Environment International 100 (2017) 1–31

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Review article

Exposure to traffic-related air pollution and risk of development of childhood asthma: A systematic review and meta-analysis

Haneen Khreis [a,*], Charlotte Kelly [a,b], James Tate [a], Roger Parslow [c], Karen Lucas [a], Mark Nieuwenhuijsen [d,e,f]

[a] Institute for Transport Studies, University of Leeds, Leeds, United Kingdom
[b] Leeds Institute of Health Sciences, University of Leeds, Leeds, United Kingdom
[c] Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, United Kingdom
[d] ISGlobal CREAL, C/Dr. Aiguader 88, 08003 Barcelona, Spain
[e] Universitat Pompeu Fabra (UPF), C/Dr. Aiguader 88, 08003, Barcelona, Spain
[f] CIBER Epidemiología y Salud Pública (CIBERESP), C/Monforte de Lemos 3-5, 28029 Madrid, Spain

ARTICLE INFO

Article history:
Received 6 July 2016
Received in revised form 4 November 2016
Accepted 10 November 2016
Available online 21 November 2016

Keywords:
Asthma
Childhood
Traffic-related air pollution
Meta-analysis
Black carbon
Transport policy

ABSTRACT

Background and objective: The question of whether children's exposure to traffic-related air pollution (TRAP) contributes to their development of asthma is unresolved. We conducted a systematic review and performed meta-analyses to analyze the association between TRAP and asthma development in childhood.
Data sources: We systematically reviewed epidemiological studies published until 8 September 2016 and available in the Embase, Ovid MEDLINE (R), and Transport databases.
Study eligibility criteria, participants, and interventions: We included studies that examined the association between children's exposure to TRAP metrics and their risk of '*asthma*' incidence or lifetime prevalence, from birth to age 18 years old.
Study appraisal and synthesis methods: We extracted key characteristics of each included study using a predefined data items template and these were tabulated. We used the Critical Appraisal Skills Programme checklists to assess the validity of each included study. Where four or more independent risk estimates were available for a continuous pollutant exposure, we conducted overall and age-specific meta-analyses, and four sensitivity analyses for each summary meta-analytic exposure-outcome association.
Results: Forty-one studies met our eligibility criteria. There was notable variability in asthma definitions, TRAP exposure assessment methods and confounder adjustment. The overall random-effects risk estimates (95% CI) were 1.08 (1.03, 1.14) per 0.5×10^{-5} m^{-1} black carbon (BC), 1.05 (1.02, 1.07) per 4 $\mu g/m^3$ nitrogen dioxide (NO_2), 1.48 (0.89, 2.45) per 30 $\mu g/m^3$ nitrogen oxides (NO_x), 1.03 (1.01, 1.05) per 1 $\mu g/m^3$ Particulate Matter <2.5 μm in diameter ($PM_{2.5}$), and 1.05 (1.02, 1.08) per 2 $\mu g/m^3$ Particulate Matter <10 μm in diameter (PM_{10}). Sensitivity analyses supported these findings. Across the main analysis and age-specific analysis, the least heterogeneity was seen for the BC estimates, some heterogeneity for the $PM_{2.5}$ and PM_{10} estimates and the most heterogeneity for the NO_2 and NO_x estimates.
Limitations, conclusions and implication of key findings: The overall risk estimates from the meta-analyses showed statistically significant associations for BC, NO_2, $PM_{2.5}$, PM_{10} exposures and risk of asthma development. Our findings support the hypothesis that childhood exposure to TRAP contributes to their development of asthma. Future meta-analyses would benefit from greater standardization of study methods including exposure assessment harmonization, outcome harmonization, confounders' harmonization and the inclusion of all important confounders in individual studies.
Systematic review registration number: PROSPERO 2014: CRD42014015448.

