The effect of outdoor air pollution on the risk of hospitalisation for bronchiolitis in infants: a systematic review

Charlotte King[1,*], Jamie Kirkham[2], Daniel Hawcutt[3,*] and Ian Sinha[4,*]

[1] Department of Women and Child's Health, University of Liverpool, Liverpool, UK
[2] Department of Biostatistics, University of Liverpool, Liverpool, UK
[3] NIHR Alder Hey Clinical Research Facility, Alder Hey Children's Hospital, Liverpool, UK
[4] Department of Respiratory Medicine, Alder Hey Children's Hospital, Liverpool, UK
* These authors contributed equally to this work.

ABSTRACT

Objective: To systematically review the evidence around the effect of ambient levels of particulate and gaseous pollutants, and the risk of hospitalisation with bronchiolitis for infants under two years of age.

Design: Systematic review of observational epidemiological studies including cohort, time series, case crossover and case control study designs.

Data sources: Medline, Scopus, and Web of Science searched to November 2017 with no language restrictions.

Eligibility criteria: Studies investigating impact of air pollution levels on particulate pollutants (diameter <2.5 µm (PM2.5) or <10 µm (PM10) and gaseous pollutants (nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), ozone (O_3)) on hospital admission for bronchiolitis.

Main outcome measure: Risk of hospitalisation from bronchiolitis.

Results: Eight studies were eligible for review. Long term exposure to PM2.5 may be associated with increased risk of hospitalisation for bronchiolitis. SO_2 may also be associated with hospitalisation, but results for other pollutants are inconsistent between studies. In three of the five studies that showed a positive association between air pollutants and hospitalisation, measured concentrations were below World Health Organization (WHO) recommended levels.

Conclusions: Certain particulate and gaseous pollutants may have a clinically relevant effect on hospital admissions for bronchiolitis in children below age two years old. Large cohort or time series studies are needed to examine this possible association.

Protocol: The protocol can be found at PROSPERO (CRD42017080643).

Subjects Global Health, Pediatrics, Respiratory Medicine
Keywords Bronchiolitis, Air pollution, Hospitalisation, Systematic review

INTRODUCTION

Bronchiolitis is a common lower respiratory infection in infancy, it is caused by respiratory syncytial virus (RSV) in 80% of cases (*Jhawar, 2003*). RSV, spread by droplet transmission (*Leung, Kellner & Davies, 2005*), causes airway inflammation (*Nicolai et al., 2013*), bronchial epithelial cell necrosis (*Leung, Kellner & Davies, 2005*), and other pathogenic

Submitted 15 May 2018
Accepted 10 July 2018
Published 28 August 2018

Corresponding author
Daniel Hawcutt,
d.hawcutt@liverpool.ac.uk

Academic editor
Yuming Guo

Additional Information and Declarations can be found on page 14

DOI **10.7717/peerj.5352**

Table 1 Air pollutants that affect the respiratory system, their major sources, and maximum mean levels recommended by WHO.

	Source	WHO ambient level
Particulate matter diameter <2.5 μm (PM2.5)	Combustion sources	10 μg/m^3 annual mean 25 μg/m^3 24 h mean
Particulate matter diameter <10 μm (PM10)	Mechanical processes such as construction activities, road dust re-suspension and wind	20 μg/m^3 annual mean 50 μg/m^3 24 h mean
Nitrogen Dioxide (NO_2)	Fuel emission and combustion related pollution i.e. road traffic	40 μg/m^3 annual mean 200 μg/m^3 1 h mean
Sulphur Dioxide (SO_2)	Fossil fuel combustion at industrial plants and other industrial facilities	20 μg/m^3 24 h mean 500 μg/m^3 10 min mean
Carbon Monoxide (CO)	Fossil fuel emission from cars, trucks and other vehicles	10 mg/m^3 8 h mean
Ozone (O_3)	Photochemical reactions in the presence of sunlight and oxides or VOCs	100 μg/m^3 8 h mean

effects (*Sinha et al., 2015*). It is a major cause of hospital admission in developed (*Green et al., 2016*; *Hasegawa et al., 2013*; *Shay et al., 1999*) and developing countries (*Berman, 1991*; *Robertson et al., 2004*) worldwide. In England, rates of hospital admission for infants with bronchiolitis have increased since the 1980s, particularly in industrialised areas (*Green et al., 2016*). Risk factors for severe disease requiring hospitalisation include those that affect structural and functional lung development, or generate airway inflammation, including prematurity (*García et al., 2010*), low birth weight (*Lanari et al., 2002*), cardiac abnormalities (*Purcell & Fergie, 2004*), and exposure to tobacco smoke (*Semple et al., 2011*).

Exposure to air pollutants in early childhood also affects pulmonary function tests, and airway inflammation (*Gotschi et al., 2008*; *Schultz et al., 2012*). Relative functional and anatomical immaturity of an infant's respiratory and immune systems, in addition to their higher tidal volume per unit body weight, may render them particularly susceptible to the adverse effects of air pollutants (*Braga et al., 2001*; *Schwartz, 2004*).

There is increasing awareness that air pollution contributes to respiratory morbidity (*Curtis et al., 2006*; *UNICEF, 2016*) and mortality (*Global Burden of Disease 2016 Risk Factors Collaborators, 2017*; *Marchal et al., 2012*), including increased risk of asthma exacerbations (*Orellano et al., 2017*) and acute lower respiratory infection in children (*Mehta et al., 2013*). Air pollutants implicated in respiratory morbidity, their major sources (*World Health Organization (WHO), 2006*; *UNICEF, 2016*) and maximum recommended World Health Organization (WHO) ambient levels (*World Health Organization (WHO), 2000*, *2006*) are listed in Table 1. The air pollutants implicated are particulate matter, which is subdivided depending on particle size as either less than 2.5 μm (PM2.5) or less than 10 μm (PM10), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3).

We aimed to systematically review observational studies which examined the impact of ambient levels of both particulate and gaseous pollutants on the risk of hospitalisation with a clinical or microbiological diagnosis of bronchiolitis in infants.

METHODS

The protocol for our review was registered on PROSPERO (CRD42017080643). Two investigators (Charlotte King and Ian Sinha) independently performed the initial screening of titles and abstracts, analysed full text reports for eligibility, extracted data, and evaluated study quality according to the steps of the PRISMA statement (*Liberati et al., 2009*). Disagreements were discussed between the two reviewers (Charlotte King and Ian Sinha) to reach an agreement, a third reviewer (DH) then assessed if agreement was not made.

