Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

REVIEW

The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies

G. Bowatte[1], C. Lodge[1], A. J. Lowe[1], B. Erbas[2], J. Perret[1], M. J. Abramson[3], M. Matheson[1]* & S. C. Dharmage[1,4,*]

[1]Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne; [2]School of Public Health and Human Biosciences, Department of Public Health, La Trobe University; [3]School of Public Health & Preventive Medicine, Monash University; [4]Murdoch Children Research Institute, Melbourne, Vic., Australia

To cite this article: Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ, Matheson M, Dharmage SC. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization: a systematic review and a meta-analysis of birth cohort studies. *Allergy* 2015; **70**: 245–256.

Keywords
air pollution; allergies; asthma; NO_2 and $PM_{2.5}$.

Correspondence
Professor Shyamali Dharmage, Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, L3, 207 Bouverie Street, Carlton, Vic. 3053, Australia.
Tel.: +61-3-83440737
Fax: +61-3-9349-5815
E-mail: s.dharmage@unimelb.edu.au

*Equal senior authorship.

Accepted for publication 10 December 2014

DOI:10.1111/all.12561

Edited by: Douglas Robinson

Abstract

The impact of early childhood traffic-related air pollution (TRAP) exposure on development of asthma and allergies remains unclear. Birth cohort studies are the best available study design to answer this question, but the evidence from such studies has not been synthesized to date. We conducted a systematic review and meta-analyses of published birth cohort studies to understand the association between early childhood TRAP exposure, and subsequent asthma, allergies and sensitization. Increased longitudinal childhood exposure to $PM_{2.5}$ and black carbon was associated with increasing risk of subsequent asthma in childhood ($PM_{2.5}$: OR 1.14, 95%CI 1.00 to 1.30 per 2 $\mu g/m^3$ and black carbon: OR 1.20, 95%CI 1.05 to 1.38 per 1×10^{-5} m^{-1}). Also, early childhood exposure to TRAP was associated with development of asthma across childhood up to 12 years of age. The magnitude of these associations increased with age, and the pattern was prominent for $PM_{2.5}$. Increasing exposure to $PM_{2.5}$ was associated with sensitization to both aero- and food allergens. There was some evidence that TRAP was associated with eczema and hay fever. In summary, exposure to TRAP was related to asthma and allergic diseases. However, the substantial variability across studies warrants long-term birth cohort studies with regular repeated follow-ups to confirm these findings.

The prevalence of asthma and allergic diseases has increased in epidemic proportions in the developed world. While some developed countries are now seeing a plateau in the prevalence of these conditions, a new epidemic is emerging in low- and middle-income countries (1, 2). While the cause of these trends is not yet clear, environmental changes have been suggested as a major driver (1). Increase in exposure to traffic-related air pollution (TRAP) is one such factor (3).

There is an emerging body of evidence about the influence of TRAP on both asthma and allergic diseases (4). The pollutants that have been implicated are particulate matter <2.5 and <10 μm in diameter ($PM_{2.5}$ and PM_{10}) and gases such as nitrogen dioxide (NO_2), nitric oxide (NO), nitrogen oxides (NO_X) and ozone (O_3). While many studies have focused on the association between TRAP and exacerbations of existing respiratory conditions (5–7), there is less evidence of the

Abbreviations
BAMSE, Barn Allergi Miljö Stockholm Epidemiologi; BCO, British Columbia birth cohort; CCAAPS, Cincinnati childhood allergy and air pollution study; CCCEH, Columbia centre for children's environmental health; COPSAC, Copenhagen prospective study on asthma in childhood; GINI & LISA, German infant nutrition intervention programme & lifestyle related factors on the human immune system and development of allergies in children; GINI plus & LISA plus, German infant nutrition intervention programme plus & lifestyle related factors on the human immune system and development of allergies in children plus; INMA, Infancia y Medio Ambiente; Oslo, Oslo birth cohort; PIAMA, prevention and incidence of asthma and mite allergy; Vancouver, Vancouver birth cohort.

impact of TRAP on the development of asthma and allergies over time (8–10).

Infants and young children are most vulnerable to the adverse effects of air pollution (11–13) because of the relative immaturity of their immune and respiratory systems (14). Furthermore, children spend more time outdoors, breathing around 50% more air per kilogram of body weight compared with adults, which exposes them to relatively higher doses of ambient pollutants (15). As the human lung continues to grow from the intra-uterine period to early adulthood (14, 16), this relatively high exposure to pollutants may increase the vulnerability of children to adverse effects of air pollution (11).

Recently, a number of narrative and systematic reviews have been conducted to evaluate the body of evidence on TRAP exposure and respiratory and allergy outcomes (17–23). A recent meta-analysis (22) has shown evidence that long-term exposure to $PM_{2.5}$ and NO_2 is associated with the incidence of asthma and wheeze symptoms. However, this review included both children and adults and did not separately consider the potentially important different effects related to exposure to TRAP in children. Birth cohort studies with frequent follow-up data provide the strongest practically available evidence to understand the incidence and progression of diseases. No systematic review to date has specifically focussed on the evidence from birth cohorts. Therefore, we aimed to systematically review and meta-analyse the evidence of the effects of childhood TRAP exposure on subsequent asthma, wheeze, allergic sensitization, hay fever and eczema.

Methods

Search strategy

MEDLINE, EMBASE and ISI Web of Science databases were searched for English language, peer-reviewed articles from 1960 to March 2014 by combining two sets of keywords. One set of keywords included terms related to TRAP exposure, while the second set of keywords included terms related to respiratory or allergic outcomes (Fig. S1). The primary TRAP exposure markers considered were particulate matter (PM_{10}, $PM_{2.5}$ and black carbon), gases (NO_2, NO and NO_X) and proximity to roads. The primary outcomes considered were asthma, wheeze, eczema, hay fever and sensitization to allergens.

Inclusion criteria

This systematic review included only birth cohort studies that have examined the association between TRAP exposure in early childhood and subsequent respiratory or allergic outcomes reported at any age.

Definitions

To overcome problems with the variation in definitions of original studies, we used the following definitions for the purpose of this systematic review.

Asthma was defined as current asthma or 'asthmatic, obstructive, spastic bronchitis diagnosis or asthma diagnosis'.

Wheeze was defined as any wheeze or current wheeze or wheeze without a cold.

Sensitization was defined as an allergen-specific immunoglobulin E (IgE) antibody level of 0.35 kU_A/l or greater.

Eczema was defined as 'doctor-diagnosed eczema' or 'parent-reported eczema'.

Hay fever was defined as 'doctor-diagnosed hay fever' or 'parent-reported hay fever'.

Black Carbon (BC) was defined as $PM_{2.5}$ absorbance or elemental carbon attributed to traffic (ECAT) with all studies using similar methods.

