# Air pollution in Hanoi, Vietnam: Evaluating effects on hospital admissions of children

**INAUGURALDISSERTATION**

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

Der Universität Basel

von

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aus Vietnam

Basel, 2018

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel auf Antrag von

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Basel, 12 December 2017

Prof. Dr. Martin Spiess

Dekan der Philosophisch-Naturwissenschaftlichen Fakultät

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## ACKNOWLEDGEMENT

First, words cannot express my deepest gratitude and thanks to my beloved mother and members of my family, especially my husband, Mr. Vo Van Binh. Without the sacrifice, support and true love of my husband, it would have been impossible for me to overcome the difficulties and challenges of accomplishing this study; he himself has worked hard, without any conditions, to take care of our lovely daughters during my overseas study in Switzerland. I also would like to extend my thanks to my sister-in-law, Ms Nguyen Thi Lan, who has provided tremendous effort and assistance as well as sharing and sympathy to my lovely daughters for the last three years.

I would like to express my heartfelt thanks to my PhD supervisor, Professor Nino Künzli, for his constructive critique, invaluable support and encouragement throughout my living and studying in Switzerland. It was a great honor for me to be his PhD student, not only in terms of research guidance, but also the research and academic freedom granted, and the problem-solving skills and innovative thinking that he trained and motivated me to successfully implement during the research project; all with the aim to provide positive impacts and optimal solutions for tackling the challenges and problems in developing countries, namely air pollution in Vietnam.

Sincere appreciation and thanks go to Dr. Christian Schindler who provided technical supports and in-depth knowledge of statistical analysis techniques and statistical modeling methods. I am truly honored to have had the opportunity to work with him, with all the amazing discussions about the research topics, and with your passion and patience.

Gratitude and acknowledgement also go to Jan Hattendorf, for his support and time taken to find and fix errors in the dataset for this research project. It was also an honor to receive support and advice from Professor Nicole Probst-Hensch and Dr Laura Perez; I am so thankful for their valuable contributions to the outcomes of the research project.

Sincere thanks go to Christine Mensch, Nora Bauer and the other administrative staff at Swiss Tropical and Public Health Institute, Basel, Switzerland. The main work and procedure of the research project would not have been successful without their support and guidance about administrative processes.

I am deeply grateful to Dr Tran Minh Dien, Vice Director of Vietnam National Children's Hospital for all his support during data collection, and for his willingness to share his understanding and extensive knowledge of the clinical issues and treatment procedures.

Big thanks go to the staffs at the Department of Administration of the Vietnam National Children's Hospital, the Center of Environmental Monitoring (Vietnam Environmental Administration), National Hydro-Meteorological Service, and the Lang Meteorological Station for all the support with data collection and documentation for the research project. Without this valuable support, data and materials, the research project could not have been successfully implemented.

My sincere thanks go to colleagues at Hanoi University of Public Health,, Vietnam, especially Dr Bui Thi Tu Quyen, Head of Biostatistics Department and Professor Vu Thi Hoang Lan, Head of Fundamental Faculty. Also, my thanks and appreciations go to Ms Hanh, Ms Ngan, Ms Linh and Mr Hoang for covering my duties at the university and for taking care of my lovely daughters during my time of studying abroad.

Lastly, I thank the Swiss Government Excellence Scholarships (ESKAS) for providing me with a scholarship and the great opportunity to obtain the PhD fellowship at Swiss Tropical and Public Health Institute, Basel, Switzerland.

Finally, special thanks go to my friends and PhD students at the office of 83 Eulerstrasse, Basel, Switzerland, for your friendships, sharing and caring. I would have been terribly homesick in Basel without you all.

# SUMMARY

## Background

Worldwide, pneumonia is responsible for approximately 1.4 million paediatric deaths per year. The prevalence of hospitalization due to pneumonia has been increasing globally, contributing to a large proportion of Disability-Adjusted Life Years (DALY). About 75% of the burden of disease occurs in low-and middle-income countries. In Vietnam, pneumonia is one of the leading causes of childhood hospitalization and deaths, thus, there is a need to determine optimal interventions for preventing childhood pneumonia. To do this, more information about potential risk factors is needed.

Air pollution, particularly outdoor air pollution, is known to be among the leading causes of pneumonia. Evidence of the link between outdoor air pollution and the risk of hospitalization and/or premature death due to pneumonia can be found in numerous epidemiological studies in high income countries. In developing countries, like Vietnam, such data is still sparse. This lack of sufficient specific evidence hinders the public health sector from implementing and promoting different interventions against air pollution in these countries.

The overall aim of the present PhD research was to investigate the short-term effects of ambient air pollution on the daily number of hospital admissions of children and adolescents in Vietnam. Specifically, the work aimed to a) study pneumonia rate trends in Vietnam; b) investigate the existing evidence linking pneumonia hospitalization and outdoor air pollution, globally; and to c) estimate the association between outdoor air pollution and the daily number of hospital admissions of Vietnamese children.

## Method

Data source

Daily means of pollutants, including particulate matter less than 10, 2.5 and 1 microns in diameter ($PM_{10}$, $PM_{2.5}$, and $PM_1$, respectively), sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), nitrogen oxides ($NO_x$), carbon monoxide (CO) and 8-hour moving average of ozone ($O_3$) were derived from fixed monitoring stations in Hanoi, namely Lang, Nguyen Van Cu. All pollutants were expressed in $\mu g/m^3$. Daily means

for temperature ($^0$C), relative humidity (%) and wind speed (m/s) were obtained by averaging values from four stations: Lang, Ba Vi, Son Tay and Ha Dong.

Study approach

Data from the Vietnam National Children's Hospital, covering the period 2007–2014, were analysed to calculate the emergency visit and hospital admissions rates caused by pneumonia in Hanoi's paediatrics unit.

The short-term association between ambient air pollution on hospital admissions of children was determined using two broad approaches: (i) a literature review and meta-analysis of the peer-review publication up to 2017, and (ii) an epidemiological study based on information from the hospital database in Hanoi, Vietnam.

First, the review study summarized existing evidence of the relationship between exposure to air pollution and hospitalization for pneumonia. Then, a time-series analysis with quasi-Poison regression was conducted to investigate the association between ambient air pollution and daily hospital admissions of Hanoi children during the period 2007–2014.

In the summary below, the associations between air pollutants and outcome are presented in percent change (excess risk-ER%).

**Results**

Among the respiratory diseases affecting Hanoi children, pneumonia was responsible for 24.5% of emergency visits (2012–2014), and 54.1% of hospital admissions (2007–2014). Infants made up the group most frequently hospitalized due to pneumonia. Moreover, pneumonia was also the biggest cause of both prolonged hospitalization time and deaths in the hospital among Hanoi children. Rates of infant hospitalization due to pneumonia increased from 19.2 per 1000 children in 2009 to 32.4 per 1000 children in 2014.

Seventeen studies reporting the association between hospitalization for pneumonia and ambient air pollution from Web of Science and PubMed were derived and summarized. Eight of these studies were conducted in high income countries. Meta-analysis using random effect models indicated the positive association between air pollutants and hospital admissions of children worldwide, except CO. The excess risk in percent (ER%) of every 10μg/m$^3$ increment of $PM_{10}$ and $PM_{2.5}$ were 1.5%

(95% confidence intervals (CI): 0.6% to 2.4%) and 1.8% (95% CI: 0.5% to 3.1%), respectively. The ER% of 1000ppb increment of CO, however, was 0.9% (95%CI: 0.0% to 1.9%).

Time series analyses showed positive associations between ambient air pollution and daily numbers of children (aged 0-17) admitted to hospital for pneumonia in Hanoi. The strongest effect was observed for $NO_2$; an interquartile increase in seven-day average $NO_2$ (21.9µg/$m^3$) resulted in a 6.1% (95%CI: 2.5% to 9.8%) increase of hospital admissions for pneumonia. This was followed by $PM_{10}$, whereby the ER% per 66.5 µg/$m^3$ increase in seven-day average concentration of $PM_{10}$ in Hanoi was a 5.8% (95%CI: 2.8% to 9.0%) increase in hospitalizations for pneumonia. The effects of $NO_2$ were stable across both pollutant models. The effects of $PM_{10}$, however, were attenuated upon inclusion of $O_3$. Stronger effects among children aged 1–5 years were observed, compared with infants. The findings also indicate a seasonal influence on the association between ozone and hospitalization due pediatric pneumonia for all ages (0-17).

**Conclusion**

This work provides evidence of the increasing trend of emergency and hospital admission rates among Vietnamese children. Pneumonia infection accounted for a large proportion of hospital admissions, prolonged hospitalization and was a primary cause of deaths at hospital among Vietnamese children.

The findings from the meta-analysis concluded that studies from North America and Europe document associations between exposure to ambient air pollution and pneumonia. This study also suggests that time series analysis is an easy and cost effective study approach for investigating the effects of ambient air pollution, as it uses routine data (i.e. hospital records). It is, thus, an appropriate method to apply in developing countries, such as Vietnam.

The time series study in Hanoi has demonstrated the link between air pollution and hospitalization for pneumonia among Vietnamese children, in which all pollutants except $SO_2$ and $O_3$ were found to have significant associations with an increase in childhood hospitalizations. It is also recommended that $NO_2$ and $PM_{10}$ levels are used as predictors for hospital admission for pneumonia in Vietnam.

# CHAPTER 1: INTRODUCTION

## 1.1 About pneumonia

### 1.1.1 Definitions of pneumonia

Pneumonia is a type of respiratory diseases that is marked by any inflammation in one or two side(s) of the lungs, or fluid or pus in small air sacs (or alveoli) within the lungs (European Respiratory Society, 2017, Marriam-Webster, 2017). This disease is mainly caused by microorganisms such as viruses, bacteria or fungi. Common symptoms of pneumonia include coughing, fever, chills, shortness of breath, and chest pain. The acute form of pneumonia is characterized by the sudden onset of the disease, particularly in young children and the elderly or a chronic form in which progress of disease development is slow.

In resource limited settings, it can be difficult to distinguish pneumonia from bronchitis because the clinical features of these diseases often overlap, particularly among young children (Lanata et al., 2004). Therefore, in some circumstances, the terms “acute lower respiratory tract illness” or “acute lower respiratory infection (ALRI)”, a combination of pneumonia and bronchitis, are used interchangeably in reporting epidemiological studies (European Respiratory Society, 2017).

The definition of childhood pneumonia has not always been consistent as definitions have often depended on the aims, design and settings of particular studies (Lanata et al., 2004, Mulholland et al., 1992, Scott et al., 2012). However, there are two main broad definitions, whereby one is based on clinical symptoms and the other on physician’s diagnosis. The typical clinical symptoms are fast and difficulty breathing, and chest wall indrawing (Lanata et al., 2004, Roth et al., 2008). Physician diagnoses are based on clinical symptoms and clinical signs from chest radiography, complete blood count, erythrocyte sedimentation rate (Harris et al., 2011, Lynn M. Taussig and Landau, 2008, Victor Chernick and Kendig, 2006) and microbiological analysis (European Respiratory Society, 2017, Harris et al., 2011, Lanata et al., 2004)

### 1.1.2 Burden and economic consequences of pneumonia

Pneumonia is a primary cause of deaths among children (Walker et al., 2013). In 2010, approximately 1.2 million children worldwide died of severe pneumonia (Walker et al., 2013). Incidence rates of pneumonia differ substantially from region to region, with rates of incidence and case-fatality in low- and middle-income countries (LMIC) being much higher than those in high-income countries. For example, in 2010 incidence of pneumonia in the Eastern Mediterranean and African regions was 0.23 and 0.27 episodes per child-year, respectively; while in European countries, it was 0.03 episodes per child-year (Walker et al., 2013). Incidence of pneumonia in Southeast Asia region including Vietnam was about 0.26 episodes per child-year in 2010. Also, total of deaths among children under five years old in the region was 443.8 thousand (Walker et al., 2013).

In Vietnam, pneumonia accounted for 11% of the total burden of disease in children under 15 years of age and for 11% of total deaths among children under five, in 2008 (Nhung et al., 2014). The incidence of acute respiratory infection in the first year of life was 1,363 per 1,000 infant-years according to data from a semi-rural cohort in Ho Chi Minh and Dong Thap (Anders et al., 2015).

Previous studies have demonstrated that the economic cost of pneumonia is enormous. A Turkish study of 130 children revealed that costs for health care services (including hospital bed, examination, laboratory analyses, scanning methods, etc.) for pneumonia patients in 2014 was about EUR 480.60 per patient. Moreover, this cost increased 1.5 times after accounting for indirect costs (including parents' lost work time, transportation expenses, etc.) of EUR 330.10 per patient (Ceyhan et al., 2017). Another study, conducted in Italy, reported mean costs to hospital management of EUR 1,435 per pneumonia patient, with costs increasing to EUR 2,553 for those using intravenous antibiotics (Di Ciommo et al., 2002). The United Kingdom annually spent GBP 13–20 million for hospitalization children with pneumonia (Harris et al., 2011). The treatment costs for a pneumonia case in Vietnam was about USD 31 (Anh et al., 2010).