Information sources and search strategy

We individually searched online databases MEDLINE, SCOPUS and Web of Science for terms related to 'bronchiolitis', 'air pollution', 'particulate matter', 'nitrogen dioxide', 'sulphur dioxide', 'carbon monoxide', 'ozone', and 'infants' (see File S1 for detailed search strategy).

Inclusion criteria and study selection

We included cohort, time series, case crossovers or case control study designs (based on previous methodology by *Shah et al. (2015)*) that evaluated the impact of air pollution levels (PM2.5, PM10, NO_2, SO_2, CO, O_3) on the pre-specified primary outcome (risk of hospitalisation with bronchiolitis, this is classified as a hospital admission only not including emergency department visits). Secondary outcomes were the risk of emergency department visits, unscheduled primary care visits, and critical care admission. Studies were included that evaluated exposure to air pollutants at any time period (lag) before hospitalisation occurred and were categorised as acute (less than 7 days), sub-chronic (1 month prior to hospitalisation), or lifetime exposure (average daily exposure from birth to hospitalisation). We specified that the primary pollutants of interest would be particulate matter and nitrogen dioxide as these are from the most common sources of pollution in urban areas (*UNICEF, 2016*).

There were no language restrictions. We excluded studies that evaluated the impact of air pollution on more than one respiratory illness if data for bronchiolitis were not presented separately. We also excluded studies examining temporal associations between air pollution levels and the number of hospitalisations for bronchiolitis in a particular hospital or region.

Assessment of quality of studies

The quality of case-control and cohort studies was evaluated using the Newcastle Ottawa quality assessment tool (*Wells et al., 2015*), and in addition the following specific methodological features of all included studies were examined.

Selection bias and additional quality criteria

Studies were considered to have low risk of selection bias if consecutive cases of hospital admission for bronchiolitis were included, and these were identified from health records rather than parental recall. We classed as higher quality those studies in which the case definition of bronchiolitis was based on the International Classification of Disease

(ICD 9) criteria (*World Health Organization, 1978*) (code 466.1, due to RSV or other infectious organisms), and whether clinical diagnosis was supplemented by microbiological testing. Also, studies were classified as higher quality if infants were less than two years old based on guidance by the National Institute for Health and Care Excellence (NICE) (*Ralston et al., 2014*).

Exposure assessment

From each study, we evaluated the reported methodology with which levels of air pollutants were measured, regarding frequency of monitoring, methodology of data collection and proximity of stations to participants. Studies were considered more methodologically robust if pollutants were measured daily, using standardised techniques, and monitors were placed within ten miles of the hospitals or residences.

Adjustment for confounders

Adjustment for meteorological confounders, socioeconomic status, age, and other clinical risk factors were examined in each study. Studies were considered to be at low risk of bias if they adjusted for at least two of these types of confounders.

Data extraction and statistical analysis

From eligible studies, we extracted data around sample size, odds ratio (OR) or relative risk of hospital admission for the stated air pollutant concentrations. We desired to only meta-analyse results from cohort studies, as they provide the strongest observational evidence in the absence of RCTs. Case crossover studies allow for case events to act as their own controls, with excess risk evaluated using conditional logistic regression (*Maclure, 1991*), thus adjust for age as a confounding variable. Time series studies use counts with analysis done using log linear regression models, adjusting for confounding variables such as the weather (*Fung et al., 2003*). Time series, case crossover studies and case control studies are reported descriptively, and results presented on forest plots without overall synthesis. This was undertaken due to the high levels of methodological heterogeneity expected between studies. For each study, we compared the mean ambient pollutant value with the recommended level by *WHO (2000, 2006)*.

Grading of evidence

For acute, sub-chronic, and lifetime exposure to each pollutant, we formulated conclusions and graded evidence according to a strategy based on recommendations from the GRADE working group (*Schünemann et al., 2013*), such that each conclusion would be based on low-, moderate- or high-quality evidence as judged by two reviewers (Ian Sinha and Charlotte King). Evidence was graded as low to begin with, as we only included observational studies, and was downgraded one level if there was only one study. Evidence was graded down if there were any studies in the analysis with one or more methodological limitations outlined in the quality assessment domains above and graded up one if there were no methodological flaws across the studies relevant to that analysis. We considered downgrading one level for inconsistency if there were no overlapping confidence intervals between studies, if the point estimate for OR across studies was either wide in variance

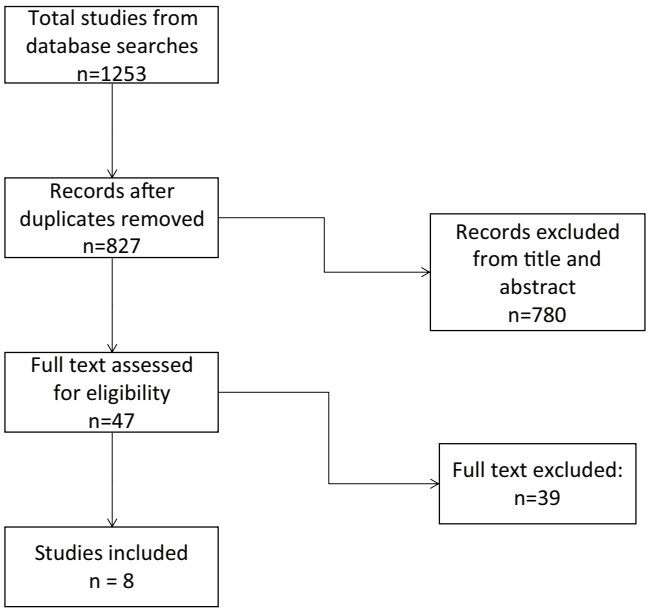

Figure 1 **PRISMA flow diagram.** Full-size DOI: 10.7717/peerj.5352/fig-1

across studies, or if the results were conflicting. We did not include criteria around indirectness this was covered in the quality assessment process. For imprecision, we graded down if there were less than 5,000 infants in the studies and graded up one if there were more than 20,000. We did not incorporate formal assessment of publication bias as there were too few studies to do this robustly.

RESULTS

Eight studies (including four case control studies and four case crossover studies *Abdul Rahman et al., 2017*; *Girguis et al., 2017*; *Karr et al., 2004*, *2006*, *2007*, *2009a*, *2009b*; *Segala et al., 2008*) were eligible for our review. The review flowchart is shown in Fig. 1, and the reasons individual studies were excluded are summarised in File S2.

Six of the studies were from overlapping research groups in North America (*Girguis et al., 2017*; *Karr et al., 2004*, *2006*, *2007*, *2009a*, *2009b*), one from France (*Segala et al., 2008*) and one from Malaysia (*Abdul Rahman et al., 2017*) a developing country. The study characteristics are summarised in Table 2. Of the eight studies, six were classed as being of low risk of bias with regards selection of participants, evaluation of air pollution, and for adjustment for confounding factors in their analysis. The study characteristics are summarised in Table 2, and the quality assessments in Table 3.

