Environmental and genomic factors that influence respiratory health in children.

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June 2018

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Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy

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Abstract

Background

Respiratory diseases are common in children. These diseases are multifactorial, with both environmental and genomic influences associated. Various epidemiological research has been carried out to understand the association between ambient air pollution and adverse outcomes in respiratory disease. Along with environmental factors, pharmacogenomics has shown that asthma medication efficacy can be affected by someone's genotype. Lately, research has examined if adverse drug reactions (ADRs) are similarly affected.

Methods

This thesis has systematically reviewed the health effects of ambient air pollution (particulate pollutants (diameter <2.5µm (PM2.5) or <10µm (PM10) and gaseous pollutants (nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), ozone (O_3)) in children, as a review of hospitalisation with bronchiolitis and as an overview of systematic reviews of all common paediatric respiratory diseases requiring healthcare utilisation (HRU). A systematic review was completed analysing studies examining the association between pharmacogenomics and adverse drug reactions in asthma medications in the whole population. A survey was subsequently sent to members of the Pharmacogenomics in Childhood Asthma (PiCA) consortia, to determine priorities for ADR pharmacogenomic studies.

Results

In the bronchiolitis systematic review eight studies were included. Long term exposure to particulate pollutants may be associated with increased risk of hospitalisation with bronchiolitis. In addition, short-term exposure to NO_2 and SO_2 may also be associated with hospitalisation, while results for other pollutants were inconsistent.

In the overview, 11 systematic reviews were included, ten had incorporated meta-analysis data. There was moderate quality evidence that risk of HRU for asthma exacerbations in children are associated with increased concentrations for each ambient air pollutant, and

that risk of HRU with pneumonia is positively correlated with concentrations of PM2.5, PM10, and O_3.

In a systematic review examining pharmacogenomics and ADRs five studies were included, one examined inhaled short acting beta-2 agonists (SABA), one long acting beta-2 agonists (LABA), and three examined corticosteroids (one included inhaled, all included oral). The ADRs and polymorphisms identified were change in lung function tests (rs1042713), adrenal suppression (rs591118), decreased bone mineral density (rs6461639) and bone mineral accretion (rs9896933, rs2074439). The priorities for future pharmacogenomic ADR studies in asthma gained from the survey were tachycardia (SABA/LABA), adrenal suppression/crisis and growth suppression (Corticosteroids), sleep/behavior disturbances (Leukotriene Receptor Antagonists), and nausea and vomiting (Theophylline).

Conclusion

This thesis highlights the need to recognize adverse effects of ambient air pollution on children's respiratory health. It also confirmed that ADR's should be recognized and examined in future pharmacogenomic studies. The combination of these factors could help to decrease the burden respiratory disease has on healthcare resources worldwide as could help limit the risk of hospitalization for both the disease and complications of management of the disease.

Acknowledgement page

This thesis would not have been possible without the encouragement, support and help of many people.

First and foremost, I would like to thank my supervisors, Dr Daniel Hawcutt and Dr Ian Sinha, for their continued support and guidance, and for providing me with the opportunity to undertake this work.

Several people have helped throughout the process, I would like to thank Dr Jamie Kirkham for supplying the invaluable advice regarding statistical analysis needed in Chapter 2. I also thank Anna Surace and Graham Jeffers for their fantastic translation skills for the research done in Chapter 3. For help, support and useful comments I thank all members of the PiCA consortia who undertook the survey in Chapter 4 and contributed to the work.

Many thanks go to the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

Finally, I must thank my friends and family who have tirelessly supported me through many ups and downs throughout this process. I would especially like to thank my parents, Sara and Alisdair, and my brother, Oliver, for their continued support throughout my studies and helping to fund this year.

Funding Statement

Charlotte King is part-funded by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC)

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.

Publications and outputs

Poster presentation:

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

Presented at the 28th European Respiratory Society Congress, Paris, France, September 2018

Publication

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

Published in PeerJ, August 2018

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List of abbreviations

ADR – Adverse Drug Reaction

ADRB2 - Beta 2 Adrenoreceptor

ALL – Acute Lymphoblastic Leukaemia

ALRI – Acute Lower Respiratory Infection

BMA – Bone Mineral Accretion

BMD – Bone Mineral Density

BNFC - British National Formulary for Children

CAMP - Childhood Asthma Management Program

CAZ – Clean Air Zones

CDSR - Cochrane Database of Systematic Reviews

CINAHL - Cumulative Index of Nursing and Allied Health Literature

CO – Carbon Monoxide

COPD – Chronic Obstructive Pulmonary Disease

DARE - Database of Abstracts of Reviews of Effects

ECJ – European Court of Justice

ED – Emergency Department

EU – European Union

GAM – Generalised Additive Models

GIS – Geographical Information Systems

GWAS – Genome Wide Association Studies

HRU - Healthcare Resource Utilisation

ICU – Intensive Care Unit

ICD – International Classification of Disease

ICS – Inhaled Corticosteroids

LABA – Long Acting Beta2 Agonists

LOESS – Locally weighted scatterplot smoothing

LRTI - Lower Respiratory Tract Infection

LTA – Leukotriene Receptor Antagonists

LUR – Land Use Regression

MDG – Millennium Development Goal

NICE - National Institute for Health and Care Excellence

NO_2 – Nitrogen Dioxide

O_3 – Ozone

OECD – Organisation for Economic Co-operation and Development

PASS - Pharmacogenetics of Adrenal Suppression with Inhaled Steroids

PDGFD - Platelet Derived Growth Gene

PiCA – Pharmacogenomics in Childhood Asthma

PM2.5 – particulate matter diameter less than 2.5 micrometres

PM10 – particulate matter diameter less than 10 micrometres

RAPGEF5 - Rap Guanine Nucleotide Exchange Factor 5 Gene

RCT – Randomised Controlled Trial

RSV – Respiratory Syncytial Virus

SABA – Short Acting Beta-2 Agonists

SDG – Sustainable Development Goal

SNP – Single Nucleotide Polymorphism

SO_2 – Sulfur Dioxide

TUBG1 – Tubulin Gamma 1 Gene

UK – United Kingdom

US/USA – United States

WHO – World Health Organisation

Chapter 1: Introduction

1.1 Background

Globally, in the paediatric population, respiratory diseases are a major burden of disease [1-3]. There are numerous different diseases that affect each part of the respiratory system, from the upper airways to the nerves responsible for breathing, at various ages across childhood [4-6]. The most susceptible group in children is those under the age of five years, a key age range for lung development [4]. Some of the common respiratory diseases in children include acute lower respiratory infections (ALRI) such as bronchiolitis and pneumonia, and asthma [7, 8]. The cause of these diseases are multifactorial, from environmental factors, such as smoking, to a genetic predisposition for a disease [9, 10]. In 2012, environmental factors had been associated with 12.6 million deaths, 26% were in children under the age of five [11]. Some environmental factors can be modified to help decrease the risk of incidence or severity of the disease. One of the environmental factors that has recently been brought to attention for its negative impact on health is air pollution [12], particularly ambient (outdoor sources) pollution. Ambient air pollution has been increasing for several decades. In 2005, with the World Health Organisation (WHO) created international guidelines for the main air pollutants [13, 14], these inform countries of safe concentration levels for air pollutants in order to minimise harm to individual's health. Ambient air pollution is known to affect childhood mortality [15], however, its effects on aspects of healthcare utilization is unclear. Apart from environmental factors, other variables influence respiratory health such as genomics. For asthma an increase susceptibility in childhood to the disease occurs if certain loci are present [16]. Interindividual variation is known with asthma medication, pharmacogenomics has been shown to have an effect alleviation of disease and reduction of symptoms [17]. The discipline of pharmacogenomics, which examines variations in genetic characteristics related to drug responses, has shown that efficacy is affected in certain populations with particular genes [18-20]. Although, medication efficacy has been examined, medicines can cause harm via adverse drug reactions (ADRs), this has not been thoroughly explored. ADRs are a significant cause of hospital admissions, with incidence rates ranging from 0.4% to

10.3% in all children [21]. To help synthesise existing primary research to assess the current knowledge on topics and possible gaps in the evidence, this MPhil has used systematic reviews [22-25]. The methodology and benefits of this technique adopted in this research are discussed below.

1.2 Respiratory Disease in Children

Respiratory disease has an impact on the health of millions of people worldwide, as a leading cause of ill health in both adults and children [2]. After birth, additional respiratory development occurs, with full functionality achieved at roughly six years old [26-28]. For example, at birth, the lung's still need to form 80% of the alveoli [29]. Also, a child's respiratory epithelium layer has greater permeability than an adult's [30]. Children spend a greater period of time outside compared to adults [31, 32], have a larger surface area per kilogram of body weight than adults [26], and have a higher minute ventilation rate [33]. Young children are also predominantly oral breathers, this means that the nasal filters are bypassed so a variety of pollutants can then enter the lower airways [34]. All of these factors make children more vulnerable and susceptible to the harmful effects of pollutants.

It is understood that lifestyle can impact on a person's respiratory health; nutritional deficiencies can impact lung growth, increase the risk of infections and decrease inflammatory control [35, 36]. Each respiratory disease has further risk factors that contribute to their incidence and prevalence [37]. Risk factors are classified as any attribute, characteristic or exposure of an individual that increases their chances of developing a disease or injury [38, 39]. In children, different respiratory diseases affect children at different ages; from bronchiolitis when an infant [40], to acute lower respiratory infections when a child [41], to asthma that can occur at any age [42]. Specific respiratory diseases, acute lower respiratory infection, asthma, and croup in children are described in the following sections.

1.2.1 Lower Respiratory Tract Infections

Acute lower respiratory infection (ALRI) is a broad term that covers a range of diseases, it is defined in the international classification of diseases as infections that manifest below the epiglottis [43, 44]. The majority of study definitions are based on signs, such as tachypnoea, difficulty breathing, chest wall indrawing, and abnormal auscultatory findings [45]. ALRI is a major cause of morbidity and mortality worldwide [46]. It is in the top three most frequent causes of mortality worldwide in children [10]. Globally, it accounts for one in five deaths in children below the age of five, in developing countries it is one of the largest causes of death in this age group [47-50]. In the past decade the admissions rates in England for children under the age of 15 years who were diagnosed with an ALRI has increased by 40% [51]. This is set to only increase if modifiable risk factors are not monitored and controlled. Risk factors for ALRI's are numerous with key factors being malnutrition, exposure to wood smoke, low birth weight, second hand smoke and ambient air pollution [49, 52-55]. The burden of disease in disability adjusted life years (DALYs) for ALRI in children under the age of five that is attributable to the environment is 57% [56]. ALRI's can be sub divided into further diseases, including bronchiolitis and pneumonia, often based on differentiation by pathogen [44]. Bronchiolitis and pneumonia are described in further detail in the following sections.

1.2.1.1 Bronchiolitis

Bronchiolitis is a respiratory infection that occurs in infancy, it has a high prevalence in the first year of life [57-59]. It is predominantly caused by the pathogen respiratory syncytial virus (RSV), responsible for approximately 80% of cases [60], although there are many other viral pathogens that cause bronchiolitis [40, 61]. The majority of children will contract bronchiolitis during their early years, however not all children who have bronchiolitis require intervention by healthcare professionals. Only 2-3% of children are admitted to hospital [59, 62, 63], with 2-6% of those admitted needing intensive care [62, 64, 65]. However, the high prevalence of the illness means that infants represent a significant proportion of overall paediatric admissions. Bronchiolitis accounts for 18% of all hospital admissions in children less than one year in the United States (US) [66], while in England, between 2004 and 2012 bronchiolitis counted for 11.8% of all intensive care admissions in

children less than one year old [67]. The healthcare utilisation burden for bronchiolitis is therefore high [67, 68]. As bronchiolitis is more prevalent during particular seasons depending on geographical location, the burden is not spread across the year but causes a marked seasonal impact on healthcare resources [67].

There are known risk factors that contribute to an infant being at a higher risk of requiring hospitalisation for bronchiolitis; low birth weight [69], exposure to smoke [70], history of atopy [71], and co-morbidities (e.g. congenital heart disease) [72]. However, 50-80% of emergency admissions that occur globally are in full term healthy infants [73, 74]. Another risk factor is a child's socioeconomic status. This risk factor has been seen in developed countries between areas of different socioeconomic status, with higher rates of admissions for bronchiolitis seen in England in areas of low socio-economic status. The greatest proportion of deaths related to RSV associated respiratory infections in children younger than five years is from low income countries [75, 76]. Other variables, such as environmental pollution, may contribute to bronchiolitis as well.

1.2.1.2 Pneumonia

Pneumonia is one of the most common infections in the paediatric cohort [77], particularly in low and middle income countries. It is a leading cause of mortality in children, particularly those under the age of five years where it contributes to 15% of childhood mortality causes [30]. In developing countries it counts for a large proportion of avoidable deaths [78]. Pneumonia is an acute infection due to viral, bacterial or fungal infections, causing alveoli function to be affected by pus and fluid (pneumonia fact sheet). There is no standard definition, clinical diagnosis varies between developed and developing countries based on healthcare resources available, such as chest radiographs, and physician judgement [79]. Not all clinical cases of pneumonia result in an hospitalisation, however, 12% of cases worldwide do progress to severe requiring hospitalisation [80]. Of the 120 million episodes of pneumonia worldwide that occur in children less than five years old, 14 million will progress to severe episodes that require hospitalisation, and 1.3 million deaths [80]. The development of pneumonia is multifactorial with the pathogen, the host, and

environmental factors contributing to the disease [78]. Numerous risk factors increase the probability of severe pneumonia; age less than six months, nutrition and diet, and indoor air pollution [41, 81, 82]. Indoor air pollution has been shown to increase the incidence of severity and mortality [83] and the effect of outdoor air pollution is understood for mortality [30].

1.2.2 Asthma

Asthma affects 334 million people worldwide [84], it is one of the most common chronic diseases in children globally [42]. Asthma is most common in children under the age of ten years old [84]. It is caused by eosinophilic activity and inflammation of the airways due to airway hyperresponsiveness from atopic or non-atopic triggers [85, 86]. Hospitalisation from asthma occurs when a child's asthma is exacerbated by a known trigger causing a severe symptomatic response [87]. There are known risk factors for the development of asthma; exposure to smoke, genetics, family history of atopy, environmental factors, and diet and nutrition [88, 89]. Environmental factors, such as air pollution have both been shown in studies to have a positive association with the development of asthma [34, 88, 90, 91]. Triggers for asthma exacerbation are varied and dependent on the individual person with the disease. Asthma has been shown to be aggravated by dust [92], allergens [93], and other environmental factors such as thunderstorms [94]. Air pollution has been shown to be another factor to aggravate asthma, studies showed that high exposure levels can increase the rate of emergency room visits and the use of asthma medication compared to other times [95]. Systematic reviews researching the effect of air pollution on asthma exacerbations have been undertaken, with evidence showing an increased risk of asthma exacerbations [96, 97].

1.2.3 Croup

Croup is a respiratory disease that often affects children aged between six months to three years [98]. It is most commonly caused by the parainfluenza virus [60, 99]. In the USA, it

annually affects 3% of children under the age of three years, with five per cent of emergency admissions in children under six years old being attributed to the disease in the USA and Canada [98]. Globally, the annual incidence rate ranged from 1.5% to 6% in children less than six years old [99-101]. The global hospitalisation rate for patients with croup is between 1.3% to 2.6% [101, 102]. The majority of croup symptoms resolves within 48 hours, with mortality being rare. However, severe croup can lead to respiratory failure and ultimately respiratory arrest [98]. The viral pathogen leads to inflammation and oedema in the upper airways as well as increased production of laryngeal mucosa, this can lead to blockages of the airways causing respiratory distress [98, 103]. Risk factors for croup are not completely clear, it has been associated with gender, boys being at greater risk of developing croup [104], as well as history of croup in the siblings [105].

1.3 Pollution

Pollution is defined as material that is unwanted, and possibly dangerous that has been introduced into the environment by human activity [106]. It has been highlighted as an important environmental hazard that needs to be addressed worldwide, although is currently undervalued [107]. Pollution can be broken down into subsections depending on the environmental material; air, water, or soil [108]. With air pollution, this is further subdivided into indoor and ambient (outdoor sources) pollution, however a lot of hazardous materials overlap between the two sub sections, such as particulate matter [109-114]. There are six main pollutants that are recognised to contribute to pollution [14, 115, 116]. They are particulate matter; diameter less than 10 micrometres (PM10) and diameter less than 2.5 micrometres (PM2.5), and gaseous pollutants; nitrogen dioxide (NO_2), sulphur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3). These are included in the recommended guidelines from the World Health Organisation (WHO) that countries and cities should follow [13, 14], see Table 1.

Sources for the ambient air pollutants are interlinked between all, thus reduction in all sources will have wide reaching effects [13, 14, 30, 117], see figure 1.

Table 1. WHO ambient air pollutant recommended concentration levels for the six main pollutants [13, 14]

	WHO ambient exposure threshold
Particulate Matter diameter <2.5µm (PM2.5)	10 µg/m^3 annual mean 25 µg/m^3 24 hour mean
Particulate Matter diameter <10µm (PM10)	20 µg/m^3 annual mean 50 µg/m^3 24 hour mean
Nitrogen Dioxide (NO_2)	40 µg/m^3 annual mean 200 µg/m^3 1 hour mean
Sulphur Dioxide (SO_2)	20 µg/m^3 24 hour mean 500 µg/m^3 10 minute mean
Carbon Monoxide (CO)	10 mg/m^3 8 hour mean
Ozone (O_3)	100 µg/m^3 8 hour mean

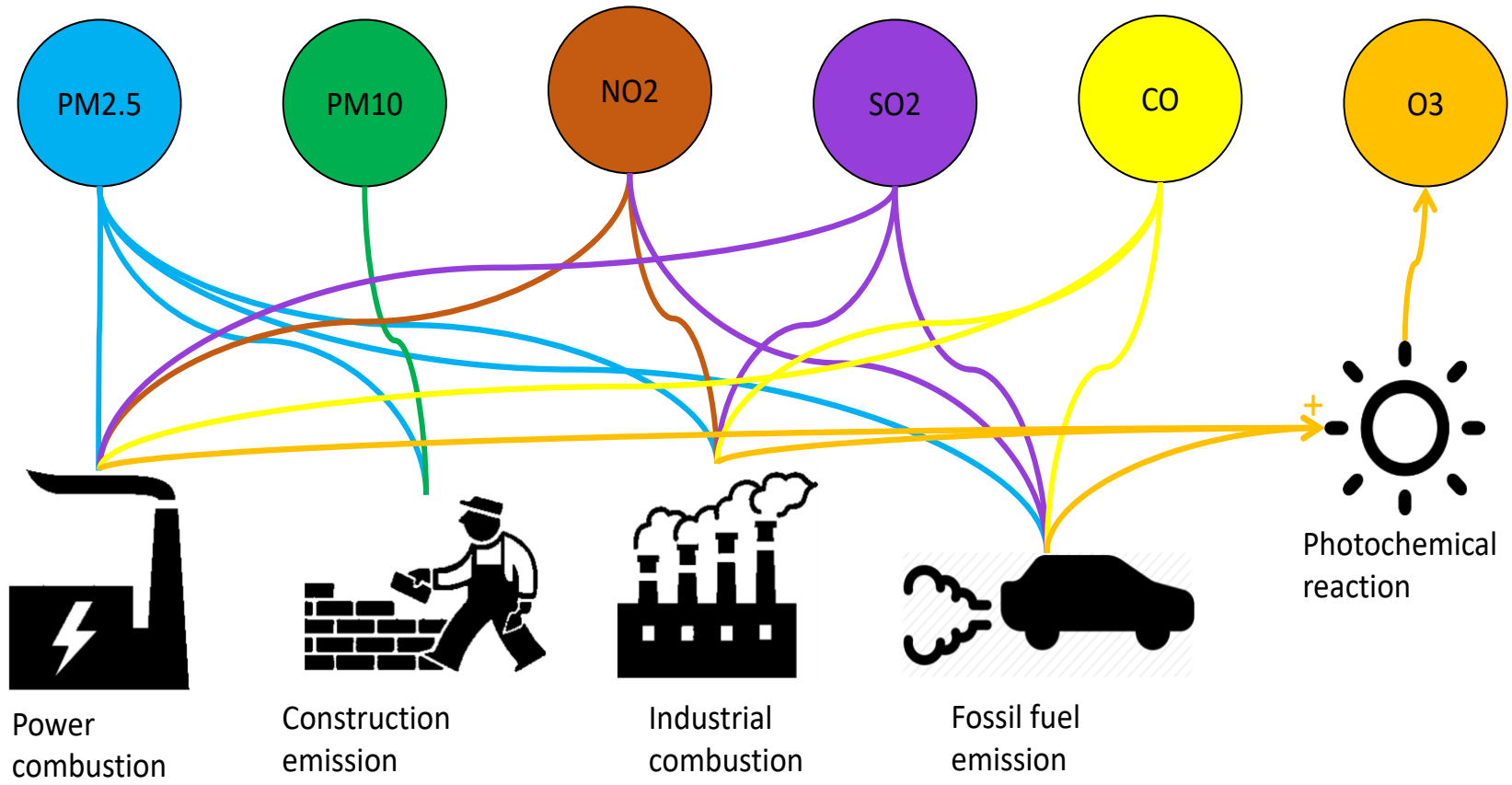


Figure 1. Major sources of production of each of the six ambient air pollutants [13, 14, 30, 114]

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm, NO2: nitrogen dioxide, SO2: sulphur dioxide, CO: carbon monoxide, O3: ozone

With indoor air pollutants, a wide range of sources cause harmful effects; household combustion, mould, dust mites, wood burning smoke and volatile organic compounds [118-120]. The effect of household fuel combustion have been highlighted to have harmful effects by WHO, in 2012 an estimated 4.3 million premature deaths were associated [120]. Indoor air pollution affects those in lower income and rural areas more, as concentration levels are higher [121]. The effects of indoor air pollution are particularly seen in Asian and African nations due to solid fuel cooking and limited ventilation methods [83, 110]. Exposure to indoor pollutants increases the risk of an adverse health event and mortality for an estimated three billion people [121]. Although, mortality rates are substantial, numbers have remained consistent between 2013 and 2015 [3], unlike ambient air pollution.

No country is unaffected by ambient air pollution [122]. Currently, the WHO ambient air pollutant guidelines are exceeded in cities worldwide; 98% of cities in low and middle income countries and 56% of cities in high income countries [123]. This means that an estimated 80% of the world population are exposed to levels above the guidelines that may be harmful to their health [123]. For particulate matter pollution a substantial number of children live in areas that exceed the international recommended levels [124], shown in figure 2, with 300 million children residing in areas exceeding levels by six times the recommended WHO threshold [124]. The highest levels of particulate matter were noted to be in South-East Asian countries, normally exceeding thresholds by five to ten times [125]. Recently, China has been making a conscious effort to address this issue [126, 127], in 2015 roughly 17% of all deaths in China were linked to air pollution [128]. The high levels of air pollution experienced by China is due to increased coal consumption, vehicle usage and industrial dust production from rapid urbanization that has occurred in the past several decades [129]. India is another low performing country for air pollution threshold adherence [30], and only increasing in concentration levels. Some nations that do not recognise air pollution as a significant problem [107, 130, 131], thus effort to decrease exposure levels does not occur. Concentration levels have improved in North America and Europe, but even in these areas places still experience levels exceeding the guidelines [30]. With new environmental regulations and the use of new technologies, the possibility of decreases in concentration levels may occur [30, 132].

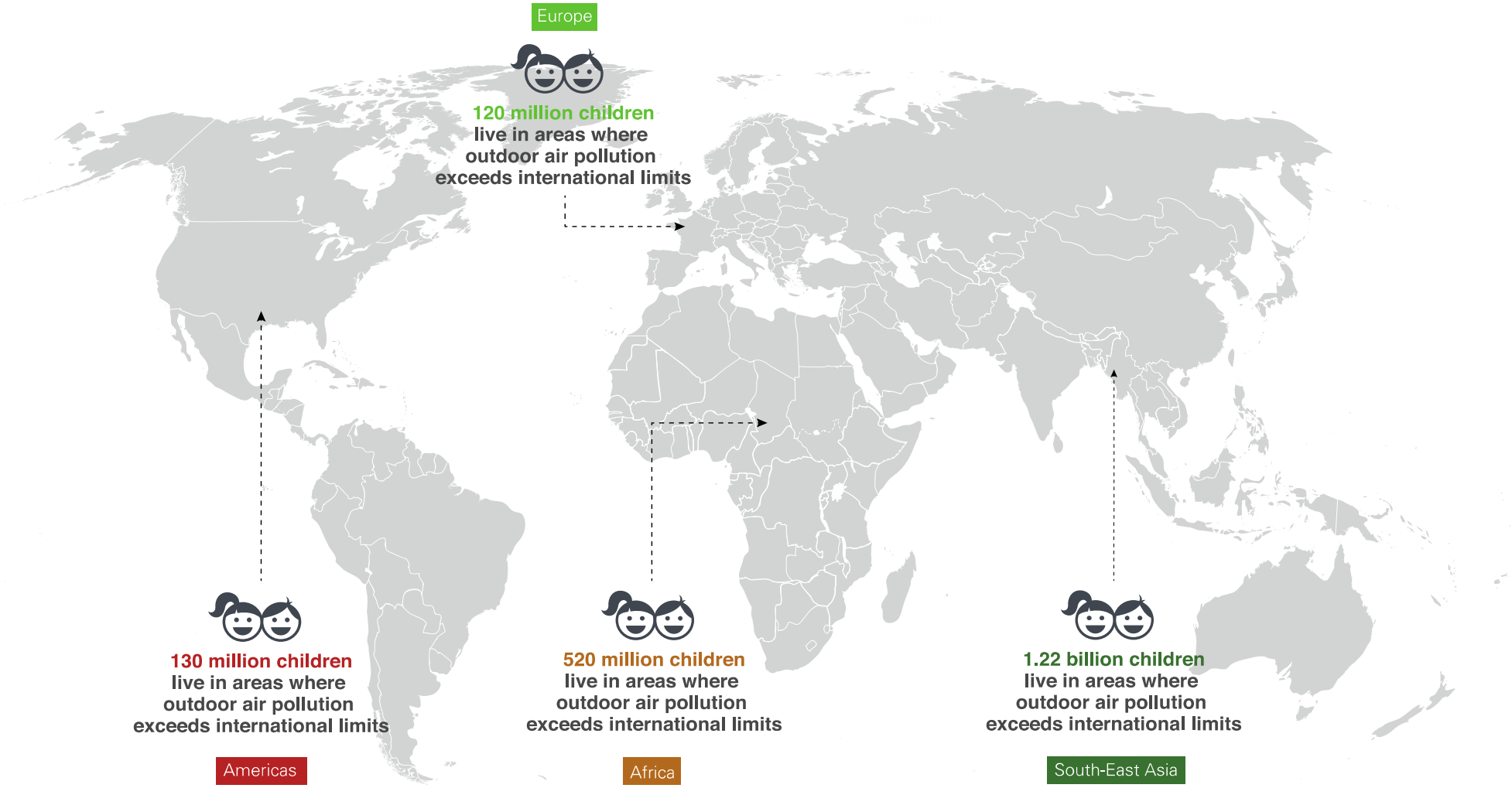


Figure 2. World map showing number of children living in areas exceeding international ambient air limits [121]

The driving forces of air pollution continue to be economic development, urbanization, energy consumption, transportation and vehicle usage [133]. WHO estimated that urban outdoor air pollution has increased by eight per cent from 2008 to 2013 alone [134], and levels are continuing to rise. It is estimated that two thirds of the world population are expected to live in an urban area by 2050 [30]. However, monitoring of air pollution levels is varied worldwide, low socio-economic and rural areas have the lowest number of monitors. In Africa, the air monitoring is sparse at ground level so it is difficult to estimate the exact levels of air pollution and thus their effect on the population [30]. This could mean that current effect estimates are understated.

Indoor and outdoor pollution are estimated to be responsible for around 6.5 million deaths worldwide, with a larger proportion being associated with outdoor air pollution [37, 49, 135]. Outdoor air pollution was responsible for around 3.7 million deaths in 2012 according to WHO, with 127,000 being in children under the age of five [121, 136, 137]. Compared to estimates from the Global Burden of Disease study in 2015, 4.2 million deaths [37], there has been a considerable increase in mortality numbers. Air pollution has been shown to be linked with one out of every eight deaths globally [15]. Estimated childhood mortality numbers for different areas worldwide due to ambient air pollution is shown in figure 3 [125]. There has been evidence to show that short-term exposure to ambient air pollution has a known effect on cardiovascular disease [138-142], and all-cause mortality for long-term exposure [143]. The current 2005 air quality guidelines are currently under review with a new set to be released in 2020 [136]. Until then, pollution remains a major problem that needs to be addressed and will continue to pose a risk to morbidity and mortality.

