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

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**ABSTRACT**

*Objective:*

To systematically review the evidence around of 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 <2.5μm (PM2.5) or <10μm (PM10) and gaseous pollutants (nitrogen dioxide(NO2), sulphur dioxide (SO2), carbon monoxide (CO), ozone (O3)) 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. SO2 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 Organisation (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).

**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 et al. 2005), causes airway inflammation(Nicolai et al. 2013), bronchial epithelial cell necrosis (Leung et al. 2005), and other pathogenic 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. 2015). 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 (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 (2006; UNICEF 2016) and maximum recommended World Health Organisation (WHO) ambient levels (2006; WHO 2000) are listed in Table 1. The air pollutants implicated are particulate matter, which is subdivided depending on particle size as either less than 2.5μm (PM2.5) or less than 10μm (PM10), nitrogen dioxide (NO2), sulfur dioxide(SO2), carbon monoxide (CO), and ozone (O3).

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

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 (CK and IS) 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 (CK and IS) 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 Supplementary 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(Shah et al. 2015)) that evaluated the impact of air pollution levels (PM2.5, PM10, NO2, SO2, CO, O3) 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 seven days), sub-chronic (one 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 (Statistics 1998) (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 (RR) 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 (2006; WHO 2000).

**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. 2009), such that each conclusion would be based on low, moderate or high quality evidence as judged by two reviewers (IS, CK). 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 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; Karr et al. 2007; Karr et al. 2006; Karr et al. 2009a; Karr et al. 2009b; Segala et al. 2008)) were eligible for our review. The review flowchart is shown in Figure 1, and the reasons individual studies were excluded are summarised in Supplementary File S2.

*Figure 1. Review flowchart showing screening and selection of included studies*

Six of the studies were from overlapping research groups in North America(Girguis et al. 2017; Karr et al. 2004; Karr et al. 2007; Karr et al. 2006; Karr et al. 2009a; Karr et al. 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

*Table 2. Characteristics of included studies*

*Table 3. Quality assessments of included studies*

***Association between air pollution and risk of hospitalisation for bronchiolitis***

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

*Figure 2. Forest plots of particulate pollutants*

*Figure 3. Forest plots of gaseous pollutants*

*Particulate Pollutants*

Based on moderate quality evidence (supplementary data S4), acute exposure to PM2.5 does not seem to increase risk of hospitalisation (Figure 2). Two studies (Karr et al. 2004; Karr et al. 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 (Figure 2). Two studies found no increased risk of hospitalisation with sub chronic or lifetime exposure (Karr et al. 2009a; Karr et al. 2009b) but two studies did find an increased risk with 30 day exposure (Karr et al. 2007) (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 (supplementary data 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 (Figure 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 (supplementary data S4), the acute, sub-chronic, and lifetime effects of NO2 are unclear, although longer term exposure may be associated with increased risk of admission for bronchiolitis (Figure 3). Two studies found no increased risk of acute exposure (Karr et al. 2004; Karr et al. 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; Karr et al. 2009b) found no association with risk 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)).

For SO2, the strength of this evidence was graded as low (supplementary data S4). The results of two studies suggest that acute, sub-chronic, and lifetime exposure to SO2 may be associated with increased risk of hospitalisation (Figure 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; Karr et al. 2006), CO does not seem to have acute effects on the risk of hospitalisation for bronchiolitis (Figure 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 (Figure 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 longer term effects of ozone but none evaluated acute exposure. . The quality of evidence for sub-chronic as moderate, but low for lifetime exposure (supplementary data S4). Most studies showed a reduction in the risk of admission associated with ozone exposure (Figure 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 longer 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; Karr et al. 2009a) and one with lifetime exposure (OR 0.92 [0.88-0.97] (Karr et al. 2007; Karr et al. 2009a).

*Secondary Outcomes*

One case crossover study (Segala et al. 2008) examined the acute effect of PM10, NO2 and SO2 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)), NO2 (OR 1.03(1.02-1.05)), and for SO2 (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; Karr et al. 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 (Girguis et al. 2017; Karr et al. 2009a) 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 NO2 and SO2, may also be associated with increased risk of hospitalisation. In some studies (Girguis et al. 2017; Karr et al. 2009a; Karr et al. 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, O3, SO2 and NO2 (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 NO2 and SO2 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 NO2, SO2 and PM10(Braga et al. 2001). In context of increased urbanisation worldwide (Landrigan et al.) 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 (Organisation 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. 2007; Karr et al. 2006; Karr et al. 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, NO2 exposure in the second trimester was positively associated with an increased risk of doctor diagnosed lower respiratory tract infection (LRTI), 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 NO2), 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 et al. 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, NO2 and SO2 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.

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**List of Figures**

*Figure 1. Review flowchart showing screening and selection of included studies*

*Figure 2. Forest plots of particulate pollutants*

*Figure 3. Forest plots of gaseous pollutants*

**List of Tables**

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

*Table 2. Characteristics of included studies*

*Table 3.Risk of Bias assessments of included studies*

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