### 1.1.3 Causes and risk factors of pneumonia

Childhood pneumonia is caused by a wide range of agents, such as bacteria, viruses, protozoa and fungi (European Respiratory Society, 2017, Ewig, 1999, Ruiz

et al., 1999). Among them, *Streptococcus pneumoniae* is the most common causative bacteriological agent of pneumonia worldwide (The World Health Organization, 1991). *Haemophilus influenzae* type b and respiratory syncytial virus are the second and third leading causative agents for childhood pneumonia (Shi et al., 2017). In the Western Pacific Region, *Mycoplasma pneumonia* is the most frequent atypical bacteria among pneumonia patients (Phuong et al., 2017). In Vietnam, *rhinovirus*, respiratory syncytial virus, and influenza virus were the most commonly detected viruses among infants with pneumonia in the South (Anders et al., 2015), while *Mycoplasma pneumonia, Legionella pneumophila,* and *Chlamydophila pneumonia* are the most common pathogens causing pneumonia in the North (Huong P et al., 2014)).

Factors that contribute to paediatric pneumonia infection include age, sex, nutrition status, quality of air, water sanitation and having other comorbidities such as HIV infection (Jackson et al., 2013, Lamberti et al., 2013). The number of hospital admissions due to pneumonia among children less than two years of age are higher than that for older children (Harris et al., 2011). Walker et al. (2013) also estimated that nearly 81% of pneumonia deaths occurred in children less than two years of age. The incidence of pneumonia was higher in boys than in girls (Harris et al., 2011). Pneumonia-related deaths usually occurred amongst children who were not breastfed optimally and/or malnourished (Chisti et al., 2009, Lamberti et al., 2013, Sonego et al., 2015). Lack of immunization for measles and/or influenza is another know risk of pneumonia infection during childhood (Harris et al., 2011, Jackson et al., 2013, Sonego et al., 2015). Environmental factors, including indoor air pollution from solid fuel, inadequate housing space and exposure to tobacco smoke were also associated with childhood pneumonia infections (Cardoso et al., 2004, Mahalanabis et al., 2002, Suzuki et al., 2009). Last but not least, ambient air pollution is an underlying factor for ALRI in children worldwide (Mehta et al., 2013).

In Vietnam, age of the child, mother's education level, having an older sibling, exposure to tobacco smoke, and lack of exclusive breastfeeding were found to be potential risk factors of childhood pneumonia (Anders et al., 2015, Hanieh et al., 2015, Huong P et al., 2014, Suzuki et al., 2009). In addition, in a study conducted in Ho Chi Minh and Dong Thap provinces (South Vietnam), Anders et al. (2015) demonstrated that influenza virus A and respiratory syncytial virus were frequently

isolated among patients with pneumonia during the rainy seasons (between July and October), whereas rhinovirus and bocavirus were mostly isolated throughout the whole year.

### 1.1.4 Management and treatment

Since pneumonia is a leading cause of hospitalization and premature deaths among children, any intervention for preventing this disease would have a positive impact on public health. To date, interventions mainly focus on eliminating risk factors and vaccinating against pathogens (Harris et al., 2011, The World Health Organization, 1991). Nutrient supplementation, such as with zinc, vitamin A, iron, and folic acid, could decrease mortality rates due to ALRI by 5% to 20% (Roth et al., 2008). Lamberti et al. (2013) indicated that breastfeeding could reduce 15% of all hospitalizations caused by ALRI in children. Vaccination with *Haemophilus influenzae* and *Streptococcus pneumoniae* is another way to prevent pneumonia infections in children, worldwide (Cohen et al., 2012, Harris et al., 2011, Shann et al., 1999).

Treatment with antibiotics is the best option to prevent bacterial pneumonia fatalities (Harris et al., 2011, Shann et al., 1984, The World Health Organization, 1991). It is estimated that 75% of acute lower respiratory patients were prescribed antibiotics (Di Ciommo et al., 2002). However, irrational use of antibiotics may cause other problems, like the so-called “super resistance” of bacteria, which is currently an emerging phenomenon (Cohen et al., 2012, Di Ciommo et al., 2002, Garau, 2002, Harris et al., 2011, Shann et al., 1984). This phenomena is even worse in developing countries, such as Vietnam, where antibiotics are used unnecessarily and irrationally (Phuong et al., 2017, The World Health Organization, 2017). Therefore, in such settings, preventative interventions against pneumonia are preferred.

## 1.2 Pneumonia and air pollution

### 1.2.1 Pollutants

Air pollutants get in the air from sources like factory chimneys or motor vehicle exhaust pipes (so called primary pollutants) or can be created by chemical reactions within the atmosphere (World Health Organization, 2006). Popularly primary pollutants are particulate matter (PM), sulfur dioxide ($SO_2$), carbon monoxide (CO), nitrogen dioxide ($NO_2$), and some volatile organic compounds (World Health

Organization, 2006). PM with diameters less than 10µm, 2.5µm and 1µm are denoted as $PM_{10}$, $PM_{2.5}$ and $PM_1$, respectively. Pollutants such as CO and $NO_2$, mainly come from vehicle emissions during the fossil fuel combustion process, also known as traffic-related air pollution.

A secondary air pollutant is ground level ozone ($O_3$), generated by reactions of $NO_x$ and hydrocarbons under the presence of ultraviolet light (World Health Organization, 2006).

### 1.2.2 Effects of air pollution on pneumonia: Evidence from experimental studies

Inhalation of PMs and other pollutants generate oxidative stress, activating inflammation in the pulmonary system (Li et al., 2008, Xing et al., 2016). Additionally, ozone, known as a highly active gas, is strongly associated with oxidative stress (Mudway et al., 1999, Saintot et al., 1999). Evidence from an animal study shows that exposure to high concentration levels of $NO_2$ also impairs the function of alveolar macrophages and epithelial cells, consequently increasing the risk of lung infections (Frampton et al., 1989).

It is hypothesized that metal compounds in $PM_{2.5}$ interact with *Mycoplasma pneumoniae* via Toll-like receptors and/or the factor-kappa B pathway to modulate the human immune system (Hou et al., 2016). Mushtaq et al. (2011) pointed out that exposure to $PM_{10}$ and $PM_{2.5}$ may increase *Streptococcus pneumoniae* adhesion to airway epithelial cells. Ambient air pollutants exacerbate the alveolar macrophage, consequently decreasing the host's ability to take up and clear inhaled *Streptococcus pneumoniae* cells (Zelikoff et al., 2003, Zhou and Kobzik, 2007).

### 1.2.3 Pneumonia and air pollution: evidences from epidemiology studies

Since 1952, when the number of deaths surged during the great smog in London, the effects of air pollution on illness and deaths have been taken much more seriously and are now well documented. The information has led researchers to conclude that there is an existing association between ambient air pollutants and pneumonia hospitalization, as well as pneumonia-related deaths. A study conducted in Utah Valley (Pope, 1991) showed that the annual number of admissions due to pneumonia increased by 17% during the years when a steel mill operated, compared with the years when the steel mill was closed. In a cross-sectional study, Hruba et al.

(2001) found that an increase in pneumonia cases was associated with an increase in $PM_{2.5}$. A cohort study showed that bronchiolitis rates in infants increased with increased pollutant concentrations, such as $PM_{2.5}$ and $O_3$ (Hertz-Picciotto et al., 2007, Karr et al., 2007). The association between $SO_2$ and numbers of children with *Streptococcus pneumonia* infections was also demonstrated in the study by Kim et al. (1996) in the United States of America, and further supported by the study by Murdoch and Jennings (2009) in New Zealand. However, the findings from seven cohort studies in Europe did not show any significant association between elements of PM and pneumonia in infancy (Fuertes et al., 2014). Both long-term effects and short-term effects of air pollutants on pneumonia in adults have been summarized in numerous reviews (Atkinson et al., 2014, Ji et al., 2011, Pinault et al., 2017).

### 1.2.4 Burden of ambient air pollution

Air pollution has been confirmed as a substantial cause of morbidity and mortality worldwide, resulting in major public health impacts and millions of dollars lost (Forouzanfar et al., 2015, Landrigan et al., 2017). The number of deaths related to air pollution is three times that of AIDS, tuberculosis and malaria combined (Landrigan et al., 2017). $PM_{2.5}$ is ranked as the fifth cause of mortality among the risk factors presented in the Global Burden of Disease 2015, accounting for 4.2 million deaths and 103.1 million disability-adjusted life-years (DALYs) (Cohen et al., 2017). Moreover, ozone caused about 254,000 deaths and 4.1 million DALYs in the same year. From an economic point of view, air pollution is costly. Annually, it is estimated that approximately USD 4.6 trillion of the global wealth is lost due to air pollution (Landrigan et al., 2017). The World Bank estimated that losses of labour income related to exposure of $PM_{2.5}$ were approximately USD 144 billion per year in 2013 (The World Bank and Institute for Health Metrics and Evaluation, 2016). Health-care costs for air pollution-related diseases accounted for 7% of total health expenses in the developing world.

## 1.3 Children and air pollution

Children are the most susceptible to ambient air pollution. Children's lungs, immune system, and other organs are still developing (Schwartz, 2004) and, hence, vulnerable to pollutants and infectious agents. The lung epithelium in children does not completely develop until six years of age. Therefore, exposure to air pollutants

may cause adverse health consequences not only in childhood but also later in life. Epidemiological studies report that children who suffered from ALRI, including pneumonia, in the early years of life might experience decreased lung function in later life or even contract chronic obstructive pulmonary diseases in adulthood (Henderson et al., 1992, Shaheen et al., 1994, Voter et al., 1988). Moreover, children tend to spend more times outside than adults, particularly in summer and in the afternoon when concentration levels of some pollutants, such as ozone or particulate matter, are high. Also, children are more active when they are outdoors, which may increase ventilation effects and lead to more exposure to air pollution.

## 1.4 Air pollution and its health impact in Vietnam

### 1.4.1 Air pollution and emitted sources of air pollution in Vietnam

Atmospheric quality in Vietnam is very poor, particularly in big cities such as Hanoi and Ho Chi Minh. Pollutant concentration in Hanoi and Ho Chi Minh cities are frequently higher than the guideline values recommended by the World Health Organization (WHO) to protect public health (Ho and Clappier, 2011). The daily mean of $PM_{2.5}$ concentration varied from 10 µg/$m^3$ to 143 µg/$m^3$ in Hanoi in 2007. The percent of days with levels of Air Quality Index (AQI) above 100 (unhealthy level for sensitive groups) accounted for 40% to 60% of total monitoring days in Hanoi between 2013 and 2014. More than approximately 60% of monitoring days in 2013 in Ho Chi Minh city exceeded the 50µg/$m^3$ (the WHO limit values for public health safety)(Ho and Clappier, 2011, Ministry of Natural Resources and Environment, 2014)

Transportation and industrial activities are the main sources of air pollution in Vietnam (Bang et al., 2017, Hai and Oanh, 2013, Ho, 2017, Huy and Kim Oanh, 2017, Ministry of Natural Resources and Environment, 2014). These emissions contribute to 80% of NO, 90% of $SO_2$, 75% CO and 60% of PM concentrations in Can Tho (Bang et al., 2017). Buses and trucks are usually old or obsolete, and some motorcycles have no pollution control (Ministry of Natural Resources and Environment, 2014). In the meantime, industrial activities, particularly the cement and construction material production sector, contributed to a large proportion of particulate matter in suburban areas. Nearly 70% of total suspended particles (TSP) in suburban areas were caused by cement factories (Ministry of Natural Resources

and Environment, 2014). Besides that, steel and metal productions are also responsible for high concentration levels of $NO_x$ and $SO_2$ (Bang et al., 2017, Ho, 2017).

Electricity power production and other daily activities have also contributed significantly to the deterioration of air quality in Vietnam (Bang et al., 2017, Ho and Clappier, 2011, Trang et al., 2015). Electricity power production in Vietnam mainly relies on coal. It is projected that the number of coal-fired power plants will increase from 38 in 2011 to 133 in 2030. If the projection is correct, it will result in the tripling of $SO_2$ and $NO_x$ concentration levels, approximately 0.63 Tg/a for $SO_2$ and 0.69 Tg/a for $NO_2$, respectively (Koplitz et al., 2017). Other sources of emission can also be indexed in Vietnam, but not in other countries, like using coal for cooking in both household and roadside restaurants, burning trash and rubbish (i.e. plastic bags) in public places (Ministry of Natural Resources and Environment, 2014). In Hanoi, commercial/residential activities accounted for 16% of $PM_{2.5}$ concentrations (Hai and Oanh, 2013).