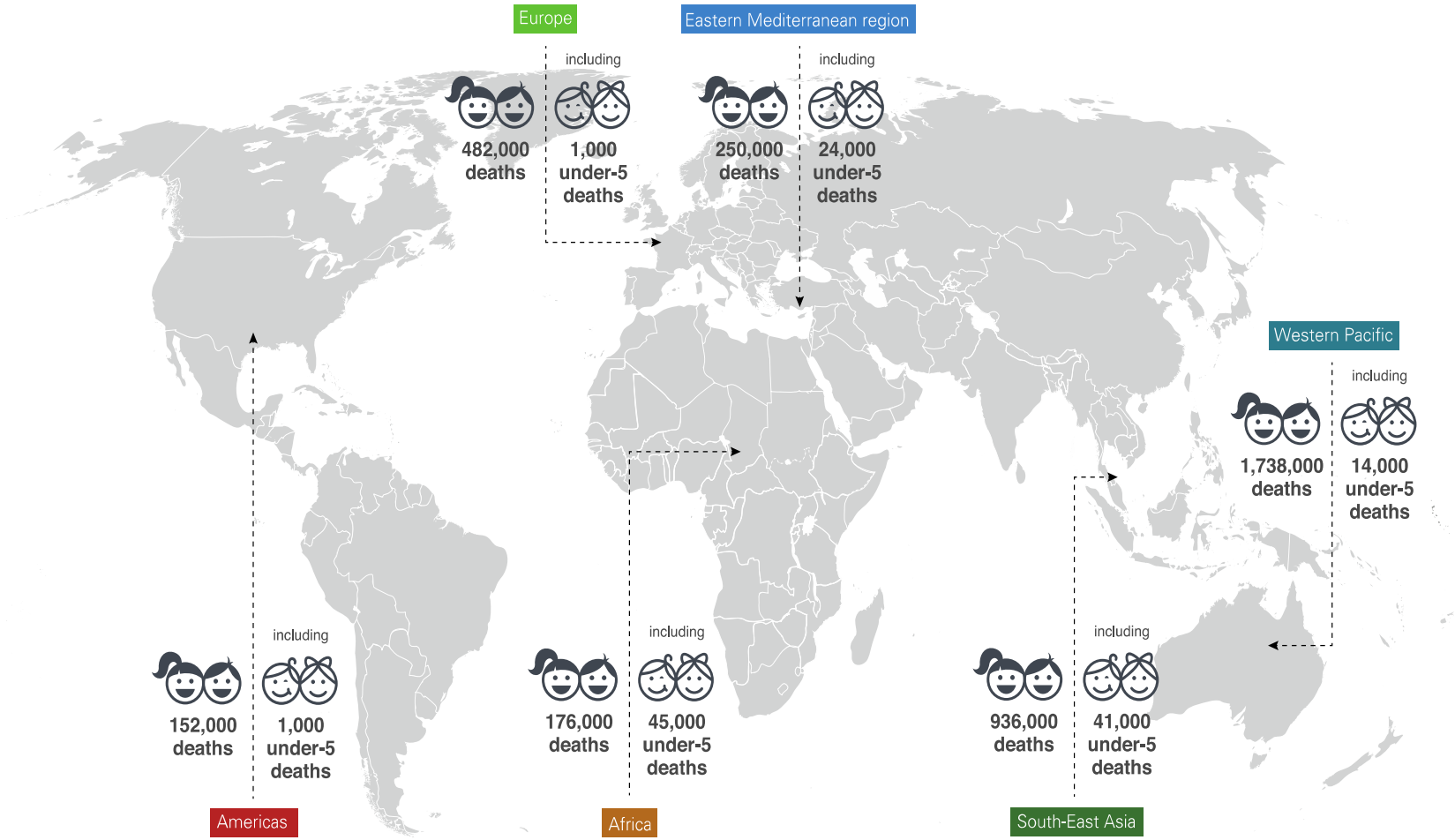


Figure 3. Estimate of overall mortality in children aged 0-18yrs, including children aged 0-5yrs associated with ambient air pollution exposure [122]

1.3.1 Particulate matter

Particulate matter is formed of a mixture of small particles and liquid droplets [144]. These consist of sulfates, nitrates, ammonia, sodium chloride, black carbon, and soil or dust particles [30]. The majority is formed from fossil fuel emissions from industrial combustion and from traffic related emissions, particularly diesel car emissions [14]. Particulate matter is further subdivided into the size of the particles and where they deposit within airways [145]. The size of particles determines the duration of stay in the atmosphere, along with the exposure window [145]. This can help to determine the effects particulate matter particles may have on the respiratory system and subsequently respiratory disease. Fine particles, those with a diameter less than 2.5μm (PM2.5), have been shown to penetrate deep inside the lungs and even enter a person's blood stream [30]. In mice, particulate matter has been shown to cause considerable pulmonary damage [146]. Particulate matter can trigger the oxidative pathway and inflammatory response in the respiratory system [147, 148]. Particulates have been thought to exacerbate existing respiratory disease, impair pulmonary mechanisms [133], and with long-term exposure lead to airway remodelling and chronic inflammation [149].

The effect of particulate matter on health is similar in both developed and developing countries [133], although different areas have high exposure levels for varying diameter sizes. For particulate matter with a diameter less than 10μm (PM10) the highest levels are shown in Asia, Africa and Latin America [133]. PM10 has been shown worldwide by WHO to increase mortality for all ages (OR 1.006(1.004-1.008)) [150, 151]. For exposure to PM2.5, WHO has estimated that it contributes to 800,000 premature deaths per year [152]. The majority of interest analysing the effect of particulate matter has been focused on the cardiovascular system with links shown with both short and long-term exposure [153, 154]. Related to the respiratory system, along-term study in children has shown that those exposed to high levels were at an increased likelihood of having a low FEV1 compared to those in low concentration level [155]. Another study has shown that those in high areas of particulate matter exposure have decreased lung function growth [156]. For PM10 exposure increases in respiratory hospital admissions have been seen at concentrations rise [157,

158]. When you combine this with the knowledge that two billion children live in areas that exceed the current WHO guidelines for particulate matter [30], the effect that particulate matter may have on children is significant.

1.3.2 Nitrogen dioxide

Nitrogen dioxide (NO_2) is a gaseous pollutant that is mainly associated with traffic-related pollution [159], but other sources contribute as well such as industrial combustion [160]. Concentrations of NO_2 may vary daily within a city, as well as average concentrations varying from distance from major roads [14]. NO_2 promotes the release of inflammatory mediators in a person [161], effecting the lungs due to oxidative and immune modulatory responses [162]. This causes irritation in the lungs increasing bronchial reactivity and susceptibility to infections and allergens [14, 163, 164]. Daily concentrations of NO_2 have been shown to increase all-cause mortality and specifically respiratory mortality [165]. In a European study, a 1.3% increase in daily mortality rates was seen for each increase of 50mg/m^3 of NO_2 [166]. Furthermore, NO_2 exposure has been associated with asthma hospital admissions [167], and in panel studies in asthmatic children it has been shown to have an effect on the incidence of viral infections [168].

1.3.3 Sulfur Dioxide

Sulfur dioxide (SO_2) is a colourless gas, with the majority produced when sulphur containing coal and oil is burned as fossil fuel or during the smelting of mineral ores [169]. In Australia, 99% of SO_2 in the air is from these human sources [169], this is similar to the other countries. Natural sources that produce SO_2 are volcanoes and the oceans, however, this accounts for a small part, around two per cent, of the overall production of SO_2 [170]. Although, there has been a decrease in SO_2 levels around the world, particularly in the USA and Europe [171], due to legislation tackling fossil fuel combustion, about 15% of cities in the WHO data between 2000 and 2005 still exceed SO_2 guidelines [14]. It has been shown in studies that SO_2 is linked with all cause respiratory and cardiovascular mortality [172]. When examining hospital admissions, cardiovascular disease admissions are significantly increased

by short-term exposure to SO_2 in adults [173, 174]. It has been shown to have an association with all respiratory hospital admissions [150], particularly in asthmatics [175]. This may be due to the effect that SO_2 has on the respiratory system by acting as an irritant on the airways, promoting airway inflammation, inducing bronchospasm, and leading to airway fibrosis [14, 163, 164, 176]. This causes coughing, mucus secretion, aggravation of asthma, and chronic bronchitis [177]. In children, these effects may contribute to their likelihood of needing hospital admission when experiencing a respiratory disease.

1.3.4 Carbon Monoxide

Carbon monoxide (CO) is a colourless, odourless gas that is mainly produced in urban areas that experience heavy traffic [178, 179]. It is a product of incomplete fuel combustion produced by vehicular emissions [170]. CO has been shown to effect both cardiovascular and respiratory diseases in all age groups. In adults, short-term exposure has been shown to have effects on both cardiovascular mortality [180], and hospital admissions for cardiovascular disease [181]. When examining the effects of CO on the respiratory system, there is less evidence available. Studies have shown that short-term exposure effects the paediatric asthmatic cohort [182], with increases in asthma visits and decrease in lung function in this sub-group [183]. For the whole population, when examining emergency room department visits CO was associated with an increase in visits for upper respiratory tract infections [184]. CO affects a person's body by interfering with oxygen's ability to bind to haemoglobin, therefore affecting oxygen transport and reducing oxygen availability to organs [163, 164]. These could have an effect on respiratory diseases particularly in children.

1.3.5 Ozone

Ozone (O_3) is formed by a photochemical reaction in the atmosphere involving sunlight, nitrogen oxides and volatile organic compounds [26, 30]. The O_3 produced is different from atmospheric O_3 as refers to ground level O_3. Due to O_3 not being directly produced from

pollutant sources like the other major pollutants, there has been shown to have strong seasonal variation in levels [185]. This pollutant has been shown to have an effect on cardio and respiratory mortality in urban USA communities, increasing mortality by 0.64% for each increase of 20mg/m^3 [186]. It has been shown that the effect of O_3 on respiratory hospital admissions is higher in the warmer seasons [133], this highlights the seasonal variation that occurs. Short term exposure to O_3 has been shown to increase emergency department visits in Californian residents for asthma, acute respiratory infections, pneumonia and upper respiratory tract infections, with results being larger in the warm season [187]. Also, chronic exposure to ozone has been indicated to decrease lung function in young adults [188]. It has been thought that O_3 is a powerful respiratory irritant that induces respiratory tract mucosal inflammations, damage the epithelium lining the airways [163, 164]. This can lead to shortness of breath, chest pain, wheezing, coughing, and exacerbation of respiratory illnesses [14, 30, 161]. Thus, examining the effect that ozone has on healthcare resource utilisation in children who suffer from respiratory disease is important.

1.3.6 Pollution and respiratory disease

A third of all disease in children has been attributed to modifiable environmental factors such as water quality, sanitation, exposures to chemical and air quality [11]. The Committee on Environment Health of American Academy of Paediatrics stated in 2004 that there is a link between ambient air pollution and children's health [33]. In children an association between exposure to air pollutants and morbidity [189, 190], and mortality [191, 192] has been highlighted. The 2018 environmental performance index stated that poor air quality is one of the greatest threats to public health [193], with the Organization for Economic Co-operation and Development (OECD) estimating that ambient air pollution will become the greatest cause of environmental related child death by 2050 [194]. The WHO air quality guidelines were produced to provide international reference for levels that cause adverse effects on human health [133], however, they may be out of date in the current environment if updated figures and evidence are to be trusted.

Respiratory diseases and air pollution have been found to have a close relationship worldwide [195-202]. Along with the hazardous effects that ambient air pollution has, especially on the oxidant pathways in the lungs [203, 204], the age of the child at the time of exposure to inhaled pollutants plays a major role in the pattern of the injury [205], with younger children being more susceptible to the effects. Even when examining adults, ambient air pollution has been linked to occurrence and exacerbations of respiratory diseases, particularly chronic obstructive pulmonary disease (COPD) and lung cancer [206-209]. Reducing air pollution has been shown to lead to improvements in children's respiratory health [156, 210, 211]. In the USA, children who relocated to areas of lower levels of ambient PM10 had an increase in their lung function compared to those still residing in high levels of pollution [156]. Lung capacity has been highlighted to reduce by an estimated 20% if children reside in highly polluted environments [212]. This can lead to respiratory problems later on it life, especially if chronically exposed to pollutants [213, 214]. Air pollution has been linked to respiratory diseases such as asthma, bronchitis and wheezing [30, 34, 215-219]. Ambient air pollution has been associated in both asthmatic [220] and non-asthmatic [221] children when it comes to adverse respiratory effects. Although in some studies increases in morbidity or mortality related to respiratory disease have been small when extrapolated to a worldwide scale then the public health concerns are significant [133, 222]. One way to help reduce the effects of air pollution is to increase the monitoring systems available at local and national levels to emphasise the effect air pollution can have on the population [30]. Reducing air pollution is a target of the sustainable development goals (SDG) [30, 223], which replaced the millennium development goals (MDGs). Thus, the targets will hopefully help force governments and policy makers to recognise the hazardous effects pollution has on respiratory health.

1.3.7 Pollution and inequalities

Air pollution is a global problem, yet, there is a difference in how it effects countries. Outdoor air pollution is an issue that needs to be resolved across all countries regardless of income, as each country contributes to the hazardous effects it has on the population [136]. This struggle is not one that will be solved quickly but is a long-term task for all [224-226]. The most susceptible groups of the population at risk are children, the elderly and those in low socioeconomic status (SES) countries [133]. Air pollution levels have been decreasing

particularly in developed countries due to the implementation of pollution management controls and legislation, yet, developing countries are undergoing a transitional period of development with their concentration levels rising [133], particularly with traffic pollutants [227, 228]. However even with the improvement seen in developed countries, a large proportion still have high concentration levels [134]. These numbers highlight the considerable problem that remains with air pollution levels and production.

When examining the effect of those in low or middle income countries the disproportionate burden experienced by this population is high, with 90% of deaths from outdoor air pollution occurring in these countries [136]. When the effect is further analysed for children, those in low and middle income countries contribute to 88% of all deaths from illnesses that are associated with outdoor air pollution [136]. With the vast bulk of the total deaths occurring in Asia, although, the proportion of deaths from Africa is increasing [30, 229]. Furthermore, the Global Burden of Disease estimated that in children less than five years old who reside in low and middle-income countries the likelihood of dying from exposure to air pollution is increased by 60% [37]. It is not just children in low and middle income countries that are most likely to be affected but even in developed countries the lower income areas is where exposure to pollutants is highest [230]. Thus, overall poorer children are more likely to be affected by air pollution. It has been shown in studies that children who live in areas where pollution levels are high regardless of country are disproportionately from poorer communities [231, 232]. In the USA, air pollution has been shown to be higher in non-white and low income neighbourhoods [233, 234]. An example is in South Bronx in New York City which is known to be a lower income community, here asthma rates are four times higher than the national average [235]. Emphasising the disparity between populations and that concentration needs to be focussed on areas that are poorer as they are at greater risk of the hazardous effects of air pollution, as concentration levels are known to be high [236].

1.3.8 Pollution and Regulations

Air pollution episodes have occurred in the United Kingdom (UK) since the early 17th century when industrialisation started. However, increased concern in this area has led to new

legislation being implemented in the past century to limit the harmful effects from pollution. For the UK, some of the first legislation that was implemented occurred in 1956, being updated in 1968, was the Clean Air Act [237]. This has since been replaced by the Air Quality Strategy, but this is now out of date [238, 239]. For the USA, the Clean Air Act, was one of the first environmental laws, it set limits for the major pollutants and stated that violations would be penalised [240-242]. Legislation has been shown to work in other environmental areas, such as smoking exposure, where it has had a positive health benefit. The smoke-free legislation in the UK has shown that since the ban a reduction in childhood asthma has occurred, with at least a 10% decrease in hospital visits for children [243]. This highlights the importance of implementing further legislation in areas of air pollution, as current legislation in areas of the world have not reduced the harmful effects of pollution so far. By highlighting these hazardous effects that air pollution has on child health, it could highlight to policy makers the need for better, updated legislation.

1.4 Epidemiological study designs

Numerous study designs have been applied in epidemiological research to assess exposure of air pollution and adverse health effects [133]. Each has the ability to assess either short or long-term exposure in the population. For short-term exposure, some study designs used are time series, case-crossover or panel studies. Whereas for long-term exposure, cohort studies are used the majority of the time.

The time series study design involves estimating the influence of temporal variations via statistical models, and assesses changes in health events in a geographically defined population using air pollution measurements [244]. The majority of evidence has been generated using this method. Increases in availability of health record data, usually computerised, and air pollution measurements has helped facilitate the use [245]. Additionally, substantial developments in statistical analysis has helped to control for confounding factors, such as weather and seasonality [246]. Flexible smoothing techniques,

such as generalised additive models (GAM) help adjust for confounders. The use of locally weighted scatterplot smoothing (LOESS) or degrees of freedom need to be applied depending on the time span examined, helping to adjust for non-linear regression [246, 247]. There are disadvantages of this design, due to the use of computerised data for health records there is reporting bias as variation in judgement may occur in diagnosis, recording or reporting of diseases, introducing variability. The advantages of this method are that socio-economic conditions, occupation, tobacco smoke exposure cannot confound relationships, and there is reduced cost involved due to data readily available.

Another study design, case-crossover, is based on the case-control design where cases act as their own control [248]. Risk estimates are based on within subject comparisons to exposure at the time of effect with exposure periods before or after the event [248]. This design is used for recent exposure as otherwise there is the possibility of increased risk of carry-over effects causing bias. Disadvantages of this design revolve around the inability to control for changes in characteristics over time, it's less precise than a time series analysis, and is not suitable for cumulative effect estimation [246]. The advantages are that cases act as their own control, so remove subject specific confounders, it's relatively easy to implement, and if performed bi-directionally can control for time trends [14].

Panel studies are an alternative design methodology for short-term exposure assessment, they allow outcomes to be explored in susceptible populations [14]. Participants are followed up prospectively for a short time period, multiple measurements are obtained from each subject at various intervals [249]. The benefit of this design is the ability to obtain health and exposure information from individuals, with the possibility of using personal monitors due to small sample sizes [14]. This design requires covariates across time to be controlled for in analysis [250].

For long-term exposure, the majority of evidence uses cohort studies that can provide larger estimates of pollution effects than time series. Cohort studies are able to compare chronic health effects in people residing in different geographical locations [244]. A key feature to confound for variables that may interfere with estimates is based on the availability of

individual information, such as smoking and occupation. Disadvantages of cohort studies are the high cost of implementation, the logistical difficulties, and follow up can result in losses.

It is difficult to determine which study design is best as the majority can provide reasonable estimates of risk for short-term exposure or long-term exposure.

1.5 Asthma and pharmacogenomics

Analysing the effects of the environment is only one component of respiratory diseases, other factors influence the natural history of diseases and their management. A key part of treatment for respiratory disease is the use of pharmacotherapy. Respiratory medications are commonly prescribed in the paediatric population [251]. The exposure level to respiratory medication is largest in early childhood. Anti-asthmatic medication accounts for a large proportion of prescribed medication in children, in a Danish cohort study a third of young children received anti-asthmatic medication [251]. In another cohort study, the prevalence rate for asthma medication for children under 14 years old was 22.6% [252]. The use of medication to help alleviate or control a child's asthma is common. Depending on a child's severity of disease and age, the exact medication used varies according to the treatment steps [253]. Even with the recommended international treatment pattern there is variation between patients [254, 255].

ADRs are a substantial health risk to children. The WHO database between 1995-2005 reported that 11% of all ADR's reports in children were due to respiratory medications [256]. ADR's have previously been reported in children in systematic reviews [257-259], where they have been highlighted as a considerable issue on healthcare resources and hospital admission rates. In children, hospitalisation rates due to ADR's have been shown to range from 0.4% to 10.3% [260]. With asthma medications in children ADRs can have a greater effect due to children still developing than in adults, such as growth restriction when on corticosteroids [261].

The discipline of pharmacogenomics is an increasingly recognised area when it comes to medication efficacy and toxicity, it refers to the effect of genetic variation on a drug's effects on the patient [20, 262, 263]. It has been shown that a person's genotype can influence the efficacy of asthma medication [264]. The beta 2 adrenoreceptor (ADRB2) has been shown at the single nucleotide polymorphism (SNP) rs1042713 to show varied outcomes to beta 2 agonists when it came to pulmonary function responsiveness [265]. With ADRs, these reactions had previously been considered to be difficult to predict in individuals, however, the application of pharmacogenomics may now allow this [266]. In a recent study, ADRs in inhaled corticosteroids were examined in the childhood population, with adrenal suppression found in a specific sub group of patients [267].

Asthma requires long-term management, with the use of pharmacotherapy being one of the components needed. The need to balance between efficacy and toxicity when it comes to medication use is an important factor to consider. By using pharmacogenomics to understand an individual's risk of ADRs, it is possible to only prescribe medication to those who are least at risk of an ADR [268]. Identifying these susceptible groups will then contribute to healthcare professionals being able to personalise treatment plans for patients.

Pharmacogenomic studies have the opportunity of being randomised controlled trials, a high standard for evaluating relations in research [269]. However, cohort studies are also known to be used due to their lower cost, wider range of patients that can be entered due to looking for certain outcomes that may have already happened and quicker timing [270]. Cohort studies are useful to look for rare events, which would require large sample sizes that are not possible except as a cohort study. Both types of studies can be assessed to determine likelihood of bias of results [271, 272] and thus determine the usefulness of conclusions.

1.5 Systematic reviews

Systematic reviews are a useful tool to help synthesise evidence, particularly in healthcare [24]. They are increasing in practice due to their methodological rigor and effectiveness in reducing bias when performed correctly [24]. Systematic reviews should be based on pre-defined eligibility criteria along with a methodical protocol that has been pre-designed [24]. This ensures that the review has been carefully considered, promoting consistency, transparency and holding the review team to accountability for the process [24]. The conclusions and decisions gathered from systematic reviews can be made and then undertaken due to the reliability of the findings if performed robustly [273, 274]. The use of overviews of systematic reviews allows authors to combine multiple systematic reviews that have been performed and assess the results in a methodological manner, increasing the chance of forming reliable results for decisions to be formed from. These methods have been undertaken in this thesis to analyse the current evidence for both air pollution and pharmacogenomics.

1.6 Conclusion

Respiratory diseases are complex, with multiple factors influencing disease and patient outcomes. Understanding these factors is vital in helping to improve respiratory health in the population, particularly for children who are at increased susceptibility to certain elements. Various environmental parts are understood to affect the risk of respiratory outcomes, one of which is ambient air pollution. The current understanding of ambient air pollution in children identifies that it has hazardous effects on mortality, however, it fails to recognise and quantify the importance when it comes to healthcare utilisations, such as hospital admissions. The susceptibility of children to ambient air pollution requires further in depth analysis and understanding to see if the current WHO air quality guidelines [13, 14] have low enough thresholds, and if current legislation in countries is acceptable to prevent adverse health outcomes. In addition to understanding air pollution, other variables that affect respiratory disease outcomes need to be tackled. Respiratory medication is commonly prescribed in children, especially anti-asthmatics [251], to help manage respiratory diseases. The use of anti-asthmatics accounts for a large proportion of

medication prescribed [251]. With asthma medication the discipline of pharmacogenomics has identified that medication efficacy is affected by a person's genotype, supporting the interindividual variation seen in patients on the same medication. Although efficacy has been shown, the identification of susceptibility to ADRs is still in progress. The use of systematic reviews in these areas will collaborate the current knowledge available. This can then help form conclusions about both ambient air pollution and respiratory health in children, as well as pharmacogenomics relating to ADRs in asthma medications. These variables then may be able to help reduce the burden of respiratory diseases on healthcare and in individuals.

1.7 Aims

The aim of this thesis is to improve the understanding of how the environment and genomics influences respiratory health in children. The systematic reviews undertaken, each contribute to this aim.

Chapter two is aimed to systematically review the current literature relating to bronchiolitis hospital admissions and ambient air pollution. This is the first systematic review to be completed in this topic area and will help to contribute to the current evidence available in other respiratory diseases and ambient air pollution.

An overview of systematic reviews is undertaken in chapter three, it aims to collaborate all current systematic reviews available to investigate the effect of ambient air pollution on all acute respiratory diseases in children. Due to the work carried out in chapter two, evidence highlighted the possible effect that current air pollution guidelines may not be sufficient to protect respiratory health in children. Therefore, the need to compare the results with other previously undertaken systematic reviews was needed. The main finding from this overview is the current evidence available for asthma exacerbations and the lack of evidence for other respiratory diseases.

Chapter four aims to examine the role of pharmacogenomics and ADRs in asthma medications. Secondly, it aims to undertake a survey to determine the priorities of future pharmacogenomic studies. This review highlighted the importance of recognising ADRs as an outcome that needs to be investigated in future studies.

In chapter five, the outcomes from these reviews are discussed, where future directions should head and the relevance of the outcomes in clinical practice.

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

2.1 Background

Bronchiolitis is a common respiratory infection that affects children during infancy, with the majority contracting the disease within their first year of life [59], although can occur later. The majority of cases are due to the pathogen respiratory syncytial virus (RSV), responsible for between 43% to 80% of bronchiolitis cases [275-280]. Although other pathogens such as rhinovirus, parainfluenza, adenovirus and influenza can cause bronchiolitis, see table 2 [275] for main viral pathogens of bronchiolitis and approximate frequency.

Table 2. Viruses detected in hospitalised children and approximate frequencies

Virus	Approximate frequency (%)
Respiratory syncytial virus	43-80
Human rhinovirus	5-25
Parainfluenza virus	5-25
Human metapneumovirus	5-10
Coronavirus	5-10
Adenovirus	5-10
Influenza virus	1-5
Enterovirus	1-5

RSV, spread through close contact via droplet transmission [281], causes bronchial cell necrosis, airway inflammation, destruction of ciliated epithelial cells and infiltration by lymphocytes [275, 281]. This leads to small airway obstruction due to mucus and oedema of the airway, as well as bronchospasm [275]. Bronchiolitis is usually mild and self-limiting in children [74], manifesting as coryzal symptoms two to three days before the development of a cough, wheeze, tachypnoea, increased work of breathing, and hypoxia [282, 283]. Hospitalisation from bronchiolitis usually occurs in severe cases, when respiratory distress

may be present [283]. Admissions due to bronchiolitis account for a third of all hospital admissions in infants due to respiratory infections [284]. The disease is one of the major causes of hospital admission in both developed countries [66, 67, 282]and developing countries [285, 286] worldwide. In the past 30 years bronchiolitis admissions have increased from one per cent to three percent [282, 287, 288], increasing the burden on healthcare resources. In England, since the 1980s rates of bronchiolitis admissions have increased, particularly in industrialised areas [67]. When analysing between viral pathogens of bronchiolitis, cases due to RSV have been associated with longer hospital length stays, and increased risks of ICU admission compared to those with non-RSV bronchiolitis[61].

Along with the viral pathogen contributing to severity of disease, there are known risk factors for severe disease that needs hospitalisation including those that affect structural and functional lung development or generate airway inflammation. Some of the risk factors include prematurity [40], low to very low birth weight [289], chronic lung disease or congenital heart disease [290], and tobacco smoke exposure [70]. However, in an English cohort study the majority of children admitted to hospital with bronchiolitis did not have any of the associated severe risk factors, with only 24% of children having a risk factor [74]. This has been shown in other studies looking at bronchiolitis admissions, with the majority having no risk factors but are usually healthy, full term infants [63].

There is known seasonal variation with admission rates for bronchiolitis with peak seasons in most regions being during the winter [291], however, this does depend on geographical variation. In tropical and subtropical areas, bronchiolitis peaks occur in the cool, rainy season, whereas in regions below the equator peaks occur in the cool, dry months [292]. Along with seasonal variation, geographical variation occurs especially in areas of industrialisation [67] and deprivation [293]. This variation may also be linked to air pollution levels, as it is known that children from lower socioeconomic backgrounds and in areas of high urbanization are more effected [133]. As urbanization has increased in the last few decades and air pollution levels rise, the effect of air pollution on bronchiolitis admissions may become more apparent in evidence available.

Air pollution is measured through various exposure lengths. Lag exposure refers to the time period from when a study participant is exposed to air pollution until when the end point is

measured. Bronchiolitis effects children at a very young age, thus their exposure to air pollution chronic lifetime exposure has been limited. Lag exposure in this systematic review refers to multiple different exposure lengths divided into acute, sub chronic and chronic exposure. For acute, lag exposure refers to the average air pollution exposure from the time of admission up to the previous seven days. Sub chronic lag exposure is when air pollution is measured from hospital admission up to one month before and averaged. Lastly, chronic exposure is the average lifetime air pollution exposure concentration from birth until hospital admission.

This chapter describes a systematic review of studies that addresses the question of whether ambient air pollution effects bronchiolitis hospital admissions in infants.

2.2 Aims

The aim of this chapter is to identify studies that have analysed ambient air pollutant levels and bronchiolitis admissions in infants. A secondary aim is to assess whether the current WHO guidelines for ambient air pollutants are sufficiently low enough to protect children's health related to bronchiolitis.

2.3 Methods

A protocol was written a priori and submitted to PROSPERO, see Appendix 1 for the submitted protocol. PROSPERO is an online registration database of prospective systematic reviews to help limit the reproduction of similar reviews by different research groups.

2.3.1 Inclusion and exclusion criteria

Studies that evaluated the impact of ambient air pollution levels (PM2.5, PM10, NO_2, SO_2, CO, and O_3) on the pre-specified outcome in the protocol (risk of hospitalisation, excluding emergency department visits, with bronchiolitis) were eligible for inclusion. Studies had to be observational in design, thus were either cohort, time series, case-crossover, or case

control studies. This inclusion criteria was determined from a previous systematic review analysing the effect of air pollution and stroke [294].

Studies were included that evaluated exposure to ambient air pollution at a time period (lag) before hospitalisation occurred and were categorised into acute exposure (less than seven days), sub-chronic exposure (one month prior to hospitalisation), and lifetime exposure (average daily exposure concentrations since birth to hospitalisation). Secondary outcomes that were examined included emergency department visits, critical care admission, length of stay and mortality.

Studies were excluded for the following reasons.

1) Evaluated the impact of ambient air pollution on more than one respiratory illness, such that bronchiolitis data could not be extrapolated.
2) Looked at temporal associations between air pollution levels and number of hospitalisations for bronchiolitis in a particular region.
3) If they examined pollutants that were not the six main ambient pollutants stated or commented on ambient air pollution levels as a general outcome with no specifics.

2.3.2 Identification of relevant studies

An array of electronic databases was searched to increase the likelihood of identifying eligible studies.

The specific databases used in this systematic review were Medline, SCOPUS, and Web of Science. Medline is an online bibliographic database with access to 24 million references from 5,200 journals, specialised for life sciences and biomedicine [295]. It has articles available from 1966 to the present day [295]. SCOPUS is a databases of peer reviewed literature from scientific journals, books, and conferences [296]. Launched in 2004, it covers approximately 34,000 journals in the areas of life sciences, social sciences, physical sciences, and health sciences [296]. Web of Science, is a citation search database that covers articles

dating back to 1900 until present [297]. It covers the sciences, social sciences, arts and humanities with access to multiple databases [297].

2.3.3 Design of search strategy

The search strategy was constructed around the main concepts of the research question, with search terms modified to include synonyms and variations identified in previous publications [298]. The search strategies are shown in Appendix 2.

The following search terms were used in the literature databases undertaken until November 2017 with no restriction placed on date or language of publication. The specific search terms “bronchiolitis”, “air pollution”, “particulate matter”, “nitrogen dioxide”, “sulphur dioxide”, “carbon monoxide”, “ozone”, and “infants” were used, these reflected the aim of the systematic review. Bronchiolitis can frequently be described by various terminology, these were included in order to capture all studies. Discussion with experts in the field of paediatric and respiratory research were consulted to insure all search terms had been identified.

Synonyms within these words were combined using the Boolean operator OR, using this function allowed for any citations that had the key terms in their abstract, title or index words to be identified. Further synonyms were included using the MeSH function within Medline. To narrow the search results further the search terms were combined using the Boolean operator AND, so that studies with at least one key word from each section would be identified. As well as the use of synonyms, truncation was applied to increase the sensitivity of the search. The use of truncation, via the denotation of an asterix, identified various derivations of key words such as infan* would locate infancy, infant etc.

Specific types of studies, “observational studies”, were not included in the search terms in order to prevent the reduction and exclusion of possible eligible evidence as they may not be included in the paper’s title, abstract or indexed words. Thus, preventing an overly precise search strategy.

2.3.4 Selecting eligible studies for inclusion

Two independent reviewers (CK and IS) independently performed the screening process on the titles and abstracts, checking the eligibility of the results in accordance with the predetermined eligibility criteria. Full studies were examined by both reviewers to determine acceptability of inclusion in the review. From included studies, references and content were scanned for additional eligible studies.

Disagreements between the two reviewers (CK and IS) were discussed to determine if an agreement could be reached, otherwise, a third reviewer (DH) assessed the information and formed a conclusion.

