pollutants [101].

Further, investigating different exposure time windows may highlight other relevant exposure windows beyond the birth year and early-life that are commonly studied. The differences between effects of early exposure versus later exposures or exposures with greater duration is yet unclear and is difficult to detangle due to the limited number of studies investigating different time windows. Some authors have suggested that exposures of longer duration at elevated TRAP levels may be necessary to generate pathophysiological changes leading to asthma development and therefore may be behind the observed effects [46].

4.4. Outlook and Recommendations

Novel approaches to exposure assessment are underway including the use of OMICS technologies that measure biological molecules and/or activity in the body (e.g., transcriptomics, proteomics, metabolomics or methylation) to identify fingerprints of air pollution [89,102]. Although still in their infancy, such approaches may provide a good way of characterising air pollution exposures inside the

body and on existing biological samples (that have been stored for a while). Furthermore, they may provide further insight in the underlying mechanisms by which air pollution cause health effects in children and others.

Although there appear to be statistical significant associations between TRAP and the development of childhood asthma, there is a further need to improve the exposure estimates, and therefore improve the exposure–response functions and the consistency of the study findings. This is important for example when these exposure–response functions are used for burden of disease and health impact assessment studies, and for better understanding the underlying mechanisms of TRAP and childhood asthma and the potential differential pollutant effects and drivers of heterogeneity. Over the past few years, there has been an epidemic increase in the number of studies in the field, and there are likely to be more studies over the next few years given the importance of the topic. Improvements in exposure assessments, as we discuss in this paper, may well increase the scientific value of these new studies. More refined exposure models are needed, and will arguably produce the most robust associations when investigating the potential health effects of TRAP. Furthermore, we also emphasize the need to incorporate mobility patterns in the exposure estimates and to undertake personal exposure monitoring to cross validate modelling estimates.

5. Conclusions

Although our previous meta-analysis found statistically significant associations for various TRAP exposures and childhood asthma, further refinement of the exposure assessment may improve the risk estimates and shed light on critical exposure time windows, putative agents, underlying mechanisms and drivers of heterogeneity.

Supplementary Materials: The following are available online at www.mdpi.com/1660-4601/14/3/312/s1, Table S1: Exposure assessment place, time and validation in the Included Studies.

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