Early childhood exposure was defined as exposure to TRAP from birth to 5 years of age.

Late childhood exposure was defined as exposure to TRAP after 5 years of age.

Longitudinal childhood exposure was defined as overall exposure to TRAP from birth to last follow-up.

Data tabulation and assessment

Data were extracted using a standardized form. The study quality was assessed by Newcastle-Ottawa scale for cohort studies (Table S1). The quality assessment of this scale is based on the selection of study sample, outcome assessment, exposure assessment and adjustment for confounders. The relevant effect estimates and 95% confidence intervals were extracted for asthma, wheeze and sensitization and tabulated according to the age at assessment and type of traffic pollution marker (Tables S2–S11). Authors of the published articles were contacted for further data when the numerical data were not fully described.

Statistical analysis

Standardization of data

Some of the extracted data were standardized to enable comparison across studies. Odds ratios and 95% confidence intervals for the exposures to NO_2, $PM_{2.5}$ and BC were standardized into increase per 10 $\mu g/m^3$, 2 $\mu g/m^3$ and 1×10^{-5} m^{-1}, respectively. To increase the number of quantitative estimates of pollution–outcome pairs, PM_{10} and NO_X were scaled into $PM_{2.5}$ and NO_2, respectively, by methods previously described (22, 24). Similarly, extracted IgE results were also scaled and standardized into the same magnitude.

Meta-analysis

Only studies with similar exposures and outcome measures were combined for meta-analysis. Studies with significant methodological or clinical heterogeneity were excluded when pooling the data.

The first series of meta-analyses included studies that investigated longitudinal childhood exposure to TRAP and asthma incidence independent of the age at which the outcome was measured. The second series of meta-analyses investigated the exposure to TRAP at birth and asthma incidence stratified by the age at which the outcome was

assessed. Age-specific summary effect estimates were plotted to investigate the temporal trends. Separate meta-analyses were conducted for allergic sensitization. Studies reporting hay fever or eczema as outcomes were not eligible for meta-analysis due to the differences in reporting of the outcome measures.

I^2 statistics (25) were calculated as measures between study heterogeneity. To estimate effect sizes and 95%CI, fixed- and random-effect meta-analyses were performed. Statistical software STATA version 13.1 (Stata Corp LP, College Station, TX, USA) was used to perform the meta-analysis.

Results

The electronic search strategy generated 1768 articles. After reading abstracts and applying inclusion criteria, 241 articles were selected for full-text reviewing. Among these, 19 articles fulfilled the inclusion criteria (Fig. S1).

Study characteristics

The 19 articles included in the review were based on eleven birth cohorts (Table 1). Of the 11 birth cohorts, seven were based in Europe (26–32) and four were based in North America (33–36). The sample sizes ranged from 186 to 37 401 and follow-up periods varied from 1 to 12 years. Some of the cohorts reported outcome data at multiple follow-up points, while others reported outcome data at a single time point (Table 2). The number of cohorts that reported associations at different ages ranged from a single follow-up (28, 32, 33, 36) to eight follow-ups (30, 37, 38) (Table 2).

Study quality

Among the 11 cohorts, eight were population-based, while three were high-risk cohorts (i.e. included those with a family history of asthma or allergies). Two cohorts recruited children born in a single referral hospital (28, 34). Three cohorts had more than 50% loss to follow-up (Table 1 and Table S1). Second-hand smoking, a potential confounder of the association between TRAP and asthma and allergy outcomes, was not adjusted for in three cohorts (33, 36, 39). Allergic predisposition, another potential confounder for the association of TRAP and allergic diseases, was not adjusted for in three population-based cohorts (28, 33, 34) (Table S1).

Variability in exposures

Substantial variability in the exposure measurements was observed across studies (Table 2). Land use regression (LUR) models were the most common methods used to assess TRAP exposure (27, 28, 32, 33, 36, 38, 39). Other methods used were dispersion models, passive samplers, a single central monitoring station and proximity to major roads (Table 2). Early childhood TRAP exposure was reported in all cohorts considered in the review, and four cohorts reported both early and late childhood exposure for TRAP (29, 32, 40, 41).

Oxides of nitrogen and PM were the most frequently reported traffic pollutant markers. Oxides of nitrogen were reported in eight cohorts (26–28, 32, 33, 36, 38, 42) where seven of them reported it in the form of NO_2 (27, 28, 32, 33, 36, 38, 42) and two as both NO_2 and NO (33, 36). PM was reported in different ways: six cohorts reported primary PM either as PM_{10} or $PM_{2.5}$ (26, 28, 31, 33, 36, 38, 42), while some of the cohorts reported PM as BC, $PM_{2.5}$ absorbance or ECAT (27, 32, 33, 35, 36, 38). Only one study measured ultrafine PM, carbon monoxide and ozone (33). All except two studies reported exposure to pollutants per interquartile range increase. One of the two reported the exposure as 5th to 95th percentile increase (41), and the other reported both as quartiles range increase and low/high exposures of average daily ECAT (35) (Table 2).

Proximity to roads was used as a TRAP marker in six cohorts (27, 32–34, 42) (Table 2). Four cohorts reported the proximity to roads as a dichotomous variable with exposed individuals defined as residents within a specified distance from roads (<50, <100 or <150 m) (32, 33, 39, 40). The unexposed were defined as individuals living further away from the roads than the exposed. Two cohorts reported exposure to proximity to roads as quartiles of increasing distance (29, 34).

Variability in outcomes

Asthma and wheeze were the most frequently measured clinical outcomes. Asthma and wheeze were reported by nine and eight cohorts, respectively. Hay fever and eczema were reported by three cohorts (Table 2). The outcomes were assessed mainly from parent-reported questionnaires (nine cohorts). Two cohorts reported the outcomes using diagnosis made by a single blinded paediatric allergist, physician billing records and hospital discharge records (Table S1).

Allergen-specific IgE was documented in five cohorts (30, 32, 34, 37, 40, 43). Of the five cohorts, two measured IgE levels at multiple stages of follow-up (30, 37, 41). IgE was reported for a range of allergens including pollen, food, furry pets, house dust mites and moulds.

Outcome variables were reported as prevalence (26, 27, 32, 34, 35, 40, 43, 44) and incidence (28, 29, 31, 33, 36, 37, 41, 43). Only one study reported the measure of association as a risk ratio (RR) (32) with the remainder reporting odds ratios (OR).

The association between TRAP and asthma and allergies

TRAP exposure, asthma and wheeze

The data concerning the incidence of asthma were meta-analysed separately for exposures of nitrogen oxides, PM and BC. The outcome of wheeze incidence was unable to be meta-analysed as of the three cohorts that reported this association (28, 31, 41), only one met the inclusion criteria for meta-analysis (41).