Association between air pollution and risk of hospitalisation for bronchiolitis

The results from the included studies are summarised below and shown in Figs. 2 and 3, see File S3 for detailed results. The summary evidence and GRADE assessments are summarised in File S4.

Table 2 Characteristics of included studies.

Study	Study design	Years conducted	Country (Region)	Bronchiolitis definition	Population	Population size	Lag exposure	Adjusted for confounders	Pollutants measured*
Karr et al. (2009a)	Case control	1999–2002	Canada (British Columbia)	ICD 9	Singleton children aged 2–12 months	11,675	Lifetime and 1 month before	Adjusted for infant sex, gestational age, First Nation status, parity, maternal age, maternal smoking during pregnancy, maternal initiation of breastfeeding at birth, income (quintile census), maternal education (quartile census). Cases and controls are matched on date of birth	PM2.5, PM10, NO_2, SO_2, CO, O_3
Karr et al. (2009b)	Case control	1997–2003	United States (Washington State)	ICD 9	Three weeks to one year	3,124	Lifetime, 30 day average and 7 day average (PM2.5 only)	Maternal education, mother's self-reported smoking during pregnancy and infant race/ethnicity	PM2.5, NO_2
Karr et al. (2006)	Case crossover	1995–2000	United States (California)	ICD 9	Three weeks to one year	19,109	Lag 1–2 and Lag 3–5 days for PM2.5, Lag 1 and 4 days for NO_2, CO	Day of week (PM2.5 only), mean daily temperature, mean daily humidity	PM2.5, NO_2, CO
Karr et al. (2004)	Case crossover	1995–2000	United States (California)	Not stated	Three weeks to one year	22,365	Lag 1–2, Lag 3–5	Not stated	PM2.5, NO_2, CO
Girguis et al. (2017)	Case control	2001–2008	United States (Massachusetts)	ICD 9	Three weeks to less than 12 months	19,374	Lifetime	High risk pregnancy, maternal age, birthweight, smoking during pregnancy, maternal education, adequacy of prenatal care, parity, income and insurance type. Matched on date of birth (± 6 days) and gestational week	PM2.5
Abdul Rahman et al. (2017)	Case crossover	2006–2010	Malaysia (Klang Valley)	Not stated	Not stated	5,779	Lifetime	Not stated	PM10, CO, O_3, NO_2

Table 2 (continued).

Study	Study design	Years conducted	Country (Region)	Bronchiolitis definition	Population	Population size	Lag exposure	Adjusted for confounders	Pollutants measured*
Karr et al. (2007)	Case control	1995–2000	United States (California)	ICD 9	Three weeks to one year	18,595	Chronic and sub-chronic	Gender, ethnicity (Hispanic vs. not Hispanic), insurance category (medical, private/health maintenance organization/ preferred provider organization, other), mother's highest level of education (0, 1–6, 7–12, or 13 years), any lung disease (chronic lung disease and pulmonary anomalies, including congenital diaphragmatic hernia), any cardiac anomalies, daily mean temperature, and daily mean humidity	PM2.5, NO_2, O_3, CO
Segala et al. (2008)	Case crossover	1997–2001	France (Paris)	Respiratory dyspnea and/or sibilants and wheezing for children	Less than three years	16,588	Lag 0–1, lag 0–4	Public holidays, holidays and weather variables	PM10, NO_2, SO_2

Note:

* PM2.5, particulate matter diameter <2.5 µm; PM10, particulate matter diameter <10 µm; NO_2, nitrogen dioxide; SO_2, Sulphur dioxide; CO, carbon monoxide; O_3, ozone.

Table 3 Risk of bias assessment of included studies.

Study	Study design	Selection of participants	Evaluation of exposure	Consideration of confounding factors	Newcastle Ottawa score
Karr et al. (2009a)	Case control	Low	Low	Low	7
Karr et al. (2009b)	Case control	Low	Low	Low	7
Karr et al. (2006)	Case crossover	Low	Low	Low	N/A
Karr et al. (2004)	Case crossover	Unclear*	Unclear*	Unclear*	N/A
Girguis et al. (2017)	Case control	Low**	Low	Low	8
*Abdul Rahman et al. (2017)****	Case crossover	High	High	High	N/A
Karr et al. (2007)	Case control	Low	Low	Low	7
Segala et al. (2008)	Case crossover	Low	Low	Low	N/A

Notes:
* Unclear as conference abstract.
** In this study, hospital admissions, observational stays, and ED visits were combined into one outcome ('clinical encounter') but data for hospitalisations only were reported separately.
*** Unclear risk of bias for selection as although all admissions were included, definition of bronchiolitis is not stated; High risk of bias for exposure evaluation based on large distance between measurement stations; no adjustment for confounding factors.

Particulate pollutants

Based on moderate quality evidence (File S4), acute exposure to PM2.5 does not seem to increase risk of hospitalisation (Fig. 2). Two studies (*Karr et al., 2004*, *2006*) found no increased risk of hospitalisation with acute exposure to PM2.5. Sub-chronic effects are unclear, but lifetime exposure may increase risk of hospitalisation (Fig. 2). Two studies found no increased risk of hospitalisation with sub chronic or lifetime exposure (*Karr et al., 2009a*, *2009b*) but two studies did find an increased risk with 30 day exposure (OR 1.09 [1.04–1.14]) and lifetime exposure (OR 1.09 [1.04–1.14] *Karr et al., 2007* and 1.09 [1.05–1.13] *Girguis et al., 2017*).

The evidence around PM10 is of lower quality (File S4). Acute and lifetime effects of PM10 on hospitalisation with bronchiolitis are unclear, but sub chronic exposure does not seem to be associated with increased risk (Fig. 2). One study (*Segala et al., 2008*) found association between PM10 and risk of hospital admission at a lag of 0–4 days (OR 1.06 [1.03–1.10]), but not at a lag of 0–1 days. Of the two studies which measured longer term effects of PM10, one (*Karr et al., 2009a*) found no association, but one (*Abdul Rahman et al., 2017*) found a statistically significant association with lifetime exposure (OR 1.115 [1.093–1.138]).

Gaseous pollutants

The association between exposure length of gaseous pollutant and risk of hospitalisation admission varied between pollutants, and results were inconsistent across studies.