2.3.5 Data extraction

For each study the following information was extracted from eligible studies by one reviewer (CK), with queries discussed with the second reviewer (IS):

1) Sample Size of Population and age range
2) Odds ratio or relative risk of hospital admission for bronchiolitis
3) Air pollutants mentioned and methodology of measuring pollution
4) Time period of measured air pollution
5) Level of air pollutants if reported

2.3.6 Assessment of quality of studies

The methodological quality of the included studies was assessed by CK, with it checked by a second reviewer. By assessing the quality of the studies, it allows the reviewers to determine the degree to which results from the literature are valid, and whether clinical implications can be determined.

The methods for quality review were dependent on the study design. For cohort and case control studies, the Newcastle-Ottawa scale has been formed as a tool for methodological appraisal [271]. This tool concentrates on a predetermined set of questions, with a star system developed for the tool, in addition a score out of nine at the end of the document depending on the results is given for studies. However, for time series and case-crossover study designs no specific quality tool exists to appraise them, thus, a modified Newcastle-Ottawa scale was created. Based on the quality appraisal tools, an assessment of risk of bias was formed with those of high methodological quality or a score greater than seven on the Newcastle-Ottawa scale was considered to be of low risk of bias.

2.3.6.1 Development of assessment quality tool for time series and case crossover study designs

Time series and case-crossover studies are similar to cohort studies, however, are designed so that cases act as their own control, therefore help to reduce confounding variables.

Three main aspects were derived from the Newcastle-Ottawa scale and adapted to assess the quality of time series and case-crossover studies. These were selection bias and other quality criteria, exposure assessment, and adjustment for confounders. A score was not attributed to each area, rather a rating of low, medium or high methodological quality depending on information in the studies.

For this review, selection bias and other quality criteria was assessed to be of high methodological quality if consecutive cases of hospital admission for bronchiolitis were included. If the cases had been identified from health records rather than parental recall. Studies were considered to be of higher quality when researchers had based the definition of bronchiolitis of the International Classification of Disease (ICD 9 or 10) criteria [43, 299, 300], or had supplemented their clinical judgement of a bronchiolitis diagnosis with microbiological testing for RSV or the other infectious organisms. Also, studies were further classified as being of higher quality if infants included were less than two years old based on guidance by the National Institute for Health and Care Excellence (NICE) [58]. However,

studies were not excluded if the age of children was over the age of two years if they included a standard bronchiolitis definition.

The other aspect examined in included studies was their exposure assessment of air pollution. From each study, the reported methodology was evaluated for how air pollutants were measured, specifically regarding the frequency of monitoring, the methodology of data collection and proximity of monitoring stations to participants. Studies were considered to be more systematically robust and thus of higher methodological quality if pollutants had been measured daily, measurements had been collected using standardised techniques, and monitors had been places within ten miles of a cases' residence or the admitting hospital.

The third area analysed in the modified quality assessment tool was adjustment for confounders. Adjustment for meteorological confounders (temperature, humidity etc), socioeconomic status, age and other clinical risk factors like maternal education and smoking were examined in each study. Studies were considered to be of high methodological quality if adjustment had occurred for at least two of these types of confounders. Due to the nature of time series and case crossover study designs age was already adjusted for as a confounding variable [248].

2.3.7 Grading of evidence

For acute, sub-chronic, and lifetime exposure to each pollutant, conclusions were formulated and evidence graded according to a strategy based on recommendations from the GRADE working group [301], such that each conclusion would be based on low, moderate or high quality of evidence as judged by two reviewers (CK and IS). The GRADE approach allows for a structured approach to be adopted when rating the quality of evidence so that recommendations can be formed in a systematic and transparent manner [302].

Evidence was graded based on three main criteria; study design, inconsistency, and imprecision, with an overall grade then given. Evidence was considered to be low at the

beginning, as only observational studies were included. Evidence was further graded down if there were any studies in the analysis with one or more design limitations based on the assessment of methodological quality above and graded up if there were no flaws in the study's methodology relevant to the analysis. Studies were considered to be further downgraded if there was inconsistency in results if there was wide variance across results, or if the results were conflicting. Evidence was further downgraded if there was imprecision in results with few patients, few outcomes and wide confidence intervals surrounding the effect estimate (odds ratio or relative risk). Specifically, evidence was downgraded if there were less than 5,000 infants in the studies and upgraded if more than 20,000 infants. Criteria surrounding indirectness was not included as this was covered in the quality assessment process. Publication bias was not formally assessed as there were too few studies to do this robustly

2.3.8 Data analysis

Meta-analysis was only considered to be undertaken in the presence of cohort studies, as they provide the strongest observational evidence in the absence of RCTs. 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 heterogeneity expected between studies. In addition, for each study the mean ambient pollutant value was compared with the recommended level by WHO.

2.4 Results

2.4.1 Study selection

A total of 1253 studies were located from databases using the search criteria, of these 47 studies were then assessed for full text eligibility, appendix 3 shows reasons for exclusion of papers. The remaining eight studies were then eligible for review. The review flowchart identifying the eligible studies is shown in Figure 4.

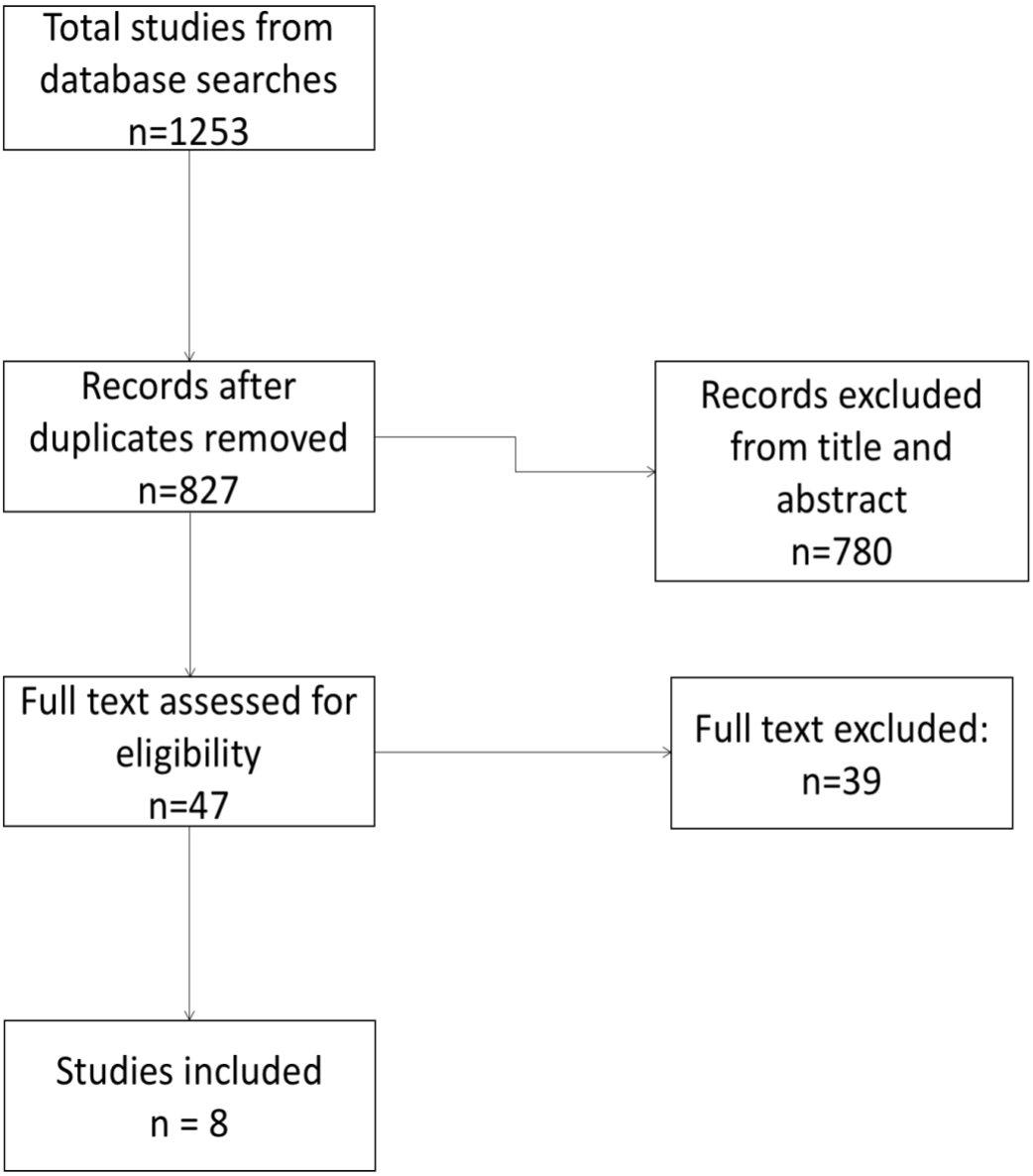


Figure 4. Review flowchart of included studies in systematic review of ambient air pollution and risk of hospitalisation with bronchiolitis

There were no cohort studies or time series studies identified from the eligible papers that analysed the effect of air pollution on risk of hospitalisation for bronchiolitis that matched the inclusion criteria. Thus, there was insufficient evidence to undertake a meta-analysis on the primary outcomes from the included studies, so results were reported descriptively.

2.4.2 Quality of included studies

Of the eight observational studies [303-310], four were case crossover studies and four case control studies.

The four case crossover studies were each assessed via the modified methodological quality assessment tool previously described above, with the four case-control studies evaluated via the Newcastle-Ottawa scale for methodological quality. The results of the quality assessment, referring to risk of bias are shown in table 3. From these six were considered to be of high quality, thus were determined to have low risk of bias with regards to selection of participants, evaluation of exposure of air pollution, and adjustment for confounding factors in their analysis. One study was reported to be of low methodological quality, thus had a high risk of bias, as for selection bias the definition of bronchiolitis was not stated nor an age range, exposure assessment was based on large distances between monitoring stations, and there was no adjustment for confounding factors. One study was a conference abstract, so was unclear when it came to the assessment of their methodological quality due to limited information supplied.

Table 3. Risk of bias assessment of studies included in systematic review of bronchiolitis and ambient air pollution

Study	Study design	Selection of participants	Evaluation of exposure	Consideration of confounding factors	Newcastle Ottawa Score
Karr 2004 [303]	Case crossover	Unclear*	Unclear*	Unclear*	N/A
Karr 2006 [304]	Case crossover	Low	Low	Low	N/A
Karr 2007 [305]	Case control	Low	Low	Low	7
Karr 2009 [306]	Case control	Low	Low	Low	7
Karr 2009 [307]	Case control	Low	Low	Low	7
Segala 2008 [308]	Case crossover	Low	Low	Low	N/A
Girguis 2017 [309]	Case control	Low**	Low	Low	8
Rahman*** 2017 [310]	Case crossover	High	High	High	N/A

Legend

*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

The GRADE assessments of the included studies are summarised in table 4 and 5, for each pollutant at each time lag.

Table 4. GRADE assessment of included studies in systematic review of bronchiolitis and particulate pollutants

Pollutant and exposure	Number of studies and design, and number of infants	Conclusion	Study limitations	Inconsistency	Imprecision	Grade of evidence
PM2.5 acute exposure	2 case-crossover studies and of 41,474 infants [303, 304]	Does not seem to affect risk of hospitalisation	No change	No change	+1	Moderate
PM2.5 sub-chronic exposure	3 case-control studies including 33,394 infants [305-307]	Unclear effect on risk of hospitalisation	+1	-1	+1	Moderate
PM2.5 lifetime exposure	4 case-control studies of 52,768 infants [305-307, 309]	May increase risk of hospitalisation	+1	-1	+1	Moderate
PM10 acute exposure	1 case crossover study of 16588 infants [308]	Unclear effect on risk of hospitalisation	+1	No change	No change	Low
PM10 sub-chronic exposure	1 case control study of 11,675 infants [307]	Does not seem to affect risk of hospitalisation	+1	No change	No change	Low
PM10 lifetime exposure	1 case crossover study and 1 case control study, including 17,454 infants[307, 310]	Unclear effect on risk of hospitalisation	-1	No change	No change	Low

Legend

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm Acute exposure: less than seven days, Sub-chronic exposure: less than 30 days, Lifetime exposure: average exposure from birth until hospitalisation

Table 5. GRADE assessment of included studies in systematic review of bronchiolitis and ambient air pollution and gaseous pollutants

Pollutant and exposure	Number of studies and design, and number of infants	Conclusion	Study limitations	Inconsistency	Imprecision	Grade of evidence
NO_2 acute exposure	3 case-crossover studies of 58,062 infants [303, 304, 308]	Unclear effect on risk of hospitalisation	+1	No change	+1	Moderate
NO_2 sub chronic exposure	2 case-control studies of 30,270 infants [305, 307]	Unclear effect on risk of hospitalisation	+1	No change	+1	Moderate
NO_2 lifetime exposure	2 case control studies and 2 case crossover studies of 39,173 infants [305-307, 310]	Unclear effect on risk of hospitalisation	-1	No change	+1	Low
SO_2 acute exposure	1 case crossover study of 16,588 infants [308]	May increase risk of hospitalisation	+1	No change	No change	Low
SO_2 sub chronic exposure	1 case crossover study of 11,675 infants [307]	May increase risk of hospitalisation	+1	No change	No change	Low
SO_2 lifetime exposure	1 case control study of 11,675 infants [307]	May increase risk of hospitalisation	+1	No change	No change	Low
CO acute exposure	2 case crossover study of 41,474 infants [303, 304]	Does not seem to affect risk of hospitalisation	+1	No change	No change	Low
CO sub chronic exposure	2 case control studies of 30,270 infants [305, 307]	Unclear effect on risk of hospitalisation	+1	No change	+1	Moderate

CO lifetime exposure	2 case control studies and 1 case crossover study of 36049 infants [305, 307, 310]	Unclear effect on risk of hospitalisation	-1	No change	+1	Low
O_3 acute exposure	No studies	No assessment can be made				
O_3 sub chronic exposure	2 case control studies of 30,270 infants [305, 307]	Does not seem to increase risk of hospitalisation and may be associated with lower risk of admission	+1	No change	+1	Moderate
O_3 lifetime exposure	2 case control studies and 1 case crossover study of 36049 infants [305, 307, 310]	Does not seem to increase risk of hospitalisation and may be associated with lower risk of admission	-1	No change	+1	Low

Legend

NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone

Acute exposure: less than seven days, Sub-chronic exposure: less than 30 days, Lifetime exposure: average exposure from birth until hospitalisation

2.4.3 Study Characteristics

Out of the eight included studies, five of the studies were from overlapping research groups in North America [303-307], one was from a different North American research group [309], one from France [308], and one from Malaysia [310]. The characteristics of the included studies are summarised in table 6. There were six studies that examined PM2.5 exposure [303-307, 309], three for PM10 exposure [307, 308, 310], seven for NO_2 [303-308, 310], two that analysed SO_2 exposure [307, 308], five examining CO [303-305, 307, 310], and three that surveyed O_3 exposure [305, 307, 310] and risk of hospitalisation with bronchiolitis.

Table 6. Characteristics of included studies

Study	Study Design	Years Conducted	Country (Region)	Bronchiolitis Definition	Population	Population Size	Lag exposure	Adjusted for confounders	Pollutants Measured*
Karr 2004 [303]	Case crossover	1995-2000	United States (California)	Not stated	Three weeks to one year	22365	Lag 1-2, Lag 3-5	Not stated	PM2.5, NO_2, CO
Karr 2006 [304]	Case crossover	1995-2000	United Stated (California)	ICD 9	Three weeks to one year	19109	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 2007 [305]	Case control	1995-2000	United States (California)	ICD 9	Three weeks to one year	18595	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,	PM2.5, NO_2, O_3, CO

								daily mean temperature, and daily mean humidity.	
Karr 2009 [306]	Case Control	1997-2003	United States (Washington State)	ICD 9	Three weeks to one year	3124	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 2009 [307]	Case control	1999 to 2002	Canada (British Columbia)	ICD 9	Singleton children aged 2-12 months	11675	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
Segala 2008 [308]	Case Crossover	1997-2001	France (Paris)	Respiratory dyspnoea and/or sibilants and wheezing for children	Less than three years	16588	Lag 0-1, lag 0-4	Public holidays, holidays and weather variables.	PM10, NO_2, SO_2

Girguis 2017 [309]	Case Control	2001-2008	United States (Massachusetts)	ICD 9	Three weeks to less than 12 months	19374	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
Rahman 2017 [310]	Case Crossover	2006-2010	Malaysia (Klang Valley)	Not stated	Not stated	5779	Lifetime	Not stated	PM10, CO, O_3, NO_2

Legend

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm, NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone

2.4.4 Primary outcome – the association between air pollution and risk of hospitalisation for bronchiolitis

The results from the included studies are summarised below and shown in figures 5-10, with the detailed results shown in in table 7 and 8.

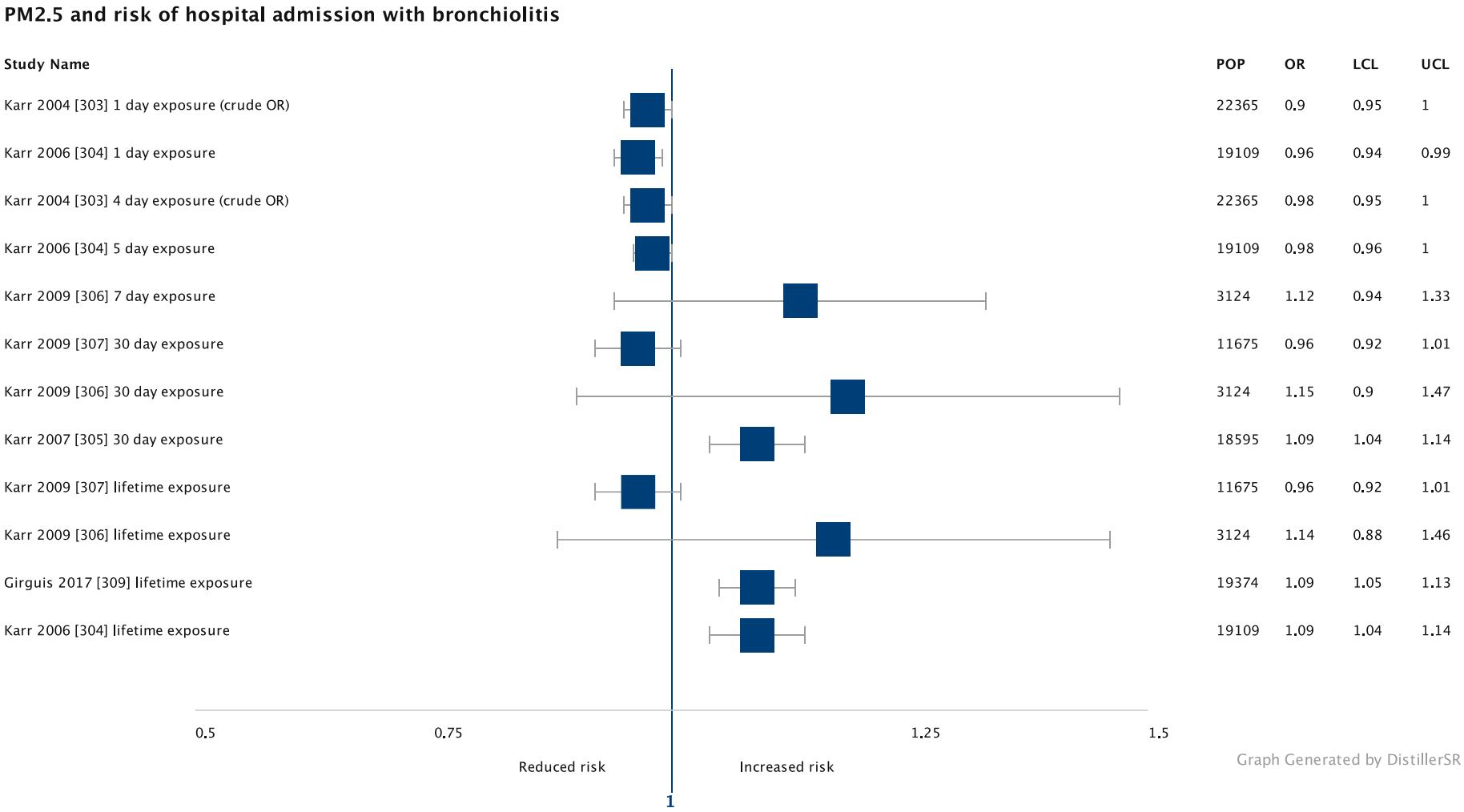


Figure 5. Forest plots of PM2.5 exposure and risk of hospitalisation with bronchiolitis without meta-analysis

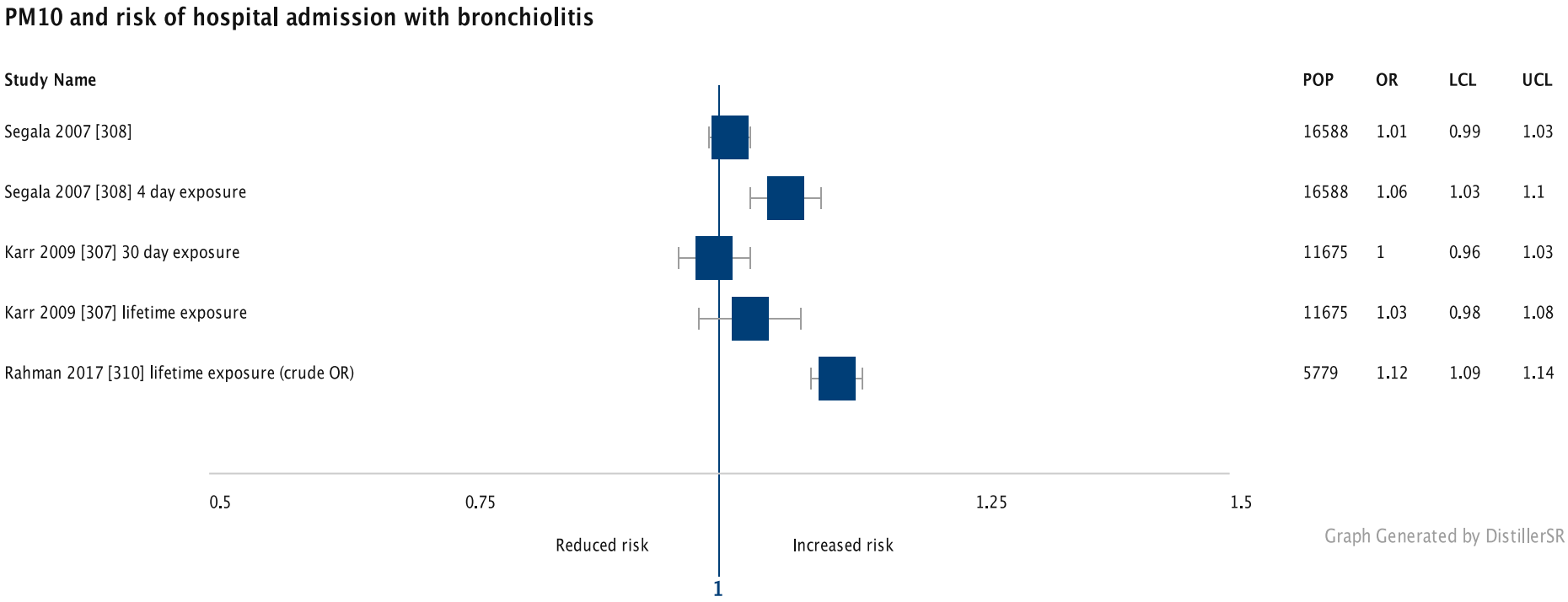


Figure 6. Forest plots of PM10 exposure and risk of hospitalisation with bronchiolitis without meta-analysis

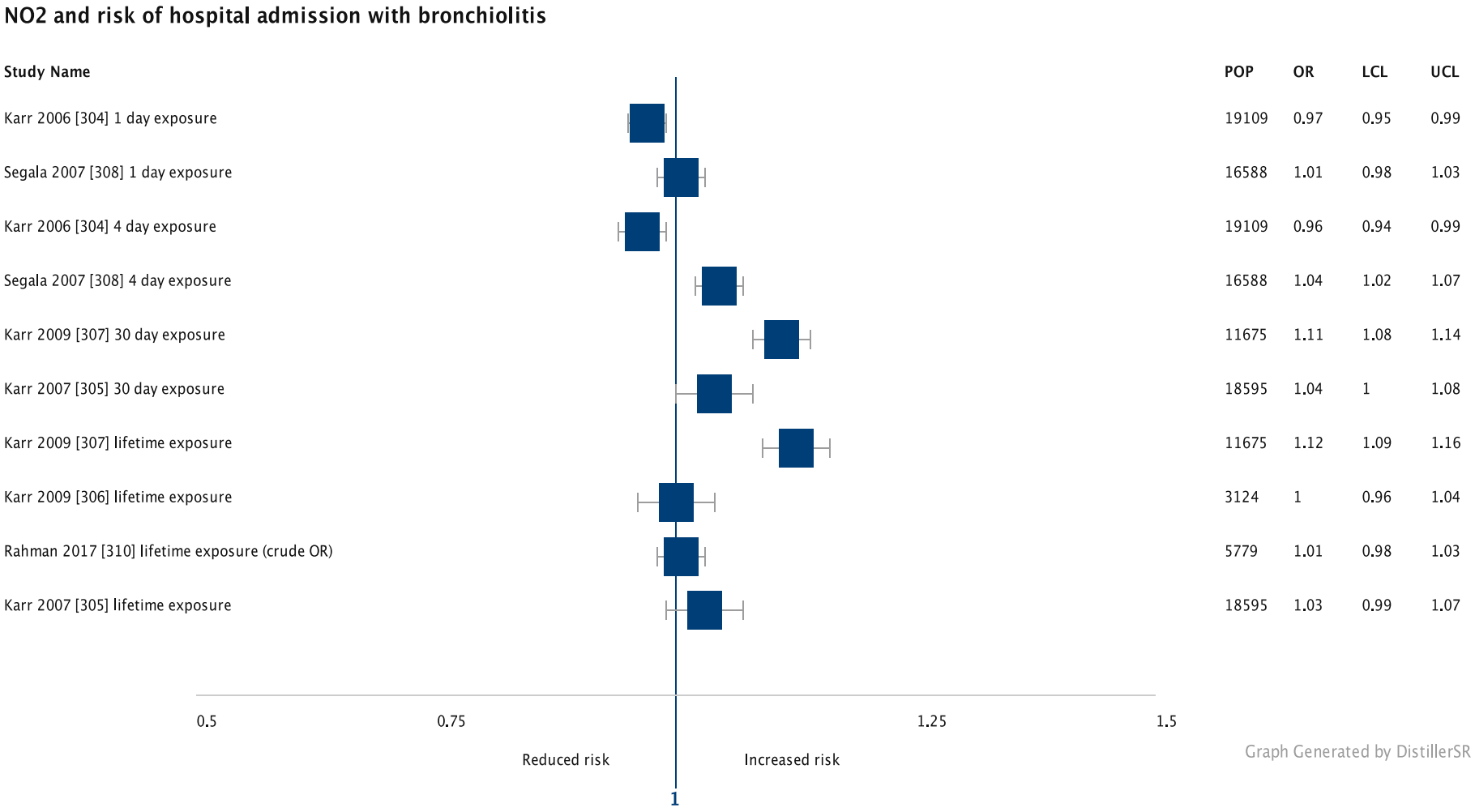


Figure 7. Forest plots of NO_2 exposure and risk of hospitalisation with bronchiolitis without meta-analysis

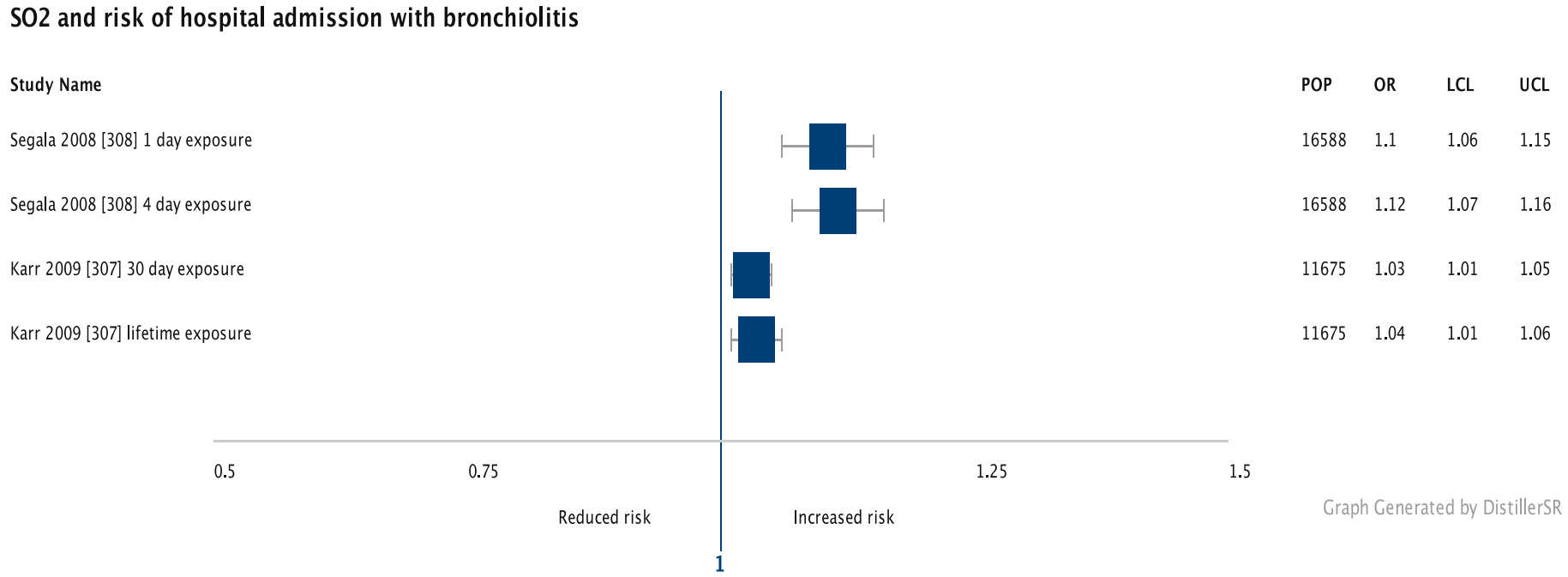


Figure 8. Forest plots of SO_2 exposure and risk of hospitalisation with bronchiolitis without meta-analysis