### 1.4.2 Health impact of air pollution in Vietnam

Table 1 shows the number of deaths attributable to $PM_{2.5}$ for all ages by all causes and by lower respiratory infection in particular, from 1990 to 2015 in Vietnam, according to the Global Burden of Disease (Cohen et al., 2017). Fine particulate matter ($PM_{2.5}$) accounted for 6.8% of total of deaths, equivalent to 42.2 thousand deaths in Vietnam in 2015. $PM_{2.5}$ contributed to 21.5% of total DALYs for lower respiratory diseases. A recent study indicated that premature deaths due to coal emissions in Vietnam was about 4,250 cases in 2011 and is projected to increase to approximately 19,223 cases in 2030 (Koplitz et al., 2017).

In the cities, existing evidence shows that $PM_{10}$ caused 1,287 deaths and 44,954 hospital admissions in 2007 in Hai Phong (Dhondt et al., 2011). The number of deaths caused by $PM_{10}$ in Hanoi was estimated at 3,200 cases in 2009 (Vu Van Hieu et al., 2013). The authors also emphasized that numbers of deaths caused by outdoor air pollution was higher than the number of deaths caused by traffic accidents in these cities (Dhondt et al., 2011, Hieu et al., 2013).

Table 1: Number of attributable deaths (in thousands) to $PM_{2.5}$ for all causes and lower respiratory infections in Vietnam from 1990 to 2015.

| Year | Number of attributable deaths (in thousands) | |
|---|---|---|
| | All causes | Lower respiratory infections |
| 1990 | 26.3 | 6.0 |
| 1995 | 29.0 | 5.0 |
| 2000 | 31.9 | 4.3 |
| 2005 | 35.8 | 4.7 |
| 2010 | 37.0 | 4.6 |
| 2015 | 42.2 | 4.9 |

### 1.4.3 Short-term effects of air pollution in Vietnam

A study in Ho Chi Minh city reported that the effects of 10 $\mu g/m^3$ increases for $NO_2$ and $SO_2$ increased hospitalization for ALRI among children under six years of age by 4.3% (95% confidence interval (CI) = 0.1% to 8.8%) and 5.0% (95%CI: 0.8% to 9.3%), respectively (Le et al., 2012). The results of the study marked different effects when the analyses stratified by season. Another study from Ho Chi Minh city estimated that a 10$\mu g/m^3$ increase in $PM_{10}$, $NO_2$ and $SO_2$ concentration was associated with a 0.7% (95% CI: 0.2% to 1.3%), 8% (95% CI, 6% to 11%), 2% (95% CI, 1.0% to 3%) increase in hospital admissions for respiratory diseases. The study did not observe any evidence of different effects between males and females (Phung et al., 2016).

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# CHAPTER 2: RESEARCH NEEDS, OBJECTIVES AND STUDY HYPOTHESES

## 2.1 Research needs

Similar to other emerging economies, Vietnam has experienced rapid economic development, industrialization and urbanization. The population in urban regions has increased dramatically (Vietnam Ministry of Health, 2016). The numbers of private cars and motorcycles in megacities like Hanoi have increased sharply in recent years. Construction areas have been expanding and are usually located near areas with dense populations. Taken together, these factors have led to concentrations of air pollutants that far exceed the limits of both Vietnam's air quality standards (Ministry of Natural Resources and Environment, 2014) and the air quality guidelines recommended by the WHO (World Health Organization, 2006), as discussed in section 1.3.1.

Though evidence of the health effects of exposure to ambient air pollution have been documented elsewhere, data from Vietnam is scarce. Concentration-response function (CRF), the essential parameter of health impact assessment (HIA) of air pollution, is usually absent. Alternatively, HIA studies of Vietnam (discussed in section 1.3.2) use CRF, which has been derived from countries where emission sources may differ, as presented in section 1.3.1. Additional lack of local evidence might pose a barrier to pursuing policies against air pollution in Vietnam. In addition, to predict the benefit of clean air policies on health — such as those documented in a Swiss landmark study (Bayer-Oglesby et al., 2005) — or to compare the cost-effectiveness of clean air strategies versus provision of health-care costs in Vietnam, information from local data is essential.

This PhD project was developed based on this background and mainly focused on understanding the role of air pollution in Hanoi, ultimately, to raise awareness among local authorities of the effects of air quality problems on health.

## 2.2 Hypotheses

The study was based on the following hypotheses

> *Hypothesis 1*: The rates of emergency visits and hospital admissions due to pneumonia in Hanoi children increased from 2007 to 2014

*Hypothesis 2*: Increased exposure to ambient air pollution would be associated with an increase in the daily number of hospital admissions of Hanoi children

## 2.3 Objectives

The aim of this project is to provide evidence of the impact of air pollution on health in Hanoi by using state-of-the-art methodologies and statistical methods. To achieve the aim, it is necessary to:

*I)* Investigate the trend of emergency visits and hospital admissions rates caused by pneumonia in Hanoi children for the period 2007–2014

*II)* Investigate the association between daily levels of pollutant concentrations and daily numbers of hospital admissions due to pneumonia in children.

## 2.4 Structure of the thesis

The topic of this work focuses on the short-term effects of ambient air pollutant exposure and hospital admissions due to pneumonia in children. **Chapter one** reviewed the basic concepts, burden of disease of pneumonia and the context of pneumonia infections in Vietnamese children. **Chapter two** presented detailed information on the study goal, specific objectives and hypotheses. General patterns, including rates of emergency visits and hospital admissions, lengths of hospital stays, and leading causes of hospital deaths among Hanoi children, is documented in **chapter three**. Next, **chapter four** presents a systematic review and meta-analysis study of the relationship between exposure to ambient air pollution and increasing daily hospital admissions of children. **Chapter five** addresses the effects in the Vietnamese context by conducting time-series analyses. This chapter is also at the heart of this work. The analysis was thoughtfully conducted for nine pollutants, combining both single-pollutant and two-pollutant models. Specific estimates by gender and seasons are provided. **Chapter six** discusses the contributions and comparisons of this work. **In chapter seven**, I will present the outlook and conclusion of this work.

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# CHAPTER 3: CHILDHOOD HOSPITALISATION AND RELATED DEATHS IN HANOI, VIETNAM: A TERTIARY HOSPITAL DATABASE ANALYSIS FROM 2007 TO 2014

The article was published as:

NGUYEN, N. T. T., DIEN, T. M., SCHINDLER, C., LIEN, N. T. B., PROBST-HENSCH, N., LAN, V. T. H., KUNZLI, N. & PEREZ, L. 2017. Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014. *BMJ Open,* 7**,** e015260.

BMJ Open

# Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014

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**To cite:** Nguyen NTT, Dien TM, Schindler C, *et al*. Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014. *BMJ Open* 2017;**7**:e015260. doi:10.1136/bmjopen-2016-015260

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/ 10.1136/bmjopen-2016-015260).

Received 23 November 2016
Revised 25 April 2017
Accepted 1 June 2017

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## ABSTRACT

**Objective** To describe hospital admission and emergency visit rates and potential risk factors of prolonged hospitalisation and death among children in Hanoi.

**Study design** A retrospective study reviewed 212 216 hospitalisation records of children (aged 0–17) who attended the Vietnam National Children's Hospital in Hanoi between 2007 and 2014. Four indicators were analysed and reported: (1) rate of emergency hospital visits, (2) rate of hospitalisation, (3) length of hospital stay and (4) number of deaths. The risk of prolonged hospitalisation was investigated using Cox proportion hazard, and the risk of death was investigated through logistic regressions.

**Results** During 2007–2014, the average annual rate of emergency visits was 2.2 per 1000 children and the rate of hospital admissions was 13.8 per 1000 children. The annual rates for infants increased significantly by 3.9 per 1000 children during 2012–2014 for emergency visits and 25.1 per 1000 children during 2009–2014 for hospital admissions. Digestive diseases (32.0%) and injuries (30.2%) were common causes of emergency visits, whereas respiratory diseases (37.7%) and bacterial and parasitic infections (19.8%) accounted for most hospital admissions. Patients with mental and behavioural disorders remained in the hospital the longest (median=12 days). Morbidities related to the perinatal period dominated mortality causes (32.5% of deaths among those admitted to the hospital. Among the respiratory diseases, pneumonia was the leading cause of both prolonged hospitalisation and death.

**Conclusions** Preventable health problems, such as common bacterial infections and respiratory diseases, were the primary causes of hospital admissions in Vietnam.

## Strengths and limitations of this study

- The study capitalised on the availability of hospital records from the biggest tertiary hospital in Northern Vietnam, with 1300 beds.
- The data compiled 8 years (2007–2014) of information, revealing hospital admission and emergency visit trends for all diagnoses and potential predictors of prolonged stays and death in hospital.
- The study does not capture information about socioeconomic conditions, environmental factors and crowding.
- No distinction was made between new visits and readmission of the same patients.
- The data come from one tertiary hospital only.

## INTRODUCTION

Many families in low-income and middle-income countries rely on hospital visits to receive a broad range of healthcare. Hospital registries in these settings are an administrative tool and can provide objective information on the state of health of the population.[1] Hospitalisation patterns can reveal opportunities for better care and prevention, identify emerging threats and assist in setting relevant public policies.[2–4]

In Vietnam, extensive information about childhood health patterns is readily available through national reports, such as the Country Report[5] or the Annual Report Statistic, published by the Vietnam Ministry of Health.[6] These reports show a declining trend in childhood mortality, from 58.0 per 1000 live births in 1990 to 23.2 per 1000 live births in 2012.[5] However, the reports are limited to presenting rates of malnutrition, immunisation coverage and the absolute number of cases of and deaths due to some vaccine-preventable infectious diseases, like measles, tuberculosis, typhoid fever, diphtheria and neonatal tetanus.[6] Evidence has shown that the leading causes of premature deaths among Vietnamese children are infectious diseases and drowning.[6–8] Yet information on rates of disease or death due to other common paediatric pathologies, as well as quality-of-care indicators for these diseases, is still missing from national records.

To address this gap, we collected data from the electronic registry of the Vietnam National Children's Hospital (VNCH) in Hanoi for all children under 18 years of age, who were residents of Hanoi (27% of the total Hanoi population) and who were hospitalised and discharged between 2007 and 2014. With 1300 beds and 13 clinical departments, VNCH is the largest tertiary care centre for children in Northern Vietnam. Every day, approximately 2000–3000 children visit the hospital for a health check-up. Of these, 200 children are admitted to the hospital as inpatients. According to the 2016 annual report of the VNCH,[9] 95% of Hanoi children visited the hospital directly via the VNCH's outpatient department. Only 5% of all patients were transferred from the provincial hospital (Saint Paul) or from other sector hospitals, such as Post Hospital. About 10% of hospital admissions went through the emergency room; these included severe cases of respiratory, liver or heart failure. Scheduled outpatient visits accounted for about 0.05% of all admissions.[9]

Our analysis aimed to understand the patterns and time trends of paediatric hospitalisations in Vietnam. We evaluated the rates of emergency visits, hospital admissions and deaths, as well as the length of hospital stay (LOS), among Hanoi children. We examined how these indicators vary by diagnoses, age, sex and residential location.

## METHODS

### Hospital data source

We obtained individual inpatient records from the VNCH electronic database, covering the period from 2007 to 2014. The hospital records included patient identification, gender, date of birth, home address, date of admission, discharge diagnoses (including codes according to the International Classification of Diseases, 10th Revision (ICD10), and disease name), date of discharge and health status at discharge. With the exception of the emergency department, all hospital departments collected data electronically from 2007. The emergency department commenced electronic data collection beginning in 2012. We included the records of children with residence in Hanoi only. Ethical approval was obtained from the ethical committee of the VNCH. Quality control and quality assurance processes were developed and implemented to ensure the validity of data (online supplementary file 1).

### Outcome indicators

We analysed the database to obtain the following indicators: (1) rates of emergency visits and hospital admissions by age group and sex, (2) percentage of emergency visits, hospital admissions and deaths by diagnoses and age group, and (3) predictors of prolonged LOS and death. Age at admission year was classified into three groups: <1 year, 1–4 years and 5–17 years.

Emergency visits were defined as admission to and discharge from the hospital on the same day. Emergency room data were only collected electronically from 2012; thus, we present data for the period 2012–2014. Average annual rates of emergency visits per 1000 children were computed by dividing the average annual number of emergency visits (in a 3-year period) by the size of the age–sex-specific population of Hanoi children in 2013.

Hospital admissions were defined as hospital stays for at least one night. Average annual rates of hospital admission per 1000 children were calculated as the average annual number of hospital admissions divided by the population of Hanoi children in 2010. Analyses were stratified by age and sex. We described disease frequencies for different discharge diagnoses according to ICD10's main chapters (online supplementary file 1). We additionally considered subgroups of respiratory diseases, including pneumonia (ICD10 J12-J18), bronchitis (ICD10 J20, J21), asthma (ICD10 J45), influenza (ICD10 J11), upper respiratory diseases (ICD10 J00-J06) and other respiratory diseases (ICD10 J07-J10, J19, J22-J44, J46-J99), as these diseases are the main causes of hospitalisation in most low-income and middle-income countries. To illustrate trends in the annual number of hospitalisations and emergency visits, we analysed these rates for children under age 5 from 2009 to 2014. Children under age 5 were chosen specifically because illnesses in this age group can affect the development of children later in life. We also derived annual hospitalisation rates of pneumonia, asthma, influenza, upper respiratory disease and gastroenteritis (ICD10 A08-A09) for children under 5.