Based on moderate quality evidence (File S4), the acute, sub-chronic, and lifetime effects of NO_2 are unclear, although longer term exposure may be associated with increased risk of admission for bronchiolitis (Fig. 3). Two studies found no increased risk of acute exposure (*Karr et al., 2004*, *2006*), and one found a statistically significant association at a lag of 0–4 days (OR 1.04 [1.02–1.07]), but not 0–1 days (*Segala et al., 2008*). Three studies (*Abdul Rahman et al., 2017*; *Karr et al., 2007*, *2009b*) found no association with risk

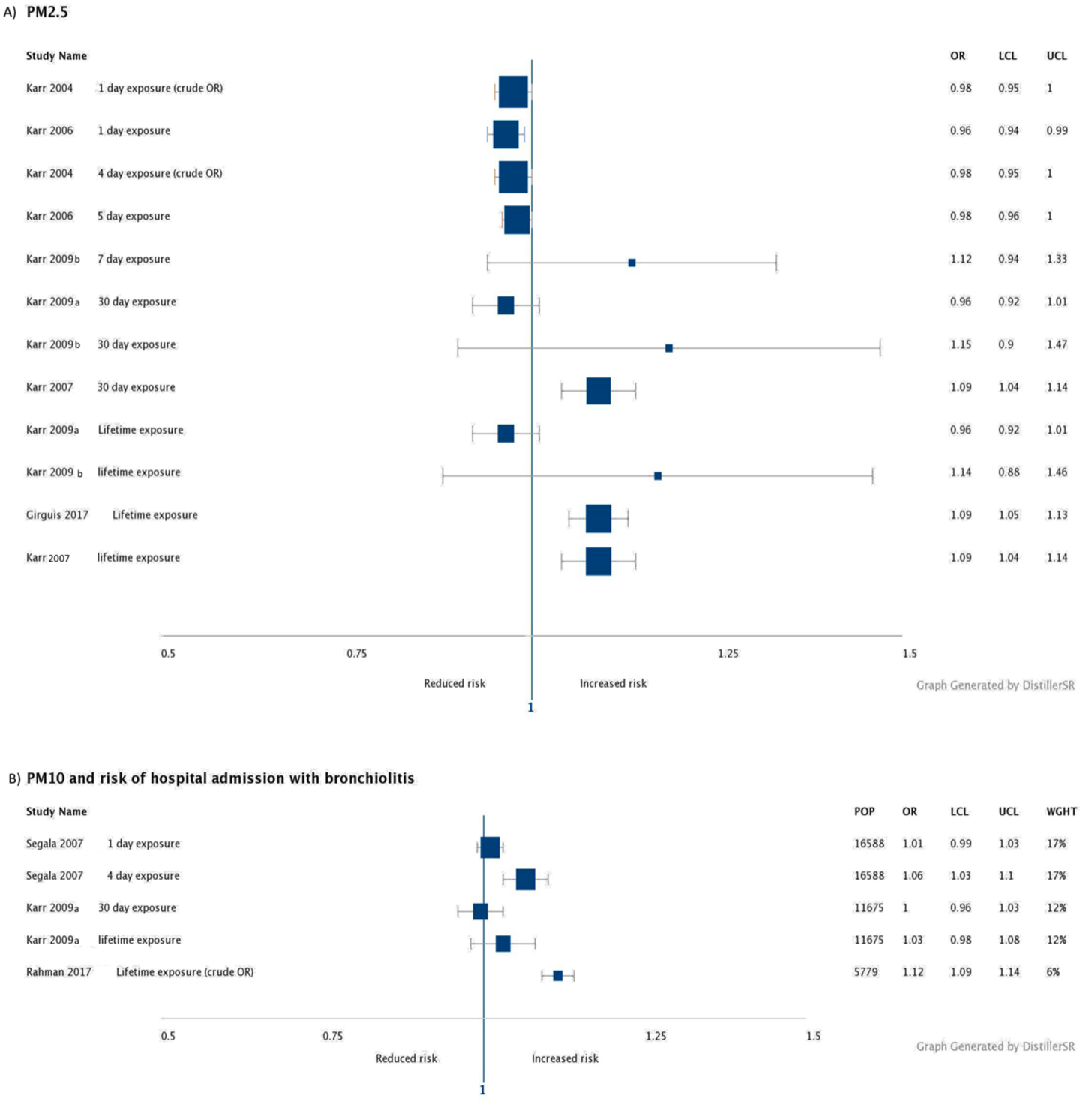

Figure 2 Forest plots of particulate pollutants. (A) PM2.5 forest plot. (B) PM10 forest plot. Full-size DOI: 10.7717/peerj.5352/fig-2

of hospitalisation admission, but one (*Karr et al., 2009a*) found statistically significant association with sub-chronic (OR 1.11 [1.08–1.14]) and lifetime exposure (OR 1.12 [1.09–1.16]).

