

CORRESPONDENCE

The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization

DOI:10.1111/all.12611

In the December 2014 issue of *Allergy*, Bowatte et al. (2014) concluded that exposure to traffic-related air pollution (TRAP) was related to asthma and allergic diseases after conducting a systematic review and meta-analysis of

the current evidence available from birth cohort studies (1). Although this is an impressive feat given the vast amount of existing literature on this topic, the authors appear to have unfortunately missed a few recent but very

Table 1 Select odds ratios and 95% confidence intervals for associations between air pollutants estimated to the birth address of participants and asthma, wheeze, allergic rhinitis or allergen sensitization outcomes from studies absent in Bowatte et al. (2014)

	Study design	Outcome	NO ₂	PM _{2.5} mass	PM _{2.5} absorbance	Ozone
Fuentes et al. (2013)*	Longitudinal analysis of GINIplus and LISAPlus birth cohorts	Asthma (from 3 to 10 years)	0.89 [0.73, 1.08]	0.97 [0.59, 1.58]	0.82 [0.55, 1.21]	1.20 [0.98, 1.48]
		Allergic rhinitis (from 3 to 10 years)	0.96 [0.85, 1.09]	0.87 [0.60, 1.26]	0.75 [0.58, 0.96]	1.02 [0.90, 1.16]
		Aeroallergen sensitization (at 6 and 10 years)	0.92 [0.84, 1.01]	1.10 [0.83, 1.45]	0.82 [0.68, 0.99]	0.99 [0.89, 1.09]
Macintyre et al. (2014)†	Pooled analysis of six birth cohorts	Current asthma (at 7/8 years)	1.14 [0.98, 1.48]	2.08 [1.35, 3.19]	1.07 [0.91, 1.26]	0.81 [0.51, 1.27]
		Ever asthma (up to 7/8 years)	1.23 [1.03, 1.46]	1.17 [0.86, 1.60]	1.06 [0.95, 1.19]	0.86 [0.66, 1.13]
		Current wheeze (at 6/7/8 years)	1.12 [0.89, 1.40]	1.33 [0.90, 1.95]	1.06 [0.93, 1.21]	1.29 [0.88, 1.88]
		Ever wheeze (up to 6/7/8 years)	1.04 [0.91, 1.18]	0.95 [0.74, 1.22]	1.00 [0.91, 1.10]	0.90 [0.74, 1.10]
Fuentes et al. (2013)‡	Pooled analysis of six birth cohorts	Allergic rhinitis (at 7/8 years)	1.10 [0.95, 1.26]	1.37§ [1.01, 1.86]	1.16 [0.96, 1.41]	0.91 [0.77, 1.08]
		Aeroallergen sensitization (at 6/7/8 years)	0.94 [0.82, 1.08]	0.92 [0.66, 1.27]	0.93 [0.76, 1.13]	0.95 [0.81, 1.12]
Gruzdeva et al. (2014)‡	Meta-analysis of five birth cohorts	Any allergen sensitization (at 4/6 years)	1.07 [0.86, 1.34]	1.26 [0.90, 1.77]	0.94 [0.63, 1.40]	na
		Any allergen sensitization (at 8/10 years)	0.99 [0.84, 1.16]	1.26 [0.93, 1.73]	1.05 [0.76, 1.44]	na
Molter et al. (2014)‡	Meta-analysis of five birth cohorts	Asthma (at 4/5 years)	1.17 [0.84, 1.62]	1.34 [0.89, 2.02]	1.33 [0.80, 2.21]	na
		Asthma (at 8/10 years)	1.10 [0.81, 1.49]	1.23 [0.78, 1.95]	1.25 [0.84, 1.86]	na

Bold: *P*-value < 0.05; na, not available.

*Results reported per interquartile range increase in pollutant.

†Results reported per 10 µg/m³ for NO₂ and ozone, 4 µg/m³ for PM_{2.5} mass and 0.5 10⁻⁵/m for PM_{2.5} mass absorbance.

‡Results reported per 10 µg/m³ for NO₂ and ozone, 5 µg/m³ for PM_{2.5} mass and 1 10⁻⁵/m for PM_{2.5} mass absorbance.