The population size of Hanoi children was derived from one of two sources, depending on the year. Population data for 2009 were extracted from the 2009 population census, as reported by the General Statistics Office.[10] Population data for all other years were obtained from the respective annual population reports published by the Hanoi Population and Family Planning Branch (HPFPB).[11] Information in the 2009 population census was published elsewhere.[10] In this study, we only used age-specific and gender-specific information for the Hanoi population. The HPFPB derives data from quarterly updated censuses conducted by collaborators at the community level.

### Predictor analysis

We used Cox proportion hazard regression to evaluate the risk of prolonged hospitalisation (or LOS) as a function of potential predictors including age, sex, residential location, year of admission and diagnosis. Stays of deceased children were not included in these analyses. Residential location was classified into three groups, namely inner city, outer city and unidentified location (online supplementary file 1). We defined LOS as the number of nights a child stayed in the hospital, calculated as the date of discharge minus the date of admission. Since LOS in the hospital was not normally distributed, both mean and median of LOS were reported. Hazard ratios (HRs) >1 mean that patients in the respective group were, on average, discharged earlier (shorter hospital stay) than

those in the reference group. Since HRs varied over time for most of the predictor variables, we presented HRs for those discharged the day after a one-night stay and following a five-night stay in the hospital ($HR_1$ and $HR_5$).

Similarly, to assess the contribution of predictors of death during hospitalisation, we performed logistic regressions with a predefined set of predictor variables consisting of age group, sex, residence location and year of admission. Separate models were computed for children who made emergency visits and for children who were admitted to the hospital. Two additional logistic regression models were developed, including indicator variables for respiratory diseases, to evaluate the risk of death from respiratory diseases. To define 'death', we combined two adverse outcomes, namely death at the hospital and 'worse' as a heath status at discharge. Culturally, Vietnamese people wish their family members to experience their last moments of life at home. Therefore, children in terminal states, with little chance of survival, were sent home at the family's request to die at home. In such cases, health status at discharge was usually coded as 'worse'. Results were considered statistically significant if two-sided p values were below 0.05. All analyses were conducted using Stata V.13.1.

## RESULTS

### Emergency room visits

Between 2012 and 2014, there were 12 389 paediatric emergency visits to the VNCH originating from Hanoi. This corresponds to an average annual rate of 2.2 visits per 1000 children (table 1). Emergency visit rates were higher among boys than among girls (2.6 vs 1.7 visits per 1000 children, respectively). The average rate of emergency visits was highest among infants, with 5.6 visits per 1000 infants, followed by children aged 1–4 years, with approximately 5.5 visits per 1000 children (table 1).

Across all ages, diseases of the digestive system accounted for the largest proportion (32.0%) of all emergency visits. Injuries ranked second (30.2%). Respiratory diseases (11.4%) and bacterial infections (7.8%) were also important causes of emergency visits (figure 1). This ranking differed across age groups. For infants, digestive diseases (39.6%) were followed by respiratory infections (17.1%) as the leading causes of emergency visits, whereas for children aged 1–4, digestive diseases (34.3%) and injuries (32.9%) were the leading causes, followed by respiratory diseases (10.3%). Injuries were the prime reason for emergency visits (41.3%) among children aged 5–17 years (figure 1). Online supplementary file 1 provides percentages of emergency visits for each group.

Of the respiratory diseases, upper respiratory illness was the primary cause (46.0%) for emergency visits. Among infants, pneumonia was the leading respiratory cause for emergency visits (41.1%) (online supplementary file 1).

### Hospital admissions

VNCH data show that 199 827 children from Hanoi were hospitalised between 2007 and 2014. This translates into an average annual hospitalisation rate of 13.8 per 1000 children. Hospitalisations were also higher among boys than among girls (16.9 per 1000 boys compared with 10.4 per 1000 girls). The hospital admission rate was more than three times higher for infants than for children aged 1–4 years (85.7 per 1000 vs 23.4 per 1000 children, respectively) (table 1).

Respiratory diseases were the most frequent, accounting for 37.7% of all hospital admissions. Bacterial and parasitic infections were the second most common disease group (19.8%), followed by digestive disorders (10.2%)

**Table 1** Number, percentage and annual rate of emergency visits and hospital admissions of Hanoi children referred to the National Children Hospital in Vietnam, by gender and age group

| | Emergency visits (2012–2014) | | | Hospital admissions (2007–2014) | | |
|---|---|---|---|---|---|---|
| Variable | N | % | Rate per 1000* | N | % | Rate per 1000† |
| All | 12 389 | 100 | 2.22 | 199 827 | 100 | 13.82 |
| Gender | | | | | | |
| Female | 4481 | 36.2 | 1.72 | 70 631 | 35.4 | 10.38 |
| Male | 7908 | 63.8 | 2.65 | 129 196 | 64.7 | 16.88 |
| Age group | | | | | | |
| <1 | 2387 | 19.3 | 5.55 | 81 648 | 40.9 | 85.74 |
| 1–4 | 7765 | 62.7 | 5.47 | 88 061 | 44.1 | 23.42 |
| 5–9 | 1883 | 15.2 | 1.13 | 23 470 | 11.8 | 6.28 |
| 10–14 | 339 | 2.7 | 0.26 | 6184 | 3.1 | 1.69 |
| 15–17 | 15 | 0.1 | 0.02 | 464 | 0.2 | 0.20 |

*Annual mean rate of emergency visits (per 1000 children)=1000×annual mean number of cases (2012–2014)/number of children in the respective gender or age group, using the midyear 2013 Hanoi children population as denominator.
†Annual mean rate of hospital admissions (per 1000 children)=1000×annual mean number of hospital admissions (2007–2014)/number of the respective gender or age using the midyear 2010 Hanoi children population as denominator.

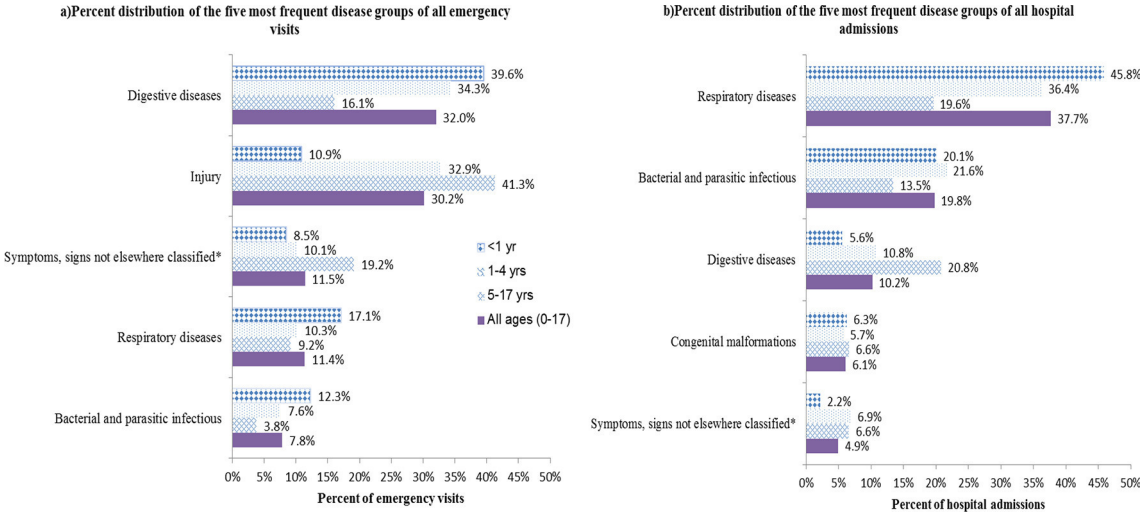


**Figure 1** Distribution of the five most frequent diagnoses among (A) emergency visits (2012–2014) and (B) hospital admissions (2007–2014) in Hanoi children, stratified by age group. *Symptoms, signs not elsewhere classified are defined as discharge diagnoses from the International Classification of Diseases, 10th Revision code from R10-R19, which included abdominal or pelvic pain, nausea and vomiting.

(figure 1). This trend was consistent across age groups, except in the case of infants where diseases related to the perinatal period (birth trauma, haemorrhagic disorder of fetus and newborn, and so on) ranked as the third leading cause of hospital admissions (9.0%) (online supplementary file 1).

Of the respiratory disease-related admissions, pneumonia accounted for 54.1% and bronchitis for 19.1%. Among infants, pneumonia accounted for 66.8% of all respiratory disease-related admissions. Pneumonia and upper respiratory diseases were the leading causes of hospital admissions among children aged 1–4 years (45.5% and 27.9%, respectively) (online supplementary file 1).

## Predictors of hospitalisation and LOS

Across all types of stays, the average length of hospitalisation was 5.2 nights. Except for infants, the average length of hospitalisation increased with age, from 4.3 nights for children aged 1–4 years to 6.9 nights for adolescents (table 2). Boys were more likely to have shorter stays than girls. Children living in the outer regions of the city had a significantly higher likelihood of longer stays than children residing in the inner city ($HR_1$=0.86, 95% CI 0.85 to 0.87). In general, having been hospitalised due to a non-communicable disease increased the LOS, compared with having been hospitalised due to a communicable disease. For instance, the average LOS of patients with mental and behaviour-related diseases was 12.2 nights, compared with 3.8 nights for those with bacterial and parasitic infections (data not shown). Table 2 shows the top 5 disease groups with the longest hospital stays; all five are non-communicable diseases, with mental health disorders at the top. Among the respiratory infections, pneumonia accounted for the longest average LOS (6.4 nights), followed by bronchitis (4.9 nights). Those admitted due to upper respiratory disease had, on average, the shortest length of stay (2.9 nights).

Table 2 also depicts the probabilities of discharge from the hospital on day 2, after having stayed one night ($HR_1$), and on day 6, after having stayed five nights ($HR_5$). In particular, the probability of discharge was higher for upper respiratory diseases than for pneumonia, but this difference decreased from day 2 to day 6, with the HRs on day 2 and day 6 being 2.06 (95% CI 1.95 to 2.19) and 1.46 (95% CI 1.40 to 1.53), respectively.

## Predictors of mortality during hospitalisation

In the period 2012–2014, 131 deaths occurred among children visiting the hospital for emergency situations, that is, 1.1% of all children making emergency visits did not survive the day of the visit (table 3). Those deaths occurred more frequently among infants (108 out of the 131 cases). Diseases relating to the perinatal period were the primary cause of death (38.9% of all emergency visit deaths). Death related to cardiovascular diseases and congenital malformations each contributed to 11.5% of the total. While perinatal-period diseases and congenital malformations were the leading causes of death among infants, cardiovascular diseases and injuries were the main causes of deaths among children aged 1–4 years (table 3).