Influence of nitrogen oxides on asthma and wheeze. The pooled results of the five cohorts [BAMSE, PIAMA, Oslo, Vancouver and BCO (29, 33, 36, 37, 41)] that estimated the

Table 1 Study characteristics of the birth cohorts

Cohort, country, recruitment and study period	References	Original participants	Follow-ups and loss to follow-up		IgE measurements in different ages
Oslo birth cohort Norway 1992/1993 – 2001/2002	(29) (42)	*n* = 2871 children born in Oslo 1992/93 and living in Oslo until 2001/02	At birth, *n* = 2871 and at 8 years, *n* = 1551 Other than the original birth cohort (*n* = 1551), a cross-sectional sample of the 1991–92 born children were included (*n* = 1320)		No IgE tests
BAMSE Sweden 1994/1996 – 2008	(26) (43) (41)	*n* = 4089 children born between 1994 and 1996 municipalities in Stockholm County	At 1 year, *n* = 4089 At 2 years, *n* = 3843 (94%) At 4 years, *n* = 3721 (91%) At 8 years, *n* = 3435 (84%) At 12 years, *n* = 3353 (82%)		IgE at 4 years *n* = 2543 IgE at 8 years *n* = 2545
GINI & LISA Germany 1995/1998 – 2005	(27) (44) (40)	GINI – original cohort *n* = 5991 LISA – original cohort *n* = 3097	At age 1 and 2 years, *n* = 1756 – a subset of cohort lived in Munich city. At age 4 years, *n* = 3577 – a subset of cohort lived in Munich city and metropolitan area At age 6 years, *n* = 2860		IgE at age 6 years *n* = 1554
GINI plus & LISA plus Germany 1995/1998 – 2005	(32)	GINI plus *n* = 3042 LISA plus *n* = 348	GINI plus At birth, *n* = 3042 At 1 year, *n* = 2301 (76%) At 2 years, *n* = 2178 (72%) At 4 years, *n* = 1975 (65%) At 6 years, *n* = 1889 (62%)	LISA plus 348 277 (80%) 262 (75%) 267 (77%) 223 (64%)	IgE at 6 years *n* = 1004 (GINI plus = 888, LISA plus = 116)
*Vancouver birth cohort** Canada 1995 – 2003	(36)	*n* = 272 children born in 1995, Vancouver, Canada, to high-risk parents	At 1 year, *n* = 272 At 7 years, *n* = 186 (68%)		No IgE tests

Table 1 (continued)

Cohort, country, recruitment and study period	References	Original participants	Follow-ups and loss to follow-up	IgE measurements in different ages
PIAMA The Netherlands 1996/1997 – 2005	(30) (38) (37)	*n* = 4146 pregnant mothers recruited from a series of communities in the north, west and central Netherlands	At 1 year, *n* = 3745 (91%) At 2 years, *n* = 3740 (90%) At 3 years, *n* = 3694 (89%) At 4 years, *n* = 3563 (86%) At 5 years, *n* = 3518 (85%) At 6 years, *n* = 3473 (84%) At 7 years, *n* = 3373 (81%) At 8 years, *n* = 3269 (79%)	IgE at age 8 years *n* = 1700
CCCEH USA 1998 – 2006	(34)	*n* = 727 at birth, mothers were recruited during pregnancy from a reference hospital	At 1 year, *n* = 559 (77%) At 2 years, *n* = 500 (69%) At 3 years, *n* = 494 (68%) At 5 years *n* = 341 (47%)	IgE at age 2 years *n* = 419 IgE at age 3 years *n* = 394 IgE at age 5 years *n* = 248
*COPSAC** Denmark 1998/2001 – 2005	(31)	*n* = 411 Danish children born to mothers with asthma; lived in Copenhagen	At birth, *n* = 205 (lived in 15 km radius of the monitoring station) At 1 year, *n* = 202 (99%) at 2 years *n* = 199 (97%) At 3 years, *n* = 194 (95%)	No IgE tests
British Columbia birth cohort Canada 1999/2000 – 2003	(33)	*n* = 37 401 a nested case–control study. Children born in 1999/2000 in South-western British Columbia	At the end of the follow-up (average age 4 years), asthma cases = 3482; controls = 33 919	No IgE tests
*CCAAPS** USA 2001/2003 – 2006	(35) (39)	*n* = 762 children born to parents who lived in Cincinnati, positive to aeroallergens	At birth, *n* = 762 At 3 years, *n* = 624 (82%)	No IgE tests
INMA Spain 2003/2005	(28)	*n* = 787 children born in Valencia in 2004/05	At birth, *n* = 787 Air pollution data available at 1st yr *n* = 352 (45%)	No IgE tests

*High-risk birth cohorts.

Table 2 Exposure and outcome measures of birth cohorts

	Exposures assessed												Exposure model					Outcome					
Cohort	PM_{10}	$PM_{2.5}$	BC	UFPM	NO_2	NO	NO_X	CO	SO_2	O_3	Proximity	Traffic / Road density	Dispersion	LUR	Passive sampler	Proximity	Central site	Asthma	Wheeze	Hay fever	IgE	Eczema	Ages where the outcomes assessed (years)
BAMSE	✓	–	–	–	–	–	✓	–	–	–	–	–	✓	–	–	–	–	✓	✓	–	✓	–	1,2,4,8 and 12
GINI & LISA	–	✓	✓	–	✓	–	–	–	–	–	✓	–	–	✓	–	✓	–	✓	✓	✓	✓	✓	1,2 and 6
GINI plus & LISA plus	–	–	✓	–	✓	–	–	–	–	–	✓	–	–	✓	–	✓	–	✓	–	✓	✓	✓	6
BCO	✓	–	✓	–	✓	✓	–	✓	✓	✓	✓	–	–	✓	–	✓	–	✓	–	–	–	–	4
INMA	–	–	–	–	✓	–	–	–	–	–	–	–	–	✓	✓	–	–	–	✓	–	–	–	1
Oslo	–	–	–	–	✓	–	–	–	–	–	✓	–	✓	–	–	✓	–	✓	✓	–	–	–	1 and 8
Vancouver*	–	✓	✓	–	✓	✓	–	–	–	–	–	–	–	✓	–	–	–	✓	–	–	–	–	7
PIAMA	–	✓	✓	–	✓	–	–	–	–	–	–	–	–	✓	–	–	–	✓	✓	✓	✓	✓	1,2,3,4,5, 6,7 and 8
CCCEH	–	–	–	–	–	–	–	–	–	–	✓	✓	–	–	–	✓	–	✓	✓	–	✓	–	1,2,3 and 5
COPSAC*	✓	–	–	✓	–	–	–	–	–	–	–	–	–	–	–	–	✓	–	✓	–	–	–	1,2 and 3
CCAAPS*	–	–	✓	–	–	–	–	–	–	–	✓	–	–	✓	–	✓	–	✓	✓	–	–	–	1,2 and 3
Total	3	3	6	1	7	2	1	1	1	1	6	1	2	7	1	6	1	9	8	3	5	3	

*High-risk birth cohorts.

association between longitudinal childhood exposure to NO_2 and incidence of asthma showed a modest association (OR 1.09 95%CI 0.96 to 1.23 per 10 μg/m^3 increase, Fig. 1A), but the association was highly variable between studies (I^2 = 75.5%). There was an increasing association between early childhood exposure to NO_2 and asthma incidence with increasing age until the age of 6 years although the heterogeneity (I^2) in age-specific meta-analysis ranged from 0% to 62.6% across the years (Fig. 2A and Table S2). After 6 years, the association between exposure to NO_2 and asthma did not show a clear pattern.