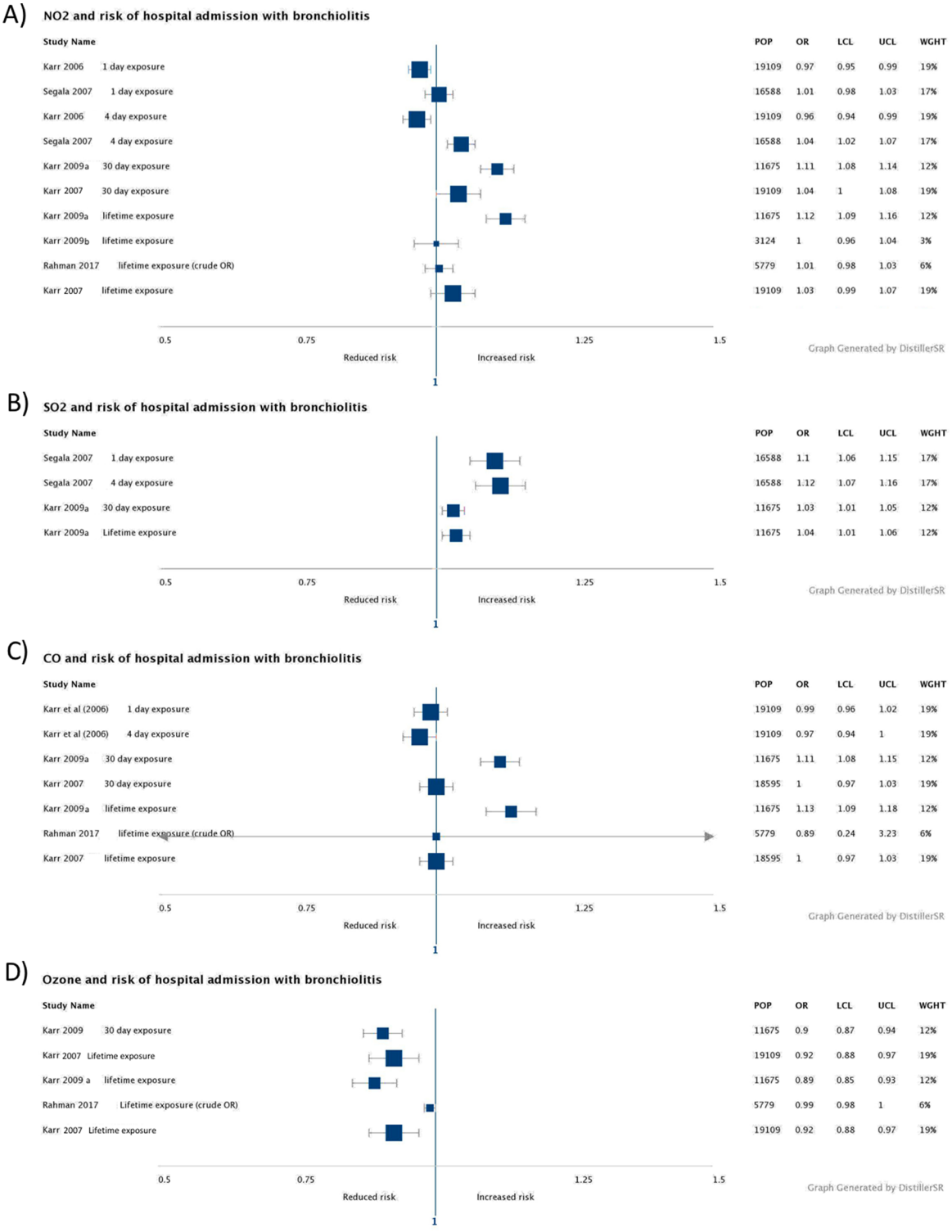

Figure 3 Forest plots of gaseous pollutants. (A) NO_2 forest plot. (B) SO_2 forest plot. (C) CO forest plot. (D) O_3 forest plot.
Full-size DOI: 10.7717/peerj.5352/fig-3

For SO_2, the strength of this evidence was graded as low (File S4). The results of two studies suggest that acute, sub-chronic, and lifetime exposure to SO_2 may be associated with increased risk of hospitalisation (Fig. 3). One study (*Segala et al., 2008*) examined the acute effects and found statistically significant associations at a lag of 0–4 days (OR 1.12 [1.07–1.16]) and 0–1 days (OR 1.10 [1.06–1.15]). One study (*Karr et al., 2009a*) assessed longer term exposure and found a statistically significant association with risk of hospitalisation for lifetime exposure (OR 1.04 [1.01–1.06]) and sub-chronic exposure (OR 1.03 [1.01–1.05]).

Based on low-quality evidence from two studies (*Karr et al., 2004*, *2006*), CO does not seem to have acute effects on the risk of hospitalisation for bronchiolitis (Fig. 3). Based on moderate quality evidence for sub-chronic effects, and low-quality evidence for lifetime exposure effects, the risks of hospitalisation for bronchiolitis in relation to longer term exposure to CO is unclear (Fig. 3). Two studies found no association with risk of hospitalisation (*Abdul Rahman et al., 2017*; *Karr et al., 2007*), but one study (*Karr et al., 2009a*) found a statistically significant association with lifetime (OR 1.13 [1.09–1.18]) and sub-chronic exposure (OR 1.11 [1.08–1.15]).

Three studies assessed long-term effects of ozone but none evaluated acute exposure. The quality of evidence for sub-chronic as moderate, but low for lifetime exposure (File S4). Most studies showed a reduction in the risk of admission associated with ozone exposure (Fig. 3). One study (*Abdul Rahman et al., 2017*) found no association between ozone levels and risk of hospitalisation for bronchiolitis. Two studies however found a statistically significant decrease in hospitalisation risk with long-term exposure to ozone, one with sub-chronic (OR 0.90 [0.87–0.94]) and lifetime (OR 0.89 [0.85–0.93]) exposure (*Karr et al., 2007*, *2009a*) and one with lifetime exposure (OR 0.92 [0.88–0.97], *Karr et al., 2007*, *2009a*).

Secondary outcomes

One case crossover study (*Segala et al., 2008*) examined the acute effect of PM10, NO_2 and SO_2 on risk of unscheduled consultation for bronchiolitis. One case control study (*Girguis et al., 2017*) evaluated lifetime exposure of PM2.5 on risk of clinical encounter for bronchiolitis and found no association.

A statistically significant association was found at a lag of 0–4 days for PM10 (OR 1.06 [1.04–1.08]), NO_2 (OR 1.03[1.02–1.05]), and for SO_2 (OR 1.12[1.09–1.15]), which was also statistically significant for a lag of 0–1 days (OR 1.08[1.06–1.11]).

Comparison between effect of air pollution and WHO recommended guidelines

Of the eight included studies, five reported that one or more pollutants was associated with an increased risk of hospitalisation for bronchiolitis (*Abdul Rahman et al., 2017*; *Girguis et al., 2017*; *Karr et al., 2007*, *2009a*; *Segala et al., 2008*). Of these, three measured mean levels of air pollutants below the WHO recommendations (*Girguis et al., 2017*; *Karr et al., 2009a*; *Segala et al., 2008*). Two studies (*Karr et al., 2009a*; *Girguis et al., 2017*) found statistically significant associations between PM2.5 and risk of hospitalisation from

bronchiolitis, at mean levels below WHO recommendations, and one (*Segala et al., 2008*) had similar findings for PM10.

DISCUSSION

This is the first systematic review analysing the effect of exposure to ambient air pollution on the risk of hospital admission with bronchiolitis. Although findings are inconsistent across studies a suggested association with longer term and lifetime exposure to particulate matter on the risk of hospitalisation for bronchiolitis is seen. Acute exposure to NO_2 and SO_2, may also be associated with increased risk of hospitalisation. In some studies (*Girguis et al., 2017*; *Karr et al., 2009a*, *2009b*), hospitalisation with bronchiolitis increased despite measured levels of the gaseous pollutants being lower than the maximum concentrations recommended in WHO guidelines.

Ozone, is known to be a unique air pollutant and is often peaked during the hot season when RSV epidemics are low. Thus, would not seem to affect risk of hospitalisation with bronchiolitis. However, the decreased risk does not necessarily mean that ozone is a protective factor. It could be that due to the increase in temperature the photochemical reaction producing ozone is increased in the high season (*Monks et al., 2014*), or that in the winter months, other pollutants confound the effects of ozone, multipollutant modelling is one way to assess this (*Karr et al., 2007*).