Among the hospitalised children, 3142 deaths were registered during 2007–2014, corresponding to 1.6% of all paediatric hospital admissions. Infants deaths contributed 2502 cases to the total (79.6%). As in emergency visits, diseases relating to the perinatal period were the leading cause of death during hospitalisation (32.5%). Respiratory diseases accounted for 18.3% of deaths during hospitalisation. As shown in table 3, disease related to the perinatal period was the dominant factor leading to death among infants (40.8%), whereas bacterial and parasitic

**Table 2** Hospital duration (mean, median, minimum, maximum) (days) by age group, gender, residential location and disease group and HR of discharge on day 2, after having stayed for one night ($HR_1$), and on day 6, after having stayed for five nights ($HR_5$), respectively, among children in Hanoi, Vietnam

| Categories | Mean | Median | Maximum | HR (95% CI)† | |
|---|---|---|---|---|---|
| | | | | After one night ($HR_1$) | After five nights ($HR_5$) |
| All | 5.20 | 4 | 80 | | |
| Age group | | | | | |
| <1 | 6.41 | 5 | 66 | Ref | Ref |
| 1–4 | 4.31 | 3 | 80 | 1.51 (1.49 to 1.52)* | 1.41 (1.39 to 1.42)* |
| 5–9 | 4.37 | 3 | 77 | 1.52 (1.49 to 1.55)* | 1.40 (1.38 to 1.42)* |
| 10–14 | 5.48 | 3 | 80 | 1.28 (1.24 to 1.32)* | 1.22 (1.19 to 1.25)* |
| 15–17 | 6.87 | 4 | 58 | 1.04 (0.93 to 1.17) | 1.01 (0.93 to 1.10) |
| Gender | | | | | |
| Female | 5.32 | 4 | 80 | Ref | Ref |
| Male | 5.13 | 4 | 80 | 1.05 (1.04 to 1.06)* | 1.04 (1.03 to 1.05)* |
| Residential location | | | | | |
| Inner city | 4.76 | 3 | 77 | Ref | Ref |
| Outer city | 5.97 | 4 | 80 | 0.86 (0.85 to 0.87)* | 0.88 (0.87 to 0.89)* |
| Unidentified location | 5.58 | 4 | 66 | 0.94 (0.91 to 0.98)** | 0.91 (0.88 to 0.94)** |
| Top 5 disease groups with the longest hospital duration‡ | | | | | |
| Mental and behavioural disorders | 12.18 | 12 | 41 | Ref | Ref |
| Factors influencing health status and contact with health services | 10.51 | 5 | 76 | 2.78 (1.87 to 4.12)* | 2.00 (1.41 to 2.84)* |
| Causes related to perinatal period | 10.29 | 7 | 61 | 2.79 (2.40 to 3.24)* | 2.18 (1.94 to 2.45)* |
| Neoplasms | 9.57 | 6 | 80 | 2.61 (2.24 to 3.03)* | 1.99 (1.77 to 2.23)* |
| Endocrinal and nutritional and metabolic diseases | 9.66 | 7 | 52 | 2.63 (2.26 to 3.06)* | 2.15 (1.92 to 2.42)* |
| Respiratory diseases§ | | | | | |
| Pneumonia | 6.42 | 6 | 30 | Ref | Ref |
| Bronchitis | 4.91 | 4 | 30 | 1.63 (1.58 to 1.68)* | 1.47 (1.44 to 1.49)* |
| Asthma | 4.28 | 4 | 27 | 1.76 (1.67 to 1.86)* | 1.44 (1.39 to 1.49)* |
| Other respiratory diseases | 4.34 | 3 | 30 | 3.67 (3.57 to 3.78)* | 2.05 (2.02 to 2.09)* |
| Influenza | 3.02 | 2 | 30 | 3.27 (3.08 to 3.46)* | 1.99 (1.90 to 2.09)* |
| Upper respiratory disease | 2.92 | 2 | 30 | 2.06 (1.95 to 2.19)* | 1.46 (1.40 to 1.53)* |

*p<0.001, **p<0.05.
†HR >1 means higher probability of earlier discharge from hospital (thus, a shorter length of stay) than in the reference group. Hospital admissions are defined as staying at the hospital for at least one night.
‡HR was estimated from Cox proportional hazard regression model with length of hospitalisation as outcome, and age group, sex, residential location, year of admission and disease groups as predictors.
§The model has adjusted for respiratory diseases instead of disease groups. Stays of deceased children were not included in these analyses.
Ref, reference group.

infections were the leading cause of death among children aged 1–4 years (representing 26.3% of deaths in this age group) (table 3).

Table 4 illustrates the association of demographic factors with death in hospital during emergency visits and hospitalisation. Boys were significantly less likely to die in the hospital than girls ($OR_{emergency\ visit}$=0.69, 95% CI 0.48 to 0.98; $OR_{hospital\ admission}$=0.83, 95% CI 0.77 to 0.90). Children living in the outer regions of the city were substantially more likely to die than those living in the inner city ($OR_{emergency\ visit}$: 3.12, 95% CI 2.13 to 4.56; $OR_{hospital\ admission}$: 2.34, 95% CI 2.18 to 2.52).

Table 4 also compares the risk of death from respiratory diseases, adjusted for demographic factors. Children admitted with pneumonia were more likely to die than those hospitalised due to asthma or bronchitis.

### Trends in children under 5

Overall, the rates of emergency visits and hospital admissions for children under 5 increased over the study period

**Table 3** Distribution of deaths across major discharge diagnoses of emergency visits (2012–2014) and hospital admissions (2007–2014) in different age groups among children visiting the National Children Hospital in Vietnam

| | All ages (0–17 years) | | | <1 year | | | 1–4 years | | | 5–17 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Case fatality ratio* | Death (%)† | N | Case fatality ratio* | Death (%)† | N | Case fatality ratio* | Death (%)† | N | Case fatality ratio* | Death (%)† |
| All emergency visits (2012–2014) | 12 389 | | | 2387 | | | 7765 | | | 2246 | | |
| Total deaths | *131* | *1.1%* | | *108* | *4.5%* | | *15* | *0.2%* | | *8* | *0.4%* | |
| Diseases related to perinatal period | 51 | | 38.9 | 51 | | 47.2 | 0 | | 0.0 | 0 | | 0.0 |
| Cardiovascular diseases | 15 | | 11.5 | 11 | | 10.2 | 4 | | 26.7 | 0 | | 0.0 |
| Congenital malformations | 15 | | 11.5 | 14 | | 13.0 | 1 | | 6.7 | 0 | | 0.0 |
| Respiratory diseases | 14 | | 10.7 | 10 | | 9.3 | 1 | | 6.7 | 3 | | 37.5 |
| Injury | 3 | | 2.3 | 0 | | 0.0 | 3 | | 20.0 | 0 | | 0.0 |
| Other diagnoses | 33 | | 25.2 | 22 | | 20.4 | 6 | | 40.0 | 5 | | 62.5 |
| All hospital admissions (2007–2014) | 199 827 | | | 81 648 | | | 88 064 | | | 30 115 | | |
| Total deaths | *3142* | *1.6%* | | *2502* | *3.1%* | | *468* | *0.5%* | | *172* | *0.6%* | |
| Diseases related to perinatal period | 1020 | | 32.5 | 1020 | | 40.8 | 0 | | 0.0 | 0 | | 0.0 |
| Respiratory diseases | 574 | | 18.3 | 448 | | 17.9 | 100 | | 21.4 | 26 | | 15.1 |
| Congenital malformations | 443 | | 14.1 | 415 | | 16.6 | 22 | | 4.7 | 6 | | 3.5 |
| Bacterial and parasitic infectious | 378 | | 12.0 | 227 | | 9.1 | 123 | | 26.3 | 28 | | 16.3 |
| Digestive diseases | 149 | | 4.7 | 126 | | 5.0 | 15 | | 3.2 | 8 | | 4.7 |
| Other diagnoses | 578 | | 18.4 | 266 | | 10.6 | 122 | | 44.4 | 104 | | 60.5 |

*Case fatality ratio=number of deaths/all emergency visits (or hospital admissions), respectively.
†Death (%)=100×number of death in each diagnosis/total number of deaths in respective age group.

**Table 4** Logistic regression of deaths with demographic and diagnosis factors for emergency visits (2012–2014) and hospital admissions (2007–2014) among children in Hanoi, Vietnam

| | Emergency visit (2012–2014) | | | Hospital admission (2007–2014) | | |
|---|---|---|---|---|---|---|
| **Predictors** | **Number of deaths** | **Death (%)** | **OR† (95% CI)** | **Number of deaths** | **Death (%)** | **OR† (95% CI)** |
| *Total* | *131* | | | *3142* | | |
| Age group | | | | | | |
| <1 | 108 | 4.5 | Ref | 2502 | 3.1 | Ref |
| 1–4 | 15 | 0.2 | 0.05 (0.03 to 0.09)* | 468 | 0.5 | 0.19 (0.17 to 0.21)* |
| 5–9 | 3 | 0.2 | 0.05 (0.01 to 0.15)* | 100 | 0.4 | 0.15 (0.12 to 0.18)* |
| 10–14 | 4 | 1.2 | 0.34 (0.12 to 0.94)** | 64 | 1.0 | 0.34 (0.27 to 0.44)* |
| 15–17 | 1 | 6.7 | 1.87 (0.24 to 14.84) | 8 | 1.7 | 0.56 (0.28 to 1.13) |
| Gender | | | | | | |
| Female | 60 | 1.3 | Ref | 1211 | 1.7 | Ref |
| Male | 71 | 0.9 | 0.69 (0.48 to 0.98)** | 1931 | 1.5 | 0.83 (0.77 to 0.90)* |
| Residence location | | | | | | |
| Inner city | 45 | 0.5 | Ref | 1197 | 1.0 | Ref |
| Outer city | 79 | 2.6 | 3.12 (2.13 to 4.56)* | 1875 | 2.6 | 2.34 (2.18 to 2.52)* |
| Not identified location | 9 | 2.0 | 2.73 (1.19 to 6.23)** | 70 | 2.2 | 2.14 (1.67 to 2.73)* |
| Respiratory diseases‡ | | | | | | |
| Pneumonia | 8 | 2.3 | Ref | 493 | 1.2 | Ref |
| Bronchitis | 0 | 0.0 | NA | 9 | 0.1 | 0.05 (0.03 to 0.10)* |
| Asthma | 1 | 1.3 | 0.78 (0.05 to 13.19) | 4 | 0.2 | 0.26 (0.10 to 0.72)** |
| Upper respiratory diseases | 0 | 0.0 | NA | 0 | 0.0 | NA |
| Influenza | 0 | 0.0 | NA | 3 | 0.2 | 0.33 (0.11 to 1.05) |
| Other respiratory diseases§ | 5 | 26.3 | 13.38 (3.24 to 55.21)* | 65 | 3.4 | 6.26 (4.59 to 8.53)* |

Death (%)=100×number of death in the category/total number of case of emergency visits (or hospital admissions) in respective category of predictor variables.
Emergency visit defined as hospital admission and discharge on same day. Hospital admission defined as hospital stay of at least one night.
*p<0.001, **p<0.05.
†Logistic regression model was built with death as outcome, and age group, gender, residence location and year of admission for emergency visits as predictors.
‡Additional predictors in models.
§All five deaths during emergency visits and 51/65 deaths among hospital admissions in this group were due to respiratory failure (International Classification of Diseases, 10th Revision code J96).
NA, not applicable; Ref, reference group.

(online supplementary file 1). The rate of emergency visits among children under 5 went from 3.3 per 1000 in 2012 up to 7.3 per 1000 in 2014. Notably, the age-specific rate of emergency visits among infants increased by 3.9 per 1000 children (from 4.3 per 1000 to 8.2 per 1000) during 2012–2014.

Hospital admission rates among children under 5 increased slightly between 2009 and 2014 (from 32.8 to 39.9 per 1000 children). However, among infants, the rate of hospital admissions increased substantially, from 69.7 per 1000 in 2009 to 97.2 in 2013, with a slightly lower rate in 2014 (94.8 per 1000 children) (online supplementary file 1).

## DISCUSSION

This study shows that Hanoi children visited the hospital for services that could be covered by primary care services. Hospital admissions reached an average rate of 13.8 per 1000 children/year, with stays lasting 5.2 days on average. These numbers are much higher than the statistics published for American children, with annual hospital admission rates for children aged 0–17 years of 7.9 per 1000 in 2012 and a mean LOS of 3.9 days.[12] Our study shows that digestive diseases and respiratory diseases were the leading causes of hospitalisation.

Intestinal obstruction was the leading cause of emergency visits due to digestive diseases, accounting for 80.9% of those emergencies. VNCH is the national referral hospital and receives, as a result, the most complex cases, including intestinal obstruction. Therefore, these results are in line with expected patterns. If not treated