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* Corresponding author at: Institute for Transport Studies, 34-40 University Road, University of Leeds, Leeds, LS2 9JT, United Kingdom.
E-mail addresses: ts12hrk@leeds.ac.uk, khreishaneen@gmail.com (H. Khreis).

http://dx.doi.org/10.1016/j.envint.2016.11.012
0160-4120/

1. Introduction

Asthma is a complex and heterogeneous chronic inflammatory disease of the airways (Wenzel, 2012; Xie and Wenzel, 2013). The condition is conservatively estimated to affect 334 million people worldwide (Global Asthma Network, G, 2014). Numerous studies show that the prevalence of childhood asthma has increased dramatically since the 1950s, with some suggestion of plateauing in developed regions (Anandan et al., 2010; Braman, 2006; Pearce et al., 2007; Anderson et al., 2007; Zhang et al., 2013; Huang et al., 2015; Chen et al., 2016). The factors driving these increases are largely unknown, but coinciding changes in environmental exposures are thought to be responsible (Gaffin et al., 2014).

One putative environmental exposure is humans' exposure to ambient air pollution. Although there is sufficient evidence that ambient air pollution can exacerbate pre-existing asthma across a variety of outcomes (Gilmour et al., 2006; Guarnieri and Balmes, 2014; Braback and Forsberg, 2009), the role of air pollution exposure in the initial development of asthma is as yet contested (Eder et al., 2006; Gowers et al., 2012; Gehring et al., 2015a; Deng et al., 2016), partly as a result of the difficulty in conducting adequate epidemiological studies required to address this question.

Earlier reviews have effectively excluded ambient air pollution as a plausible cause of the rise in asthma incidence, with one argument being that the available evidence was inconsistent (Koenig, 1999). Furthermore, previous studies showed that asthma prevalence did not mirror changes in ambient air pollution concentrations, and reductions in levels of ambient sulfur dioxide (SO_2) and total suspended particles (TSP), for example, seemed to synchronize with rapid increases of the condition (Eder et al., 2006; Gowers et al., 2012; Heinrich et al., 2002; Anderson, 1997). However, positive associations were subsequently shown between the incidence and prevalence of asthma and wheeze and exposure contrasts at the intra-urban scale, mainly dominated by traffic-related air pollution (TRAP) (Gasana et al., 2012; Anderson et al., 2013; Bowatte et al., 2014; Health Effects Institute, H.E.I, 2010; Favarato et al., 2014). Traffic-related air pollutants are ubiquitous, are of different chemical and physical nature compared to the classical air pollution mix associated with domestic heating and power plant emissions, and thus necessitate specific examination.

Early-life and childhood could represent critical exposure windows for asthma development due to the plasticity and susceptibility of target organs and systems during these developmental periods and the long maturation period of the respiratory, immune and detoxification systems (Schwartz, 2004; Wright and Brunst, 2013; Deng et al., 2015; Bateson and Schwartz, 2007). Moreover, when compared to adults, infants and children exhibit higher ventilation rates (Wright and Brunst, 2013), reduced nasal deposition efficiencies for inhaled particles (Bennett et al., 2007), are more typically mouth-breathers invalidating the nasal filtering and conditioning of the inhaled air in temperature and relative humidity (Bateson and Schwartz, 2007), and tend to be more active outdoors where their exposure to TRAP is generally higher (Braback and Forsberg, 2009; Bateson and Schwartz, 2007).

2. Objective

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

Four meta-analyses were previously published on asthma and TRAP (Gasana et al., 2012; Anderson et al., 2013; Bowatte et al., 2014; Favarato et al., 2014). Unlike these analyses, our review is specifically focused on TRAP exposures and childhood asthma development only. Studies of TRAP exposures and childhood wheeze, included by Gasana et al. (Gasana et al., 2012), Anderson et al. (Anderson et al., 2013) and their follow-up synthesis by Favarato et al. (Favarato et al., 2014), were not included in our analyses as childhood wheeze is a non-specific symptom, represents different disease patterns at different ages (Gehring et al., 2002; Piippo-Savolainen and Korppi, 2008; Brunst et