It is biologically plausible that air pollutants might increase the likelihood of severe bronchiolitis, because of known effects on lung function (*Gotschi et al., 2008*; *Yu et al., 2001*) and airway inflammation (*Barraza-Villarreal et al., 2008*). In systematic reviews of epidemiological studies, risk of asthma exacerbations in children was increased with exposure to particulate pollutants, O_3, SO_2 and NO_2 (*Orellano et al., 2017*), and the risk of acute lower respiratory infections is associated with PM2.5 exposure (*Mehta et al., 2013*). The possible differences between pollutants with regards to the chronicity of their association with hospitalisation for bronchiolitis may reflect different pathogenic processes. PM2.5 and PM10 may have a more chronic pro-inflammatory effect (*Calderón-Garcidueñas et al., 2003*), while NO_2 and SO_2 may be associated with more acute damage to airways (*Chen et al., 2007*), but further work is required to better understand the in vivo pathogenic effects of these pollutants in the airways of infants and children (*Aguilera et al., 2013*).

Maximum levels of air pollutants in current WHO air quality guidelines may not be sufficiently low to protect infants, who may be particularly vulnerable to their harmful effects (*Salvi, 2007*). In a study that examined adverse effects of air pollution exposure on children's health, infants younger than two years of age were most susceptible to the health effects of air pollutants, particularly NO_2, SO_2, and PM10 (*Braga et al., 2001*). In context of increased urbanisation worldwide (*Landrigan et al., 2018*) it is important that the impact of air pollution on infants is considered when writing guidelines about air quality. Currently, 98% of cities in low and middle income countries with populations greater than 100,000 people, and 56% of such cities in high income countries, demonstrate air pollution levels above the WHO guidelines (*World Health Organization (WHO), 2016*).

This review was conducted in a systematic manner, but the validity of the conclusions is hampered by variation between studies. From current evidence, it is difficult to estimate the proportion of cases of hospitalisation from bronchiolitis that may be attributable to air pollution but given the ubiquity of this infection even the modest associations identified in this review are likely to have a substantial impact on morbidity and global burden of illness. Seasonality is a known to affect the variability of air pollution, with the majority of studies accounting for temperature and humidity along with matching within the same time period for time-series and case crossover studies to limit this confounder (*Girguis et al., 2017*; *Karr et al., 2006*, *2007*, *2009b*; *Segala et al., 2008*).

Although this systematic review only analysed the effects of air pollution to risk of hospitalisations after birth, emerging evidence suggests an association between antenatal air pollution exposure and low birthweight (*Smith et al., 2017*) which may also affect risk of severe bronchiolitis. In a Spanish cohort study, NO_2 exposure in the second trimester was positively associated with an increased risk of doctor diagnosed lower respiratory tract infection, with 98% of the diagnosis being classified as bronchiolitis or bronchitis (*Aguilera et al., 2013*), and also highlights the possibility of antenatal exposure to air pollutants being a risk factor for bronchiolitis. A recent study, published after the search period, has further highlighted positive associations between traffic related pollutants, PM2.5, CO, and nitrogen oxides (this includes NO_2), and bronchiolitis clinical encounters (*Kennedy et al., 2018*). This further supports that air pollution may have an association with increased risk of bronchiolitis hospital admissions.

The results of the included studies were unable to be synthesised as no studies were identified that utilised a cohort design. One source of imprecision is that the diagnosis of bronchiolitis, even when made according to standardised definition, relies upon the subjective judgements by individual clinicians. Variation in the age definition between the studies may have resulted in viral wheeze being misclassified as bronchiolitis, particularly when including over the age of one year (*Abdul Rahman et al., 2017*; *Segala et al., 2008*). Differences in the way in which air pollution was measured was observed, and the confounding factors that were considered in the analyses of the studies. As expected, crude odds ratios that showed statistical significance were found (*Girguis et al., 2017*; *Karr et al., 2009a*), but adjusted ORs did not, and this highlights the importance of considering confounding factors in observational studies. It was noted that studies measuring exposure to more than one pollutant did not describe a pre-specified primary analysis with regards to clinical outcome, pollutant, and lag time. It is possible, therefore, that individual studies may be at risk of selective outcome reporting, a practice that is commonplace in RCTs (*Dwan et al., 2013*). International consensus, around potential confounding factors and a core outcome set (*Kirkham, Clarke & Williamson, 2017*; *Sinha et al., 2012*) to measure and report in observational studies of air pollution, may help reduce these problems.

CONCLUSION

This review suggests an association between different air pollutants and risk of hospitalisation for bronchiolitis, particularly with particulate matter, NO_2 and SO_2

exposure. There is a need for a multicentre cohort or time series to examine this possible association, and these would be strengthened by development of standardised methodological approaches. Revision of international recommendations around air quality is warranted and this should incorporate specific consideration around the impact of outdoor air pollution on infants.

ACKNOWLEDGEMENTS

The views expressed here are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

Charlotte King is partly funded by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC). There was no additional external funding received for this study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Grant Disclosures

The following grant information was disclosed by the authors:
National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Charlotte King analysed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.
- Jamie Kirkham contributed reagents/materials/analysis tools, approved the final draft.
- Daniel Hawcutt authored or reviewed drafts of the paper, approved the final draft.
- Ian Sinha analysed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper, approved the final draft.

Data Availability

The following information was supplied regarding data availability:

The research in this article did not generate any data or code as it is a systematic review.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.5352#supplemental-information.

REFERENCES

Abdul Rahman SR, Ismail SNS, Sahani M, Ramli MF, Latif MT. 2017. A case crossover analysis of primary air pollutants association on acute respiratory infection (ARI) among children in urban region of Kiang valley, Malaysia. *Annals of Tropical Medicine and Public Health* **10(1)**:44–55 DOI 10.4103/atmph.atmph_75_17.

Aguilera I, Pedersen M, Garcia-Esteban R, Ballester F, Basterrechea M, Esplugues A, Fernandez-Somoano A, Lertxundi A, Tardon A, Sunyer J. 2013. Early-life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the INMA study. *Environmental Health Perspectives* **121(3)**:387–392 DOI 10.1289/ehp.1205281.

Barraza-Villarreal A, Sunyer J, Hernandez-Cadena L, Escamilla-Nuñez MC, Sienra-Monge JJ, Ramírez-Aguilar M, Cortez-Lugo M, Holguin F, Diaz-Sánchez D, Olin AC, Romieu I. 2008. Air pollution, airway inflammation, and lung function in a cohort study of Mexico City schoolchildren. *Environmental Health Perspectives* **116(6)**:832–838 DOI 10.1289/ehp.10926.