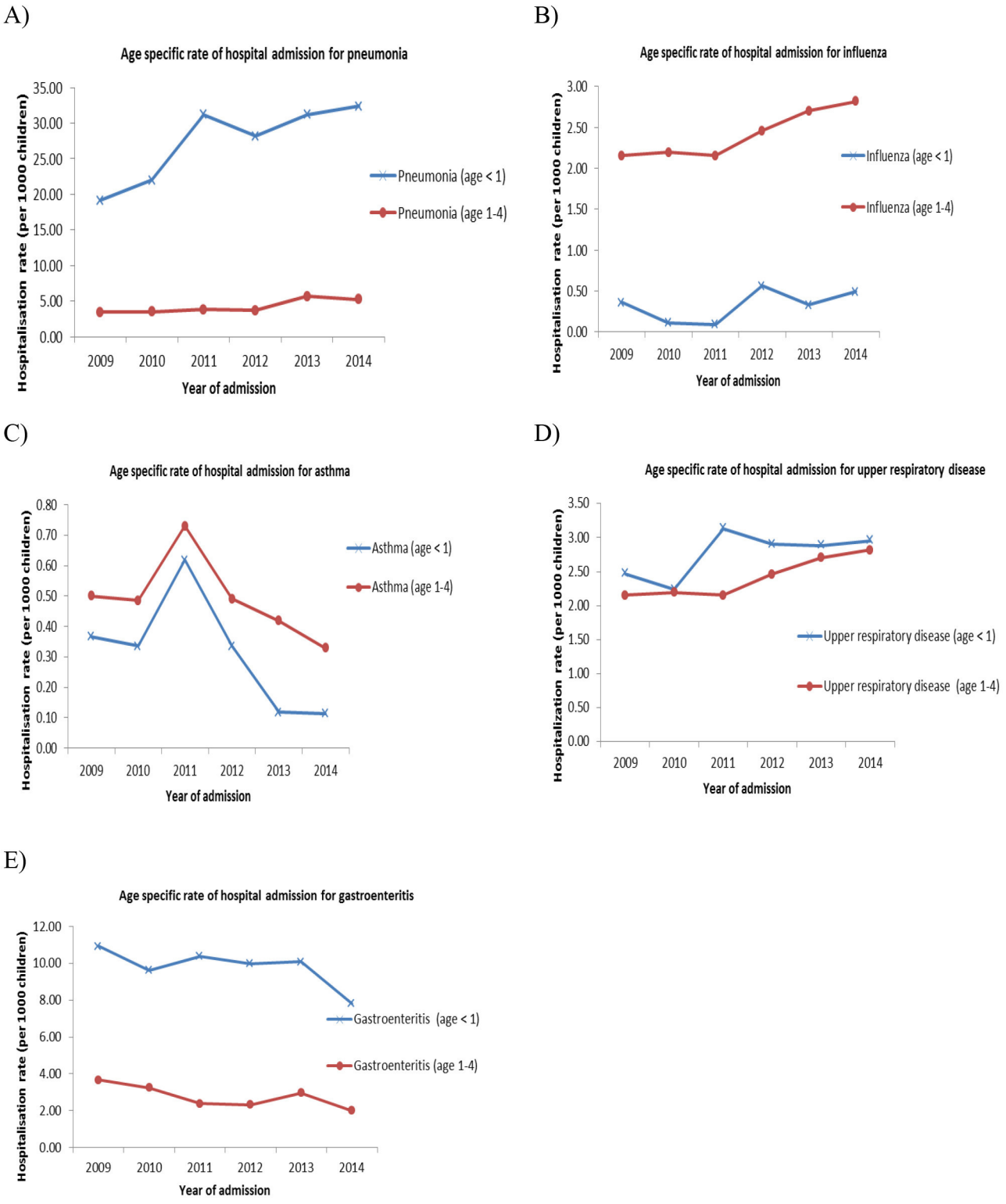


**Figure 2** Illustrates the time trend of annual hospital admission rates for five specific diseases, namely (A) pneumonia, (B) influenza, (C) asthma, (D) upper respiratory disease and (E) gastroenteritis, for infants and children aged 1–4 years, from 2009 to 2014. Trends were similar for infants and children aged 1–4, in which hospitalisation rates tended to decrease for asthma and gastroenteritis. Admissions due to asthma peaked in 2011 but declined thereafter in both age groups. However, an increasing trend was observed for pneumonia, influenza and upper respiratory diseases. For instance, infant admission rates due to pneumonia increased from 19.2 per 1000 in 2009 to 32.4 per 1000 in 2014.

early, intestinal obstruction is a severe and potentially lethal condition for children.[13] Therefore, research on the causes and prevention of this disease is warranted in Vietnam.

We found that injuries were the second leading cause of emergency room visits, accounting for 30% of all emergency visits. According to the Vietnam National Injury report, the main causes of injury in children under 14 years of age were burns with fire or hot water.[14] The low rate of injury-related hospital admissions is explained by the fact that severe injuries were transferred to other specialised hospitals, such as the National Burn Institute for burn cases or Viet Duc Hospital for other injury types. Our results add to the evidence showing that injury affects the health of Vietnamese children and highlight the need to strengthen injury prevention activities.[14]

Respiratory diseases are still the most important causes of hospital admissions for children, with pneumonia causing 24.5% of all emergency visits and 54.1% of total hospital admissions for respiratory diseases. As reported in other countries,[15 16] pneumonia was a primary cause of prolonged hospitalisation and a major reason for death due to respiratory diseases. These findings are also consistent with the results from the Vietnam Burden of Disease and Injury in 2008, in which pneumonia was the leading cause of illness and premature death in children, especially those under the age of 5.[7] We reported all data according to the ICD coding scheme used by VNCH; therefore, some data should be interpreted with caution. In the case of asthma, for example, reactive airway disease may be a better diagnostic description among the youngest children; asthma may be used inconsistently by physicians.

A further concern related to pneumonia is the upward trend shown in figure 2, predominantly among infants. There is a need to identify the causes of this severe disease and the reasons behind the increase to implement preventive strategies. Pneumonia in children has many possible causes, including individual characteristics, nutrition, vaccination, environmental tobacco smoking and air pollution.[17 18] In Vietnam, the prevalence of smoking has declined among both women and men over the last decades.[19] Similarly, as a result of implementing several nutrition and vaccination programmes, the rate of malnutrition has declined and the rate of vaccination has increased.[5] Therefore, we hypothesise that atmospheric pollution may play a role in the risk of hospitalisation for pneumonia, as seen in Hong Kong,[20] given the high concentrations reported for Hanoi.[21 22] Further investigations are required to determine a possible relationship.

The findings in this study show that the rates of emergency visits and of hospital admissions were higher for boys than for girls, although death rates were lower for the former. These findings are consistent with results from other studies.[23] For example, Axelson *et al*[23] reported that the infant mortality rate ratio of men:women in 2006 in Vietnam was 14.0:20.8, whereas the men:women ratio of the prevalence of diarrhoea in the 2 weeks preceding the interview was 7.5:6.1. Gender preferences among parents may explain these findings. In Vietnamese culture, boys are the privileged gender.[24] As a consequence, parents may pay more attention to and act earlier on health problems for boys than for girls.

Our descriptive study has several limitations. First, while this is the first study to provide an overview of hospital admissions and emergency visits among children in Hanoi, the cross-sectional data do not allow us to examine possible causes of the observed patterns or the role of potentially relevant factors, such as socioeconomic conditions, environmental factors, crowding or infectious disease epidemics. Second, the study is based on registry data — that is, the number of visits or admissions — with limited additional information and no distinction between new visits and readmissions of the same patients. Therefore, we cannot derive information about patterns among diseased patients where readmissions may be relevant. Indeed, the rate of hospital admissions or emergency visits might be higher among patients with non-infectious diseases than among those with infectious diseases. Third, data come from one hospital in Hanoi; hence, the results do not represent all children of Hanoi. Nonetheless, the VNCH has 1300 beds compared with 50 beds in the second national hospital (Paediatric Department, Bach Mai Hospital). Thus, the former hospital represents an important fraction of all hospitalisations. Fourth, given that children above 13 years of age could be transferred to adult health facilities, rather than to the VNCH, particularly for injuries or heart disease, the total hospitalisation rate among adolescents in the Hanoi region may be underestimated.

Our analysis raises several questions for future investigations. First, what are the reasons behind the upward trends in hospitalisations due to largely preventable diseases, such as respiratory disease? This issue could be addressed by using hospital data combined with data about environmental factors, like air quality and weather. Second, what is the relevance of the household's social class, hospital capacity, residential distance to hospitals or changes in insurance policies with regard to admission patterns and the LOS at the hospital? Third, the LOS in the hospital showed no particular trend over time (data not shown), yet improvements in treatment and technology may result in shorter stays. This raises the question of how best to increase the efficiency of the hospital system and possibly reduce costs without jeopardising quality of care. Understanding those factors will provide the information needed to plan and implement evidence-based strategies of prevention and treatment.

## CONCLUSION

Utilisation of the hospital was common among children in Hanoi, particularly among children under 5 years of age. Respiratory and digestive diseases were the prime causes of both emergency visits and hospital admissions. Study results show that pneumonia was the most common

respiratory disease, causing both prolonged hospitalisation and death. As seen in other parts of the world,[3] many of these respiratory and digestive diseases could be prevented. The data collected in this study show that further research is needed to characterise the aetiologies of respiratory diseases and digestive diseases in Hanoi. This will provide the basis for targeted public health interventions to reduce these burdens.

**Acknowledgements** We thank the staff from the Administration Department in the VNCH for contributing time for data cleaning work. The Vietnam General Statistic Office provides data on population census in 2009, and the Hanoi Population and Family Planing Branch provides data on population from 2010 to 2014. Ms Le Thi Thu Hien (Public Health Freelance Professional) edited the English language for the initial draft, and Amena Briët (Swiss TPH) edited the English language for the final version.

**Contributors** NTTN and LP conceived the study. NTTN drafted the initial manuscript. NTTN, TMD, NK, NPH and LP developed the study design. NTBL integrated and extracted data from electronic system. NTTN undertook the data analyses. CS provided expertise in the data management and data analysis. All authors contributed to the interpretation of the results. Each of the author contributed to the preparation and editing of the manuscript. All authors have seen and approved the submission of this version of the manuscript and take full responsibility for the manuscript.

**Competing interests** None declared.

**Patient consent** Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

**Ethics approval** The National Hospital of Pediatrics Ethics Committee.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** Individual record of hospital admissions and emergency visits collected for this study were given approval limited to use for this study only. However, the authors would be happy to make the data available upon request. Individuals may contact nhung.nguyen@unibas.ch.



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BMJ Open

# Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014

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*BMJ Open* 2017 7:
doi: 10.1136/bmjopen-2016-015260



## Notes

Supplementary file for article with title **"Childhood hospitalisation and related deaths in Hanoi, Vietnam: a tertiary hospital database analysis from 2007 to 2014"**

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This supplemental document contains

Part A: Data quality control and quality assurance procedures for hospital data
Part B: Disease classification
Part C: Outcome indicator measurement
Part D: Expanded summary results including tables S4, S5, S6

**P**art A: Data quality control and quality assurance procedures for hospital data

Diagram S1 depicts the process of data quality control in this study. The process involved three steps: 1) check missing values in variables; 2) check inconsistent information between variables and duplicated records, 3) Testing of the validity of data in a random sample.
In the first stage of the process, no missing values have been found in the date of birth, date of admission, date of discharge, the name of disease or ICD code of disease in the database. We found 12% of the total records with 'commune address' missing and 1.2% of the records with 'district address' missing. These missing values were coded as “not identified home address”.
In stage $2^{nd}$, we also found 300 inconsistent records where the date of admission or the date of discharge was before the date of birth. These records were corrected by matching electronic files with hard copy documents and checked with parents by phone. Also, we checked all records where the length of hospital stay was longer than three months (612 records). These records were checked with the financial database of the National Hospital of Pediatrics and/or by calling the parents. Inaccurate records were corrected in the database. Duplicate records were defined as an admission re-entered into the hospital system $\leq$ 24 hours after discharge. We found 3326 such records. Duplicate records were combined into one record according to the following rules; 1) date of admission is entry date in the first department; 2) discharge date is time patients existed the hospital from the last unit; 3) name of disease and ICD code of disease were taken from the last record.
Final, we carried out cross checks of electronic data with hard copy documents (medical documents) and individual data in a random sample of 400 records. After checking in hard copy of medical document, phone to the parent to check date of admission, date of birth and date of discharge, we did not find any mistake in any variables.

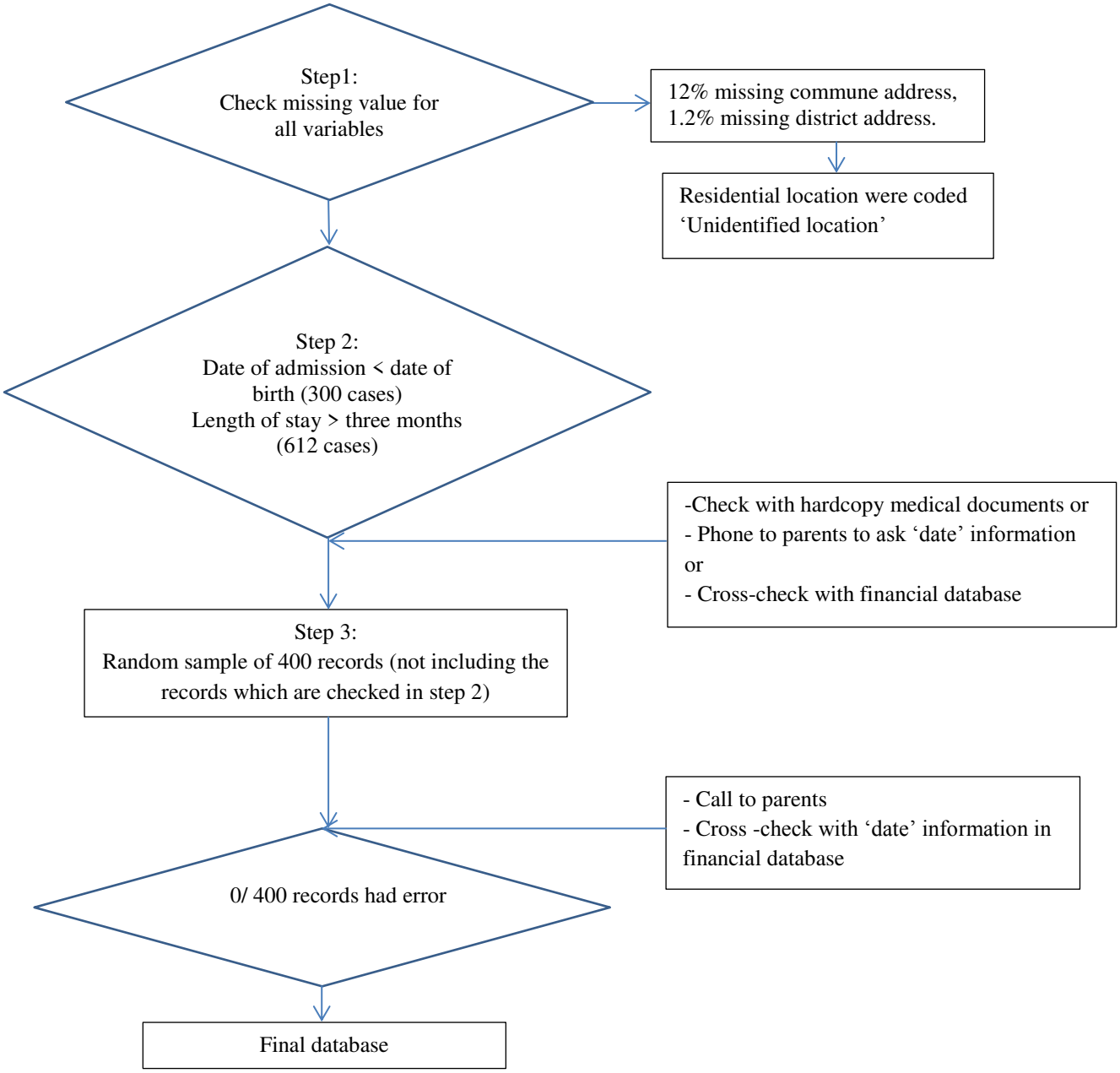


Diagram S1: Pilot testing process for data quality control.