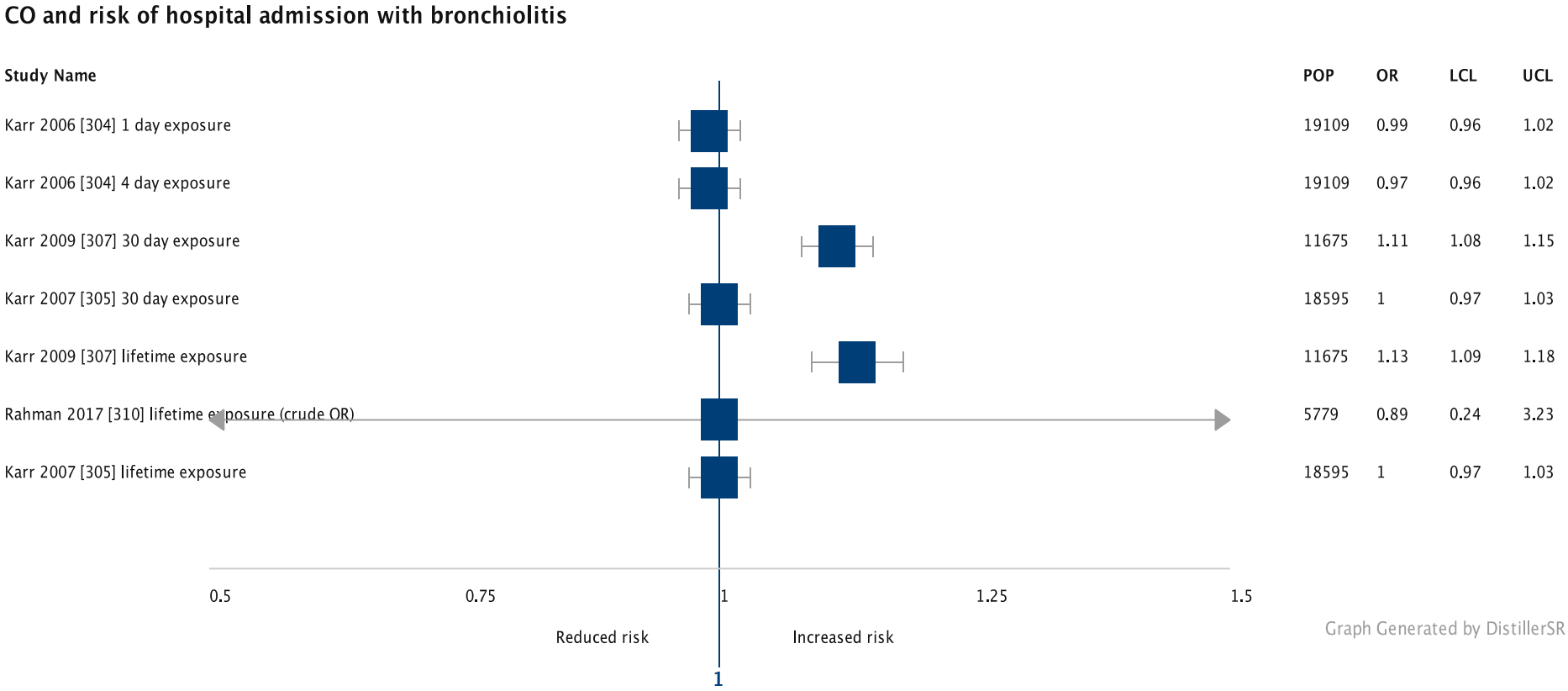


Figure 9. Forest plots of CO exposure and risk of hospitalisation with bronchiolitis without meta-analysis

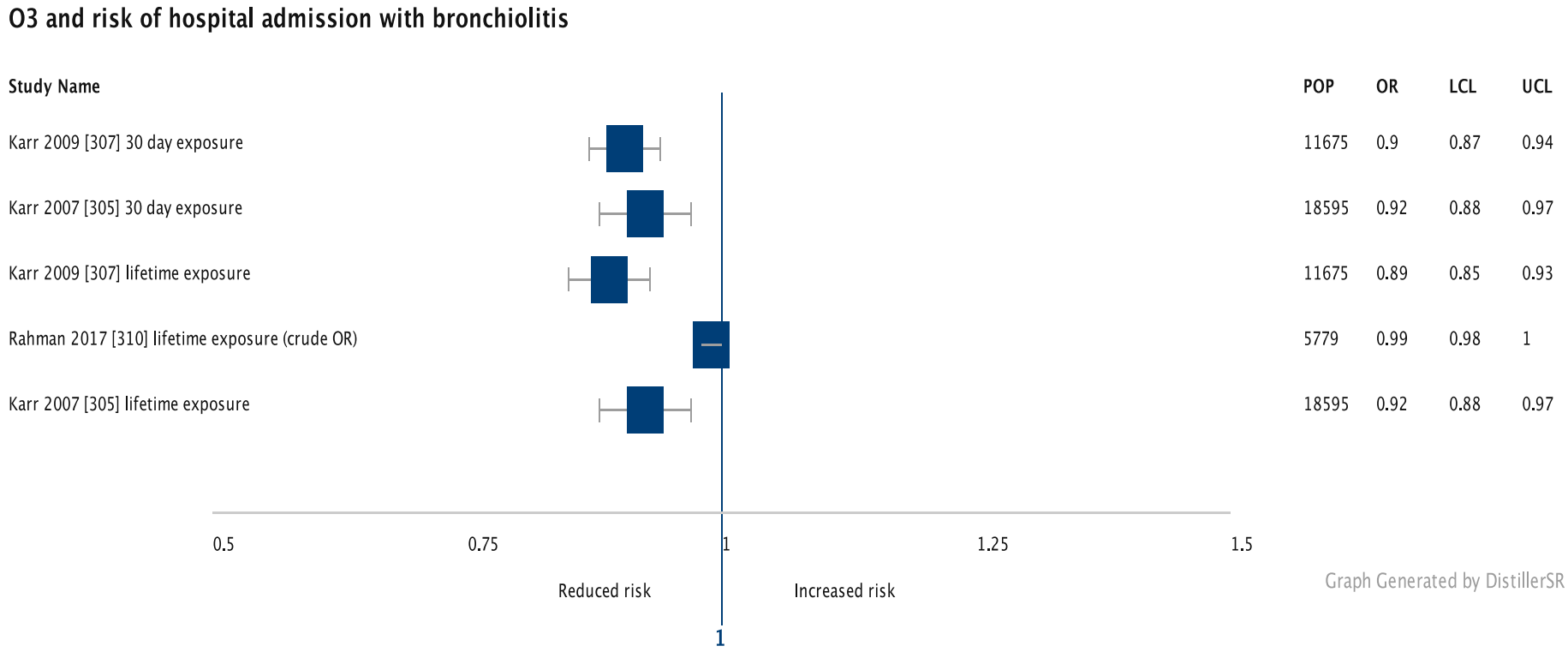


Figure 10. Forest plots of O_3 exposure and risk of hospitalisation with bronchiolitis without meta-analysis

Table 7. Results of included studies for particulate pollutants

Pollutant	Study	Lag Exposure	Crude Odds Ratio	Adjusted Odds Ratio
PM2.5	Karr 2009 [307]	1 month Exposure	0.93 (0.89–0.97)	0.96 (0.92-1.01)
		Lifetime	0.90 (0.84–0.97)	0.97 (0.90-1.04)
	Karr 2009 [306]	7 days	Not stated	1.12 (0.94-1.33)
		30 day	Not stated	1.15 (0.90-1.47)
		Lifetime	Not stated	1.14 (0.88-1.46)
	Karr 2006 [304]	1-2 days	Not stated	0.96 (0.94-0.99)
		3-5 days	Not stated	0.98 (0.96-1.00)
	Karr 2004 [303]	1-2 days	0.98 (0.95-1.00)	Not stated
		3-5 days	0.98 (0.96-1.00)	Not stated
	Girguis 2017 [309]	Lifetime	1.05 (1.02, 1.07)*	1.09 (1.05-1.13)*
	Karr 2007 [305]	Sub-chronic (30 days)	Not stated	1.09 (1.04-1.14)*
		Chronic (Lifetime)	Not stated	1.09 (1.04-1.14)*
PM10	Karr 2009 [307]	1 month Exposure	0.97 (0.94–10.01)	1.00 (0.96-1.03)
		Lifetime	0.99 (0.94–1.04)	1.03 (0.98-1.08)
	Rahman 2017 [310]	Lifetime	1.12 (1.09-1.14)*	Not stated
	Segala 2008 [308]	0-1 day	Not stated	1.01 (0.99-1.03)
		0-4 day	Not stated	1.06 (1.03-1.10)*

Legend

*statistically significant

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm,

Acute exposure: less than seven days, Sub chronic exposure: less than one month, Lifetime exposure: average exposure from birth until hospitalisation

Odds ratio refers to increase in PM2.5 and PM10 with a unit increase of 10 µg/m^3

Table 8. Results of included studies for gaseous pollutants

Pollutant	Study	Lag Exposure	Crude Odds Ratio	Adjusted Odds Ratio
NO_2	Karr 2009 [307]	1 month Exposure	1.06 (1.03–1.09)*	1.11 (1.08-1.14)*
		Lifetime	1.06 (1.02–1.09)*	1.12 (1.09-1.16)*
	Karr 2009 [306]	Lifetime	Not stated	1.00 (0.96-1.04)
	Karr 2006 [304]	1 day	Not stated	0.97 (0.95-0.99)
		4 days	Not stated	0.96 (0.94-0.99)
	Karr 2004 [303]	1 day	Not available	Not available (stated as not statistically significant association)
		4 day	Not available	Not available (stated as not statistically significant association)
	Rahman 2017 [310]	Lifetime	1.01 (0.98-1.03)	Not stated
	Karr 2007 [305]	Sub-chronic (30 day)	Not stated	1.04 (1.00-1.08)
		Chronic (Lifetime)	Not stated	1.03 (0.99-1.07)
	Segala 2008 [308]	0-1 day	Not stated	1.01 (0.98-1.03)
		0-4 day	Not stated	1.04 (1.02-1.07)*
SO_2	Karr 2009 [307]	1 month Exposure	1.00 (0.98–1.02)	1.03 (1.01-1.05)*
		Lifetime	1.00 (0.98–1.02)	1.04 (1.01-1.06)*
	Segala 2008 [308]	0-1 day	Not stated	1.10 (1.06-1.15)*
		0-4 day	Not stated	1.12 (1.07-1.16)*
CO	Karr 2009 [307]	1 month Exposure	1.03 (1.00–1.06)	1.11 (1.08-1.15)*
		Lifetime	1.03 (0.99–1.07)	1.13 (1.09-1.18)*
	Karr 2006 [304]	1 day	Not stated	0.99 (0.96-1.02)

		4 day	Not stated	0.97 (0.94-1.00)
	Karr 2004 [303]	1 day	Not available	Not available (stated as not statistically significant association)
		4 day	Not available	Not available (stated as not statistically significant association)
	Rahman 2017 [310]	Lifetime	0.89 (0.24-3.23)	Not stated
	Karr 2007 [305]	Sub-chronic (30 day)	Not stated	1.00 (0.97-1.03)
		Chronic (Lifetime)	Not stated	1.00 (0.97-1.03)
O_3	Karr 2009 [307]	1 month Exposure	0.97 (0.94–1.01)	0.90 (0.87-0.94)
		Lifetime	0.98 (0.94–1.02)	0.89 (0.85-0.93)
	Rahman 2017 [310]	Lifetime	0.99 (0.98-1.00)	Not stated
	Karr 2007 [305]	Sub-chronic (30 day)	Not stated	0.92 (0.88-0.97)
		Chronic (Lifetime)	No	0.92 (0.88-0.97)

Legend

*statistically significant

NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone

Acute exposure: less than seven days, Sub chronic exposure: less than one month, Lifetime exposure: average exposure from birth until hospitalisation

Odds ratio refers to increase in NO_2, SO_2 and O_3 with a unit increase of 10 $\mu g/m^3$, and for CO a unit increase of 1 mg/m^3

2.4.4.1 Particulate Pollutants

Based on moderate quality evidence (according to the GRADE assessment), acute exposure to PM2.5 does not seem to increase the risk of hospitalisation (figure 5). Three studies [303, 304, 306], found no association with an increased risk of hospitalisation with bronchiolitis due to PM2.5 at different time lags in the acute exposure window. Sub-chronic effects are unclear, with two studies discovering no increased risk with 30 day exposure [306, 307], however, one study did find an increased risk with sub-chronic exposure [305](OR 1.09, 95% CI 1.04-1.14). For lifetime exposure, there may be an increased risk of hospitalisation with bronchiolitis associated. Two studies [306, 307] found no increased risk of hospitalisation, yet, in two studies there was an increased risk of hospitalisation shown (OR 1.09, 95% CI 1.04-1.14 [305] and OR 1.09, 95% CI 1.05-1.13 [309]).

There is less evidence around PM10, and the evidence available is of low quality (see GRADE assessment). Acute effects of PM10 on hospitalisation is unclear, with one study [308] having found an association at a lag of 0-4 days (OR 1.06, 95% CI 1.03-1.10), but not at a smaller lag of 0-1 days. Sub-chronic exposure does not seem to be associated with an increased risk of hospitalisation, however, there was only one study that examined these effects [307]. Of the two studies that examined lifetime exposure, the results were unclear, as one [307] found no association, but one [310] found a statistically significant association with lifetime exposure (OR 1.115, 95% CI 1.093-1.138).

2.4.4.2 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 (see GRADE assessment), the acute, sub-chronic, and lifetime effects of NO_2 are unclear, although longer term exposure may be associated with an increased risk of admission for bronchiolitis (figure 7) Two studies found no increased risk of acute exposure [303, 304], and one study found a statistically significant association

at a lag of 0-4 days (OR 1.04, 95% CI 1.02-1.07), but not at a lag of 0-1 days [308]. For sub-chronic and lifetime exposure, three studies [305, 306, 310] found no association with risk of hospitalisation with bronchiolitis, but one study [307] found a statistically significant association with sub-chronic (OR 1.11, 95% CI 1.08-1.14) and lifetime exposure (OR 1.12, 95% CI 1.09-1.16).

For SO_2, the quality of evidence was graded as low (see GRADE assessment). The results of two studies suggest that acute, sub-chronic, and lifetime exposure to SO_2 may be associated with increased risk of hospitalisation (figure 8). One study [308] that examined acute exposure found that statistically significant associations were seen at lags of 0-1 days (OR 1.10, 95% CI 1.06-1.15) and 0-4 days (OR 1.12, 95% CI 1.07-1.16). In another study [307], the effects of longer term exposure were assessed, and s statically significant association was found with risk of hospitalisation for sub-chronic exposure (OR 1.03, 95% CI 1.01-1.05) and lifetime exposure (OR 1.04, 95% CI 1.01-1.06).

Based on low quality graded evidence from two studies [303, 304], CO does not seem to have an acute effect on the risk of hospitalisation for bronchiolitis (figure 9). For sub-chronic effects, based on moderate quality graded evidence, the risk of hospitalisation with bronchiolitis is unclear. One study [305] found no association with risk of hospitalisation, but one study [307] found a statistically significant association (OR 1.11, 95% CI 1.08-1.15). With lifetime exposure, based on low quality graded evidence, the risk of hospitalisation is difficult to determine, two studies [305, 310] found no association, but one study [307] did find a statistically significant association (OR 1.13, 95% CI 1.09-1.18).

Three studies assessed the longer terms effects of O_3 exposure, but none evaluated acute effects. The quality of evidence for sub-chronic was graded as moderate, but low for lifetime exposure. Most studies showed a reduction in the risk of admission associated with ozone exposure (see figure 10). Two studies [305, 307] found no association with increased risk for sub-chronic exposure, with both finding a statistically significant decrease in hospitalisation risk (OR 0.90, 95% CI 0.87-0.94 [307] and OR 0.92, 95% CI 0.88-0.97 [305]). For lifetime exposure, three studies [305, 307, 310] found no increased risk of

hospitalisation, with two studies finding a statistically significant decrease (OR 0.89, 95% CI 0.85-0.93 [307] and OR 0.92, 95% CI 0.88-0.97 [305]).

2.4.5 Secondary outcomes

There were two studies that had assessed a secondary outcome as well as the primary outcome. One case crossover study [308], examined the acute effects of PM10, NO_2 and SO_2 on the risk of emergency visit consultations for bronchiolitis. A statistically association was found in all three pollutants for a lag of 0-4 days, PM10 (OR 1.06, 95% CI 1.04-1.08), NO_2 (OR 1.03, 95% CI 1.02-1.05), and for SO_2 (OR 1.12, 95% CI 1.09-1.15). For SO_2 exposure, a positive association was also seen at a lag of 0-1 days (OR 1.08, 95% CI 1.06-1.11). There was nearly triple the amount of average number of patients in this cohort, 139 cases per day, compared the average number of hospitalisations, 45 cases per day. There was one case control study [309] that evaluated the lifetime exposure of PM2.5 on the risk of a clinical encounter (emergency department visits and hospital admissions combined) for bronchiolitis with no association found after adjustment for confounding variables.

2.4.6 Comparison between effect of air pollution and WHO recommended guidelines

Of the eight included studies, five reported that one or more of the ambient air pollutants was associated with an increased risk of hospitalisation with bronchiolitis [305, 307-310]. Of these, four measured air pollutant average levels, comparing these to WHO recommended guidelines, three [307-309] had levels below the recommendations where pollutant exposure had reached statistical significance for risk of hospitalisation with bronchiolitis. One study [305], that measured air pollutant levels, that had found an association with longer term exposure and risk of hospitalisation, had PM2.5 mean levels above those recommended. One study [309] found statistically significant associations with lifetime exposure to PM2.5 at levels below WHO guidelines, this was similarly seen in one study for acute PM10 exposure [308], one study for longer term exposure to NO_2 [307], two studies for all exposure windows for SO_2 [307, 308], and one study for longer term exposure for CO [307].

2.5 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 the findings are inconsistent across studies a suggested association with longer term exposure to the all pollutants, apart from ozone, and risk of hospitalisation with bronchiolitis is seen. Acute exposure to NO_2 and SO_2, may also be associated with increased risk of hospitalisation with bronchiolitis, with SO_2 exposure association seen in low levels of SO_2 concentrations. In some of the studies [307-309], where you would expect risk of hospitalisation with bronchiolitis to be decreased association was seen at concentration levels lower than the recommended WHO guidelines.

The effects seen with ozone should not be assumed to suggest a decrease in risk of hospitalisation with bronchiolitis, and that ozone is a protective factor. Ozone is known to be a unique air pollutant that doesn't correlate to the pattern seen in the other pollutants. Due to how ozone is produced the peak exposure window is usually during the hot, summer months when there is plenty of sunshine, which is when bronchiolitis epidemics especially due to RSV are low. The negative association seen could be due to that in the winter months, other pollutants confound the effects of ozone, with multipollutant modelling a possible way to assess this reasoning [305]. Furthermore, due to the seasonal variation seen with ozone, it may be that bronchiolitis as it is also considered to be seasonal in its peaks may not be as affected as respiratory diseases that occur all year round, or effect infants as strongly compared to children who are more active outdoors in the summer when exposure levels are high. This idea should be considered when comparing the effect of ambient air pollutants against a range of respiratory diseases in the future.

Maximum levels of air pollutants in current WHO air quality guidelines may not be sufficiently low enough to protect infants, who may be particularly vulnerable to their harmful effects [311]. 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 [312]. This systematic review highlights that even at low levels associations are still seen with pollutants. This emphasises the need for the current legislation to be stricter when it involves ambient air pollutants, as there is a high proportion of areas that exceed the current guidelines, and for a review of the current WHO guidelines as over time new hazardous effects of air pollutants are being realised.

This review was conducted in a systematic manner, but the validity of the conclusions is hampered by the variation seen 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 the morbidity and global burden of the disease. Seasonality is known to affect the variability of air pollution, with traffic associated air pollutants increasing in the winter and ozone higher in the summer months. The majority of studies included accounted for temperature and humidity along with matching within the same time period for time-series and case crossover studies to limit these confounding variables [304-306, 308, 309].

Although there were inconsistencies found between the results in this review, a recent study [313] analysing bronchiolitis in a different cohort has been released after the search period. This study has further highlighted positive associations between traffic related pollutants, PM2.5, CO and nitrogen oxides (this includes NO_2), and bronchiolitis clinical encounters. The results from this study increasingly highlight the association seen in some of the studies in this review where statistically significant results were seen. This supports the view that air pollution may have an association with increased risk of hospitalisation with bronchiolitis.

2.5.1 Limitations

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. Although bronchiolitis usually occurs within the first year of life, there was variation in age cut offs in the studies. Variation in the age definition may have resulted in viral wheeze or mild cases of pneumonia being misclassified as bronchiolitis, particularly when including children over the age of one year [308, 310]. There were differences in the confounding factors that were considered in the analyses of each of the studies, with some adjusting for a wider range of covariates than others. As expected, crude odds ratios that showed statistical significance were found [307, 309], yet the adjusted ORs did not, highlighting 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 [314]. International consensus, around potential confounding factors and a core outcome set [315, 316] to measure and report in observational studies of air pollution, may help reduce these problems.

2.6 Conclusion

As hospitalisation for bronchiolitis and ambient air pollution effects had not been considered in previous studies, the aim of this chapter was to assess this association that has already been highlighted in other respiratory diseases in children. This review suggests an association between different air pollutants and risk of hospitalisation with bronchiolitis in infants, particularly with particulate matter, NO_2 and SO_2 exposure. The review has highlighted the need for a multicentre cohort or time series study to examine this possible association further comparing with the recent study seen with traffic air pollution and bronchiolitis, and this would be strengthened by development of a standardised methodological approach. A combination of the current evidence around air pollution and respiratory disease, including this systematic review, would be beneficial to assess the differences and similarities that may appear in relation to air pollution concentrations and respiratory disease. Revision of the international recommendations around air quality levels

may be warranted and should incorporate specific consideration around the impact of outdoor air pollution on infants.

Chapter 3 – The effects of ambient air pollution on the risk of hospitalisation with acute respiratory illnesses in children: an overview of systematic reviews.

3.1 Background

The effects of outdoor air pollution on respiratory disease outcomes is rapidly growing in evidence. The previous chapter highlights how outdoor air pollution effects bronchiolitis, yet this is not the only systematic review that has analysed a respiratory diseases and pollution. A systematic review [317] analysing Canadian epidemiological studies showed a positive association of healthcare services utilisation and general respiratory conditions in children. This result was further evidenced when concentrating on asthma in children, where positive associations were also seen, specifically with acute exposure to NO_2, SO_2 and CO. In this systematic review similar to the bronchiolitis review in chapter two, positive associations were seen at low levels of pollutant exposure. Increased frequency of asthma exacerbations and wheeze has been shown in in a meta-analysis examining exposure to traffic related air pollution [318]. With the increasing levels of air pollution [133, 319, 320], the evidence from these systematic reviews will help to emphasise the importance of monitoring and controlling pollution levels.

Children are at particular risk of the harmful effects of air pollution, even when levels are low [321]. This age group are known to be susceptible due to the developmental growth periods that occur [322], the increased proportion of time that they spend outside exposed to pollution [323], the higher volume of air exchange relative to body mass compared with adults [27], and the increased normal respiratory rate of 20 to 40 breaths per minute [324] compared to a adults 12 to 20 breaths [325]. All these factors contribute to the adverse effect air pollution can have on respiratory health. The adverse effect on a child's lung function is well described [326], and there is emerging evidence regarding prenatal traffic air pollutant exposure and low birth weight, which can further affect the respiratory system [327].

Air pollutants have been implicated as risk factors for pulmonary exacerbations in children with chronic illnesses such as cystic fibrosis [328-330], and respiratory infections in children without comorbidities [331, 332]. The possible mechanism that increases susceptibility to respiratory infections due to air pollution may be a result of oxidative stress and allergic sensitisation of the respiratory system [333].

Acute respiratory events such as infection and asthma exacerbations are a major burden on healthcare utilisation and a significant contributor to global childhood mortality rates [334-337]. A paper analysing asthma outcomes estimated that the total health care costs from 34 countries was around $1.7 trillion in 2010 [338], this estimation has only likely increased as air pollution have risen along with adverse health effects. By identifying factors, such as outdoor air pollution, that may influence healthcare utilisation rates, efforts can be made to address this large cost on the health service and help to reduce the part that respiratory diseases in children may contribute to it.

This chapter describes an overview of systematic reviews that was undertaken to determine the current evidence available that examined the effects of ambient air pollution on unscheduled healthcare resource utilisation (HRU) due to acute respiratory events such as infection and asthma exacerbations.

3.2. Aims

1) To perform an overview to collate and appraise current evidence from systematic reviews examining the risk of air pollution and unscheduled healthcare resource utilisation (HRU) for acute respiratory events in children.
    a. Specifically, the impact of ambient levels of particulate and gaseous pollutants on the risk of hospitalisation for asthma exacerbations, pneumonia, bronchiolitis, acute lower respiratory infection, bronchitis, acute wheeze, croup, influenza, and pertussis will be examined.

3.3 Methods

The protocol for this was published a priori in PROSPERO, see appendix 4.

3.3.1 Inclusion and exclusion criteria

Systematic reviews were included if analysed observational studies, that had evaluated the impact of air pollution levels, PM2.5, PM10, NO_2, O_3, SO_2 and/or CO, on unscheduled HRU for acute respiratory events in children and adolescence, under the age of 20 years. The pre-specified primary outcome was the risk of unscheduled HRU defined as a composite of outcomes of acute hospitalisation and/or emergency department (ED) visits. Secondary outcomes will be analysed in included systematic reviews, looking at the risk of critical care admission, unscheduled primary care visits and mortality.

Air pollution exposure analysed at any time period (lag) before unscheduled HRU, and subsequently categorised results in short-term (less than seven days) or lifetime exposure (average daily from birth to hospitalisation). No primary pollutant of interest was specified out of PM2.5, PM10, NO_2, SO_2, CO and O_3 as each may contribute differently to illnesses to varying degrees.

Systematic reviews were excluded if they were narrative reviews, did not analyse the specific ambient air pollutants and commented generally on outdoor pollution levels, or had solely meta-analysed studies without a systematic review.

3.3.2 Identification of relevant systematic reviews

Relevant reviews were identified via an array of electronic databases in order to optimise the chances of locating eligible reviews. The specific databases Medline, Embase (via OVID), Database of Abstracts of Reviews of Effects (DARE), and Cochrane Database of Systematic Reviews (CDSR) (via the Cochrane Library) were searched until January 2018. Medline is the same as reported in chapter two. With the database Embase, it is a biomedical database

that has coverage of articles since 1947 [339]. DARE uses a comprehensive search strategy to capture reviews including unpublished work, and is a complement system to CDSR as identifies studies not carried out via the Cochrane Collaboration, however, it has not been updated since 31st March 2015 [340]. The database CDSR is a leading source of information for systematic reviews in healthcare and includes Cochrane reviews and protocols, with coverage since 2003 [341].

3.3.3 Search Strategy

The search strategy applied for the databases was constructed around relevant search terms for acute respiratory events; “respiratory infection”, “asthma”, “pneumonia”, “bronchiolitis”, “acute lower respiratory infection”, “bronchitis”, “acute wheeze”, “croup”, “influenza” and “pertussis”. Synonyms, MeSH terms and the use of truncation was used to increase the likelihood of identifying systematic reviews, similar to the search technique described in chapter two. The respiratory search terms were joined using the Boolean operator term OR, and then combined with other key words for “child”, “air pollution”, and “systematic review”. The full search strategy is shown in appendix 5.

3.3.4 Identification of eligible studies

Eligible studies were identified by two independent investigators (CK and IS) who executed the initial screening of the titles and abstracts. Included screened abstracts then had their full text examined for eligibility, with the quality of eligible systematic reviews evaluated by the two reviewers (CK and IS) as well.

3.3.5 Data extraction

From the included systematic reviewers, one reviewer (CK) extracted the predefined review characteristics into a table. These included:

- Respiratory outcome

- Time period of exposure
- Pollutant measured (and if average concentrations mentioned or supplied)
- Effect size (relative risk or percentage increase)

Effect size refers to the risk per unit of increase for each pollutant of the outcome occurring, stated as either relative risk or percentage increase. For PM2.5, PM10, NO_2, SO_2 and O_3 the unit increase is per 10 $\mu g/m^3$, and for CO a unit increase is per 1 mg/m^3.

From systematic reviews with meta-analysis, we extracted pooled effect estimates with 95% confidence interval, and I^2 measures of between-study heterogeneity.

3.3.6 Quality assessment of studies

Eligible systematic reviews were assessed using AMSTAR-2 criteria, which assesses the methodological quality of the systematic reviews using a 16-item tool [342] which enables ranking of the confidence in the results of individual reviews as high (zero or one non-critical weakness), moderate (one or more non critical weakness but no critical flaw that would affect the confidence in the quality of results), or low/critically low grade (at least one critical flaw that may reduce the validity of the results).

In order to fully evaluate the quality of the evidence we evaluated risk of bias in individual studies using the following criteria:

3.3.6.1 Selection bias and additional quality criteria

Studies were considered to be of low risk of selection bias if the study sample included consecutive cases of hospitalisations and/or emergency visits for acute respiratory events, and if these were identified from healthcare records. We also considered studies to be of higher quality if the case definition of the acute respiratory event was based on International Classification of Disease Criteria (ICD 9 or 10) [300, 343].

3.3.6.2 Assessment of Exposure

Within each individual study, we evaluated the methodology with which the individual air pollutants were measured, the frequency of monitoring, technique of data collection and the proximity of monitoring stations to the participants or hospitals. Studies were considered to be of higher quality if pollutants were measured daily, using standardised techniques, and monitors were within 20 kilometres of the hospitals or residences of included participants.

3.3.6.3 Adjustment for confounding variables

Confounding variables were examined in each study such as meteorological confounders, socioeconomic status, environmental confounders and other clinical risk factors. Studies were considered to be of low risk of bias if two or more types of confounders were accounted for when results were adjusted.

In addition, systematic reviews were graded along with the included individual studies to form a judgement regarding the overall quality of the reviews. The grade of evidence around the association between each pollutant and the risk of unscheduled HRU for each disease was classes as high quality, if both the systematic review and included studies had high methodological quality and a high AMSTAR-2 score, moderate quality, if there was a flaw in the systematic review or if the included studies were of moderate methodological quality, or low quality, if there was a critical flaw in the systematic review according to the AMSTAR-2 criteria or had low methodological quality of the included studies.

3.3.7 Data Analysis

Systematic reviews were reported descriptively for each respiratory disease due to the variation in methodology undertaken in the reviews.

3.4 Results

3.4.1 Results of search

The search yielded 1331 possible eligible articles once duplicates had been removed. Of these 1269 records were excluded through screening of titles and abstract. The remaining 60 records had full text reports retrieved and 50 were subsequently excluded, see appendix 6 for reasons of exclusion. The systematic review from the previous chapter was included for analysis. Thus, eleven systematic reviews were then eligible for inclusion, the review flowchart is shown in figure 11.