Associations between nitrogen oxides (NO, NO_2 and NO_X) and wheeze were reported in 10 papers (26–31, 37, 38, 41, 44), in relation to six cohorts (GINI & LISA, PIAMA, BAMSE, Oslo, COPSAC and INMA). Six papers reported the outcome as prevalence and four reported the outcome as incidence. Among the six cohorts, only two (PIAMA and COPSAC) (31, 37) reported significant associations of an increased risk of wheeze following exposure to nitrogen oxides at the age of 1, 2, 3, 4 and 6 years (Table S3).

Influence of PM on asthma and wheeze. Four birth cohort studies [BAMSE, PIAMA, Vancouver and BCO (33, 36, 37, 41)] showed that increased longitudinal childhood exposure to $PM_{2.5}$ was significantly related to the incidence of asthma, but there was substantial heterogeneity (OR 1.14 95%CI 1.00 to 1.30 per 2 μg/m^3, I^2 = 77.1%, Fig. 1B). The age-specific meta-analysis showed that early childhood exposure to $PM_{2.5}$ was associated with increasing trend of asthma risk from 3 years up to 12 years. The heterogeneity (I^2) of the age-specific meta-analysis ranged from 0% to 52.3% (Fig. 2B and Table S4).

Long-term exposure to PM and wheeze was reported by eight papers (26, 27, 30, 31, 37, 38, 41, 44) from four cohorts (GINI & LISA, PIAMA, BAMSE and COPSAC). Five of those reported the association as prevalence and three as incidence. Only one cohort (PIAMA) (37) showed a significantly increased risk of wheeze related to early childhood PM exposure at the ages of 1, 2, 3, 4, 5, 6 and 8 years (Table S5).

Influence of BC on asthma and wheeze. The meta-analysis of studies that reported the OR for the association between BC and asthma [PIAMA, Vancouver and BCO (33, 36, 37)] showed that longitudinal childhood exposure to traffic-related BC was significantly related to asthma incidence (OR 1.20 95%CI 1.05 to 1.38, I^2 = 19.3%, Fig. 1C). The age-specific meta-analysis for early childhood exposure to BC up to the age of 6 years showed an increasing trend of incidence of asthma with minimal heterogeneity (I^2 from 0% to 23.7%, Fig. 2C and Table S6).

The prevalence of wheeze associated with exposure to PM related to BC was reported in five papers based on two cohorts (GINI & LISA and PIAMA) (27, 37) with only one study (PIAMA) (37) reporting significantly increased risk of wheeze at the ages of 2, 3, 4 and 6 years (Table S7).

Influence of road proximity to asthma and wheeze. The association between proximity to roads and asthma was reported by six cohorts [GINI & LISA, GINI plus & LISA plus,

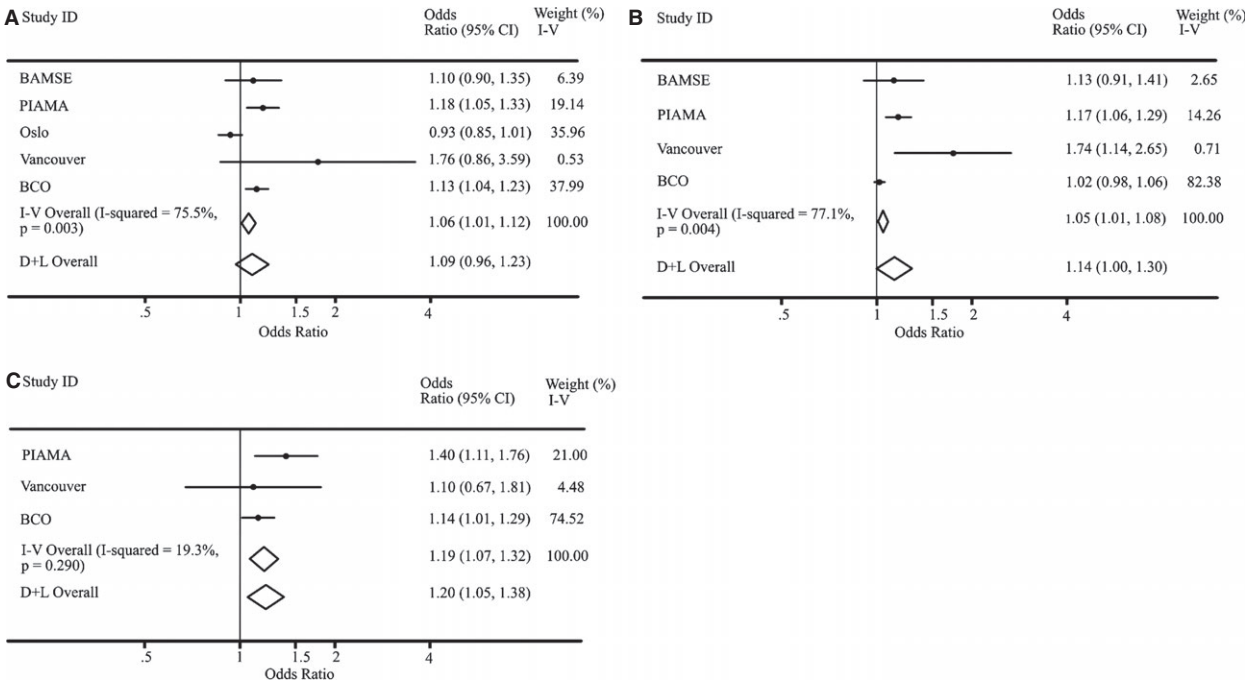

Figure 1 Longitudinal childhood exposure to TRAP and asthma incidence in childhood. (A) Exposure per 10 μg/m^3 increase in NO_2. (B) Exposure per 2 μg/m^3 increase in $PM_{2.5}$. (C) Exposure per 1 × 10^{-5} m^{-1} increase in BC.