Part B. Disease classification
The following table lists disease groups and ICD10 codes of disease groups

Table S1: International Classification of Disease (ICD) 10th revision for disease groups

| Disease groups | ICD code |
|---|---|
| Bacterial and parasitic infection | A00-B99 |
| Neoplasms | C00-D48 |
| Blood diseases and immunologic disorders | D50-D89 |
| Endocrinal and nutritional and metabolic diseases | E00-E90 |
| Mental and behavioural disorders | F00-F99 |
| Nervous system diseases | G00-G99 |
| Eye and adnexal diseases | H00-H59 |
| Ear and mastoid process diseases | H60-H95 |
| Cardiovascular diseases | I00-I99 |
| Respiratory diseases | J00-J09 |
| Digestive diseases | K00-K93 |
| Skin and subcutaneous tissue diseases | L00-L99 |
| Musculoskeletal system diseases | M00-M99 |
| Genitourinary diseases | N00-N99 |
| Childbirth and the puerperium diseases | O00-O99 |
| Diseases relating to perinatal period | P00-P96 |
| Congenital malformations | Q00-Q99 |
| Symptoms, signs not elsewhere classified | R00-R09 |
| Injury | S00-Y98 |
| Factors influencing health status and contact with health services | S00-Y98 |

Table S2: Classification of residential location for the Hanoi area

| Name of district | Residential location |
|---|---|
| Ba Dinh, Dong Da, Hoan Kiem, Gia lam, Bac Tu Liem, Nam Tu Liem, Cau Giay, Ha Dong, Hai Ba Trung, Hoang mai, Long Bien, Tay Ho, and Thanh Xuan | Inner city |
| Ba vi, Chuong My, Dan Phuong, Dong Anh, Hoai Duc, Me linh, My Duc, Phu Xuyen, Phuc Tho, Quoc Oai, Soc Son, Thach That, Thanh Oai, Thanh Tri, Thuong Tin, Ung Hoa, and Son Tay Town | Outer city |
| Missing name of district | Unidentified location |

Part C: Expanded summary results

Table S3: Percent distribution of cases across diseases within each age group of emergency visits (2012-2014) and hospital admissions (2007-2014) of Hanoi children

| Disease subgroups | Emergency visits (2012-2014) | | | | | | Hospital admission (2007-2014) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1-4 | 5-9 | 10-14 | 15-17 | Total | <1 | 1-4 | 5-9 | 10-14 | 15-17 | Total |
| All diseases | 2387 (100%) | 7765 (100%) | 1883 (100%) | 339 (100%) | 15 (100%) | 12389 (100%) | 81648 (100%) | 88061 (100%) | 23470 (100%) | 6184 (100%) | 464 (100%) | 199827 (100%) |
| Bacterial and parasitic infection | 12.3% | 7.6% | 3.6% | 5.3% | 0.0% | 7.8% | 20.1% | 21.6% | 13.2% | 14.5% | 13.8% | 19.8% |
| Neoplasms | 2.2% | 0.8% | 1.0% | 2.7% | 0.0% | 1.2% | 1.6% | 3.3% | 5.8% | 9.0% | 9.7% | 3.1% |
| Blood diseases and immunologic disorders | 0.1% | 0.1% | 0.1% | 1.2% | 0.0% | 0.2% | 1.3% | 1.3% | 2.7% | 4.1% | 5.0% | 3.1% |
| Endocrinal, nutritional and metabolic diseases | 0.1% | 0.0% | 0.1% | 0.3% | 6.7% | 0.1% | 0.9% | 0.5% | 0.9% | 1.7% | 2.2% | 0.7% |
| Mental and behavioural disorders | 0.0% | 0.0% | 0.0% | 0.9 % | 0.0% | 0.0% | 0.1% | 0.5% | 0.4% | 1.2% | 1.3% | 0.3% |
| Nervous system diseases | 0.1% | 0.2% | 0.6% | 0.9% | 0.0% | 0.3% | 1.2% | 1.6% | 1.8% | 2.9% | 3.5% | 1.5% |
| Eye and adnexal diseases | 0.0% | 0.0% | 0.1% | 0.0% | 0.0% | 0.0% | 0.8% | 0.1% | 0.1% | 0.1% | 0.2% | 0.3% |
| Ear and mastoid process diseases | 0.2% | 0.1% | 0.1% | 0.0% | 0.0% | 0.1% | 0.3% | 0.5% | 0.3% | 0.1% | 0.2% | 0.4% |
| Cardiovascular diseases | 0.7% | 0.2% | 0.6% | 0.9% | 0.0% | 0.4% | 0.6% | 0.4% | 0.9% | 1.5% | 1.5% | 0.6% |
| Respiratory diseases | 17.1% | 10.3% | 9.2% | 9.1% | 6.7% | 11.4% | 45.8% | 36.4% | 21.5% | 13.3% | 9.9% | 37.7% |
| Digestive diseases | 39.6% | 34.3% | 15.9% | 17.4% | 6.7% | 32.0% | 5.6% | 10.8% | 21.3% | 19.7% | 11.2% | 10.2% |
| Skin and subcutaneous tissue diseases | 1.7% | 0.8% | 1.2% | 1.2% | 0.0% | 1.0% | 1.2% | 2.5% | 2.8% | 1.8% | 1.7% | 2.0% |
| Musculoskeletal system diseases | 0.4% | 1.0% | 1.7% | 7.1% | 0.0% | 1.2% | 0.4% | 0.9% | 1.6% | 3.5% | 5.8% | 0.9% |
| Genitourinary diseases | 0.7% | 1.2% | 3.4% | 3.0% | 13.3% | 1.5% | 1.8% | 3.6% | 7.5% | 9.4% | 11.2% | 3.5% |
| Childbirth and the puerperium diseases | 0.0% | 0.0% | 0.1% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Diseases relating to perinatal period | 3.6% | 0.1% | 0.0% | 0.0% | 0.0% | 0.7% | 9.0% | 0.1% | 0.1 % | 0.1% | 0.2% | 3.7% |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Congenital malformations | 1.8% | 0.3% | 0.1% | 0.3% | 0.0% | 0.5% | 6.3% | 5.7% | 6.3% | 7.3% | 13.4% | 6.1% |
| Symptoms, signs not elsewhere classified | 8.5% | 10.1% | 19.0% | 20.1% | 26.7% | 11.5% | 2.2% | 6.9% | 7.0% | 5.1% | 4.5% | 4.9% |
| Injury | 10.9% | 32.9% | 43.3% | 29.8% | 40.0% | 30.2% | 0.8% | 3.4% | 5.8% | 4.8% | 4.3% | 2.7% |
| Factors influencing health status and contact with health services | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% | 0.1% | 0.2% | 0.4% | 0.0% |

Table S4: Percent distribution of respiratory diseases in each age group of all emergency visits (2012-2014) and hospital admissions (2007-2014) of Hanoi children

| | Emergency visits (2012-2014) | | | | | | Hospital admission (2007-2014) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <1 | 1-4 | 5-9 | 10-14 | 15-17 | Total | <1 | 1-4 | 5-9 | 10-14 | 15-17 | Total |
| Total (N) | 409 | 797 | 174 | 31 | 1 | 1412 | 37425 | 32009 | 5043 | 820 | 46 | 75343 |
| Pneumonia | 41.1% | 19.8% | 8.6% | 12.9% | 100.0% | 24.5% | 66.8% | 45.5% | 19.6% | 21.7% | 30.4% | 54.1% |
| Bronchitis | 31.8% | 15.3% | 8.1% | 12.9% | 0.0% | 19.1% | 23.7% | 15.8% | 7.8% | 9.2% | 6.5% | 19.1% |
| Asthma | 0.5% | 4.6% | 16.7% | 35.5% | 0.0% | 5.6% | 0.8% | 5.5% | 10.5% | 14.5% | 8.7% | 3.6% |
| Upper respiratory disease | 23.0% | 54.1% | 64.4% | 38.7% | 0.0% | 46.0% | 7.3% | 27.9% | 39.5% | 26.8% | 23.9% | 18.4% |
| Influenza | 1.0% | 5.4% | 1.2% | 0.0% | 0.0% | 3.5% | 0.6% | 2.8% | 8.4% | 9.8% | 10.9% | 2.2% |
| Other respiratory diseases | 2.7% | 0.8% | 1.2% | 0.0% | 0.0% | 1.4% | 0.6% | 2.6% | 14.2% | 18.1% | 19.6% | 2.6% |

Table S5: Age specific annual rates of emergency visits (2012-2014) and hospital admissions (2009-2014) of Hanoi children below 5 years of age

| | Emergency visit (EV) | | | | | | Hospital admission (HA) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 2012 | | 2013 | | 2014 | | 2009 | | 2010 | | 2011 | | 2012 | | 2013 | | 2014 | |
| | EVs | Rate* | EVs | Rate* | EVs | Rate* | HAs | Rate* | HAs | Rate* | HAs | Rate* | HAs | Rate* | HAs | Rate* | HAs | Rate* |
| All children under 5 yrs** | 1'900 | 3.25 | 3'759 | 6.09 | 4'493 | 7.32 | 18'462 | 32.78 | 19'018 | 32.29 | 21'140 | 35.76 | 22'994 | 39.37 | 28'603 | 46.36 | 24'528 | 39.98 |
| 1-4 yrs | 1'392 | 2.99 | 2'811 | 5.94 | 3'562 | 7.13 | 10'096 | 22.78 | 10'107 | 21.50 | 10'619 | 22.14 | 11'737 | 25.24 | 14'662 | 30.96 | 13'703 | 27.44 |
| Girl, 1-4 yrs | 503 | 2.36 | 1'000 | 4.63 | 1'257 | 5.46 | 3'621 | 17.32 | 3'642 | 16.38 | 3'782 | 16.89 | 4'137 | 19.41 | 5'333 | 24.67 | 5'033 | 21.88 |
| Boy, 1-4yrs | 889 | 3.53 | 1'811 | 7.04 | 2'305 | 8.56 | 6'475 | 27.65 | 6'465 | 26.11 | 6'837 | 26.73 | 7'600 | 30.17 | 9'329 | 36.25 | 8'670 | 32.19 |
| < 1 | 508 | 4.27 | 948 | 6.61 | 931 | 8.16 | 8'366 | 69.72 | 8'911 | 74.86 | 10'521 | 94.35 | 11'257 | 94.61 | 13'941 | 97.18 | 10'825 | 94.85 |
| Girl, < 1 yrs | 202 | 3.94 | 344 | 5.58 | 344 | 6.74 | 2'799 | 49.91 | 2'990 | 55.13 | 3'552 | 72.63 | 3'943 | 76.92 | 4'861 | 78.78 | 3'863 | 75.64 |
| Boy, <1 yrs | 306 | 4.52 | 604 | 7.39 | 587 | 9.31 | 5'567 | 87.10 | 5'921 | 91.39 | 6'969 | 111.32 | 7'314 | 107.99 | 9'080 | 111.08 | 6'962 | 110.40 |

*The rates were calculated as 1000* (number of emergency visits (or hospital admissions) of the respective gender and age in a particular year /appropriate age-specific population of Hanoi child population in the year) as denominator. Hanoi children population 2010-2014 was obtained from Hanoi population and Family Branch. Hanoi children population 2009 was derived from the 2009 population Census by the General Statistics Office.
**Age was defined as patient's age at emergency visit or hospital admission.