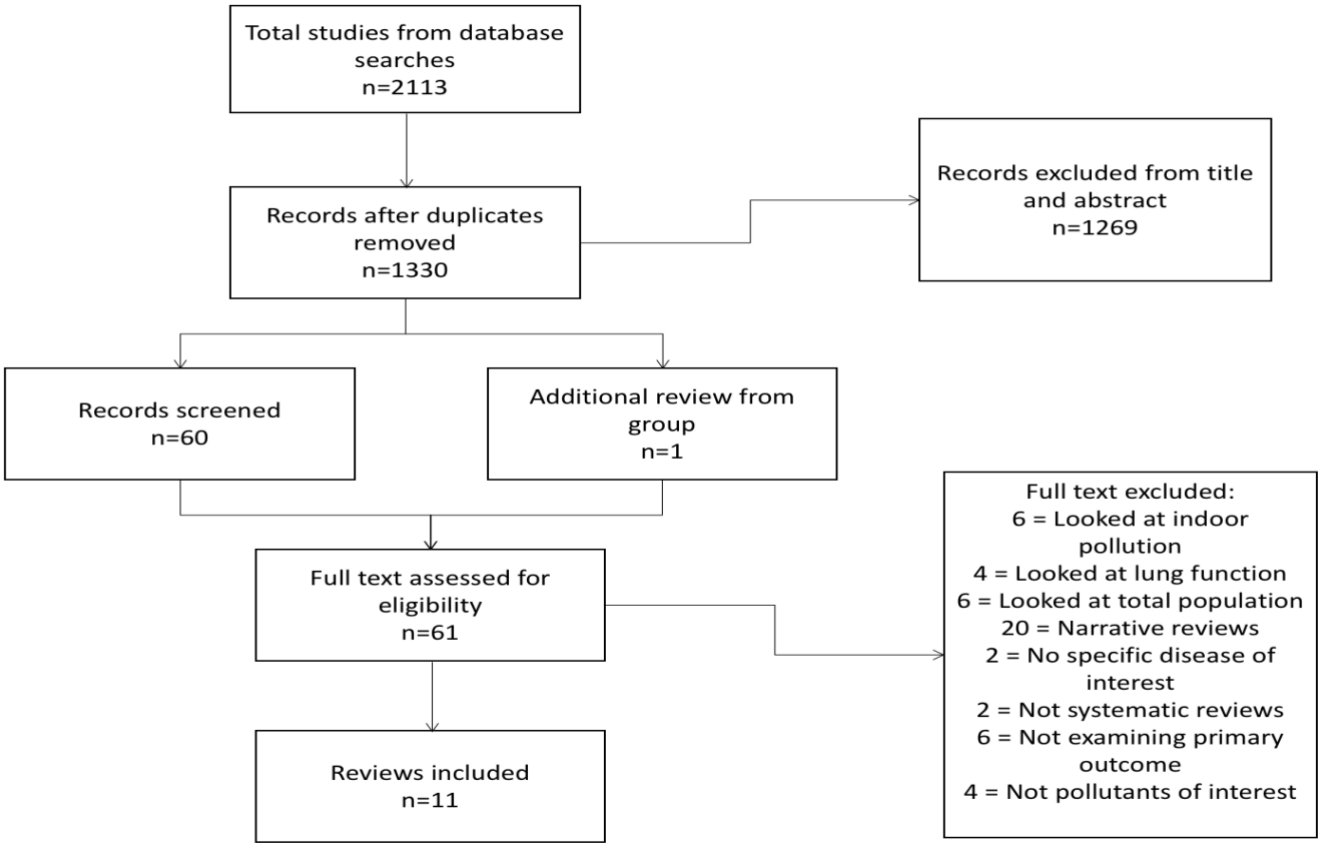


Figure 11. Review flowchart of included systematic reviews in overview examining acute respiratory events and ambient air pollution

No reviews were found that examined the other respiratory diseases; acute lower respiratory infection, bronchitis, acute wheeze, croup, influenza and pertussis.

3.4.2 Description of included studies

Of the eleven included reviews, ten had conducted meta-analysis on the included individual studies. Unscheduled HRU was reported in all eleven systematic reviews [344-354]. These were defined as hospital admission in five reviews [344, 346, 347, 349, 350], ED visits in one review [345],and a composite of both outcomes in four reviews [351-354]. Nine systematic reviews examined asthma exacerbations related to HRU, one examined risk of HRU with pneumonia, and one examined the risk of HRU with bronchiolitis.

Eight reviews included individual studies from high income countries such as United States of America, Canada and Western Europe [344-350, 352, 353]. Six reviews had at least one study from a low or middle-income country in Asia, South America or Eastern Europe [344-347, 350, 353]. No reviews analysed studies from Africa. Two of the eligible reviews did not state locations of individual studies.

Only the systematic review relating to bronchiolitis considered long-term exposure of air pollutants [347]. The other ten reviews assessed only short-term exposure up to a maximum of seven days of air pollutants and unscheduled HRU.

The characteristics of the included studies are summarised in table 9.

Table 9. Characteristics of included systematic reviews

Author (reference)	Databases searched (end date)	No. of studies	No. of participants	Countries analysed in systematic Reviews (continents)	Study designs included	Pollutant(s) measured	Respiratory disease(s) analysed	Outcome(s) measured
Romeo [352]	Pubmed (2003)	33 (16 for asthma hospitalisations)	n/a	n/a (Europe and other including America)	Time series studies and panel studies	PM10	Asthma	Hospital admission or emergency room visits
Koranteng [348]	Pubmed, Medline, Embase (December 2004)	13 (7 studies for asthma, 2 for respiratory illness)	n/a	Canada	Time series and Case Crossover Studies	PM2.5, PM10, O_3, NO_2, SO_2, CO	Asthma and Respiratory Illness (definition stated)	Hospital admission or Emergency Department. Visit
Meng Ji [346]	Pubmed (2008)	96 (29 studies for children)	n/a (children 0-14 years)	n/a (North America, Europe and some Asian cities)	Time series and Case Crossover Studies	Ozone	Asthma and Respiratory Illness (definition stated)	Hospital admission and ED visit
Ding [344]	Pubmed, EBSCO, Ovid, China Biomedical Literature, Wei Pu Chinese Science Technology Database, Wang Fang Database, CNKI (China National Knowledge Infrastructure) (December 2013)	18	n/a (children from 0-18 years)	Denmark, UK, USA, Brazil, South Korea, Greece, Northern Ireland, Canada, Italy, Turkey, China	Time series and Case Crossover Studies	PM2.5, PM10	Asthma	Hospital admission

Zhang [353]	Pubmed, Web of Science (December 2014)	26 (8 studies for children)	n/a (children aged 0-14yrs)	China, Hong Kong, Taiwan, Japan, Korea	Time series and Case Crossover Studies	PM2.5, PM10, O_3, NO_2, SO_2, CO	Asthma	Hospital utilization (all types, general admissions, emergency admissions)
Fan [345]	Embase, Pubmed, Cochrane Library, Web of Science, China Biomedical Literature Database (January 2015)	16 (7 papers specifically for children)	777,563 asthma ED visits for whole population (children <18 years old)	USA, Canada, Finland, Taiwan	Peer reviewed studies - did not specify a design	PM2.5	Asthma	Emergency Department Visits
Zheng [354]	Embase, Pubmed, Cochrane Central Register of Controlled Trials and EMB reviews, Cochrane Database of Systematic Reviews, Web of Science, Ovid, Highwire (March 2015)	87 studies (50 studies for children)	n/a	n/a	Time series and Case Crossover Studies	PM2.5, PM10, O_3, NO_2, SO_2, CO	Asthma	Hospital admission and ED visit
Lim [349]	Pubmed, Embase (March 2016)	26	n/a (children from 0-20 years)	n/a (Europe and North America)	Time series and Case Crossover Studies	PM2.5	Asthma	Hospital admission or emergency department visits
Orellano [351]	Pubmed, SCOPUS, Google Scholar (October 2016)	22 (19 studies for children)	267,413 asthma visits for whole population	n/a	Case crossover design	PM2.5, PM10, O_3, NO_2, SO_2, CO	Asthma	Hospital admission or emergency department visits

Nhung [350]	Pubmed, Web of Science (January 2017)	17	425,000 pneumonia cases	United States, Brazil, Chile, New Zealand and Australia, Italy, Spain, China	Time series and Case Crossover Studies	PM2.5, PM10, O_3, NO_2, SO_2, CO	Pneumonia	Hospitalisations (hospital admissions and ED visits combined)
King [347]	Medline, SCOPUS, Web of Science (November 2017)	8	116,609 (children aged 0-2years	North America, France, Malaysia	Cohort, Time series, Case crossover and Case control studies	PM2.5, PM10, O_3, NO_2, SO_2, CO	Bronchiolitis	Hospital admission

Legend

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm, NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone
n/a : no data available

3.4.3 Quality assessment of included studies

Of the eleven systematic reviews, according to the AMSTAR-2 criteria there was one review rated as high quality [351], five as moderate quality [344, 345, 347, 350, 354], two as low quality [346, 353], and three as critically low quality [348, 349, 352]. The majority of critical flaws reflected the assessment of risk of bias in individual studies and failing to reflect this in the subsequent meta-analysis, table 10 shows the AMSTAR-2 criteria.

Table 10. AMSTAR-2 results for systematic reviews included in overview

	Romeo 2006 [352]	Koranteng 2017 [348]	Meng Ji 2011 [346]	Ding 2015 [344]	Zhang 2016 [353]	Fan 2015 [345]	Zheng 2016 [354]	Lim 2016 [349]	Orellano 2017 [351]	Nhung 2017 [350]	King 2018 [347]
Were components of PICO included in the review?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was an a priori design (protocol) provided?	No	No	No	Partial Yes	No	No	No	No	Yes	No	Yes
Was an explanation for study design selection included?	No	No	No	No	No	No	No	No	No	No	Yes
Was a comprehensive literature search performed?	No	Yes	No	Yes	Partial yes	Yes	Partial yes	Partial yes	Partial yes	Partial yes	Partial Yes
Was study selection performed in duplicate?	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Was data extraction performed in duplicate?	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

Was a list of excluded studies provided and justified?	No	No	Partial yes	Partial Yes	Partial yes	Partial yes	Partial yes	Partial yes	Partial yes	Partial yes	Yes
Were the characteristics of the included studies provided?	No	Partial yes	Partial yes	Yes	Yes	Partial yes	Yes	Yes	Partial yes	Partial yes	Partial Yes
Was risk of bias assessed in individual studies?	No	No	No	No	No	Yes	Yes	No	Yes	Partial yes	Yes
Were sources of funding for studies included?	No	No	No	Yes	No	Yes	No	No	No	No	No
For meta-analysis: were appropriate methods used for statistical combination?	Yes	No meta-analysis conducted	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
For meta-analysis: was the impact of risk of bias in individual studies on the results assessed?	No	No meta-analysis conducted	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Did the authors account for risk of bias when discussing results?	No	No	No	Yes	No	No	Yes	No	Yes	Yes	Yes
Did the authors provide explanation for any heterogeneity observed?	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No

Was the likelihood of publication bias assessed?	Yes	No meta-analysis conducted	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Was a conflict of interest included?	Yes	No	No	No	No	Yes	No	Yes	No	Yes	Yes
Rating overall confidence in results	Critically Low	Low	Low	Moderate	Low	Low	Moderate	Critically Low	Moderate	Moderate	Moderate
	Critical flaw - no risk of bias assessment	Critical flaw - no risk of bias assessment	Critical flaw - risk of bias in studies		Critical flaw - risk of bias in studies	Critical flaw - risk of bias when meta-analyse		Critical flaw - risk of bias and heterogeneity			

From each of the included systematic reviews, CK extracted the individual study name to assess for potential overlap and risk of bias from the individual studies, due to a large proportion of systematic reviews not commentating on risk of bias. There were 203 individual included studies between all the included reviews before de-duplication, after exclusion of duplicates 119 studies remained. Within this, 94 studies evaluated HRU for asthma exacerbations, with 15 were considered to have high risk of bias. Of the 17 studies evaluating HRU for pneumonia, one was considered to be at high risk of bias. Lastly of the eight studies examining HRU for bronchiolitis, two were considered to be at high risk of bias. See appendix 7 for assessment of included individual studies and risk of bias. Specific outcomes from each individual study was not extracted, rather the meta-analysis performed by the included systematic reviews was used to assess association between air pollution and HRU, this is due to the low proportion of high risk of bias individual studies for each disease.

The overall GRADE summary for association between each pollutant and the risk of unscheduled HRU is shown in Table 11.

Table 11. GRADE assessment of systematic reviews for each pollutant

Pollutant	Disease	Quality of review	Quality of included studies	Number of studies	Overall grade	Conclusion
PM2.5	Asthma	Moderate	Low-Moderate	46	Moderate	Appears to increase risk of HRU
PM10	Asthma	Moderate	Moderate	43	Moderate	Appears to increase risk of HRU
NO_2	Asthma	Moderate-High	Moderate	55	Moderate	Appears to increase risk of HRU
O_3	Asthma	Low-Moderate	Moderate	70	Moderate	Appears to increase risk of HRU
SO_2	Asthma	Moderate-High	Moderate	48	Moderate	Appears to increase risk of HRU
CO	Asthma	Moderate	Moderate	31	Moderate	Appears to increase risk of HRU
PM2.5	Pneumonia	Moderate	Low- moderate	13	Moderate	Appears to increase risk of HRU: OR 1.02 (1.01, 1.03)
PM10	Pneumonia	Moderate	Low-moderate	13	Moderate	Appears to increase risk of HRU: 1.02 (1.01,1.02)
NO_2	Pneumonia	Moderate	Low-moderate	12	Moderate	May or may not increase risk of HRU 1.01 (1.00,1.02)
O_3	Pneumonia	Moderate	Low-moderate	16	Moderate	Appears to increase risk of HRU: 1.02 (1.01, 1.03)
SO_2	Pneumonia	Moderate	Low-moderate	10	Moderate	May or may not increase risk of HRU: 1.03 (1.00, 1.05)
CO	Pneumonia	Moderate	Low-moderate	7	Moderate	May or may not increase risk of HRU 1.01 (1.00, 1.02)

PM2.5	Bronchiolitis	Moderate	Moderate	3	Moderate	Does not seem to affect risk of HRU
PM10	Bronchiolitis	Moderate	Moderate	1	Moderate	Unclear effect on risk of HRU
NO_2	Bronchiolitis	Moderate	Moderate	4	Moderate	Unclear effect on risk of HRU
O_3	Bronchiolitis	Moderate	N/A	0	N/A	No assessment can be made
SO_2	Bronchiolitis	Moderate	Moderate	1	Moderate	Unclear effect on risk of HRU
CO	Bronchiolitis	Moderate	Moderate-High	2	Low	Does not seem to affect risk of HRI

Legend

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm, NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone

3.4.3 Primary outcome

The results of the eleven systematic reviews are shown in table 12 and presented in figure 12 for risk of asthma hospitalisations and figure 13 for pneumonia hospitalisations.

Table 12. Results from overview for each disease and acute exposure to pollutants

	Pollutant	**Review (number of studies)**	**Effect size (relative risk)**	**Heterogeneity if I^2 performed in systematic review**
Asthma Hospitalisation (Either combination, hospital admission or ER visit)	PM2.5	Zheng (20)	1.025 (1.013,1.037)	82%
		Zhang (4)	1.022 (1.019, 1.026)	n/r
		Orellano (14)	1.022 (1.000, 1.045)	n/r
		Lim (10)	1.048 (1.029,1.067)	77.70%
		Ding (10)	1.0345 (1.0099,1.3358)	70%
		Fan (7)	1.036 (1.018,1.053)	n/r
	PM10	Zheng (25)	1.013 (1.008,1.018)	83%
		Zhang (5)	1.021 (1.017, 1.024)	n/r
		Romeo (16)	1.017 (1.008,1.025)	43%
		Ding (16)	1.0175 (1.0102,1.0249)	62%
	NO_2	Zheng (39)	1.018 (1.013,1.023)	87%
		Zhang (6)	1.035 (1.025, 1.046)	n/r
		Orellano (12)	1.040 (1.001, 1.081)	n/r
	O_3	Zheng (42)	1.008 (1.005,1.012)	89%

		Zhang (7)	1.029 (1.022,1.037)	n/r
		Meng Ji (6)	-0.68 (-6.56,5.57) (percentage increase)	n/r
	SO_2	Zheng (37)	1.016 (1.011,1.022)	53%
		Zhang (4)	1.057 (1.008, 1.108)	n/r
		Orellano (10)	1.047 (1.009, 1.086)	n/r
	CO	Zheng (29)	1.018 (1.013,1.023)	70%
		Zhang (2)	1.141 (1.093, 1.191)	n/r
Pneumonia Hospitalisations	PM2.5	Nhung (13)	1.02 (1.01,1.03)	38.10%
	PM10	Nhung (13)	1.02 (1.01,1.02)	66.10%
	NO_2	Nhung (12)	1.01 (1.00,1.02)	71.10%
	O_3	Nhung (16)	1.02 (1.01,1.03)	75.20%
	SO_2	Nhung (10)	1.03 (1.00,1.05)	71.10%
	CO	Nhung (7)	1.01 (1.00,1.02)	68.10%

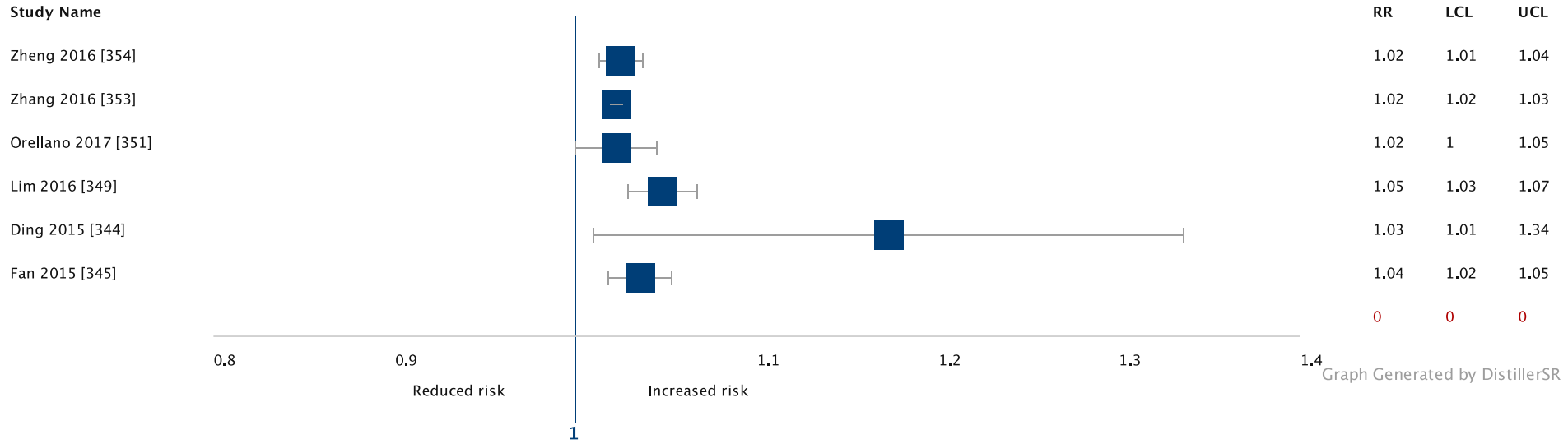
Legend

PM2.5: particulate matter diameter <2.5µm, PM10: particulate matter diameter <10µm, NO_2: nitrogen dioxide, SO_2: sulphur dioxide, CO: carbon monoxide, O_3: Ozone

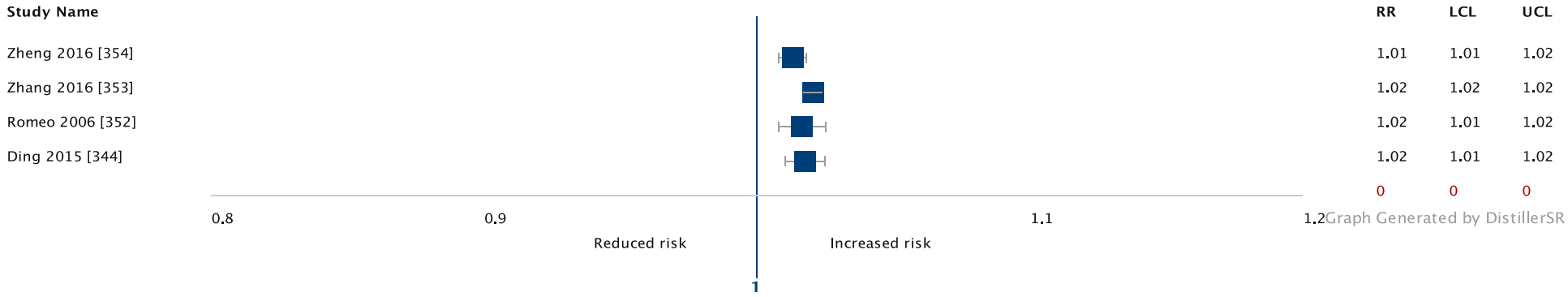
n/r: no data reported

Effect size refers to increase in PM2.5, PM10, NO_2, SO_2 and O_3 with a unit increase of 10 µg/m^3, and for CO a unit increase of 1 mg/m^3

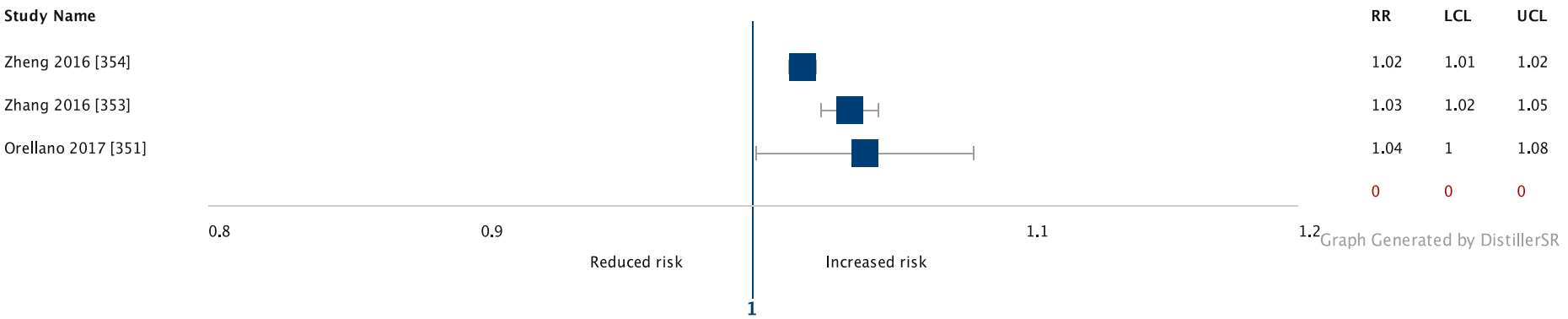
A) **Risk of asthma hospitalisation due to acute exposure to PM2.5**



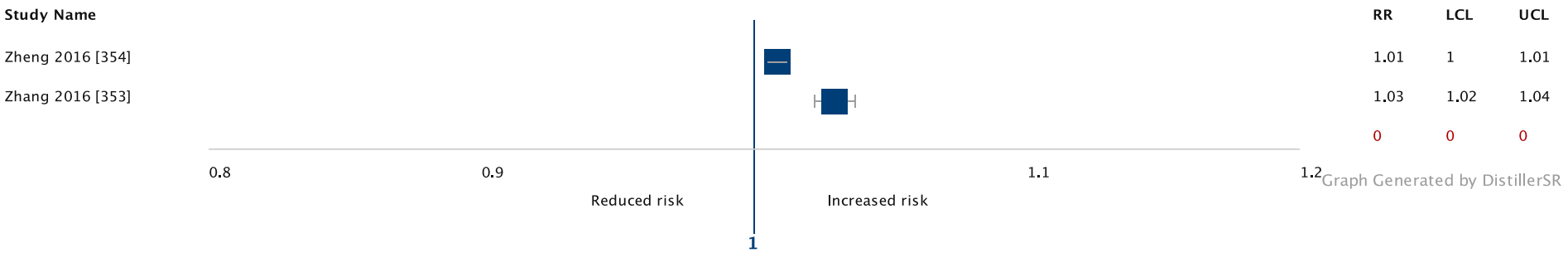
B) **Risk of asthma hospitalisation due to acute exposure to PM10**



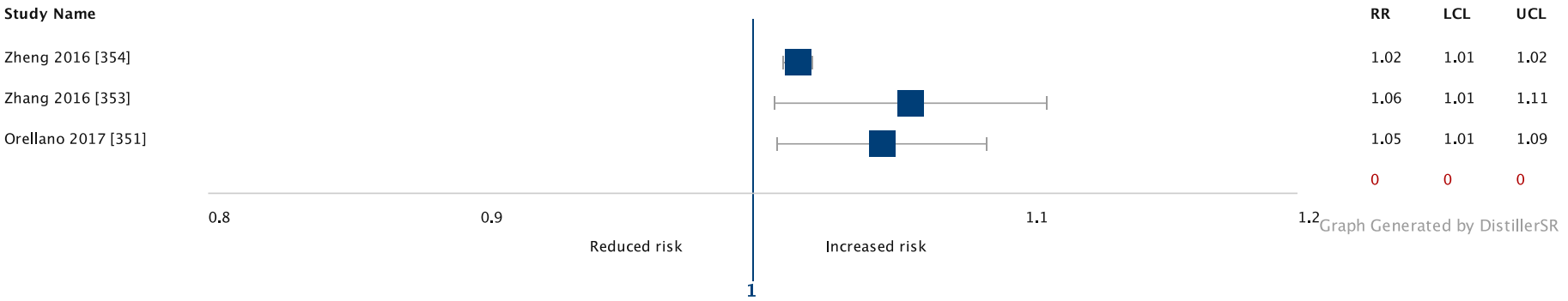
C) **Risk of asthma hospitalisation due to acute exposure to NO2**



D) **Risk of asthma hospitalisation due to acute exposure to O3**



E) **Risk of asthma hospitalisation due to acute exposure to SO2**



F) **Risk of asthma hospitalisation due to acute exposure to CO**

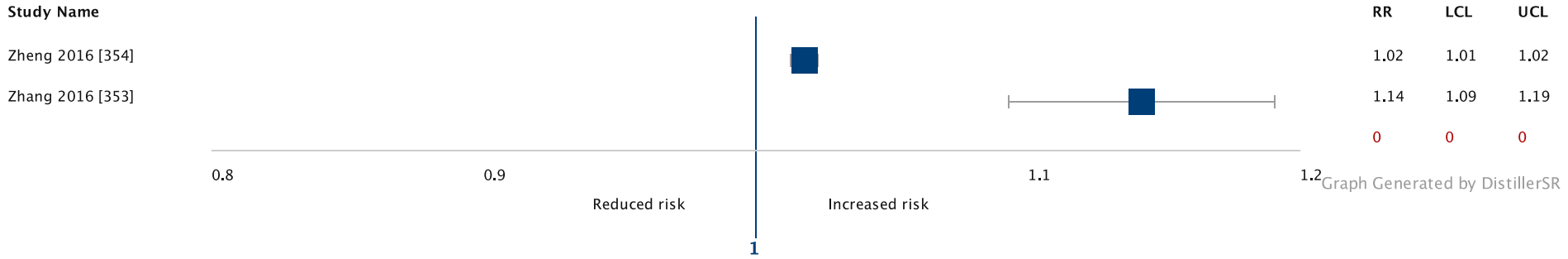


Figure 12. Forest plots of risk of asthma exacerbation needing HRU admission and acute exposure to pollutants

A) PM2.5 exposure
B) PM10 exposure
C) NO2 exposure
D) O3 exposure
E) SO2 exposure
F) CO exposure

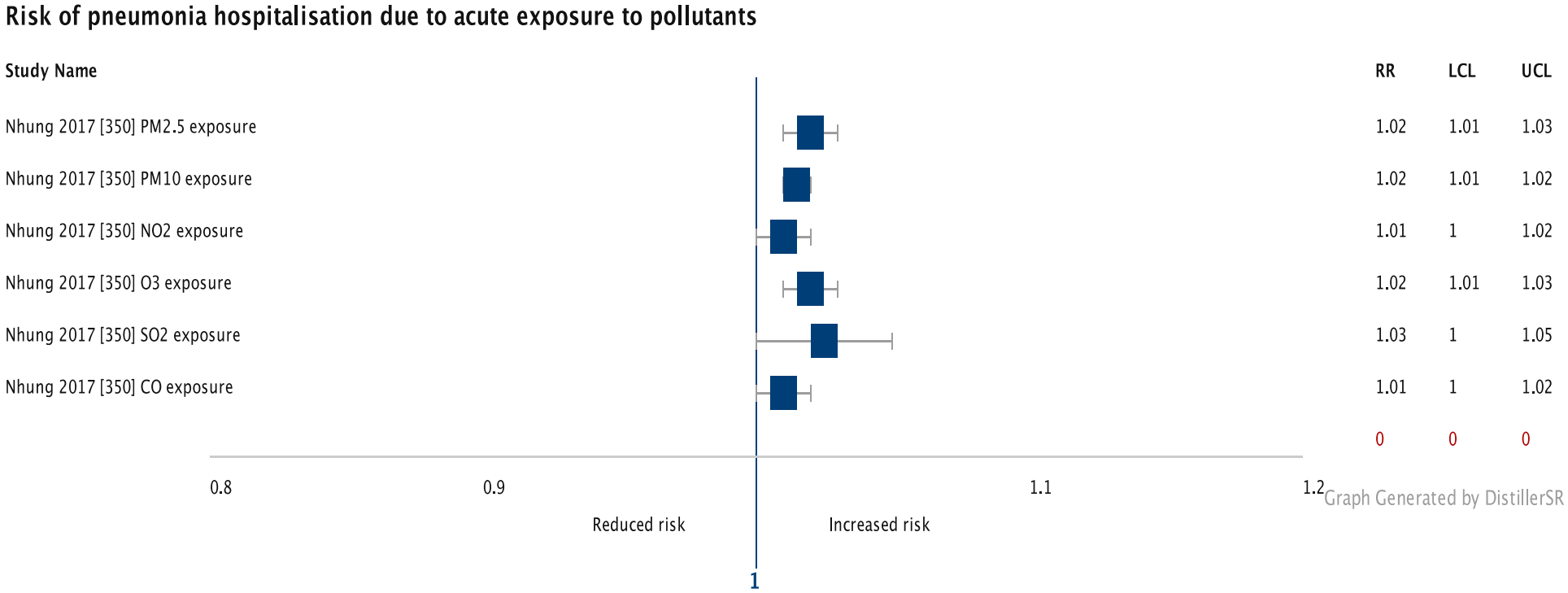


Figure 13. Forest plot of risk of pneumonia needing HRU admission and acute exposure to pollutants

Nine systematic reviews examined the effects of ambient air pollution on risk of hospitalisation with an asthma exacerbation [344-346, 348, 349, 351-354]. Of those, eight meta-analysed the results from individual studies [344-346, 349, 351-354].