Berman S. 1991. Epidemiology of acute respiratory infections in children of developing countries. *Clinical Infectious Diseases* **13(Supplement_6)**:S454–S462 DOI 10.1093/clinids/13.supplement_6.s454.

Braga ALF, Saldiva PHN, Pereira LAA, Menezes JJC, Conceição GMS, Lin CA, Zanobetti A, Schwartz J, Dockery DW. 2001. Health effects of air pollution exposure on children and adolescents in São Paulo, Brazil. *Pediatric Pulmonology* **31(2)**:106–113 DOI 10.1002/1099-0496(200102)31:2<106::aid-ppul1017>3.0.CO;2-M.

Calderón-Garcidueñas L, Mora-Tiscareño A, Fordham LA, Valencia-Salazar G, Chung CJ, Rodriguez-Alcaraz A, Paredes R, Variakojis D, Villarreal-Calderón A, Flores-Camacho L, Antunez-Solis A, Henríquez-Roldán C, Hazucha MJ. 2003. Respiratory damage in children exposed to urban pollution. *Pediatric Pulmonology* **36(2)**:148–161 DOI 10.1002/ppul.10338.

Chen TM, Gokhale J, Shofer S, Kuschner WG. 2007. Outdoor air pollution: nitrogen dioxide, sulfur dioxide, and carbon monoxide health effects. *American Journal of the Medical Sciences* **333(4)**:249–256 DOI 10.1097/MAJ.0b013e31803b900f.

Curtis L, Rea W, Smith-Willis P, Fenyves E, Pan Y. 2006. Adverse health effects of outdoor air pollutants. *Environment International* **32(6)**:815–830 DOI 10.1016/j.envint.2006.03.012.

Dwan K, Kirkham JJ, Williamson PR, Gamble C. 2013. Selective reporting of outcomes in randomised controlled trials in systematic reviews of cystic fibrosis. *BMJ Open* **3(6)**:e002709 DOI 10.1136/bmjopen-2013-002709.

Fung KY, Krewski D, Chen Y, Burnett R, Cakmak S. 2003. Comparison of time series and case-crossover analyses of air pollution and hospital admission data. *International Journal of Epidemiology* **32(6)**:1064–1070 DOI 10.1093/ije/dyg246.

García CG, Bhore R, Soriano-Fallas A, Trost M, Chason R, Ramilo O, Mejias A. 2010. Risk factors in children hospitalized with RSV bronchiolitis versus Non–RSV bronchiolitis. *Pediatrics* **126(6)**:e1453–e1460 DOI 10.1542/peds.2010-0507.

Global Burden of Disease 2016 Risk Factors Collaborators. 2017. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet* **390(10100)**:1345–1422 DOI 10.1016/s0140-6736(17)32366-8.

Girguis MS, Strickland MJ, Hu XF, Liu Y, Chang HH, Belanoff C, Bartell SM, Vieira VM. 2017. Chronic PM2.5 exposure and risk of infant bronchiolitis and otitis media clinical encounters. *International Journal of Hygiene and Environmental Health* **220(6)**:1055–1063 DOI 10.1016/j.ijheh.2017.06.007.

Gotschi T, Heinrich J, Sunyer J, Kunzli N. 2008. Long-term effects of ambient air pollution on lung function: a review. *Epidemiology* **19(5)**:690–701 DOI 10.1097/EDE.0b013e318181650f.

Green CA, Yeates D, Goldacre A, Sande C, Parslow RC, McShane P, Pollard AJ, Goldacre MJ. 2016. Admission to hospital for bronchiolitis in England: trends over five decades, geographical variation and association with perinatal characteristics and subsequent asthma. *Archives of Disease in Childhood* **101(2)**:140–146 DOI 10.1136/archdischild-2015-308723.

Hasegawa K, Tsugawa Y, Brown DFM, Mansbach JM, Camargo CA. 2013. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics* **132(1)**:28–36 DOI 10.1542/peds.2012-3877.

Jhawar S. 2003. Severe bronchiolitis in children. *Clinical Reviews in Allergy & Immunology* **25(3)**:249–258 DOI 10.1385/criai:25:3:249.

Karr C, Kaufman J, Lumley T, Davis R, Shepherd K, Ritz B, Larson T. 2004. Effect of ambient air pollution on infant bronchiolitis. *Epidemiology* **15(4)**:S31–S32 DOI 10.1097/00001648-200407000-00068.

Karr CJ, Demers PA, Koehoorn MW, Lencar CC, Tamburic L, Brauer M. 2009a. Influence of ambient air pollutant sources on clinical encounters for infant bronchiolitis. *American Journal of Respiratory and Critical Care Medicine* **180(10)**:995–1001 DOI 10.1164/rccm.200901-0117OC.

Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, Kaufman J. 2007. Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. *American Journal of Epidemiology* **165(5)**:553–560 DOI 10.1093/aje/kwk032.

Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, Kaufman J. 2006. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. *Environmental Health Perspectives* **114(2)**:277–281 DOI 10.1289/ehp.8313.

Karr CJ, Demers PA, Koehoorn MW, Lencar CC, Tamburic L, Brauer M. 2009b. Infant exposure to fine particulate matter and traffic and risk of hospitalization for RSV bronchiolitis in a region with lower ambient air pollution. *Environmental Research* **109(3)**:321–327 DOI 10.1016/j.envres.2008.11.006.

Kennedy CM, Pennington AF, Darrow LA, Klein M, Zhai X, Bates JT, Russell AG, Hansen C, Tolbert PE, Strickland MJ. 2018. Associations of mobile source air pollution during the first year of life with childhood pneumonia, bronchiolitis, and otitis media. *Environmental Epidemiology* **2**:e007 DOI 10.1097/ee9.0000000000000007.

Kirkham JJ, Clarke M, Williamson PR. 2017. A methodological approach for assessing the uptake of core outcome sets using ClinicalTrials.gov: findings from a review of randomised controlled trials of rheumatoid arthritis. *BMJ* **357**:j2262 DOI 10.1136/bmj.j2262.

Lanari M, Giovannini M, Giuffre L, Marini A, Rondini G, Rossi GA, Merolla R, Zuccotti GV, Salvioli GP. 2002. Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. *Pediatric Pulmonology* **33(6)**:458–465 DOI 10.1002/ppul.10047.

Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu N, Baldé AB, Bertollini R, Bose-O'Reilly S, Boufford JI, Breysse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndahimananjara JD, Perera F, Potočnik J, Preker AS, Ramesh J, Rockström J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart RB, Suk WA, van Schayck OCP,

Yadama GN, Yumkella K, Zhong M. 2018. The Lancet Commission on pollution and health. *Lancet* **391(10119)**:462–512 DOI 10.1016/S0140-6736(17)32345-0.