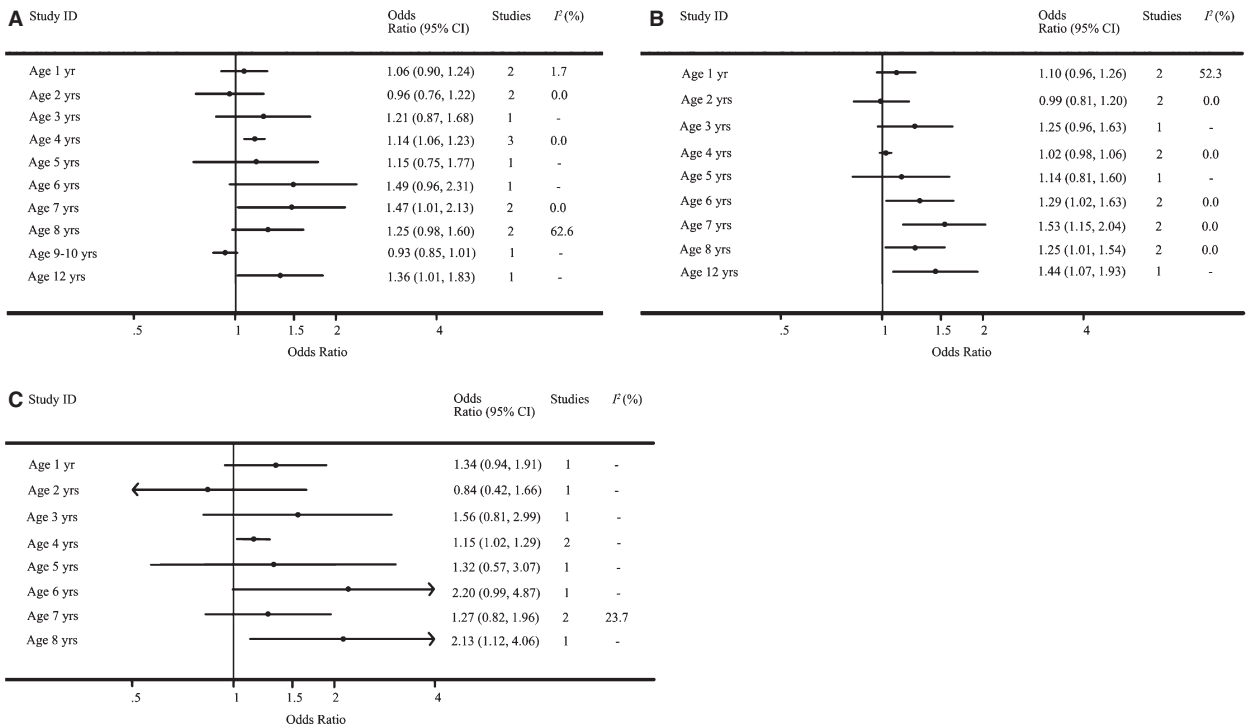

Figure 2 Early childhood exposure to TRAP and age-specific incidence of asthma from birth to childhood. (A) Exposure per 10 μg/m^3 increase in NO_2. (B) Exposure per 2 μg/m^3 increase in $PM_{2.5}$. (C) Exposure per 1 × 10^{-5} m^{-1} increase in BC.

BCO, Oslo, CCCEH and CCAAPS (29, 32–34, 39, 40)]. Only two of these studies reported significant associations at the ages of 2 and 6 years (GINI & LISA) (27, 40). The associations between proximity to roads and wheeze was reported by four cohorts, from which two (CCAAPS and CCCEH) (34, 39) showed significant associations at ages 1 and 5 years (Tables S8 and S9).

TRAP exposure and allergic sensitization

The association between exposure to TRAP and sensitization was assessed in five cohorts, where four [BAMSE, GINI & LISA, GINI plus & LISA plus and PIAMA (30, 32, 40, 43)] defined the TRAP as oxides of nitrogen and PM, and two [GINI plus & LISA plus and CCCEH (32, 34)], as proximity to roads. All the studies assessed sensitization using serum IgE levels. GINI plus & LISA plus reported the associations as RR, while the other cohorts reported OR. The measured allergens were diverse including 'indoor aeroallergens' comprising cat, dog and moulds; 'outdoor aeroallergens' comprising pollens and grass; 'food allergens' comprising egg, milk, peanut, soya and wheat; and 'any allergens' comprising any inhalant or food allergens. Sensitization to any allergen was reported by three cohorts, indoor aeroallergens by two cohorts, outdoor aeroallergens by three cohorts and inhalant allergens by three cohorts (Table S12).

The meta-analysis for indoor aeroallergens did not show any significant associations with early childhood exposure to NO_2 or $PM_{2.5}$ (Figs 3B and 4B). The meta-analysis for outdoor aeroallergens showed a significantly increased risk associated with increase in $PM_{2.5}$, although there was a high degree of heterogeneity observed between studies (I^2 = 73.7%), and no association was found with NO_2 (Fig. 4A). Early childhood exposure to NO_2 significantly increased the risk for sensitization to food allergens at the age of 4 years (Fig. 3D). However, these associations were found to be modest at the age of 8 years for both NO_2 and $PM_{2.5}$ (Figs 3D and 4D).

TRAP exposure and hay fever/eczema

The association of TRAP exposure on eczema and hay fever was reported by five papers from three birth cohorts (PIAMA, GINI & LISA and GINI plus & LISA plus) (30, 32, 37, 38, 40). GINI & LISA showed an adverse impact of NO_2 on the prevalence of eczema and an adverse impact of BC on the prevalence of hay fever (32, 40). GINI plus & LISA plus showed that greater exposure to BC both at birth and at the age of 6 years was significantly associated with the prevalence of eczema, but not with hay fever (32). Living near a major road, especially within 50 m, was found to be associated with increased prevalence of eczema and hay fever in childhood (GINI & LISA) (40). However, early childhood exposure to NO_2, $PM_{2.5}$ and BC was not associated with eczema and hay fever in the PIAMA study (37) (Tables S10 and S11).