Seven systematic reviews analysed the short-term effects of PM2.5 on risk of HRU for asthma exacerbation. Six reviews showed statistically significant association, with RR ranging from 1.022 (95% CI 1.019 to 1.026) [353] to 1.048 (95% CI 1.029,1.067) [349], and one review reported results of borderline statistical significance (RR 1.022, 95% CI 1.000,1.045) [351]. Five systematic reviews analysed the effects of PM10 on short-term risk of HRU for asthma exacerbations. A statistically significant association between exposure to PM10 and risk of HRU was found in all four reviews, with RR ranging from 1.013, (95% CI 1.008,1.018) [354] to (1.021, 95% CI 1.017,1.024) [353].

NO_2 was evaluated in four reviews, and of the three which presented meta-analysis data, all showed statistically significant association with unscheduled HRU for asthma. The effect size ranged from 1.018 (95% CI 1.013,1.023) [354] to 1.040 (95% CI 1.001,1.081) [351]. O_3 was examined in four reviews. Pooled estimates of association with unscheduled HRU for asthma showed statistical statistically significant results in two reviews, with RR ranging from 1.008 (95% CI 1.005,1.012) [354] to 1.029 (95% CI 1.022,1.037) [353]. No association was seen in one review that measured effect size using percentage increase (-0.68, CI -6.56,5.57) [346]. For SO_2, a positive association was seen in four reviews; with three analysing results. Effect size ranged from 1.016 (95% CI 1.011,1.022) [354] to 1.057 (95% CI 1.008,1.1.08) [353]. With CO three reviews examined the effects; two reviews showed statistically significant results ranging from 1.018 (95% CI 1.013, 1.023) [354] to 1.141 (95% CI 1.093,1.191) [353]. For each pollutant reviews demonstrated that there was significant heterogeneity between results of individual studies.

Risk of hospitalisation for pneumonia was associated with PM2.5 (1.02, CI 1.01,1.03), PM10 (1.02, CI 1.01,1.02), and O_3 (1.02, CI 1.01,1.03) in the single systematic review for this disease [350]. This systematic review covered a large cohort of children with pneumonia (425,000 cases). The heterogeneity in the meta-analysis was greater than 50% for all pollutants apart from PM2.5, which was 38.10%.

Bronchiolitis was examined in one systematic review and descriptively reported on [347]. The systematic review assessed both short-term exposure to pollutants and long-term exposure (greater than seven days) with varying results for all pollutants. Exposure to PM2.5, NO_2 and SO_2 all demonstrated statistically significant results for both short-term exposure and long-term exposure [347] and risk of unscheduled HRU.

3.4.4 Secondary outcomes

None of our pre-specified secondary outcomes (risk of critical care admission, unscheduled primary care visits, and mortality) were reported in the included systematic reviews.

Furthermore, no systematic reviews remarked on concentration levels of the ambient air pollutants in relation to outcomes and WHO concentrations guidelines.

3.5 Discussion

This is the first overview of systematic reviews evaluating the effect of ambient air pollution on the risk of unscheduled HRU with respiratory illness in children. On the basis of moderate quality evidence, risk of unscheduled HRU with asthma was increased in all prespecified pollutants (PM2.5, PM10, NO_2, O_3, SO_2 and CO), while for pneumonia only PM2.5, PM10, and O_3 were associated with an increase in risk. The evidence was not clear for bronchiolitis. There were no systematic reviews found for either the other common acute respiratory diseases of childhood (acute lower respiratory infection, bronchitis, acute wheeze, croup, influenza and pertussis) or the secondary outcomes, risk of critical care admission or length of stay.

Children are known to be an at-risk population with regards to air pollution [355-358], and an exposure – response relationship was seen in several studies. Although the relative risks produced from the meta-analysis are small, the results are derived from large cohorts of cases, covering a range of ethnicities and socioeconomic statuses [345, 350]. Acute

respiratory diseases in children are common and a major burden of disease [359], therefore the impact of air pollution on unscheduled HRU is likely to be high.

A paucity of evidence regarding the long-term effects of ambient air pollution, or secondary outcomes such as critical care admission was also identified. Studies were concentrated in high income countries, with none undertaken in Africa. This may be due to the lack of monitoring stations available in developing countries, with the majority of monitors usually in urban areas. This disproportionate balance should be rectified as it is known that children in poorer and developing settings are at greater risk to harmful effects of pollution. To address the needs of low and middle-income countries, a broader range of locations should be included in future studies to reduce worldwide health inequalities [321].

This overview was conducted according to a pre-specified protocol, using robust methodology. A comprehensive search strategy was utilised to capture all relevant systematic reviews that matched the eligibility criteria, and only reviews with standard definitions of disease were included to reduce subjectivity. We also conducted a rigorous process to grade the validity of the results, which is an important factor when presenting evidence and using findings of this overview to make decisions about air pollution and childhood respiratory health.

The main limitations relate to a lack of standardisation in methodological reporting of air pollution measurement. Ambient air pollution was measured in a variety of ways including personal exposure, up to average levels for an entire city. The varied methodologies may affect the accuracy of exposure within individuals. However, we are reassured by the generalised agreement between studies, with similar effect sizes noted, regardless of methodology used. Standardisation of data collection methodology would help future study meta-analysis. In addition, consensus around which confounding factors to account for, and a core outcome set [315, 316] for epidemiological studies in air pollution would help improve data quality.

3.6 Conclusion

Increased concentrations of all types of air pollution correlate with unscheduled HRU for children with acute respiratory illnesses, but there are considerable gaps in the evidence. Reductions in ambient air pollution are likely to produce significant respiratory health benefits in children. The results in this chapter efficiently describes the current evidence available examining ambient air pollution, thus other variables such as genetics need to be assessed.

Chapter 4 – Pharmacogenomic associations of adverse drug reactions in asthma: systematic review and research prioritization

4.1 Background

Another variable that can contribute to the burden of respiratory disease on healthcare resources is the role that genetics plays in relation to medication. It is known that genetics is a risk factor for incidence of respiratory diseases, particularly asthma in childhood. However, since the human genome project the area of pharmacogenomics has gained momentum. This discipline may help to explain the variation seen in patients using the same medication, such as with anti-asthmatic medication.

Asthma is a common chronic condition, affecting over 230 million people worldwide [360-362]. The management for asthma is guided by national and international evidence based guidelines [363, 364], but there is inter-individual variability in treatment response. This variation may be related to several factors, including adherence, disease subtype and severity, and environmental factors. In addition, a patient's genotype can affect outcomes of treatment in asthma [365-367]. The data from these pharmacogenomic studies of asthma medication efficacy in children have progressed to the point where there are now polymorphisms approaching clinical utility [368].

However, the overall effectiveness of a medicine is a balance between the intended benefits and the potential risks. ADRs in asthma patients need to be considered alongside the efficacy already assessed in these classes of drugs. Asthma medication accounts for a large proportion of respiratory medicine prescribed in childhood. The medications used in asthma have a well described set of ADRs associated with their use (Table 13) [369].

Table 13. List of ADR's of asthma medication from the BNFC [366]

Short Acting ß2 Agonist	Long Acting ß2 Agonist	Corticosteroids	Leukotriene antagonist	Theophylline
Arrhythmias	Arrhythmias	Adrenal crisis	Abdominal Pain	Arrhythmias
Fine tremor	Arthralgia	Adrenal suppression	Abnormal dreams	CNS stimulation
Headache	Fine tremor	Aggression/ behavioral changes	Aggressive behavior	Convulsions
Hyperglycemia	Headache	Candidiasis	Agitation/ Anxiety	Diarrhea
Hypersensitivity reactions	Hyperglycemia	Cushing's syndrome	Dizziness	Gastric irritation
Hypokalemia	Hypersensitivity reactions	Hyperglycemia	Hallucinations	Headache
Lactic acidosis	Hypokalemia	Hypertension	Headache	Hypokalemia
Muscle cramps	Muscle cramps	Reduced growth velocity	Hyperkinesia	Hypotension
Nausea	Nausea	Reduced mineral bone density	Sleep disturbances	Nausea and vomiting
Rash	Rash		Thirst	Tachycardia
Sleep/ behavior disturbance	Sleep/ behavior disturbance			
Tachycardia	Tachycardia			

In adult patients, ADRs are responsible for 6.5% of all admissions, while 14.7% of adult inpatients experience an ADR [370, 371]. For pediatrics, 3% of all admissions are related to ADRs [372], while over 17% of all pediatric inpatients experience one or more ADR [373]. For asthmatic patients, ADR's represent a significant burden, reducing their quality of life, and extract an economic cost on healthcare systems worldwide [374, 375].

There is also inter-individual variability in the type and severity of ADR experienced by patients. Factors such as adherence, and disease subtype influence this, but genomic factors

are also important [376], with several genetic polymorphisms associated with severe ADRs identified [377, 378]. Regulatory information to guide prescribers has been updated to reflect these findings [379].

While the effect size in pharmacogenomic studies is often larger than that seen in genetic epidemiology studies [380], large cohorts are still required, and replication of findings is essential if findings are to be adopted into clinical practice [381]. International consortia, utilizing the data from multiple groups, have been developed to facilitate this process [382]. Within asthma, the pharmacogenomics in childhood asthma (PiCA) consortia is well established, containing multiple cohorts from studies around the world [383].

This chapter describes a pilot review undertaken in pharmacogenomics that examines ADR's in asthma medications. It also includes a survey undertaken amongst members of the PiCA consortia to identify priorities in pharmacogenomic studies relating to ADRs.

4.2 Aims

1) To undertake a systematic review of pharmacogenomic studies of ADRs related to asthma medication across the entire population.
2) To complete a survey establishing the current prioritization of ADRs within asthma pharmacogenomic research, and to determine future research priorities.

4.3 Methods

4.3.1 Inclusion and exclusion of studies

Studies were eligible for inclusion if they were either randomized control trials (RCTs) or observational studies, such as cohort studies. The studies had to undertake genome analysis, with the researchers examining a known asthma treatment medication and if they stated ADRs. If ADRs had been stated as either the primary or secondary outcome the

studies were included. An ADR was classified according to the WHO definition [384]. Studies had to state the specific ADRs related to asthma medication.

Studies were excluded if ADRs were stated to be seen but no report was produced with data. Studies that commented asthma exacerbations as ADRs were excluded as are deemed to be classified as a failure of medication efficacy, thus an adverse event, rather than an ADR.

4.3.2 Identification of studies and search strategy

Electronic databases were searched to identify eligible studies. These online databases included Medline and Embase previously described in chapters two and three, as well as cumulative index of nursing and allied health literature (CINAHL). CINAHL is a database of around 3000 journals, books, articles, conference proceedings and abstracts related to research in nursing, biomedicine, and the allied health professions. Coverage has been from 1981. The databases were searched until January 2018 to locate eligible studies.

The search terms used included “asthma”, “pharmacogenomics”, and “asthma medication”, see appendix 8 for search strategy. A list of asthma medication based on drugs extracted from the British National Formulary for Children (BNFC) with both generic and brand names included was used. Synonyms and truncations were used based on previous strategies applied. Each search term within the groups were combined using the Boolean operator OR with the groups then combined using the operator AND.

References of included studies were analysed to locate any relevant studies of interest. Comments from the survey regarding possible eligible studies was also considered.

No limit was placed on language, publication date or age of study population. Reviewer CK constructed the search strategy and undertook the relevant searches in each strategy.

4.3.3 Study selection

Studies were reviewed by two independent reviewers (CK and DH), who after removal of duplicates, screened titles and abstracts for inclusion. Full text was then analysed for eligibility with data extraction completed collectively by the two reviewers. Disagreements between the two reviewers was discussed and resolved mutually.

4.3.4. Data extraction and statistical analysis

From each study, data was extrapolated by reviewer CK into the predefined characteristics and results tables. These included:

- Drug examined, with both the class and generic name of the medication
- The ADR stated in the study
- Method of gene identification and the associated single nucleotide polymorphism (SNP) and gene
- Asthma severity
- Study design and characteristics of participants
- Effect of SNP in discovery cohort

From studies with replication cohorts, the effect estimate in this group of participants was extracted.

A qualitative analysis was conducted on the extracted data, with each asthma medication then individually reported.

4.3.5 Quality assessment

Methodological quality assessment was undertaken in the included studies using the Newcastle Ottawa quality assessment scale [385] for cohort and case-control studies, and the Cochrane Risk of Bias tool for randomised controlled trials (RCTs) [386].

The Newcastle Ottawa scale has been described in chapter two. The Cochrane risk of bias tool [387] is a standard method for evaluating the risk of bias in RCTs. The tool comprises of seven domains that aim to cover the fundamental areas of bias that may occur in RCTs. These domains are selection bias, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias that may be apparent. A judgement is then formed on a high, low or unclear risk of bias score for each of the domains.

These tools although do not cover all areas of bias allow for standardised comparisons to be developed between studies based on their methodological strength.

4.3.6 Survey

An online survey was undertaken of PiCA consortia members to establish if the review had identified all possible pharmacogenomic studies analysing ADRs and asthma medication. In addition, the survey aimed to collate responses regarding the importance of capturing ADRs in future studies, as well as identifying which ADRs survey members felt should be investigated in future studies as priorities.

The anonymous survey included ten questions with comments sections supplied for issues regarding the questions, these are shown below:

1) Member of PiCA consortia?
2) Name of institution
3) Do you think adverse drug reactions should be captured in pharmacogenomic studies of paediatric asthma?
4) To date how well have studies captured these adverse drug reactions?
5) What adverse drug reaction concerns you the most relating to beta-2 agonists?
6) What adverse drug reaction concerns you the most relating to inhaled corticosteroids?
7) What adverse drug reaction concerns you the most relating to leukotriene receptor antagonists?

8) What adverse drug reaction concerns you the most relating to theophylline?
9) For each class of drugs please give your top three ADR's you would wish to see captured in future studies.
10) Any other comments

The survey was open for two weeks with remainders sent to participants during the time period.

4.4 Results

4.4.1 Results of search

There were 1409 results after removal of duplicated generated from the search strategy, of these three were eligible for inclusion [267, 388, 389]. From the survey sent, two additional studies were discovered [390, 391]. The review flowchart is shown in figure 8.

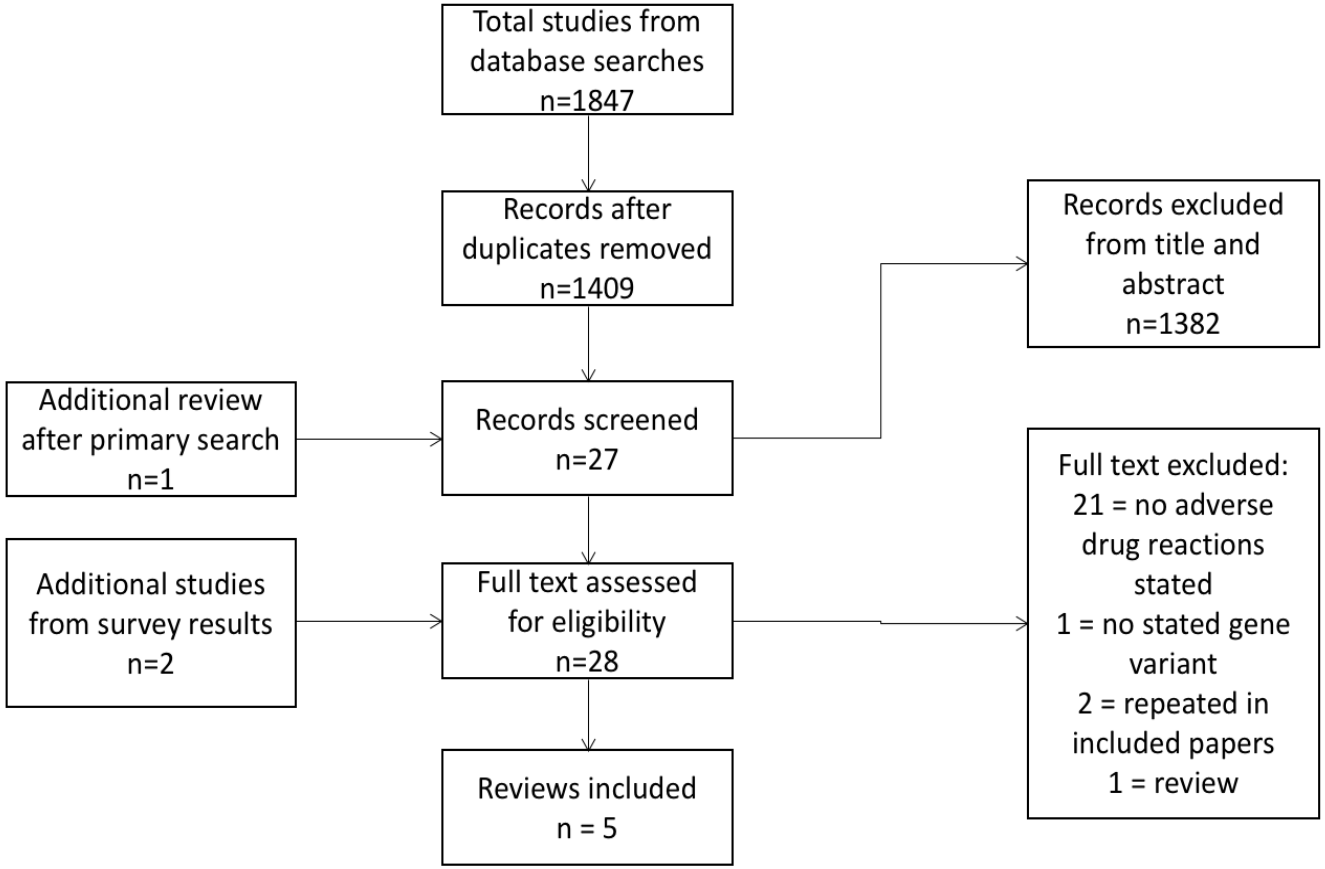


Figure 14. Review flowchart of studies included in systematic review of pharmacogenomics and ADRs in asthma medication

4.4.2 Description of included studies

There were few studies that reported ADRs specifically and as a primary outcome. Adverse events such as decreased efficacy or increased asthma exacerbations were reported in other papers not included. Within the eligible studies, a small proportion reported on ADR's as an end point of their studies.

In the included studies, four were randomized control trials [388-391], and one was a cohort study [267]. Two of the studies were undertaken in the United Kingdom with the other three having been carried out in the USA. The overall sample size of the studies was small, 1457 participants, with the largest proportion of participants being from a child population. The characteristics of the included studies are shown in Table 14.

Table 14. Characteristics of included studies.

RCT: Randomised controlled trial. GWAS: genome wide association study

Study	**Drug**	**Asthma Severity**	**Study Design and number of participants**	**Method of gene identification**	**Ethnicity (number recruited)**	**Age range recruited years (mean)**
Israel 2004 [388]	Inhaled SABA	Mild asthma	RCT, 78	Candidate gene	White (56), Black (15), Hispanic (6), Other (11)	18-55yrs
Tan 1997 [389]	Inhaled LABA	Moderately severe asthma	RCT, 22	Candidate gene	Not stated	No mean age given
Park 2015 [390]	Oral corticosteroids	Mild to moderate asthma	RCT, 489	GWAS	Caucasian	5-12yrs
Park 2017 [391]	Oral corticosteroids	Mild to moderate asthma	RCT, 461	GWAS	Caucasian	5-12yrs
Hawcutt 2018 [267]	Inhaled +/- Oral Corticosteroids	All severities	Cohort study, 407	GWAS	Caucasian	5-18 (11.6)

One study examined ADR's with inhaled short acting beta-2 agonists (SABA) [388], one analyzed long acting beta-2 agonists (LABA) [389], three studies examined the use of corticosteroids [267, 390, 391], and no studies examined either leukotriene receptor antagonists (LTA) or theophylline. For the SABA and LABA studies the candidate gene approach was applied [388, 389], whereas in the three corticosteroid studies genome wide association studies (GWAS) locating novel SNPs was used [267, 390, 391].

All included studies had a low risk of bias, the results are shown in appendix 9.

4.4.3 ADR's and asthma medication

When analyzing the genes identified in the studies, the candidate gene studies examined the same SNP, rs1042713, which is associated with the beta-2 adrenergic receptor gene (*ADRB2*). In contrast the platelet derived growth gene (*PDGFD*), the rap guanine nucleotide exchange factor 5 gene (*RAPGEF5*), the tubulin folding cofactor D (*TBCD*), and the tubulin gamma 1 gene (*TUBG1*) were all identified through GWAS. The ADR's associated with each SNP, and presence of replication, is shown in Table 15.

Table 15. Adverse drug reaction for each SNP in included studies

Drug	**Adverse Drug Reaction**	**Associated SNP & Gene**	**Effect of SNP in discovery cohort**	**Replication cohort (Y/N) and effect(s) (p-value)**
Inhaled Salbutamol [388]	Decrease in PEFR	rs1042713, *ADBR2*	23L/min improvement of PEFR on discontinuation of Albuterol in Arg16/Arg16 group (p=0.0162)	N
Inhaled Formoterol [389]	Desensitization to bronchodilator effects	rs1042713, *ADBR2*	Homozygous Gly16/Gly16 patients exhibited greater desensitization, measured using FEV_1, and FEF_{25-75}	N
Oral prednisone [390]	Decreased bone mineral accretion	rs9896933, *TBCD*	Decreased bone mineral accretion (p-value= $3.15x10^{-8}$ in GWAS)	N
Oral prednisone [390]	Decreased bone mineral accretion	rs2074439, *TUBG1*	Decreased bone mineral accretion (p-value= $2.74x10^{-4}$ in GWAS)	N
Oral prednisone [391]	Decrease in BMD-z score	rs6461639, *RAPGEF5*	One of top 100 SNPs but did not achieve genome wide significance	Y. Statistically significant decrease BMD-z score in pediatric ALL cohort (p=0.016)
Inhaled corticosteroids +/- additional corticosteroids [267]	Adrenal suppression (peak cortisol <350nmol/L)	rs591118, *PDGFD*	Increased risk of adrenal suppression (OR 7.32, 95% CI 3.15-16.99)	Increased risk of adrenal suppression in pediatric asthma cohort (OR 3.86, 95% CI 1.19–12.50) and adult COPD cohort (OR 2.41, 95% CI 1.10-5.28). Meta-analysis of all 3 cohorts achieved genome wide significance.

ALL: acute lymphoblastic leukaemia. FEV_1: forced expiratory volume in 1 second. FEF_{25-75}: forced expiratory flow at 25-75% of pulmonary volume. PEFR: Peak expiratory flow rate. BMD: Bone mineral density. GWAS: genome wide association study. COPD: Chronic Obstructive Pulmonary Disease. SNP: Single Nucleotide Polymorphism. CI: confidence interval

Regarding the ADR's in SABAs, one study [388], examining 78 adults found that if participants had the homozygous Arg16/Arg16 allele then the performance was lower when on albuterol compared to the placebo, with the peak expiratory flow rate being 23L/min better when albuterol was stopped. However, when this was replaced with ipratropium bromide, an anti-muscarinic, this group of participants had higher peak flow rates than when on albuterol or placebo.

For LABAs, one study [389], that had examined 22 adult participants found that participants with the homozygous Gly16/Gly16 genotypes their maximum FEV_1, maximum FEF_{25-75}, 6hr FEV_1 and 6h FEF_{25-75} was lower compared to the Arg16/Arg16 genotype when given formoterol.

With inhaled corticosteroids, one study [267], examining 407 children from the PASS (Pharmacogenetics of Adrenal Suppression with Inhaled Steroids) study aged 5-18 years found that the SNP rs591118, located at the *PDGFD* gene, was associated with a higher risk of adrenal suppression (odds ratio in the pediatric asthma replication cohort 3.86, 95% CI 1.19–12.50).

For oral corticosteroids, two studies [390, 391] examined children aged 5-12 years, from the CAMP (Childhood Asthma Management Program) trial, and the effect of prednisone on bone mineral density (BMD) z scores and bone mineral accretion (BMA). For decreases in BMD z scores one SNP was identified, rs6461639, and in the ALL (acute lymphoblastic leukemia) replication cohort it was significant (p-value=0.016)[391]. With the other study [390], two associated SNPs were found to worsen BMA with increased prednisone dosage, rs989633 and rs207439.

Internal replication was undertaken in two of the studies, both that examined corticosteroids [267, 391]. However, additional publications attempting external replication of these polymorphisms have not been identified.

4.4.4 Results from survey

There were 20 participants that undertook the survey, all members of the PiCA consortia, representing 15 institutes in eight countries. 95% identified ADRs as an area that should be captured in pharmacogenomic studies, and 80% of respondents agreed that only a small percentage of studies currently assessed this area. The survey respondents undertook a prioritization exercise to establish the ADRs for each asthma medication they believe should be subject to further pharmacogenomic research. The results of this prioritization exercise are shown in table 14 (ranked in order of highest priority to lowest). The most important ADR's by consensus for each drug class varies; for beta 2 agonists (SABA or LABA) it was tachycardia, corticosteroids it was both adrenal suppression/crisis and reduced growth, for leukotriene receptor antagonists it was sleep/behaviour disturbances, and for theophylline it was nausea and vomiting. Not all participants completed the survey for ADRs of each drug. For theophylline, 39% reported that the drug was no longer used in current treatment steps.

Table 16. ADR's from survey and number of people who prioritized each ADR ranked from highest

ß 2 agonists	**Corticosteroids**	**Leukotriene receptor antagonists**	**Theophylline**
Tachycardia (14)	Adrenal suppression crisis (11)	Sleep/behavior disturbances (12)	Nausea and vomiting (9)
Arrhythmias (9)	Reduced growth (11)	Headache (7)	Arrhythmias (7)
Fine Tremor (8)	Candidiasis (4)	Nausea and vomiting (5)	Headache (5)
Hypokalemia (6)	Hyperglycemia (4)	Tachycardia (3)	Tachycardia (4)
Tachypnoea (4)	Sleep/behavior disturbances (3)	Hypersensitivity reactions (2)	Sleep/behavior disturbances (3)
Lactic acidosis (3)	Bone complications (3)	Rash (2)	Hypokalemia (2)
Nausea and vomiting (3)	Fine Tremor (2)	Fine Tremor (1)	Tachypnoea (2)
Headache (2)	Headache (2)	Abdominal pain (1)	Fine tremor (2)
Asthma exacerbation (2)	Nausea and vomiting (2)	Hypokalemia (1)	Lactic acidosis (1)
Hyperglycemia (2)	Rash (1)	Lactic acidosis (1)	Hyperglycemia (1)
Sleep/behavior disturbances (1)	Asthma Exacerbation (1)	Candidiasis (1)	Rash (1)
Tachyphylaxis (1)		Dizziness (1)	CNS problems (1)
		Agitation/anxiety (1)	
		Infection/immunosuppression (1)	
		Asthma Exacerbation (1)	

4.5 Discussion

This is the first systematic review that considers the harms of anti-asthma medications and their relationship to an individual's genetic variability. This systematic review has identified six different ADRs that have pharmacogenomic associations, but these are a small subset of the overall pharmacogenomic research in asthma. In addition, there is a lack of replication cohorts within the current evidence with only two studies including internal replication cohorts in their research. In both of these studies these replication cohorts successfully demonstrated the associations with individual polymorphisms identified in the discovery cohort.

The survey of PiCA consortia members supported future pharmacogenomic research into ADRs in asthma, and prioritized ADRs for each anti-asthma medication. Although it is not surprising for consortia members to support future research, the lack of current evidence highlights that it has previously not been of importance by the members, through the survey the aim was to change this perception so that ADR's are a priority. For most of the prioritized ADRs, we have not been able to identify any published pharmacogenomic data. In addition, we note that while ADRs associated with SABA/LABA medications were identified in the evidence these ADR's are not the ones members prioritized in the survey. However, for corticosteroids the ADRs identified in publications did correlate well with the ADRs prioritized in the survey. Asthma is a disease that is particularly suitable for personalization of therapy to either select efficacious medicines or avoid harms, as there are several possible medications, and so alternate drug selections are possible.

A minority of participants in the survey commented that asthma exacerbations concerned them as an ADR for beta-2 agonists, corticosteroids and LTA's. They are included in the results of the survey. The protocol used excluded these a priori as they were considered a failure of treatment, not a worsening of disease. However, we note the core outcome set for childhood asthma does include risk of hospitalization secondary to asthma exacerbations. Reviewing the literature, asthma exacerbations have been defined as adverse events rather than ADRs in previous pharmacogenomic studies [365, 392, 393]. A

study, examining children with asthma who were on ICS plus LABA identified an increase of asthma exacerbations of 52% in those homozygous for the Arg16/Arg16 allele of *ADRB2* [392]. However, it needs to be determined if asthma exacerbations should be classified as an adverse drug reaction in future studies or is to do with efficacy instead.

Along with understanding how pharmacogenomics affects asthma medication efficacy by using the evidence discovered in this systematic review, and the potential future evidence for ADR's, the area of personalization of medication can grow. Personalizing medication will help patients to improve the control of their disease through pharmacotherapy. The practice of personalizing medicine is currently limited with asthma medication currently used in a stepwise approach [394]. The information from this systematic review may help to recognize that each patient is unique, thus each pharmacotherapy treatment plan should be unique.

A limitation of this study is that, as for any systematic review, the quality of the data produced is dependent on the quality of existing publications, and there were a paucity of eligible papers covering a range of drugs and ADRs. These studies all had relatively small sample sizes, and the diversity of ADRs identified precluded meta-analysis. However, the identification and prioritization of ADRs by members of the PiCA consortia is a positive indicator that future pharmacogenomic studies may include more ADRs as well as markers of efficacy.

4.6 Conclusion

There are few pharmacogenomic studies of ADRs in asthma that have been undertaken. None of the studies that have been undertaken have been externally replicated. Future pharmacogenomic studies in asthma should collect relevant ADR data as well as markers of efficacy. Drug specific ADR priorities have been established to guide researchers.

Chapter 5 – Discussion and main findings

5.1 Main findings

Several findings can be obtained from the evidence contained within this work. In chapter two, a systematic review of studies regarding the association between ambient air pollution and risk of bronchiolitis in infants is described. There were few eligible studies that analysed the specific outcome of hospitalisation, with half of these studies commenting on measured concentration levels of ambient air pollutants in their study. Positive associations were discovered for different pollutants at various time lags, even at low air pollutant concentrations.

It is biologically plausible that air pollutants might increase the likelihood of severe bronchiolitis, because of the known effects exposure has on lung function [395, 396] and airway inflammation [397]. 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 [351], and the risk of acute lower respiratory infections is associated with PM2.5 exposure [331]. The possible differences between pollutants with regards to the chronicity of their association with hospitalisation for bronchiolitis may reflect different pathogenic processes. With particulate pollution, PM2.5 and PM10 may have a more chronic pro-inflammatory effect [398], whereas NO_2 and SO_2 may be associated with more acute damage to airways as are considered to be more irritative to the lung epithelium [399]. Further work is required to better understand the in vivo pathogenic effects of these pollutants in the airways of infants and children [400], and thus understand the difference seen in lag exposures between the pollutants and hospitalisation risks.