§Significant association dependent on inclusion of the Dutch PIAMA cohort. Pooled result based on remaining five cohorts after PIAMA is excluded: 1.02 [0.62–1.67].

relevant publications. The results of these omitted studies are overall more conservative than the conclusions reached by Bowatte et al. (2014) and may have altered the authors' findings had they been included in the review. We thus find it important to highlight these missing studies here (select results provided in Table 1) to provide a more comprehensive picture of the state of the art at the end of 2014.

Although the authors reported on the two- and six-year follow-ups of the GINIplus and LISAplus birth cohorts, the most recent 10-year results, which are publically available since 2013, are lacking (2). This omitted large longitudinal study evaluated associations between TRAP and asthma, allergic rhinitis and aeroallergen sensitization using data collected during regular repeated follow-ups, thus directly answering the call raised by Bowatte et al. (2014) in their conclusions. Despite a highly standardized outcome and exposure assessment methodology, this missing analysis did not yield consistent evidence across three study areas in Germany that TRAP increases the risk of any of the studied outcomes. These results would have decreased the strength of the evidence for an association with TRAP, especially for asthma and aeroallergen sensitization, had they been included in the recently published meta-analysis.

Several large multicentre studies were also overlooked. Data from six birth cohorts were used to calculate combined and cohort-specific air pollution and gene–environment effects of TRAP on asthma and wheeze at 7–8 years [(3); advanced publication January 2014]. Of the 16 tested associations between asthma and wheeze outcomes with air pollutants, two were significant. However, several gene–environment interactions were also noted. A similar study conducted for allergic rhinitis and aeroallergen sensitization found one statistically significant association between allergic rhinitis and PM_{2.5} mass, which was entirely dependent on the inclusion of a single cohort (4).

The results of a further two multicentre studies, both conducted as part of the European Study of Cohorts for Air Pollution Effects, were also not highlighted. The meta-analysis on sensitization by Gruziova et al. (2014) is referenced in the article by Bowatte et al. (2014) (5); however, the results

of these two studies are not compared. Interestingly, Bowatte et al. (2014) reported that exposure to TRAP is associated with increased risk of sensitization to common allergens during childhood, whereas the larger, more standardized multicentre study that included data from five birth cohorts found no clear associations. Finally, the fifth missing study found no significant associations between air pollution exposure and childhood asthma prevalence in five European birth cohorts (6). This last article is an important contribution to the field but was only published in October 2014. Thus, in contrast to the previous four articles, it would not have been captured by the search strategy employed by Bowatte et al. (2014), which only included articles published up to March 2014.

The authors may have chosen to exclude pooled or multicentre analyses as there is often overlap in the participating cohorts. However, this strategy goes against the calls for combined analyses of available standardized data to obtain more accurate estimates and examine effect heterogeneity. Furthermore, some cohort- and outcome-specific associations included in these combined analyses had not been previously published.

Author contributions

Elaine Fuertes and Joachim Heinrich drafted and revised the manuscript and approved the final manuscript as submitted. Both authors agree to be accountable for this work.

Conflicts of interest

Both authors have no conflicts of interest.

E. Fuertes and J. Heinrich

*Institute of Epidemiology I, Helmholtz Zentrum München –
German Research Center for Environmental Health,
Neuherberg, Germany
E-mail: elaine.fuertes@helmholtz-muenchen.de*

References

1. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ et al. The influence of childhood traffic-related air pollution exposure on asthma, allergy and sensitization. *Allergy* 2015;**70**:245–256.
2. Fuertes E, Standl M, Cyrus J, Berdel D, Von Berg A, Bauer CP et al. A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts. *PeerJ* 2013;**1**:e193.
3. MacIntyre E, Brauer M, Melen E, Bauer C-P, Bauer M, Berdel D et al. GSTP1 and TNF gene variants and associations between air pollution and incident childhood asthma: The Traffic, Asthma and Genetics (TAG) Study. *Environ Health Perspect* 2014;**122**:418–424.
4. Fuertes E, Brauer M, MacIntyre E, Bauer M, Bellander T, von Berg A et al. Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: results from the TAG Study. *J Allergy Clin Immunol* 2013;**132**:342–352.
5. Gruziova 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.
6. Mölter A, Simpson A, Berdel D, Brunekreef B, Custovic A, Cyrus J et al. A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. *Eur Respir J* 2015;**45**:610–624.