Discussion

This systematic review and meta-analyses showed that both early and late childhood exposure to TRAP were associated

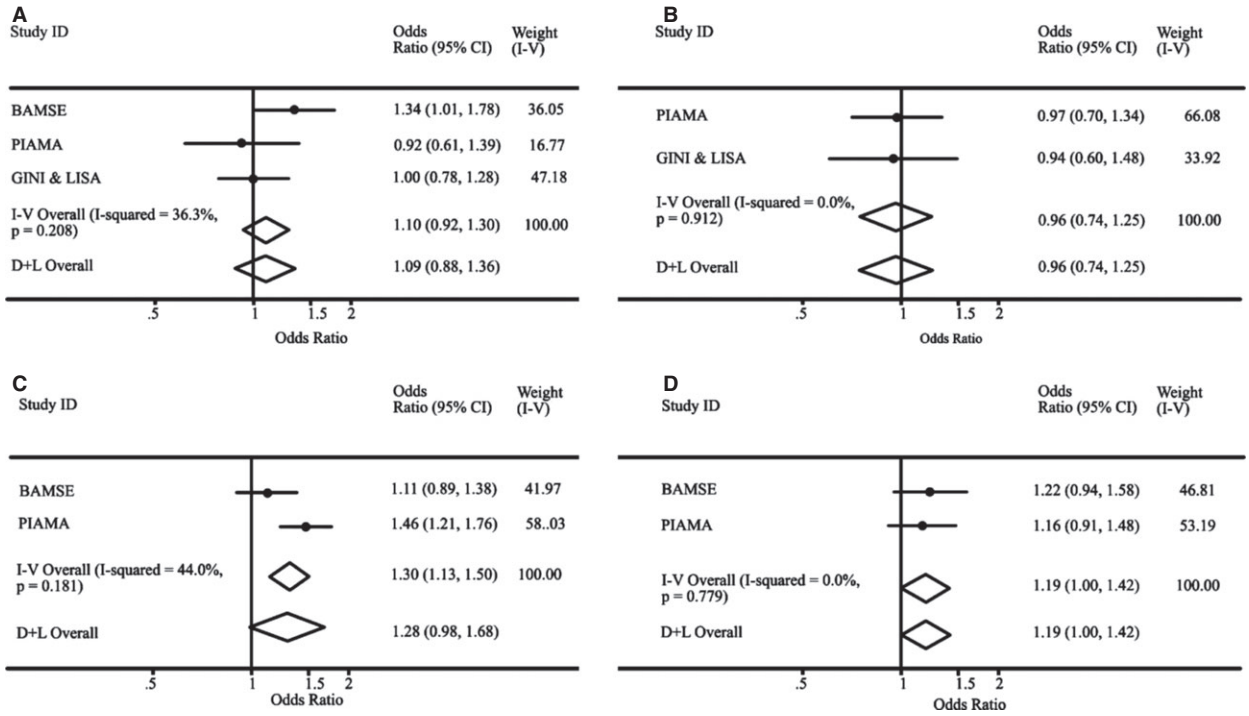

Figure 3 Early childhood exposure per 10 μg/m^3 increase in NO_2 and sensitization to (A) outdoor allergens, (B) indoor allergens, (C) food allergens at the age 4 of years and (D) food allergens at the age of 8 years.

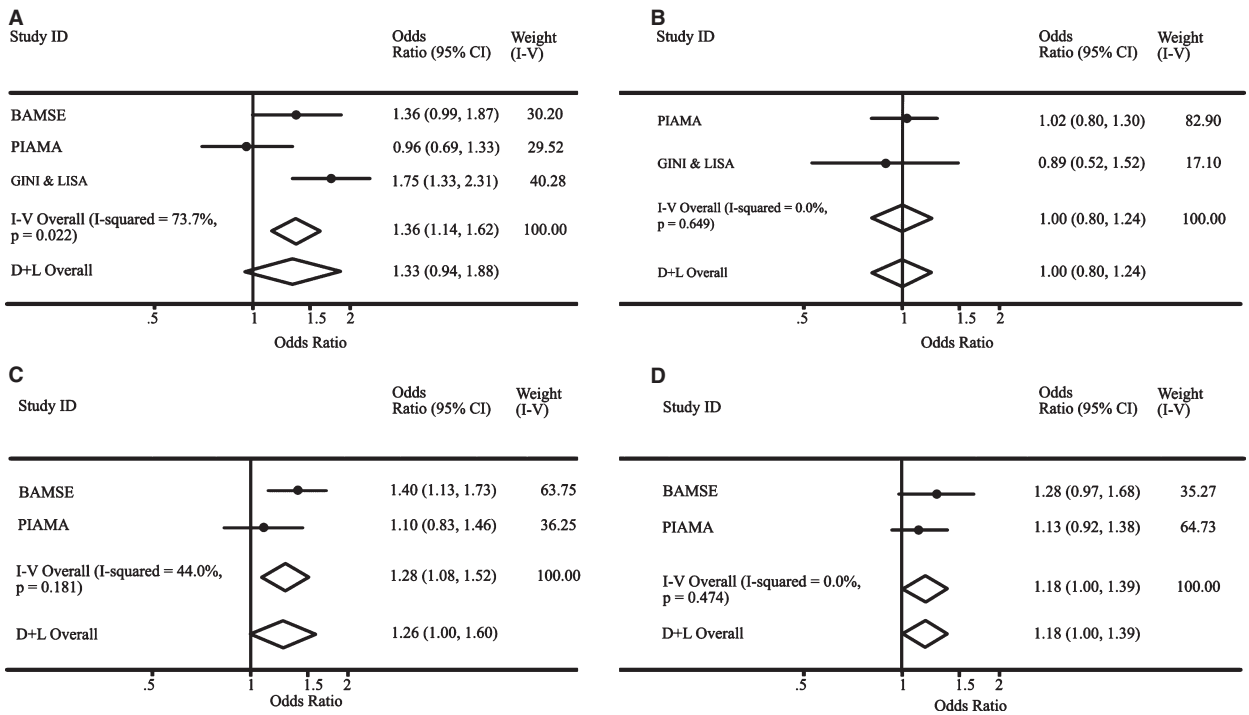

Figure 4 Early childhood exposure per 2 μg/m^3 increase in $PM_{2.5}$ and sensitization to (A) outdoor allergens, (B) indoor allergens, (C) food allergens at the age of 4 years and (D) food allergens at the age of 8 years.

with increased incidence of asthma throughout childhood and the magnitude of this risk increased with age. However, this pattern varied between different TRAP pollutants. Asthma incidence was related to early childhood exposure to NO_2 and BC with a trend of increasing risk over the first 6 years of life. The association between exposure to $PM_{2.5}$ and asthma incidence showed a similar pattern over the first 12 years of life. Compared to NO_2, $PM_{2.5}$ was more strongly associated with outdoor aeroallergen sensitization. While exposure to both NO_2 and $PM_{2.5}$ was significantly associated with food sensitization at the age of both 4 and 8 years, the association seemed to diminish in magnitude from age 4 to 8 years. There was some evidence that childhood exposure to TRAP may also be associated with increased risks of eczema and hay fever.