Although the systematic review in chapter two analysed the effects of air pollution to the risk of hospitalisations after birth, emerging evidence suggests an association between antenatal air pollution exposure and low birthweight [327] 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 (LRTI), with 98% of the diagnosis being classified as bronchiolitis or bronchitis [400], and this study highlights the possibility that antenatal exposure to air pollutants should be considered as a risk factor for bronchiolitis.

Differences in the methodological process for air pollution measurements between studies was observed, with no set standard. Some studies geocoded pollutant exposure levels to cases residential addresses, whereas others just measured the average concentrations between monitors in area. When using air pollutant monitors in a set area and then averaging the levels there may be some degree of misclassification of exposure levels, this may be due to the inclusion of remote monitoring sites that alter the concentrations. Furthermore, even though some studies correlated air pollution level concentrations to the patient's residences or the admitting hospitals, in urbanised city areas monitoring sites will experience high concentrations along with greater fluctuations in those concentrations that may affect the results. Thus, overall these observational studies may then underestimate the overall association seen between hospitalisation with bronchiolitis and ambient air pollution.

In the overview of systematic reviews to determine an association between acute respiratory events requiring healthcare resource utilisation and ambient air pollution exposure, described in chapter three, the link between the respiratory disease morbidity outcomes and air pollution was positively associated, particularly for short-term exposure. There were gaps in the evidence available regarding certain respiratory diseases and with time periods around asthma and pneumonia. These two respiratory diseases were only assessed according to short-term exposure with ambient air pollution by authors. Measurements surrounding exposure concentrations of ambient air pollutants in the systematic reviews was limited, with only a few reviews comparing concentrations observed to the WHO guidelines. Although, the need to review the WHO exposure threshold guidelines is apparent as positive associations were discovered in concentration levels below the set guidelines.

Quantifying the potential benefits related to reductions in ambient air pollution on unscheduled HRU would require sophisticated modelling methodology, outside the scope of

the overview in chapter three. However, there are reasons to be optimistic about potential impact. In European countries asthma causes around 0.6% of hospital admissions [401], to help tackle the incidence of asthma admissions legislation on a known risk factors has previously been introduced. Smoke-free ban has been successful in reducing hospital attendances for asthma in children [402, 403]. It is not just national legislation that has shown to be successful, policies at the local level have shown similar results, improvements in asthma outcomes have been seen in Boston with the Asthma Prevention and Control Program [404-406]. Even modest reductions in ambient air pollution may therefore have the potential to avoid a significant number of unscheduled HRUs. Detailed health economic analysis would be required to quantify these potential benefits.

The work undertaken to examine the environmental factor, air pollution, on respiratory disease is only one part of the larger picture. Respiratory disease is known to be multifactorial with interindividual variation shown in people suffering from the same respiratory disease. This variation may be due to differences in a person's environment, as shown in the work above, however other variables may contribute that need to be explored as well. One of these variables is the speciality of pharmacogenomics, this area has been shown to effect treatment of respiratory diseases, with asthma medication efficacy shown to be affected in previous studies [392, 407]. The emphasise in this area has been medication efficacy, however, ADR's are of equal importance in this cohort, with no systematic review of current evidence previously undertaken. In chapter four, a pilot review was carried out and highlighted the limitations in the current evidence and emphasised the need for increased inclusion of examination of ADRs in studies. This recommendation was further supported through results from the survey, where international professionals recognised it as an undervalued but important area of future research. To help prospective studies a development of a list of ADR's prioritized from highest to lowest for each class of asthma drugs has been completed.

The main recommendations from this work are twofold. The first refers to recommendations revolving around ambient air pollution and adverse effects. Methodology between exposure assessment of air pollutant and associating this with outcomes, needs improved classification on the most appropriate study design and statistical analysis for

situations. Additionally, ambient air pollution is increasing, there is now sufficient evidence to move the discussion onto how interventions may help to reduce the impact seen by air pollution on health at both the national and personal exposure level. These are needed to reduce estimates of future hazardous effects air pollution will concur if the current path is continued. The second revolves around pharmacogenomics and recognising ADRs as an important factor to be considered in future studies, one that is equal to medication efficacy. The areas highlighted concerning the methodology of epidemiological studies and possible future interventions to limit air pollution exposure and are discussed in the sections below.

5.2 Methodology of epidemiological exposure studies and adverse health outcomes

When discussing pollution exposure there are various methods available to researchers to assess the effect, one of these is a general hierarchy system that has been proposed in literature to help [14, 408], figure 9 depicts the best approximation of exposure levels to the poorest.

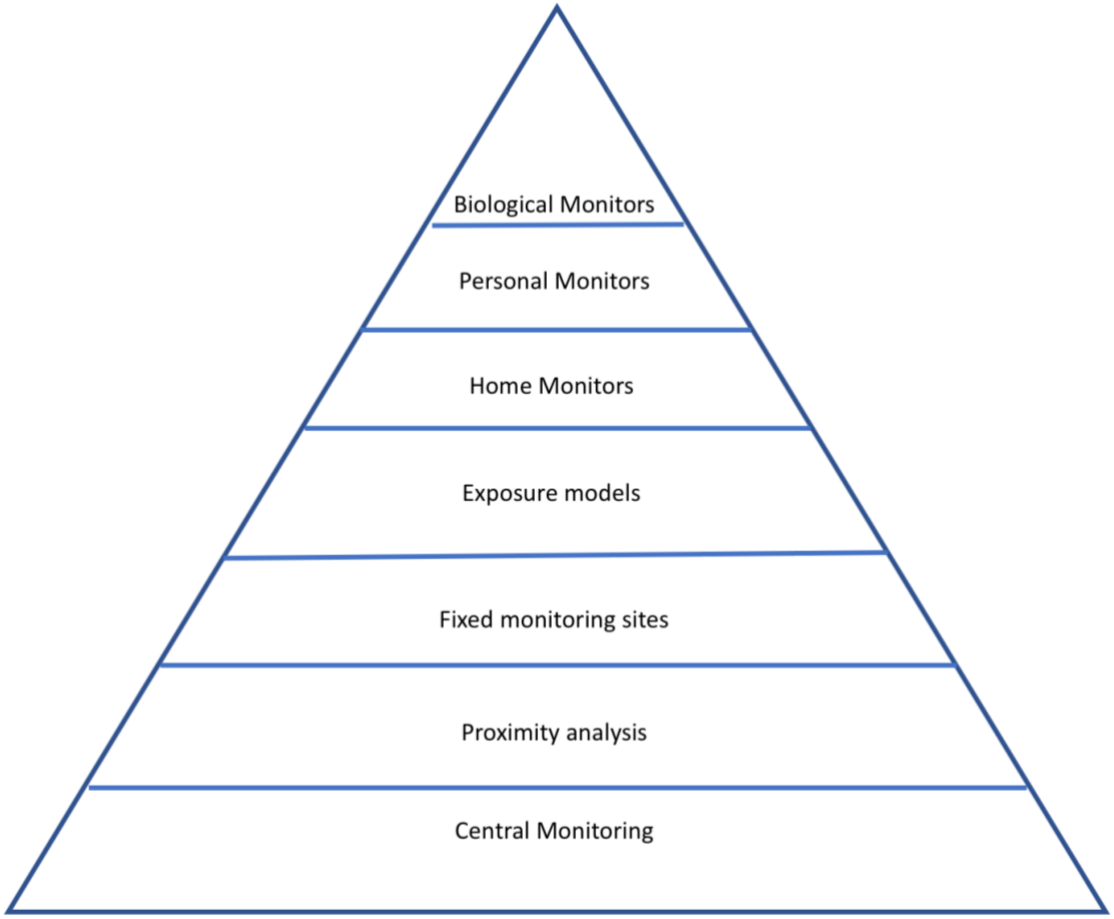


Figure 15. Hierarchy of exposure assessment from least accurate in estimates to best for estimates [14]

Estimates of exposure levels decrease in accuracy the greater the distance a monitor is positioned away from a person, exposure models, multiple fixed sites and the use of proximity monitors further decrease the quality of exposure yet are better than the use of central monitoring sites due to spatial variation between individuals. The following paragraphs discuss the use of different exposure assessment systems.

Despite the fact that for certain specific pollutants biological markers offer the best exposure assessment they are rarely used for various reasons. Biological markers are useful at the individual level, a common marker that is used is carboxyhaemoglobin levels as an assessment for CO exposure. Yet, there are high costs associated with this method, not all pollutants have biomarkers available that can assess for exposure, and unless the study is undertaken on a small scale it is difficult to obtain results.

Another useful method to measuring at the individual level is the use of personal monitors. Personal monitors provide one of the better pieces of evidence for estimates of exposure at the individual level. As the name suggests the equipment is attached to a person as they carry out their normal day to day activities with additional information then supplied such as locations travelled each day by the participant. Although they are useful, there are some downfalls to this method, so in practice it is rarely used. Some of these issues are that the devices can be a burden on participants, particularly active devices that are battery operated due to the noise that is admitted, and often need regular re-calibration to provide valid measurement. This method is not feasible for measuring long-term exposure or assessing exposure retrospectively.

A possible alternative method to personal monitors is the use of home monitors or monitors measuring microenvironments. This method doesn't depend on a participant's involvement as measures personal exposure indirectly. However, this method is not feasible for large scale use due to the set up and running of the monitors.

A recent method that is gaining in popularity is the use of exposure modelling. This method can help to improve the equilibrium, missing from previous methods mentioned, between scale of study and exposure accuracy. Exposure modelling has the possibility of providing

individual exposure estimates in large studies without the need to interact with participants. There are two main types currently used; air dispersion models and land use regression (LUR) models. Air dispersion models use mathematical functions to predict the concentration of pollutants in the atmosphere dependent on source of pollutant and meteorological conditions. The method follows a logical path from source of pollutant to monitoring sites to help predict results. The advantage of this model is that is allows for the prediction of individual pollutants at specified locations if enough data is available surrounding that area. However, the main issue with this way is that it is very expensive and time consuming particularly when applied to large study areas. An alternative method that is being applied is LUR modelling, this uses multiple pollutant concentrations at multiple sites in a specific area and then with the development of stochastic models using predictor variables through geographical information systems (GIS) a model can then be applied to an location without monitoring in that area [409]. This model has been applied in epidemiological studies in urban areas in Europe and North America, such as in the European Study of Cohorts for Air Pollution Effects [410]. Advantages of this method is that it can be readily applied in studies with large cohorts of participants and are relatively cost effective. However, the model is area specific thus for each new geographical area it has to be redone.

Another method is the use of measurements from fixed monitoring sites. This provides periodic, accurate concentration information related to the monitoring site but cannot be applied to reflect exposures of individuals. This method assumes that individuals in areas will all have the same exposure concentration level, thus ignores the spatial distribution that occurs with air pollution and the idea that individuals will have differences in exposures. A disadvantage of this fixed site monitoring measurements is that it is difficult to assess the effect total exposure from indoor pollution when concentrations are large as correlation with the monitors is poor. However, it is good as can be used to reflect daily changes in ambient air pollutant levels, it is not too expensive due to the presence of monitoring sites already in most urban developed areas. This method has often been used in studies examining health effects of air pollution and short-term exposure.

Proximity analysis uses a geospatial method, such as the distance from a pollution source as a measure of exposure rather than specific concentration levels. An example of this is with traffic related pollution where researchers use distance from major roadways to determine exposure levels. The advantage of proximity analysis is that with advances in GIS software and the use of digital maps it has become an easy method to implement. Disadvantages of this method is that it cannot distinguish between specific pollutants, does not consider meteorological confounding variables, nor explains for spatial distribution of air pollution, can only be used to describe categorical variables, and has low precision due to the geocoding method used as relies on postcodes which can correspond to a large area when variables are produced in reference to metres.

An important aspect of exposure assessment found in the included studies and in the systematic reviews related to whether studies had examined exposure at the individual or community level. At the community level it is assumed that air pollutant concentrations are similar throughout the area with little spatial variation present. Here studies would use central monitors and assign the same pollution exposure level to all, however this may not be the case as even in urban areas concentrations have been shown to fluctuate over very short distances. For the studies that assessed long-term exposure and used modelled data, this can create issues as data is modelled on a previous year's concentrations and over a number of years this can change, thus may not be comparable to the year being examined.

With confounding variables in the epidemiological studies, not all of them considered the same confounding factors such seasonal variation, indoor air pollutants, and meteorological factors. These variables are known to have an effect on ambient air pollution concentrations so need to be considered when designing exposure assessment methodology. This can lead to exposure misclassification if not assessed and thus add uncertainty to study results.

The method for assessing exposure will vary depending on the time period being assessed i.e. for short-term exposure the use of modelling and fixed sites which are geocoded to a person's residence would be more beneficial. If looking at population or community levels these methods provide a more accurate and valid exposure assessment than the use of proximity monitoring and even personal exposure is limited in these studies as they may be

influenced by confounding pollutants and unrealistic for the large scale. In regard to using exposure models the ideas of combing dispersion and land use regression models has been used to help maximise the benefits with both without the drawbacks of using them individually.

The ideal methodology would consider temporal and spatial variation of pollutants, variation between indoor and outdoor environmental concentrations and variation in location of participants at different times.

5.3 Interventions

The evidence that has been described supplies sufficient information to understand the hazardous effect of air pollution on respiratory health in children. With this effect known a new branch has to be addressed regarding possible interventions that can be developed and implemented into society to reduce pollution. These can be divided into governmental interventions or ones at the personal exposure level.

Increasing air monitoring sites and data collection worldwide will help to reflect exposure levels and give people the information they require to be decisive when it comes to protecting their health. The current WHO guidelines on air pollution are recommendations for countries and policy makers to follow, thus do no need to be abided strictly. Policy makers and countries can produce their own legislative levels they deem reasonable.

Recently, 22 countries in Europe, such as England, Germany, France, Hungary, Italy and Romania have been given warnings by the European court of justice (ECJ) regarding illegal high levels above those set out by the European Union (EU) [13, 106]. Even in the presence of fines and having to attend court, these countries are not rectifying the situations and failing to enact adequate clean air plans. Regarding the levels in the United Kingdom, a new clean air strategy has been produced, although this has received strong backlash from politicians and environmental activists [411]. One of these goals is to reduce the number of the population residing in places where particulate matter levels are above the WHO

guidelines by half by 2025, currently there are 90% of people in the UK residing in high level areas [412, 413].

There is a large need for both manufacturers and countries to tackle air pollution, however without them on board the health impact will continue to grow. In 2015, the manufacture Volkswagen highlighted one of the major issues when it comes to tackling air pollution, diesel-gate occurred [414]. The deception in nitrous oxide (NOx) emissions above those legally allowed may have led to an uncertain amount of deaths due to excess pollution, particularly in Europe where the proportion of diesel vehicles is roughly half [415]. Since the diesel-gate scandal, countries have tried to tackle their diesel exhaust emissions through monetary fines for diesel owners and the introduction of car free days in cities [415]. In 2017, another blow to tackling air pollution happened when the USA pulled out of the Paris Climate Change agreement, a decision which will have long lasting impacts on pollution emissions [416]. Countries and manufacturers need to implement policies and equipment that will have an impact on reducing air pollution to help reduce the impact it has on health and will continue to have.

A possible intervention that could be introduced to decrease city and town levels of ambient air pollution is the introduction of clean air zones (CAZ) [412]. These zones would help to deter cars from entering certain areas, limiting the pollution due to vehicular emissions in these areas. Although these areas exist in locations in London and have been given the approval to be used in other local authorities there has been little action in other areas to introduce them. Another intervention to decrease vehicular emissions is the increased use of public transport and cycling in cities. In Norway, the government have aimed to ban all cars from city centres by 2019 [417]. Whereas, in Copenhagen they have low levels of vehicular emissions due to half of the population cycling to work [417].

Some personal interventions that could be applied in areas with high levels is the use of air pollution estimates on weather maps. This allows people to take control of their risk to ambient air pollution levels, if people are warned that particular days may be high then they can limit the exposure. Another possibility is the use of home air filters which could act on

both indoor and outdoor air pollution entering the house. Although these would rely on the financial situation of families to install.

Some physical barriers to exposure could be the use of facemasks [418, 419], with some being shown to be 90% effective in limiting air pollution exposure. However, the use of facemasks is variable depending on the type and if they are used correctly by the population wearing them[412]. Another idea that would be useful for infants who are a highly susceptible group is the use of pram covers when near main roads or on the school runs [420]. This would be particularly useful in London which has over 800 institutes for education such as nurseries in areas with illegal high levels of NO_2.

Overall, there are various interventions that can be introduced to help tackle air pollution. Although, even with these interventions the best route to addressing the problem is by reducing our emissions of pollution around the world and make a conscious effort as humans to do so for the good of our health.

5.4 Conclusion

This thesis emphasises the need for ambient air pollution to be recognised as a major risk factor for hospitalisation with respiratory disease in children. It is encouraging that in certain respiratory diseases such as asthma and pneumonia this association has been recognised in this vulnerable group, with further work still needed in other illnesses. However, there is a long way before air pollution levels will be improved to combat the consequences of exposure. Currently, although gaining in recognition, action to combat concentration levels is being hindered by individuals and policy makers who are opposed to change. Further effort at the local and national level needs to occur to reduce concentrations and limit dangerous exposure levels in areas around the world. Recognising environmental factors is not enough, other variables need to be considered in relation to respiratory disease to reduce the burden that it has on healthcare resources. This thesis has shown that a possibility is addressing ADRs in children related to pharmacogenomics. This could lead to a more personalised approach to medicine for children suffering from

respiratory disease. The combination of these variables it vital to reduce the burden of respiratory disease on individuals and resources.

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Appendix

Appendix 1 – Protocol for systematic review submitted to PROSPERO

Review title

A systematic review of the effect of outdoor air pollution on the risk of hospitalisation for bronchiolitis in infants

Review team members and their organisational affiliations

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Funding sources/sponsors

Charlotte King is part-funded by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

Conflicts of interest

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.

Collaborators

Mr Jamie Kirkham. University of Liverpool, Department of Biostatics

Review Question

Objective – to systematically review the evidence exploring the association between air pollution and bronchiolitis, including hospital admissions, length of stay, emergency department visits and mortality.

Searches

Studies will be identified using electronic search databases: MEDLINE, SCOPUS and Web of Science to find eligible studies for review.

Search terms will include the general subject term 'bronchiolitis' as well as for the target age population that is of interest. Each search strategy will be tailored depending to the search database because of syntax, limits and available fields vary between databases.

There will be no restriction for language or publication date.

Types of studies to be included

Studies that examine the relationship between air relationship and bronchiolitis. Cohort studies and case crossover study designs including time series study designs will be included. Animal studies and duplicates are to be excluded.

Condition or domain being studied

Bronchiolitis

Participants/Population

Children aged less than or equal to 2 years old.

Intervention(s), Exposure(s)

Exposure to air pollution both short-term and cumulative.

Exposure to any outdoor air pollutant will be examined:

Gaseous pollutants including carbon monoxide, nitrogen dioxide, ozone and sulphur dioxide
Particulate matter including PM2.5 and PM10

Comparator/Control

These will vary according to the individual study design.

Context

Primary Outcomes

Bronchiolitis admission to hospital

Secondary Outcomes

Length of Stay in Hospital.
Critical Care admission.
Emergency Department visits.
Unscheduled visits to healthcare professional.
Bronchiolitis mortality.

Data Extraction

All abstracts and titles will be screened independently by two reviewers to determine potential studies for review.
Full text articles that meet the study selection criteria will be reviewed for eligibility for the systematic review and meta-analysis. If there is disagreement a third review will be sought for consensus.

Data to be extracted will vary depending on outcomes in each individual study that meet the primary and secondary outcomes being analysed.

Risk of bias (quality) assessment

Publication bias will be assessed by constructing a funnel plot.

The Newcastle-Ottawa Scale will be used to assess quality of non-randomised studies. A 'star system' in the Newcastle-Ottawa Scale will be used to judge a study on three broad perspectives:

a) the selection of the study groups;

b) the comparability of the groups; and

c) the ascertainment of the exposure or outcome of interest.

The studies will be graded as poor (1-3 stars), intermediate (4-6 stars) and high (7-9 stars) quality. Heterogeneity will be examined using the standard I2 test.

Strategy for data analysis

Characteristics from studies will be presented in tables and narrative forms, guided by the use of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement.

Exposure effect will be measured using risk ratio as a measure of effect size.

We anticipate heterogeneity between studies due to different study designs, methods of analysis, lag exposures, and geographical and population differences. A random effects model will therefore be used to account for heterogeneity between and within studies.

Analysis of subgroups or subsets

We will undertake sub group analysis between developing and developed countries

Appendix 2 – Search strategy used for systematic review on risk of hospitalisation with bronchiolitis and ambient air pollution

Web of Science, Medline and Scopus were searched.

Web of Science

TOPIC: (baby) *OR* **TOPIC:** (infan*) *OR* **TOPIC:** (pediatric*) *OR* **TOPIC:** (paediatric*) *OR***TOPIC:** (peadiatric*) *AND* **TOPIC:** (child*) *AND* **TOPIC:** (toddler*) *AND* **TOPIC:** (pre-school*)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

TOPIC: (Bronchiolitis) *OR* **TOPIC:** (RSV) *OR* **TOPIC:** ("respiratory syncytial virus")
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(sulphur dioxide) *OR* **TOPIC:** (SO2) *OR* **TOPIC:** (sulphur dioxide)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

TOPIC: (nitrogen dioxide) *OR* **TOPIC:** (NO2)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(carbon monoxide) *OR* **TOPIC:** (CO)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(ozone) *OR* **TOPIC:** (O3)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(particulate matter) *OR* **TOPIC:** (PM)
Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(TS=(air OR ambient OR atmospher* OR outdoor))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

(TS=(pollution OR quality))

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#8 AND #9

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#3 OR #4 OR #5 OR #6 OR #7 OR #10

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

#11 AND #1 AND #2

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Scopus

TITLE-ABS-KEYS (baby OR infan* OR pediatric* OR paediatric* OR peadiatric* OR child* OR toddler* OR pre-school*)

TITLE-ABS-KEYS (bronchiolitis or RSV or "respiratory syncytial virus")

TITLE-ABS-KEYS (sulphur AND dioxide OR SO2)

TITLE-ABS-KEYS (nitrogen AND dioxide OR NO2)

TITLE-ABS-KEYS (ozone OR O3)

TITLE-ABS-KEYS (carbon AND monoxide OR CO)

TITLE-ABS-KEYS (particulate AND matter OR PM*)

TITLE-ABS-KEYS (air OR ambient OR atmospher* OR outdoor)

TITLE-ABS-KEYS (pollution OR quality)

#8 AND #9

#10 OR #7 OR #6 OR #5 OR #4 OR #3

#11 AND #1 AND #2

MEDLINE via OVID

Sulfur dioxide/ or (sulphur dioxide or SO2 or sulphur dioxide).mp.

(nitrogen dioxide or NO2).mp. or Nitrogen Dioxide/

(ozone or O3).mp. or ozone/

(carbon monoxide or CO).mp. or Carbon Monoxide/

(particulate matter or PM*).mp. or Particulate Matter/

((air or ambient or atmospher* or outdoor) adj1 (pollution or quality)).mp.

(bronchiolitis or RSV or "respiratory syncytial virus").mp.

(baby or infan* or pediatric* or paediatric* or peadiatric* or child* or toddler* or pre-school*).mp.

or/1-6

7 and 8 and 9

Appendix 3 – Table of excluded studies in bronchiolitis review after full text assessment

Study Name and Year	Reason for Exclusion
Air pollution and admissions for acute lower respiratory infections in young children of Ho Chi Minh City [421]	Bronchiolitis and pneumonia admissions not separated
Clinical risk factors for life-threatening lower respiratory tract infections in children: A retrospective study in an urban city in Malaysia *[422]*	Pneumonia admissions as clinical outcome
Do environmental pollutants influence the onset of respiratory syncytial virus epidemics or disease severity? *[423]*	Review paper
Effect of air pollution on respiratory emergency room visits and hospital admissions *[424]*	Asthma and bronchiolitis combined
Health effects of air pollution exposure on children and adolescents in Sao Paulo, Brazil *[312]*	All acute lower respiratory infections combined
Impact of air pollution on physician office visits for common childhood conditions in Ontario, Canada *[425]*	Air pollution sensitive conditions, does not separate out bronchiolitis visits

Ozone related respiratory morbidity in a low pollution region *[426]*	Combined acute lower respiratory admissions for ages 0-14 years
Part 4. Interaction between air pollution and respiratory viruses: time series study of daily mortality and hospital admission in Hong Kong *[427]*	All ages of lower respiratory infections included
Residential proximity to large airports and potential health impacts in New York State *[428]*	Cross sectional study
Respiratory hospital admissions in young children living near metal smelters, pulp mills and oil refineries in two Canadian provinces *[429]*	Asthma and bronchiolitis combined
Seven day cumulative effects of air pollutants increase respiratory ER visits up to threefold *[430]*	Lower respiratory obstructive disease in less than 5 year olds, incorrect age group and combination of diseases
Short term risk of hospitalization for asthma or bronchiolitis in children living near an aluminium smelter *[431]*	Combined admissions for asthma and bronchiolitis
Spatial clusters of child lower respiratory illnesses associated with community level risk factors *[432]*	Not specific to bronchiolitis and air pollutant chemicals

The effect of traffic related air pollution on infantile bronchiolitis and susceptibility to childhood asthma *[433]*	Experience of bronchiolitis, no data available
The effects of air pollution on children *[434]*	Respiratory symptoms combined
Effects of short-term exposure on hospital admissions for acute lower respiratory infections in young children of Ho Chi Minh City, Vietnam *[435]*	All acute lower respiratory infections combined
A preliminary assessment of the role of ambient nitric oxide exposure in hospitalization with respiratory syncytial virus bronchiolitis *[436]*	Looked at Nitric Oxide only, ineligible pollutant
Air pollution and acute respiratory infections among children 0-4 years of Age: An 18 year time-series study *[437]*	Bronchiolitis and bronchitis admissions combined
Air pollution and environmental tobacco smoking during infancy may increase the risk of bronchiolitis *[438]*	Incorrect ages and too retrospective

Early life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the INMA study *[400]*	Doctor diagnosed lower respiratory infection not specific to bronchiolitis
Effects of fine particles on children's hospital admissions for respiratory health in Seville, Spain *[439]*	Looked at city wide levels of pollution rather than to specific admission
Exposure to traffic and early life respiratory infection: a cohort study *[440]*	All acute lower respiratory infection not specific to bronchiolitis
Fine Particulate Matter Pollution linked to respiratory illness in infants and increased hospital costs *[441]*	Cross sectional study
Haze is a risk factor contributing to the rapid spread of respiratory syncytial virus in children *[67]*	Examines at geographical level
Modifiable demographic factors that differentiate bronchiolitis from pneumonia in Nepalese children less than two years – a hospital based study *[442]*	General outdoor air pollution – non-specific to pollutants
Modifiable risk factors associated with bronchiolitis *[443]*	General outdoor air pollution – non-specific to pollutants

Outdoor, but not indoor, nitrogen dioxide exposure is associated with persistent cough during the first year of life *[444]*	Looked at respiratory problems not at outcome of interest
Respiratory syncytial virus bronchiolitis, weather conditions and air pollution in an Italian urban area: An observational study *[445]*	Association was between temperature and pollution levels in known RSV seasons
Respiratory Syncytial virus infection in infants and correlation with meteorological factors and air pollutants *[446]*	Not examine clinical outcome
Association of acute bronchiolitis with environmental variables *[447]*	City wide levels of pollutants examined
Air pollution and acute respiratory diseases in children: regression analysis of morbidity data *[448]*	Bronchitis and bronchiolitis cases combined
Effect of air pollution upon the hospitalisation for acute lower respiratory tract infections among the Bucharest municipality's residents *[449]*	Not age specific examines 0-14 year olds

Effect of environmental air pollutants on wheezing airways respiratory infections in emergency room *[450]*	Definition of bronchiolitis is for wheezing disorder
Exposure to fine particles and bronchiolitis in infants *[451]*	Same paper as written by Karr et al in 2009 that has been included
Exposure to vehicular traffic is associated to a higher risk of hospitalisation for bronchiolitis during the first year of life *[452]*	Vehicular traffic not specific pollutants
Impact of air pollution in paediatric consultations in primary health care: Ecological Study *[453]*	Unclear definition of bronchiolitis
Influence of respiratory viruses, cold weather and air pollution in the incidence of lower respiratory tract infections in infants and children *[454]*	Combines respiratory syncytial virus across all ages
Relationship of hospital admissions with respiratory syncytial virus (RSV) bronchiolitis to environmental nitric oxide [455]	Looking at nitric oxide, incorrect pollutant
The influence of respiratory syncytial virus infections and environmental conditions on	Not look at bronchiolitis separately

pediatric health care demand during winter-2002 in Santiago, Chile *[456]*	

Appendix 4 – Protocol for overview of systematic reviews submitted to PROSPERO

Review title

Ambient air pollution and respiratory illnesses in children: an overview of systematic reviews

Review team members and their organisational affiliations

Dr Ian Sinha. Alder Hey Children's Hospital
Dr Daniel Hawcutt. Alder Hey Children's Hospital
Miss Charlotte King. University of Liverpool Institute of Translational Medicine, Department of Women's and Child Health

Funding sources/sponsors

Charlotte King is part-funded by The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North West Coast (NIHR CLAHRC NWC).

Conflicts of interest

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.

Review Question

What is the evidence synthesised in systematic reviews and meta analyses about the association between ambient air pollution and the risk of hospital admission with respiratory illnesses in children?
What is the relationship between air pollution and risk of hospitalisation for children with respiratory illnesses synthesised in systematic reviews and meta analyses of observational studies?

Searches

Comprehensive searches of four electronic databases (MEDLINE, Embase, DARE and Cochrane) will be conducted to find eligible systematic reviews and meta analyses evaluating the association between ambient air pollution and childhood respiratory illnesses.
Search terms will include general search terms for respiratory illnesses, air pollution, the selected age population, and systematic reviews. Each search strategy will be tailored depending to the search database because syntax, limits and available fields vary between databases. There will be no restriction on language or publication date.

Types of study to be included

We will include systematic reviews of observational studies (cohort, time series, cross sectionals, case crossover and case control studies), with or without meta-analysis. Reviews included will examine the association between childhood respiratory illnesses and ambient air pollution. Narrative reviews of literature will be excluded. To be included, a review must provide qualitative or quantitative results from observational studies about the association between one or more ambient air pollutant and one or more respiratory outcome.