Leung AK, Kellner JD, Davies HD. 2005. Respiratory syncytial virus bronchiolitis. *Journal of the National Medical Association* **97**:1708–1713.

Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* **339**:b2700 DOI 10.1136/bmj.b2700.

Maclure M. 1991. The case-crossover design: a method for studying transient effects on the risk of acute events. *American Journal of Epidemiology* **133(2)**:144–153 DOI 10.1093/oxfordjournals.aje.a115853.

Marchal V, Dellink R, Van Vuuren D, Clapp C, Chateau J, Magné B, Van Vliet J. 2012. *OECD Environmental Outlook to 2050*. Paris: Organization for Economic Co-operation and Development DOI 10.1787/9789264122246-en.

Mehta S, Shin H, Burnett R, North T, Cohen AJ. 2013. Ambient particulate air pollution and acute lower respiratory infections: a systematic review and implications for estimating the global burden of disease. *Air Quality, Atmosphere, & Health* **6(1)**:69–83 DOI 10.1007/s11869-011-0146-3.

Monks P, Archibald A, Colette A, Cooper O, Coyle M, Derwent R, Fowler D, Granier C, Law K, Stevenson D. 2014. Tropospheric ozone and its precursors from the urban to the global scale from air quality to short-lived climate forcer. *Atmospheric Chemistry & Physics Discussions* **14(23)**:32709–32933 DOI 10.5194/acpd-14-32709-2014.

Nicolai A, Ferrara M, Schiavariello C, Gentile F, Grande ME, Alessandroni C, Midulla F. 2013. Viral bronchiolitis in children: a common condition with few therapeutic options. *Early Human Development* **89**:S7–S11 DOI 10.1016/j.earlhumdev.2013.07.016.

Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J. 2017. Effect of outdoor air pollution on asthma exacerbations in children and adults: systematic review and multilevel meta-analysis. *PLOS ONE* **12(3)**:e0174050 DOI 10.1371/journal.pone.0174050.

Purcell K, Fergie J. 2004. Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatric Infectious Disease Journal* **23(5)**:418–423 DOI 10.1097/01.inf.0000126273.27123.33.

Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM, Johnson DW, Light MJ, Maraqa NF, Mendonca EA. 2014. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* **134(5)**:e1474–e1502 DOI 10.1542/peds.2015-2862.

Robertson SE, Roca A, Alonso P, Simoes EA, Kartasasmita CB, Olaleye DO, Odaibo GN, Collinson M, Venter M, Zhu Y. 2004. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. *Bulletin of the World Health Organization* **82**:914–922.

Salvi S. 2007. Health effects of ambient air pollution in children. *Paediatric Respiratory Reviews* **8(4)**:275–280 DOI 10.1016/j.prrv.2007.08.008.

Schultz ES, Gruzieva O, Bellander T, Bottai M, Hallberg J, Kull I, Svartengren M, Melen E, Pershagen G. 2012. Traffic-related air pollution and lung function in children at 8 years of age: a birth cohort study. *American Journal of Respiratory and Critical Care Medicine* **186(12)**:1286–1291 DOI 10.1164/rccm.201206-1045OC.

Schünemann H, Brożek J, Guyatt G, Oxman A. eds. 2013. *GRADE handbook for grading quality of evidence and strength of recommendation*. The GRADE Working Group. Updated October 2013. *Available at guidelinedevelopment.org/handbook*.

Schwartz J. 2004. Air pollution and children's health. *Pediatrics* **113**:1037–1043.

Segala C, Poizeau D, Mesbah M, Willems S, Maidenberg M. 2008. Winter air pollution and infant bronchiolitis in Paris. *Environmental Research* **106(1)**:96–100 DOI 10.1016/j.envres.2007.05.003.

Semple MG, Taylor-Robinson DC, Lane S, Smyth RL. 2011. Household tobacco smoke and admission weight predict severe bronchiolitis in infants independent of deprivation: prospective cohort study. *PLOS ONE* **6(7)**:e22425 DOI 10.1371/journal.pone.0022425.

Shah ASV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, Langrish JP, Newby DE, Mills NL. 2015. Short term exposure to air pollution and stroke: systematic review and meta-analysis. *BMJ* **350**:h1295 DOI 10.1136/bmj.h1295.

Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. 1999. Bronchiolitis-associated hospitalizations among US children, 1980–1996. *JAMA* **282(15)**:1440–1446 DOI 10.1001/jama.282.15.1440.

Sinha IP, Altman DG, Beresford MW, Boers M, Clarke M, Craig J, Alberighi ODC, Fernandes RM, Hartling L, Johnston BC. 2012. Standard 5: selection, measurement, and reporting of outcomes in clinical trials in children. *Pediatrics* **129(Supplement 3)**:S146–S152 DOI 10.1542/peds.2012-0055h.

Sinha IP, McBride AKS, Smith R, Fernandes RM. 2015. CPAP and high-flow nasal cannula oxygen in bronchiolitis. *Chest* **148(3)**:810–823 DOI 10.1378/chest.14-1589.

Smith RB, Fecht D, Gulliver J, Beevers SD, Dajnak D, Blangiardo M, Ghosh RE, Hansell AL, Kelly FJ, Anderson HR, Toledano MB. 2017. Impact of London's road traffic air and noise pollution on birth weight: retrospective population based cohort study. *BMJ* **359**:j5299 DOI 10.1136/bmj.j5299.

World Health Organization. 1978. *International classification of diseases*. Ninth Revision, basic tabulation list with alphabetic index. Geneva: World Health Organisation. *Available at http://www.who.int/iris/handle/10665/39473*.

UNICEF. 2016. *Clear the air for children: the impact of air pollution on children.* New York: UNICEF.

Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. 2015. Newcastle-Ottawa quality assessment scale cohort studies. *Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp*.

World Health Organization (WHO). 2000. *Air quality guidelines for Europe*. European series: World Health Organisation Publications.

World Health Organization (WHO). 2006. *Air quality guidelines: Global Update 2005: particulate matter, ozone, nitrogen dioxide, and sulfur dioxide*. Copenhagen: World Health Organization.

World Health Organization (WHO). 2016. WHO's urban ambient air pollution database—update 2016. *Available at http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/* (accessed 21 November 2017).

Yu TS, Wong TW, Wang XR, Song H, Wong SL, Tang JL. 2001. Adverse effects of low-level air pollution on the respiratory health of schoolchildren in Hong Kong. *Journal of Occupational and Environmental Medicine* **43(4)**:310–316 DOI 10.1097/00043764-200104000-00004.