One of the main strengths of this review is the in-depth evaluation of the evidence from birth cohorts with frequent follow-ups. The age-stratified meta-analysis allowed us to demonstrate trends across age strata. However, substantial heterogeneity was observed across the studies, which may be related to diverse definitions in exposure (LUR, dispersion models and proximity to roads) and outcomes (asthma and wheeze as well as allergic sensitization) (Table S12). In the age-stratified meta-analysis, some age categories had only a small number of studies with few age categories having only one study. Therefore, the age-specific estimates may be less accurate in some categories. The heterogeneity of the study findings may also be related to unmeasured confounding. There are multiple other environmental factors such as pollens, fungal spores and meteorological conditions and their complex interactions that drive asthma and allergies, which can confound or modify the effects of TRAP exposure. Similarly, socio-economic factors that lead to living in more polluted areas may also increase risk of asthma and allergic diseases and thus confound the effect of TRAP.

There is considerable support from the existing literature for the hypothesis that early childhood exposure to air pollution is an important predictor of respiratory morbidity among children (33). One proposed mechanism behind the lag between early childhood exposure and subsequent risk of asthma is that TRAP exposure in early childhood leads to structural changes in growing lungs with subsequent expression of asthma symptoms at an age when asthma can be clearly identified (11). It is also possible that ongoing exposures to other pollutants when children spend more time outdoors (45), especially during preschool and school years, may increase the impact of early childhood exposures leading to the expression of symptoms.

Our systematic review highlights that early childhood exposure to TRAP is associated with new onset of asthma throughout childhood and there is evidence to suggest that TRAP exposure may have an ongoing effect with a lag time of about 3 years. This is a phenomenon that was previously proposed for second-hand smoking exposure and onset of respiratory diseases (46). In our review, BC is also an important predictor of asthma onset during late childhood; however, the results of the age-specific meta-analysis for BC were dominated by the PIAMA study. BC is a product of diesel combustion and emitted mostly by diesel-fuelled vehicles, especially from poorly maintained heavy vehicles, such as trucks. In our review proximity to a major road, a TRAP marker did not show a strong association with asthma and allergic diseases. The null findings may be related to exposure misclassification or due to most available cohort studies being primarily designed for purposes other than investigating air pollution and respiratory morbidity. Additional well-designed birth cohorts with frequent follow-ups, especially for TRAP markers and respiratory diseases, are needed to investigate these associations further in a robust manner.

Our systematic review provides evidence that early childhood $PM_{2.5}$ exposure increases the subsequent risk of sensitization among children. It has been shown that major allergens in pollen can bind to the diesel exhaust particles, which in turn leads to aggregation of pollen allergens that can lead to IgE-mediated reactions (47). Previous systematic reviews report that the association between air pollution and allergic sensitization was debatable due to the inconsistent results across studies. This may, in part, because they did not separately examine the different allergens such as outdoor and indoor aeroallergens and food allergens (19). However, the substantial heterogeneity across studies suggests that more studies focused on the effects of TRAP on sensitization to specific allergens are required to draw firm conclusions. Furthermore, attempts to explain the apparent variation in study results are needed.

In summary, our findings have public health and policy implications as we have shown that exposure to TRAP levels well below the guidelines provided by the World Health Organization ($PM_{2.5}$ 10 $\mu g/m^3$ annual mean and NO_2 40 $\mu g/m^3$ annual mean) is associated with increased incidence of asthma and increased risk of sensitization to common allergens during childhood. However, the substantial heterogeneity of the findings suggests more long-term studies investigating specific exposure ages, and lifetime outcomes are needed to fill this gap in the literature.

Acknowledgments

Gayan Bowatte and Caroline Lodge are supported by the Centre for Air Quality and Health Research and Evaluation (CAR) – a National Health & Medical Research Council (NHMRC) Centre of Research Excellence. Caroline Lodge is also supported by the NHMRC Centre of Research Excellence for Food Allergy. Adrian Lowe, Melanie Matheson and Shyamali Dharmage are supported by the NHMRC. Jennifer Perret is supported by the Lung Foundation of Australia.

Conflict of interest

The authors declare that they have no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Summary of literature search.

Table S1. Study quality by Newcastle-Ottawa scale.

Table S2. Exposure per 10 $\mu g/m^3$ increase in NO_2 and incidence/prevalence of asthma.

Table S3. Exposure per 10 $\mu g/m^3$ increase in NO_2 and incidence/prevalence of wheeze.

Table S4. Exposure per 2 $\mu g/m^3$ increase in $PM_{2.5}$ and incidence/prevalence of asthma.

Table S5. Exposure per 2 $\mu g/m^3$ increase in $PM_{2.5}$ and incidence/prevalence of wheeze.

Table S6. Exposure per 1×10^{-5} m^{-1} increase in black carbon and incidence/prevalence of asthma.

Table S7. Exposure per 1×10^{-5} m^{-1} increase in black carbon and prevalence of wheeze.

Table S8. Exposure to proximity to road and asthma.

Table S9. Exposure to proximity to road and wheeze.

Table S10. Exposure to TRAP and eczema.

Table S11. Exposure to TRAP and hay fever.

Table S12. IgE categories reported in cohorts.

Appendix S1. Supplementary figures and tables.