Condition or domain being studied

Childhood respiratory illnesses including: respiratory infection, croup, asthma, acute lower respiratory infections, acute wheeze, bronchiolitis, bronchitis, pneumonia, influenza, and whooping cough.

Participants/Population

Systematic reviews that synthesise evidence for the study populations: infants, children and adolescents up to the age of 20 years old will be considered.

Intervention(s), Exposure(s)

Exposure to any outdoor air pollutant will be examined for any lag period (acute, sub-acute, lifetime): a) particulate matter including PM2.5 and PM10
b) gaseous pollutants including nitrogen dioxide, sulphur dioxide, carbon monoxide, and ozone
c) traffic pollution including outdoor volatile organic compounds

Comparator/Control

Will be based on observational studies in the specific reviews.

Context

Primary Outcomes

The primary outcomes of interest are effect estimates (pooled odds ratios, risk ratios) of the association between one or more air pollutant and the subsequent risk of hospitalisation or emergency visits with the stated respiratory illnesses above.

Secondary Outcomes

Secondary outcomes of interest include effect estimates (pooled odds ratios, risk ratios) of the association between one or more air pollutant and the subsequent risk of mortality, critical care admissions and physician/ambulatory care visits for the respiratory illnesses listed above.

Data Extraction

Two reviewers will independently screen titles and abstracts generated from the searches to identify potentially relevant systematic reviews. The full text of articles deemed relevant and those whose abstracts and titles provide insufficient information will be retrieved for a

closer inspection. Two reviewers will independently apply the eligibility criteria to all potentially relevant systematic reviews for inclusion in the overview. Disagreements about eligibility will be settled by a third reviewer.

General information from all included systematic reviews will be extracted: first author, publication year, country, comprehensive literature search and evaluation process (e.g. years, databases, languages, inclusion/exclusion criteria, duplicate study selection), number of included studies, study designs of the primary studies, methods for quality assessment/risk of bias of primary studies, populations of interest, age group (s), air pollutants evaluated, respiratory illnesses reported, risk of hospitalisation or secondary outcome, method to analyse the results from primary studies (quantitative or qualitative), mention of confounders, results and review conclusions.

For meta-analyses, we will extract information of the pooled effect estimates along with the 95% confidence intervals, and the I2 values reported to inform heterogeneity across individual studies included in the reviews. Heterogeneity will be characterized as small (I2 less than and including 25%), moderate (I2 between 26% and 74%) and high (I2 equal to and greater than 75%).

Data from systematic reviews will be extracted by one reviewer and then independently verified for accuracy and completeness by a second reviewer. Any discrepancies in data extraction will be resolved by consensus between the data extractor and the data verifier.

Risk of bias (quality) assessment

Two researchers will independently appraise the methodological quality of systematic reviews using the Assessment of Multiple Systematic Reviews-Revised tool (AMSTAR-R). To the extent that Amstar works with scores, we will also evaluate the information extracted qualitatively.

Strategy for data analysis

A PRISMA flow diagram will be used to inform review selection in the overview. We will produce evidence tables and forest plots to aid in data presentation when appropriate.

Appendix 5 – Search strategy for overview of systematic reviews

- Respiratory Health
    - Respiratory infection
        - Respirat* infect*
        - Vir* infect*
        - Bacteria* infect*
        - Respiratory disease
        - Respiratory tract diseases
        - Respiratory infection Mesh
    - Croup
        - Crou*
        - Parainfluenza virus
        - Croup Mesh
    - Asthma
        - Asthma Exacerbat*
        - Asthm*
        - Asthma Mesh
    - Acute lower respiratory infections
        - ALRI
        - ARI
        - LRI
        - Acute Lower respiratory infection
    - Acute wheeze
        - Wheez*
        - Acute wheeze
        - Wheeze Mesh (respiratory sounds)
    - Bronchiolitis/ Bronchitis
        - Bronchitis Mesh
        - Bronchi*
        - Respiratory Syncytial Virus
        - RSV
        - Bronchiolitis Mesh
    - Pneumonia
        - Pneumon*
        - Pnemon*
        - Streptococcus
        - Pneumonia Mesh
    - Influenza
        - Haemophilus influenza
        - Influenz*
        - Influenza Mesh
    - Whooping Cough
        - Pertussis
        - Whooping cough
        - Whooping cough Mesh

- Child
    - Child search terms
        - Infant* or infant (MeSH)
        - Infancy
        - Newborn*
        - Baby*
        - Babies
        - Neonat*
        - Preterm*
        - Prematur*
        - Postmatur*
        - Child* or Child (MeSH)
        - Schoolchild*
        - School age*
        - Preschool*
        - Kid*
        - Toddler*
        - Adolescent (MeSH) or adoles*
        - Teen*
        - Boy*
        - Girl*
        - Minors (MeSH) or Minors*
        - Puberty (MeSH) or Pubert*
        - Pubescen*
        - Prepubescen*
        - Pediatrics (MeSH) or Pediatric*
        - Paediatric*
        - Peadiatric*
        - Schools (MeSH) or school*
        - Nursery school*
        - Elementary school*
        - High school*
    - Air Pollution
        - Ambient air pollution
            - Outdoor air pollut*
            - Ambient air pollut*
            - Air pollut*
            - Air pollution Mesh
        - Particulate Matter
            - Particulate
            - PM10
            - PM2.5
            - Particle*
            - Particulate Matter Mesh
        - Nitrogen Dioxide
            - Nitrogen
            - NO2

        - Nitrogen dioxide Mesh
    - Sulfur Dioxide
        - Sulfur
        - Sulphur
        - SO2
        - Sulfur dioxide Mesh
    - Carbon Monoxide
        - Carbon
        - CO
        - Carbon Monoxide Mesh
    - Ozone
        - O3
        - Ozone Mesh
    - Traffic pollution
        - Vehicle Emission
        - Traffic
        - Volatile Organic Compound*
        - VOC
        - Volatile Organic Compound Mesh
- Systematic review
    - Systematic review
    - Meta-analysis
    - Intervention*
    - Exposure*

Appendix 6 – Table of excluded articles from overview of systemic reviews after full text analysis

Author and year	Reason for exclusion
J R Balmes 1993 [457]	Narrative Review
F Barone-Adesi 2015 [117]	Looked at lung function
C Black 2017 [458]	Narrative Review
M Brauer 2010 [459]	Narrative Review
C I R Froes Asmus 2016 [460]	No specific disease outcome
M Chan Yeung 2002 [461]	Narrative Review
M Dherani 2008 [83]	Looked at indoor pollution
R Etzel 2003 [462]	Narrative Review
A Falck 2015 [463]	Narrative Review
A Ferguson 2017 [464]	Narrative Review
F D Gilliland 2009 [465]	Narrative Review
L Gochicoa Rangel 2011 [466]	Narrative Review
N Gouveia 2017 [467]	Not a systematic review
A Heinzerling 2016 [468]	Not pollutant of interest
T W Hesterberg 2009 [469]	Looked at total population
W Hou 2016 [470]	Not pollutant of interest
S Jackson 2013 [471]	Looked at indoor pollution
H D Kan 2005 [472]	Looked at total population
Hak Kan Lai 2013 [473]	Looked at total population
P Landrigan 2002 [474]	Narrative Review

U Latza 2008 [475]	Looked at total population
S Li 2012 [476]	Looked at lung function
J C Liu 2015 [477]	Looked at total population
Q Liu 2017 [478]	Not examining primary outcome
E C Matsui 2013 [479]	Looked at indoor pollution
D Mckee 1991 [480]	Not examining primary outcome
P Misra 2012 [481]	Looked at indoor pollution
M Nitschke 1999 [482]	Looked at indoor pollution
S Petruzzi 1994 [483]	Narrative Review
P Eggleston 2008 [484]	Narrative Review
M Raizenne 1998 [485]	Narrative Review
M Saric 1999 [486]	Narrative Review
E Schultz 2017 [487]	Looked at lung function
M Sonego 2015 [53]	Not pollutant of interest
D Strachen 1998 [488]	Not pollutant of interest
A O Tuazon 2012 [489]	Narrative Review
M Veras 2016 [490]	No specific disease outcome
S Vieira 2015 [491]	Narrative Review
D J Ward 2004 [250]	Looked at lung function
S Weichenthal 2007 [492]	Looked at indoor pollution
G Weinmayr 2009 [493]	Not examining primary outcome
D Zmirou 1997 [494]	Not examining primary outcome
J Voynow 2015 [495]	Narrative Review
M A Vigotti 1999 [496]	Not a systematic review

J Heinrich 2002 [497]	Narrative Review
S Baldacci 1993 [498]	Narrative Review
Biela-Mazur 2017 [499]	Not examining primary outcome
Biggeri 2004 [500]	Looked at total population
Yarborough 2011 [501]	Not examining primary outcome
Chauhan 1998 [502]	Narrative Review

Appendix 7 – Risk of bias assessment of individual included studies within systematic reviews for each disease

Appendix 7.1 Asthma Individual Studies Risk of Bias

Individual Study	Pollutant	Selection Bias	Exposure Assessment	Adjustment for Confounders	Risk Of Bias
Abe 2007	SO2, CO	High	Medium	Low	High
Babin 2007	O3	Low	High	Low	High
Carlin 1999	O3	High	Medium	Low	High
Dales 2000	?in ozone review	High	Medium	Low	High
Evans 2014	PM2.5, CO, SO2, O3	High	Low	Low	High
Jazbec 1999	NO2	High	Low	High	High
Laurent 2008	PM10, NO2, SO2, O3	High	Low	Low	High
Stieb 1996	O3	High	Medium	Low	High
Tao 2014	PM10, SO2, NO2	Low	Medium	High	High
Tsai 2006	PM10, NO2, SO2, CO, O3	High	Medium	Medium	High
Yamazaki 2009	O3, PM2.5, NO2	High	High	Low	High
Yamazaki 2013	NO2, O3, PM10, PM2.5	High	Medium	Low	High
Yang 2007	SO2, NO2, CO, O3, PM10	Low	Medium	High	High
Meng 2010	CO, NO2, O3, PM10, PM2.5	High	Medium	Low	High

Thompson 2001	PM10, SO2, NO2, O3, CO	Medium	High	Low	High
Alhanti 2016	O3, CO, NO2, SO2, PM2.5	Low	Low	Low	Low
Andersen 2007	PM10	Low	Low	Low	Low
Andersen 2008	PM10 and PM2.5	Low	Low	Low	Low
Atkinson 2001	PM10	Low	Low	Low	Low
Byers 2016	SO2, PM2.5, O3	Low	Low	Low	Low
Delfino 2014	PM2.5, NO2, CO, O3	Low	Low	Low	Low
Erbas 2005	NO2, O3, PM10	Low	Low	Low	Low
Glad 2012	O3, PM2.5	Low	Low	Low	Low
Gleason 2014	PM2.5, O3	Low	Low	Low	Low
Gleason 2015	O3, PM2.5	Low	Low	Low	Low
Halonen 2010	O3, PM2.5	Low	Low	Low	Low
Iskandar 2012	PM10, PM2.5, NO2	Low	Low	Low	Low
Lee 2006	SO2, NO2, PM10, PM2.5, O3	Low	Low	Low	Low
Norris 1999	PM10, CO, NO2, SO2, O3	Low	Low	Low	Low
Silverman 2010	PM2.5, O3	Low	Low	Low	Low
Weichenthal 2016	PM2.5, O3, NO2	Low	Low	Low	Low

Halonen 2008	PM2.5, CO, NO2, PM10,	Low	Low	Low	Low
Smargiassi 2009	SO2	Low	Low	Low	Low
Alman 2016	PM2.5	Medium	Low	Low	Medium
Amancio 2012	PM10, SO2, O3	Low	Medium	Low	Medium
Anderson 1998	O3, NO2, SO2	Low	Medium	Low	Medium
Anderson 2001	PM10 and PM2.5	Low	Medium	Low	Medium
Atkinson 1999	NO2, CO, O3, PM10 SO2	Low	Medium	Low	Medium
Babin 2008	O3, PM2.5, PM10	Low	Medium	Low	Medium
Barnett 2005	NO2	Low	Medium	Low	Medium
Bates 1990	SO2, NO2, O3	Low	Medium	Low	Medium
Chakraborty 2014	O3, PM10	Low	Medium	Low	Medium
Chen 2013	PM2.5, O3	Low	Medium	Low	Medium
Chew 1999	SO2, NO2, O3	Low	Medium	Low	Medium
Chimonas 2007	PM10, PM2.5	Medium	Medium	Low	Medium
Ding 2016	PM10, PM2.5, SO2, NO2, O3, CO	Low	Medium	Low	Medium
Fauroux 2000	O3, SO2, NO2	Low	Medium	Low	Medium
Fletcher 2000	PM10, SO2, NO2, O3, CO	Low	Medium	Low	Medium

Fusco 2001	Particles, SO2, NO2, CO, O3	Low	Medium	Low	Medium
Grineski 2011	PM2.5, NO2	Low	Medium	Low	Medium
Hajat 1999	SO2, NO2, CO, O3, PM10	Low	Medium	Low	Medium
Hua 2014	PM2.5, NO2, SO2	Low	Medium	Low	Medium
Jalaludin 2008	PM10, PM2.5, NO2, O3, CO, SO2	Low	Medium	Low	Medium
Ko 2007	NO2, O3, PM10, PM2.5, SO2	Low	Medium	Low	Medium
Lavigne 2012	NO2, SO2, CO, PM2.5, O3	Low	Medium	Low	Medium
Lee 2002	SO2, NO2, CO, O3, PM10	Low	Medium	Low	Medium
Lee 2006	CO, SO2, NO2, O3, PM10	Low	Medium	Low	Medium
Lee 2010	O3	Low	Medium	Low	Medium
Li 2011	CO, NO2, SO2, PM2.5	Low	Medium	Low	Medium
Lin 2003	PM10, PM2.5, SO2, NO2, O3, CO	Low	Medium	Low	Medium

Lin 2004	CO, SO2, NO2, O3	Low	Medium	Low	Medium
Magas 2007	NO2	Low	Medium	Low	Medium
Mar. 2009	O3, PM2.5	Low	Medium	Low	Medium
Medina 1997	NO2, SO2, O3	Medium	Medium	Low	Medium
Mohr 2008	O3, PM2.5, SO2	Low	Medium	Low	Medium
Morgan 1998	PM2.5, O3, NO2	Low	Medium	Low	Medium
Neidell 2010	O3	Low	Medium	Low	Medium
Park 2013	PM10, CO, O3, NO2, SO2	Low	Medium	Low	Medium
Paulu 2008	O3, PM2.5	Low	Medium	Low	Medium
Pereira 2010	PM10, O3, NO2, CO	Low	Medium	Low	Medium
Petroeschevsky 2001	SO2, NO2, O3	Low	Medium	Low	Medium
Romieu 1995	SO2, NO2, O3	Low	Medium	Low	Medium
Sacks 2014	O3	Low	Medium	Low	Medium
Samoli 2011	PM10, SO2, NO2, O3	Low	Medium	Low	Medium
Santus 2012	PM10, PM2.5, SO2, NO2, O3, CO	Medium	Medium	Low	Medium
Son 2013	PM10, NO2, SO2, CO, O3	Low	Medium	Low	Medium

Strickland 2010	CO, NO2, SO2, O3, PM10, PM2.5	Low	Medium	Low	Medium
Strickland 2015	PM2.5	Low	Medium	Low	Medium
Sunyer 1997	SO2, NO2, O3	Low	Medium	Low	Medium
Szyszkowicz 2008	CO, NOW, SO2, O3, PM10, PM2.5	Low	Medium	Low	Medium
Tecer 2008	PM2.5, PM10	Low	Medium	Low	Medium
Tolbert 2000	O3, PM10	Medium	Medium	Low	Medium
Ueda 2010	NO2, SO2	Low	Medium	Low	Medium
Villneneuve 2007	SO2, NO2, CO, O3, PM2.5, PM10	Low	Medium	Low	Medium
Wendt 2014	PM2.5, O3, NO2	Medium	Medium	Low	Medium
Wilson 2005	SO2, O3	Low	Medium	Low	Medium
Winquist 2012	O3, PM2.5	Low	Medium	Low	Medium
Yamazaki 2015	PM2.5, PM10, O3, NO2	Medium	Low	Low	Medium
Lewin 2013	SO2, PM2.5	Medium	Low	Medium	Medium
Lin 2002	PM10, PM2.5, SO2, NO2, O3, CO	Low	Medium	Low	Medium
Morgan 2010	PM10	Low	Medium	Low	Medium
Strickland 2014	CO, NO2, O3, PM10, PM2.5	Medium	Medium	Low	Medium
Sunyer 2003	SO2	Low	Medium	Low	Medium

White 1994		N/A	N/A	N/A	N/A

Appendix 7.2 Pneumonia Individual Studies Risk of Bias

Individual Study	**Pollutant**	**Selection Bias**	**Exposure Assessment**	**Adjustment for Confounders**	**Risk Of Bias**
Barnett 2005	PM2.5, PM10, NO2, SO2, CO, O3	Medium	Medium	Low	Medium
Darrow 2014	O3, NO2, CO, PM10, PM2.5	Low	Low	Low	Low
Farhat 2005	PM10, SO2, NO2, O3, CO	Low	Medium	Low	Medium
Gouveia 2000	PM10, SO2, NO2, CO, O3	Low	Medium	Low	Medium
Ilbabaca 1999	PM10, PM2.5, SO2, NO2, O3	Low	Medium	Low	Medium
Lv 2016	PM2.5, PM10, CO, SO2, NO2	High	Medium	Low	High
Malig 2016	O3	Low	Low	Low	Low
Negrisoli 2013	PM10, NO2, O3	Low	Medium	Low	Medium
Ostro 2009	PM2.5	Low	Medium	Low	Medium
Pablo-Romero 2015	PM2.5	Low	Medium	Medium	Medium
Patto 2016	PM2.5	Low	Medium	Low	Medium
Santus 2012	NO2, CO, O3, PM10, PM2.5, SO2	Low	Medium	Low	Medium

Souza 2016	NO2, O3, PM10	Low	Medium	Low	Medium
Strickland 2016	PM2.5	Low	Low	Low	Low
Tuan 2016	PM10, SO2, O3	Low	Medium	Low	Medium
Winquist 2012	O3, PM2.5	Low	Medium	Low	Medium
Xiao 2016	CO, NO2, SO2, O3, PM10, PM2.5	Low	Low	Low	Low

Appendix 7.3 Bronchiolitis Individual Studies Risk of Bias

Individual Study	**Pollutant**	**Selection Bias**	**Exposure Assessment**	**Adjustment for Confounders**	**Risk Of Bias**
Karr 2009	PM2.5, PM10, NO2, SO2, CO, O3	Low	Low	Low	Low
Karr 2009	PM2.5, NO2	Low	Low	Low	Low
Karr 2006	PM2.5, NO2, CO	Low	Medium	Low	Medium
Karr 2004	PM2.5, NO2, CO	Medium	Medium	High	High
Girguis 2017	PM2.5	Low	Low	Low	Low
Rahman 2017	PM10, CO, O3, NO2	High	Medium	Medium	High
Karr 2006	PM2.5, NO2, O3, CO	Low	Low	Low	Low
Segala 2007	PM10, NO2, SO2	Medium	Medium	Low	Medium

Appendix 8 – Search strategy for systematic review analysing pharmacogenomics and ADR's in asthma medication

Medline

1. asthma.mp.
2. asthma/
3. 1 or 2
4. Pharmacogenetics.mp.
5. PHARMACOGENETICS/
6. genetic polymorphism.mp.
7. Polymorphism, Genetic/
8. pharmacogenomics.mp.
9. pharmacogenomics/
10. single nucleotide polymorphism/
11. single nucleotide polymorphism.mp.
12. SNP.mp.
13. "Singl* nucleotid* polymorph*".mp.
14. allele/
15. allele.mp.
16. Muscarinic Antagonists/

17. muscarinic antagonist.mp.

18. ipratropium.mp.

19. ipratropium bromide.mp.

20. IPRATROPIUM/

21. atrovent.mp.

22. respontin.mp.

23. Adrenergic beta-2 Receptor Agonists/

24. adrenergic beta-2 receptor agonists.mp.

25. formoterol/

26. formoterol.mp.

27. formoterol fumarate.mp.

28. oxis.mp.

29. atimos.mp.

30. easyhaler.mp.

31. foradil.mp.

32. salmeterol.mp.

33. salmeterol/

34. neovent.mp.

35. serevent.mp.

36. vertine.mp.

37. salbutamol.mp.

38. salbutamol/

39. albuterol/

40. albuterol.mp.

41. ventolin.mp.

42. airsalb.mp.

43. airomir.mp.

44. asmavent.mp.

45. salamol.mp.

46. salbulin.mp.

47. terbutaline.mp.

48. terbutaline/

49. terbutaline
sulfate.mp.

50. bricanyl.mp.

51. 23 or 24 or 25 or 26
or 27 or 28 or 29 or 30
or 31 or 32 or 33 or 34
or 35 or 36 or 37 or 38
or 39 or 40 or 41 or 42
or 43 or 44 or 45 or 46
or 47 or 48 or 49 or 50

52. corticosteroids/

53. corticosteroids.mp.

54. hydrocortisone.mp.

55. hydrocortisone/

56. sodium
succinate.mp.

57. solu-cortef.mp.

58. prednisolone/

59. prednisolone.mp.

60. pevanti.mp.

61. deltacortril.mp.

62. dilacort.mp.

63. beclometasone/

64. beclometasone.mp.

65. beclometasone dipropionate.mp.

66. clenil modulite.mp.

67. clenil.mp.

68. qvar.mp.

69. asmabec.mp.

70. budesonide.mp.

71. budesonide/

72. budelin.mp.

73. pulmicort.mp.

74. symbicort.mp.

75. ciclesonide.mp.

76. ciclesonide/

77. alvesco.mp.

78. fluticasone.mp.

79. fluticasone/

80. flixotide.mp.

81. flutiform.mp.

82. seretide.mp.

83. relvar.mp.

84. mometasone furoate.mp.

85. mometasone furoate/

86. asmanex.mp.

87. beclomethasone.mp.

88. beclomethasone/

89. 52 or 53 or 54 or 55
or 56 or 57 or 58 or 59
or 60 or 61 or 62 or 63
or 64 or 65 or 66 or 67
or 68 or 69 or 70 or 71
or 72 or 73 or 74 or 75
or 76 or 77 or 78 or 79
or 80 or 81 or 82 or 83
or 84 or 85 or 86 or 87
or 88
90. omalizumab.mp.
91. omalizumab/
92. monoclonal
antibodies.mp.
93. monoclonal
antibody.mp.
94. Antibodies,
Monoclonal/
95. xolair.mp.
96. 90 or 91 or 92 or 93
or 94 or 95
97. leukotriene receptor
antagonists.mp.
98. LEUKOTRIENES/
99. leukotrienes.mp.
100. montelukast.mp.
101. Singulair.mp.
102. zafirlukast.mp.
103. accolate.mp.

104. 97 or 98 or 99 or
100 or 101 or 102 or 103
105. mast cell
stabilisers.mp.
106. cromoglicate.mp.
107. mast cells/
108. cromoglicate/
109. nedocromil.mp.
110. tilade.mp.
111. sodium
cromoglicate.mp.
112. sodium
cromoglycate.mp.
113. cromoglycate.mp.
114. cromoglycate/
115. nalcrom.mp.
116. intal.mp.
117. 105 or 106 or 107
or 108 or 109 or 110 or
111 or 112 or 113 or 114
or 115 or 116
118. xanthine.mp.
119. xanthine/
120. aminophylline.mp.
121. aminophylline/
122. phyllocontin.mp.
123. theophylline.mp.
124. theophylline/
125. neulin.mp.
126. uniphyllin.mp.

127. slo-phyllin.mp.

128. slophyllin.mp.

129. 118 or 119 or 120
or 121 or 122 or 123 or
124 or 125 or 126 or 127
or 128

130. 16 or 17 or 18 or 19
or 20 or 21 or 22

131. 51 or 89 or 96 or
104 or 117 or 129 or 130

132. 4 or 5 or 6 or 7 or 8
or 9 or 10 or 11 or 12 or
13 or 14 or 15

133. 3 and 131 and 132

EMBASE

1. asthma.mp.

2. asthma/

3. 1 or 2

4. pharmacogenetics.mp.

5. pharmacogenetics/

6. genetic polymorphism.mp.

7. genetic polymorphism/

8. pharmacogenomics.mp.

9. pharmacogenomics/

10. single nucleotide polymorphism.mp.

11. single nucleotide polymorphism/

12. SNP.mp.

13. singl* nucleotid* polymorph*.mp.

14. allele/

15. allele.mp.

16. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. beta 2 adrenergic receptor stimulating agent/

18. adrenergic beta-2 receptor agonists.mp.

19. formoterol.mp.

20. formoterol/

21. formoterol fumarate.mp.

22. oxis.mp.

23. atimos.mp.

24. easyhaler.mp.

25. foradil.mp.

26. salmeterol.mp.

27. salmeterol/

28. neovent.mp.

29. serevent.mp.

30. vertine.mp.

31. salbutamol.mp.

32. salbutamol/

33. albuterol/

34. albuterol.mp.

35. ventolin.mp.

36. airsalb.mp.

37. airomir.mp.

38. asmavent.mp.

39. salamol.mp.

40. salbulin.mp.

41. terbutaline.mp.

42. terbutaline/

43. terbutaline sulfate.mp.

44. bricanyl.mp.

45. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46. muscarinic antagonist.mp.

47. muscarinic receptor blocking agent/

48. ipratropium.mp.

49. ipratropium bromide.mp.

50. ipratropium/

51. atrovent.mp.

52. respontin.mp.

53. 46 or 47 or 48 or 49 or 50 or 51 or 52

54. corticosteroids/

55. corticosteroids.mp.

56. hydrocortisone.mp.

57. hydrocortisone/

58. sodium succinate.mp.

59. solu-cortef.mp.

60. prednisolone.mp.

61. prednisolone/

62. pevanti.mp.

63. deltacortril.mp.

64. dilacort.mp.

65. beclometasone/

66. beclometasone.mp.

67. beclometasone dipropionate.mp.

68. clenil modulite.mp.

69. clenil.mp.

70. qvar.mp.

71. asmabec.mp.

72. budesonide.mp.

73. budesonide/

74. budelin.mp.

75. pulmicort.mp.

76. symbicort.mp.

77. ciclesonide/

78. ciclesonide.mp.

79. alvesco.mp.

80. fluticasone.mp.

81. fluticasone/

82. flixotide.mp.

83. flutiform.mp.

84. seretide.mp.

85. relvar.mp.

86. mometasone furoate.mp.

87. mometasone furoate/

88. asmanex.mp.

89. beclomethasone.mp.

90. beclomethasone/

91. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90

92. omalizumab.mp.

93. omalizumab/

94. monoclonal antibodies.mp.

95. monoclonal antibody/

96. monoclonal antibody.mp.

97. xolair.mp.

98. 92 or 93 or 94 or 95 or 96 or 97

99. leukotriene receptor antagonists.mp.

100. leukotriene/

101. leukotrienes.mp.

102. montelukast.mp.

103. Singulair.mp.

104. zafirlukast.mp.

105. accolate.mp.

106. 99 or 100 or 101 or 102 or 103 or 104 or 105

107. mast cell stabilisers.mp.

108. cromoglicate.mp.

109. mast cells/

110. cromoglicate/

111. nedocromil.mp.

112. tilade.mp.

113. sodium cromoglicate.mp.

114. sodium cromoglycate.mp.

115. cromoglycate.mp.

116. cromoglycate/

117. nalcrom.mp.

118. intal.mp.

119. 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118

120. xanthine/

121. xanthine.mp.

122. aminophylline/

123. aminophylline.mp.

124. phyllocontin.mp.

125. theophylline.mp.

126. theophylline/

127. neulin.mp.

128. uniphyllin.mp.

129. slophyllin.mp.

130. slo-phyllin.mp.

131. 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130

132. 45 or 53 or 91 or 98 or 106 or 119 or 131

133. 3 and 16 and 132

CINAHL

S101 S99 AND S100

S100 S10 AND S18

S99 S9 OR S40 OR S69 OR S76 OR S87 OR S92 OR S98

S98 S93 OR S94 OR S95 OR S96 OR S97

S97 respontin

S96 atrovent

S95 ipratropium bromide

S94 ipratropium

S93 muscarinic antagonist

S92 S88 OR S89 OR S90 OR S91

S91 xolair

S90 monoclonal antibody

S89 monoclonal antibodies

S88 omalizumab

S87 S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86

S86 intal

S85 nalcrom

S84 cromoglycate

S83 sodium cromoglycate

S82 sodium cromoglicate

S81 tilade

S80 nedocromil

S79 cromoglicate

S78 mast cells

S77 mast cell stabilisers

S76 S70 OR S71 OR S72 OR S73 OR S74 OR S75

S75 accolate

S74 zafirlukast

S73 singulair

S72 montelukast

S71 leukotriene

S70 leukotriene receptor antagonists

S69 S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57

OR S58 OR S59 OR S60 OR S61 OR S62 OR
S63 OR S64 OR S65 OR S66 OR S67 OR S68

S68 beclomethasone

S67 asmanex

S66 mometasone furoate

S65 relvar

S64 seretide

S63 flutiform

S62 flixotide

S61 fluticasone

S60 alvesco

S59 ciclesonide

S58 symbicort

S57 pulmicort

S56 budelin

S55 budesonide

S54 asmabec

S53 qvar

S52 clenil

S51 clenil modulite

S50 beclometasone dipropionate

S49 beclomethasone

S48 dilacort

S47 deltacortril

S46 pevanti

S45 prednisolone

S44 solu-cortef

S43 sodium succinate

S42 hydrocortisone

S41 corticosteroids

S40 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39

S39 bricanyl

S38 terbutaline sulfate

S37 terbutaline

S36 salbulin

S35 salamol

S34 asmavent

S33 airomir

S32 airsalb

S31 ventolin

S30 albuterol

S29 salbutamol

S28	vertine
S27	serevent
S26	neovent
S25	salmeterol
S24	foradil
S23	easyhaler
S22	atimos
S21	formoterol fumarate
S20	formoterol
S19	adrenergic beta-2 receptor agonists
S18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S17	allele
S16	singl* nucleotid* polymorph*
S15	SNP
S14	single nucleotide polymorphism
S13	pharmacogenomics
S12	genetic polymorphism
S11	pharmacogenetics
S10	asthma
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S8	slophyllin

S7 slo-phyllin

S6 uniphyllin

S5 neulin

S4 theophylline

S3 phyllocontin

S2 aminophylline

S1 xanthine

Appendix 9 – Risk of bias assessment for each study

	Cochrane risk of bias tool	**Newcastle Ottawa Score**	**Risk of bias**
Hawcutt[267]	-	9/9	Low
Tan[389]	Low	-	Low
Israel[388]	Low	-	Low
Park[391]	Low	-	Low
Park[390]	Low	-	Low