Reply

We thank Fuertes and Heinrich for their interest in our systematic review (1). Our main conclusions were drawn from the results of meta-analyses of incidence data, although inclusion criteria for the systematic review included both prevalence and incidence (as presented in the supplementary file). We found that increased childhood exposure to PM_{2.5} and black carbon was associated with risk of subsequent asthma in childhood. Furthermore, we found that early life traffic-related PM_{2.5} exposure was associated with sensitization to both aero- and food allergens. Fuertes and Heinrich have suggested that there were five additional papers relevant to our systematic review, and considering the findings of these papers may have made our conclusions more conservative.

We agree that we overlooked the paper by Fuertes et al. (2). However, this study would not have qualified to be included within our meta-analyses, as the authors reported the association between early life TRAP exposure and asthma prevalence after 3–10 years of follow-up. We did not include the study by Mölter et al. (3), as it was published in October 2014 after our final search in March 2014. Similar to Fuertes et al. (4), this European Study of Cohorts for Air Pollution Effects analysis would not have met the inclusion criteria for our meta-analysis because the outcome was childhood asthma prevalence. Therefore, inclusion of these two papers in our systematic review would not have changed the conclusions drawn from the meta-analyses.

As acknowledged in the letter, inclusion of pooled results in a meta-analysis often overlaps with the participating cohorts. The two papers by Fuertes et al. (4) (focusing on allergic rhinitis) and MacIntyre et al. (5) (focusing on asthma/whoeeze) analysed the same six birth cohort studies to investigate the impact of exposure to TRAP at birth on different outcomes. Of the six cohorts, results from three were

included in our review. Of the remaining three birth cohort studies included in their reviews, two had not been published at the time of our literature search, and inclusion of unpublished data in a systematic review is debatable as critical evaluation of study methods is a major part of the methodology. Only Fuertes et al. (2) was missed, but as mentioned above, this study was not eligible for the meta-analyses.

The authors also raised the issue of including the review by Gruzieva et al. (6) which pooled five studies to investigate the relationship between TRAP exposure and sensitization to any allergen. As these relationships were not grouped by type of allergen, as we have done in our review, it did not meet our inclusion criteria.

In summary, consideration of these five papers would not change our main findings. However, we agree that summarizing and synthesizing the growing body of evidence on TRAP exposure is not trivial, and decisions made during the review process will influence the final conclusions.

G. Bowatte¹, C. J. Lodge^{1,2}, A. J. Lowe^{1,2}, B. Erbas³, J. Perret¹, M. J. Abramson⁴, M. C. Matheson^{1,*}, S. C. Dharmage^{1,2,*}

¹Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne,

²Murdoch Children Research Institute,

³School of Psychology and Public Health, La Trobe University,

⁴School of Public Health & Preventive Medicine, Monash University, Melbourne, Vic., Australia
E-mail: s.dharmage@unimelb.edu.au

References

1. Bowatte G, Lodge C, Lowe AJ, Erbas B, Perret J, Abramson MJ et al. 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.
2. Fuertes E, Standl M, Cyrus J, Berdel D, von Berg A, Bauer CP et al. A longitudinal analysis of associations between traffic-related air pollution with asthma, allergies and sensitization in the GINIplus and LISAplus birth cohorts. *PeerJ* 2013;**1**:e193.
3. Mölter A, Simpson A, Berdel D, Brunekreef B, Custovic A, Cyrus J et al. A multicentre study of air pollution exposure and childhood asthma prevalence: the ESCAPE project. *Eur Respir J* 2015;**45**:610–624.
4. Fuertes E, Brauer M, MacIntyre E, Bauer M, Bellander T, von Berg A et al. Childhood allergic rhinitis, traffic-related air pollution, and variability in the GSTP1, TNF, TLR2, and TLR4 genes: results from the TAG Study. *J Allergy Clin Immunol* 2013;**132**:342–352.
5. MacIntyre EA, Brauer M, Melen E, Bauer CP, Bauer M, Berdel D et al. GSTP1 and TNF Gene variants and associations between air pollution and incident childhood asthma: the traffic, asthma and genetics (TAG) study. *Environ Health Perspect* 2014;**122**:418–424.
6. 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.