References

1. Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.
2. Braun-Fahrländer C, Gassner M, Grize L, Takken-Sahli K, Neu U, Stricker T et al. No further increase in asthma, hay fever and atopic sensitisation in adolescents living in Switzerland. *Eur Respir J* 2004;**23**:407–413.
3. Guarnieri M, Balmes JR. Outdoor air pollution and asthma. *Lancet* 2014;**383**:1581–1592.
4. Braback L, Forsberg B. Does traffic exhaust contribute to the development of asthma and allergic sensitization in children: findings from recent cohort studies. *Environ Health* 2009;**8**:17.
5. Carlsten C, Melen E. Air pollution, genetics, and allergy: an update. *Curr Opin Allergy Clin Immunol* 2012;**12**:455–460.
6. Evans KA, Halterman JS, Hopke PK, Fagnano M, Rich DQ. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. *Environ Res* 2014;**129**:11–19.
7. Li S, Batterman S, Wasilevich E, Elasaad H, Wahl R, Mukherjee B. Asthma exacerbation and proximity of residence to major roads: a population-based matched case-control study among the pediatric Medicaid population in Detroit, Michigan. *Environ Health* 2011;**10**:34.
8. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. *J Allergy Clin Immunol* 2008;**121**:1133–1139.
9. Delfino RJ, Staimer N, Tjoa T, Gillen D, Kleinman MT, Sioutas C et al. Personal and ambient air pollution exposures and lung function decrements in children with asthma. *Environ Health Perspect* 2008;**116**:550–558.
10. Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. Urban air pollution, and asthma and COPD hospital emergency room visits. *Thorax* 2008;**63**:635–641.
11. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. *Curr Opin Pediatr* 2013;**25**:232–239.
12. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol* 2005;**115**:689–699.
13. Schaub B, Lauener R, Prescott SL. Immunology and defence mechanism of the developing lung. In: Frey U, Gerritsen J, editors. *Respiratory Diseases in Infants and Children*. *Eur Respir Mon*, Wakefield, UK: European Respiratory Society Journals Ltd, 2006: 60–78.
14. Dietert RR, Etzel RA, Chen D, Halonen M, Holladay SD, Jarabek AM et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems work group summary. *Environ Health Perspect* 2000;**108**:483–490.
15. Schwartz J. Air pollution and children's health. *Pediatrics* 2004;**113**(Suppl 3):1037–1043.
16. Dunnill MS. Postnatal growth of the lung. *Thorax* 1962;**17**:329–333.
17. Bloomberg GR. The influence of environment, as represented by diet and air pollution, upon incidence and prevalence of wheezing illnesses in young children. *Curr Opin Allergy Clin Immunol* 2011;**11**:144–149.
18. Gowers AM, Cullinan P, Ayres JG, Anderson HR, Strachan DP, Holgate ST et al. Does outdoor air pollution induce new cases of asthma? Biological plausibility and evidence; a review. *Respirology* 2012;**17**:887–898.
19. Gruzieva O, Gehring U, Aalberse R, Agius R, Beelen R, Behrendt H et al. Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts. *J Allergy Clin Immunol* 2014;**133**:767–776.
20. Patel MM, Miller RL. Air pollution and childhood asthma: recent advances and future directions. *Curr Opin Pediatr* 2009;**21**:235–242.
21. Tzivian L. Outdoor air pollution and asthma in children. *J Asthma* 2011;**48**:470–481.
22. Anderson HR, Favarato G, Atkinson R. Long-term exposure to air pollution and the incidence of asthma: meta-analysis of cohort studies. *Air Qual Atmos Health* 2013;**6**:47–56.
23. Sousa SIV, Alvim-Ferraz MCM, Martins FG. Health effects of ozone focusing on childhood asthma: what is now known - a review from an epidemiological point of view. *Chemosphere* 2013;**90**:2051–2058.
24. Cohen A, Anderson HR, Ostro BPK, Krzyzanowski M, Künzli N, Gutschmidt K et al. Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors. In: Ezzati M, Lopez AD, Rodgers A, Murray CJL, editors. *Mortality Impacts of Urban air Pollution*. Geneva: World Health Organization, 2004: 1353–1434.
25. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;**21**:1539–1558.
26. Nordling E, Berglind N, Melen E, Emenius G, Hallberg J, Nyberg F et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 2008;**19**:401–408.
27. Gehring U, Cyrys J, Sedlmeir G, Brunekreef B, Bellander T, Fischer P et al. Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur Respir J* 2002;**19**:690–698.
28. Esplugues A, Ballester F, Estarlich M, Llop S, Fuentes-Leonarte V, Mantilla E et al. Outdoor, but not indoor, nitrogen dioxide exposure is associated with persistent cough during the first year of life. *Sci Total Environ* 2011;**409**:4667–4673.
29. Oftedal B, Nystad W, Brunekreef B, Nafstad P. Long-term traffic-related exposures and asthma onset in schoolchildren in Oslo, Norway. *Environ Health Perspect* 2009;**117**:839–844.
30. Brauer M, Hoek G, Smit HA, de-Jongste JC, Gerritsen J, de Jongste JC et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 2007;**29**:879–888.

31. Andersen ZJ, Loft S, Ketzel M, Stage M, Scheike T, Hermansen MN et al. Ambient air pollution triggers wheezing symptoms in infants. *Thorax* 2008;**63**:710–716.
32. Krämer U, Sugiri D, Ranft U, Krutmann J, von Berg A, Berdel D et al. Eczema, respiratory allergies, and traffic-related air pollution in birth cohorts from small-town areas. *J Dermatol Sci* 2009;**56**:99–105.
33. Clark N, Demers P, Karr C, Koehoorn M, Lencar C, Tamburic L et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 2010;**118**:284–290.
34. Patel MM, Quinn JW, Jung KH, Hoepner L, Diaz D, Perzanowski M et al. Traffic density and stationary sources of air pollution associated with wheeze, asthma, and immunoglobulin E from birth to age 5 years among New York City children. *Environ Res* 2011;**111**:1222–1229.
35. Ryan P, Bernstein D, Lockey J, Reponen T, Levin L, Grinshpun S et al. Exposure to traffic-related particles and endotoxin during infancy is associated with wheezing at age 3 years. *Am J Resp Crit Care* 2009;**180**:1068–1075.
36. Carlsten C, Dybuncio A, Becker A, Chan-Yeung M, Brauer M. Traffic-related air pollution and incident asthma in a high-risk birth cohort. *Occup Environ Med* 2011;**68**:291–295.
37. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M et al. Traffic-related air pollution and the development of asthma and allergies during the first 8 years of life. *Am J Resp Crit Care* 2010;**181**:596–603.
38. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Resp Crit Care* 2002;**166**:1092–1098.
39. Ryan PH, LeMasters G, Biagini J, Bernstein D, Grinshpun SA, Shukla R et al. Is it traffic type, volume, or distance? Wheezing in infants living near truck and bus traffic. *J Allergy Clin Immunol* 2005;**116**:279–284.
40. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Koletzko S, Kramer U et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Resp Crit Care* 2008;**177**:1331–1337.
41. Gruzieva O, Bergström A, Hulchiy O, Kull I, Lind T, Melén E et al. Exposure to air pollution from traffic and childhood asthma until 12 years of age. *Epidemiology* 2013;**24**:54–61.
42. Oftedal B, Brunekreef B, Nystad W, Madsen C, Walker S-E, Nafstad P. Residential outdoor air pollution and lung function in schoolchildren. *Epidemiology* 2008;**19**:129–137.
43. Gruzieva O, Bellander T, Eneroth K, Kull I, Melén E, Nordling E et al. Traffic-related air pollution and development of allergic sensitization in children during the first 8 years of life. *J Allergy Clin Immunol* 2012;**129**:240–246.
44. Morgenstern V, Zutavern A, Cyrys J, Brockow I, Gehring U, Koletzko S et al. Respiratory health and individual estimated exposure to traffic-related air pollutants in a cohort of young children. *Occup Environ Med* 2007;**64**:8–16.
45. Wiley JA, Robinson JP, Cheng YT, Piazza T, Stork L, Pladsen K. *Study of Children's Activity Patterns*. Prepared for California Air Resources Board under contract No. A733-149. Berkeley, CA: University of California, 1991.
46. Maritz GS, Harding R. Life-long programming implications of exposure to tobacco smoking and nicotine before and soon after birth: evidence for altered lung development. *Int J Environ Res Public Health* 2011;**8**:875–898.
47. Knox RB, Suphioglu C, Taylor P, Desai R, Watson HC, Peng JL et al. Major grass pollen allergen Lol p 1 binds to diesel exhaust particles: implications for asthma and air pollution. *Clin Exp Allergy* 1997;**27**:246–251.