# CHAPTER 4: A SYSTEMATIC REVIEW AND META-ANALYSIS OF SHORT-TERM ASSOCIATION BETWEEN AMBIENT AIR POLLUTION AND PNEUMONIA IN CHILDREN

The article was published as:

NHUNG, N. T. T., AMINI, H., SCHINDLER, C., KUTLAR JOSS, M., DIEN, T. M., PROBST-HENSCH, N., PEREZ, L. & KUNZLI, N. 2017. Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies. *Environ Pollut,* 230**,** 1000-1008

Environmental Pollution 230 (2017) 1000–1008

Contents lists available at ScienceDirect

Environmental Pollution

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

# Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies☆

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ARTICLE INFO

*Article history:*
Received 2 June 2017
Received in revised form
17 July 2017
Accepted 19 July 2017

*Keywords:*
Air pollution
Systematic review
Meta-analysis
Meta-regression
Pediatric pneumonia
Hospital admissions
Children

ABSTRACT

Ambient air pollution has been associated with respiratory diseases in children. However, its effects on pediatric pneumonia have not been meta-analyzed. We conducted a systematic review and meta-analysis of the short-term association between ambient air pollution and hospitalization of children due to pneumonia. We searched the Web of Science and PubMed for indexed publications up to January 2017. Pollutant-specific excess risk percentage (ER%) and confidence intervals (CI) were estimated using random effect models for particulate matter (PM) with diameter $\leq$ 10 ($PM_{10}$) and $\leq$2.5 μm ($PM_{2.5}$), sulfur dioxide ($SO_2$), ozone ($O_3$), nitrogen dioxide ($NO_2$), and carbon monoxide (CO). Results were further stratified by subgroups (children under five, emergency visits versus hospital admissions, income level of study location, and exposure period). Seventeen studies were included in the meta-analysis. The ER% per 10 μg/$m^3$ increase of pollutants was 1.5% (95% CI: 0.6%–2.4%) for $PM_{10}$ and 1.8% (95% CI: 0.5%–3.1%) for $PM_{2.5}$. The corresponding values per 10 ppb increment of gaseous pollutants were 2.9% (95% CI: 0.4%–5.3%) for $SO_2$, 1.7% (95% CI: 0.5%–2.8%) for $O_3$, and 1.4% (95% CI: 0.4%–2.4%) for $NO_2$. ER% per 1000 ppb increment of CO was 0.9% (95% CI: 0.0%–1.9%). Associations were not substantially different between subgroups. This meta-analysis shows a positive association between daily levels of ambient air pollution markers and hospitalization of children due to pneumonia. However, lack of studies from low-and middle-income countries limits the quantitative generalizability given that susceptibilities to the adverse effects of air pollution may be different in those populations. The meta-regression in our analysis further demonstrated a strong effect of country income level on heterogeneity.



## 1. Introduction

The adverse effects of air pollution on cardiorespiratory diseases have been demonstrated in a series of studies (Fuertes et al., 2014; Künzli et al., 2000). The Global Burden of Disease Study 2013 estimated that ambient particulate matter (PM) pollution was responsible for nearly three million premature deaths worldwide (Forouzanfar et al., 2015). Other studies reveal that children living near roadways or wood industries are likely to have a higher risk of pneumonia, while a ban on diesel-powered motor vehicles may reduce the hospital admissions for the disease (El-Zein et al., 2007). Indeed, children are particularly susceptible to PM pollution, as they inhale more air per unit body weight than adults (World Health Organization, 2005). Furthermore, early exposure to ambient air pollution may affect children's normal growth and lung development, as the immune and organ systems are still evolving

☆ This paper has been recommended for acceptance by David Carpenter.

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http://dx.doi.org/10.1016/j.envpol.2017.07.063
0269-7491/

at this stage (Chen et al., 2015; Sunyer, 2008).

Pneumonia is the leading cause of childhood death, accounting for about 1.3 million deaths among children under five years of age in 2010–2011 (Walker et al., 2013). About 75% of the burden occurs among children from low-and-middle-income-countries, where poverty and severe ambient air pollution are common (Brauer et al., 2016). The current evidence suggests that many risk factors may be involved in the onset of pediatric pneumonia (Jackson et al., 2013; Sonego et al., 2015; Walker et al., 2013). These might include a broad range of personal (e.g. age or sex), family, and socio-economic characteristics; environmental factors (e.g. indoor air pollution, low quality of drinking water, second hand smoke, etc.); as well as comorbidities (e.g. HIV in children).

Acute effects of air pollution are efficiently captured by statistical time-series analyses that investigate the association between daily concentrations of air pollution and daily counts of health outcomes while controlling for other time-varying – thus potentially confounding – co-factors, such as meteorological conditions, seasonality, and other time-trends. So far, several systematic reviews have been conducted to evaluate the short-term association of ambient air pollution and lower respiratory tract infections in children (Atkinson et al., 2014; Mehta et al., 2013a; Romieu et al., 2002). However, there is no published meta-analysis of the acute effects of ambient air pollution on pediatric pneumonia to date. Meta-analyses play a vital role in the assessment of evidence, impact assessments, and public health policy making. Thus, we systematically evaluate this association using hospital admissions due to pneumonia as the main outcome.

## 2. Material and methods

### 2.1. Data sources and search strategy

We conducted a systematic review and meta-analysis of studies indexed in PubMed and Web of Science and published until January 3rd, 2017, that reported on the acute effects of outdoor air pollutants on hospitalization due to pneumonia. The search was not restricted by language, but we solely focused on original research articles published in peer reviewed journals. Database-specific search queries were developed using relevant keywords (See supplementary material A).

### 2.2. Eligibility criteria

Studies were included in the review if they (1) investigated the short-term association of ambient air pollutants with hospitalization due to pneumonia (whereby short-term effects were defined as those occurring within zero to seven days after exposure), (2) reported estimates for children up to 18 years of age, and (3) provided quantitative results for the effects (i.e. point estimate and confidence interval (CI)).

The following exclusion criteria were defined: (1) studies conducted among the general population without specific estimation for children, (2) studies of the long-term effects of air pollution on pneumonia, (3) studies that do not include pneumonia as an endpoint, (4) studies that do not measure pollutants, such as those comparing outcomes before and after an intervention like fuel bans, (5) review articles, and (6) studies limited to an abstract.

### 2.3. Study selection

First, two reviewers (NTTN and HA) independently screened the retrieved records. If there was a disagreement between the two reviewers, third and fourth reviewers (LP and NK) were called upon to help make a final decision. Afterwards, one reviewer (NTTN) examined the full text to evaluate eligibility according to the set criteria, which were then double checked by the second reviewer (HA). Finally, both reviewers (NTTN and HA) were involved independently in data extraction.

### 2.4. Data collection process

Data extraction forms were pre-designed to collect all relevant information. Data included citation information (title, author, and year of publication); the study setting (study location or country, and study period); the study design (time series, case-crossover analyses, etc.); daily mean number of events or total events; definition of health outcome; measurement of exposure, with air pollutant level; time of exposure; covariates in the models; and study results.

### 2.5. Meta-analysis approach

Meta–analysis was performed across available studies to summarize the short-term effects of pollutants on hospitalization of children due to pneumonia. Studies were eligible for meta-analyses if they used either time series or case-crossover analyses. Time series analyses use Poisson regressions to investigate associations of short-term changes in ambient concentrations of pollutants with daily changes in health outcomes. The case-crossover approach compares concentrations at the time of an event with those during a control time, within the same person. Both methods are widely used to assess short-term relationships between ambient levels of air pollution and the daily frequency of adverse health conditions (Yun Lu and Zeger, 2007).

Many studies have published a variety of estimates to accommodate various lags, multiple pollutants, or sub-groups defined by location (e.g. single cities versus multiple cities), among others. To prevent over-representation of a single study in the pooled estimation, only one estimate was selected from each study, according to the following rules: a) in the case of studies that reported several lags, we used the shortest one in the pooled estimate; b) cumulative lags (e.g. lag 0–2 or 0–4 days) were used if no single lag estimates were provided; c) in the case of multi-city studies, we included the single city results, one by one; and d) where more than one publication was available for a given population or region, we included the one that had the longest time-series period and/or the largest number of events.

To pool the effects, all relative risks (RR) were standardized to an increase of 10 $\mu g/m^3$ of $PM_{10}$ and $PM_{2.5}$ concentration; 10 ppb of sulfur dioxide ($SO_2$), nitrogen dioxide ($NO_2$), and ozone ($O_3$) concentration; and 1000 ppb of carbon monoxide (CO). In case of small relative risks, odds ratios and relative risks can be considered the same. For studies reporting $RR_u$ per U units instead of standard level (e.g. 10 units), the $RR_{standardised}$ was calculated by:

$$RR_{\text{standardised}} = RR_u^{\frac{increment\ \ unit\ \ (e.g.\ \ 10)}{u}}$$

where U is the increment used in the original study to estimate the effects.

For studies reporting the excess risk (ER), we transformed the ER to RR, using the formula: RR = 1 + ER. Some studies used $\mu g/m^3$ to describe the concentrations of gaseous pollutants; thus, we converted all estimates to ppb (Danish Centre For Environment And Energy).

For those pollutants where the effects were expressed for different exposure time metrics, such as one-hour or eight-hour instead of 24-h means, we converted the results to reflect a 24-h scale. This was the case for $SO_2$, $NO_2$ and CO. The relationship

among pollutant metrics depends on the emission source, season and level of pollutants in the community. For $SO_2$, we used community-specific ratios based on the data provided in the given study. For $NO_2$, we applied a ratio of one-hour maximum/24 h of 2:1 (EPA, 1993). We used an eight-hour moving average for $O_3$ in this review. As no study reported sufficient data for converting $O_3$, we used ratios of one-hour maximum/eight-hour maximum/24-h mean as 1.76/1.53/1, based on data from across 78 communities in the United States (Anderson and Bell, 2010). We also assumed that an eight-hour mean of ozone concentration in a specific time period (e.g. noon to 9 p.m.) is approximately equal to the moving eight-hour maximum. This assumption has been applied elsewhere (Ji et al., 2011). We also contacted the study authors for additional data, where values were not presented in the article or in supplementary documents. If no response was received from the corresponding authors, confidence intervals were estimated manually, based on the graphs in the article. The overall estimates were calculated for each pollutant if at least three individual estimates were available. This criterion has also been used elsewhere (Anoop S V Shah et al., 2016; Ji et al., 2011).

Forest plots were used to visually explore the summary of individual studies. To assess heterogeneity between studies in the pooled analyses, we used $I^2$ statistics to indicate the proportion of total variability between effect estimates due to heterogeneity by the methodology of Der Simonian and Laird (DerSimonian and Laird, 1986). $I^2$ ranges from 0 to 30%, 30%–50% and above 50% where they represent low, moderate, and high heterogeneity, respectively. We used random effects if $I^2$ exceeded 25% and fixed effects otherwise (Higgins et al., 2003; Woodward, 2013). We then carried out sensitivity analysis by repeating meta-analysis, one-by-one, with each study left out to test whether single studies were influential in the pooled estimates (Normand, 1999). The asymmetry of results for all pollutants was investigated by funnel plots. We further analyzed results by subgroup according to outcome (namely, hospital admissions versus emergency visit), children's age (namely, those under five years of age), income level of study location. Moreover, analyses were conducted for single lag and cumulative lag. The income level was based on the latest World Bank definition, classifying economies into high-income economies (HIE) and NOT-high-income economies (N-HIE) (World Bank, 2017).

Statistical analyses were performed using STATA 14 (Stata Corporation, College Station, Texas 77,845 USA). Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement was used for reporting the results in our study (Moher et al., 2009). Summary statistics are presented as the percentage change (excess risk − ER%) in pneumonia hospitalization per increment in pollutant concentration (ER% = (RR-1) × 100%) (Shah et al., 2013).

## 3. Results

The initial search yielded 1493 records. After screening the titles and abstracts, 1409 records were excluded because the articles were not relevant, were unavailable online, related to animal or cell experiments, and/or reported on longitudinal studies. We reviewed the full-texts of the remaining 84 publications and further excluded 67 records because the studies (1) did not report results specific to children (n = 30), (2) did not include pediatric pneumonia (n = 33), (3) did not provide point estimates for pollutants (n = 1), (4) had fewer than three point estimates for a pollutant (n = 1), or (5) covered a period that overlapped with several publications, therefore those with fewer events or without confidence intervals were removed (n = 2) (Fig. S1, supplementary material).

Of the 17 remaining studies, 11 used time-series analysis (Darrow et al., 2014; Farhat et al., 2005; Gouveia and Fletcher, 2000; Ilabaca et al., 1999; Negrisoli and Nascimento, 2013; Ostro et al., 2009; Pablo-Romero et al., 2015; Patto et al., 2016; Souza and Nascimento, 2016; Tuan et al., 2015; Winquist et al., 2012) and six used a case-crossover approach (Barnett et al., 2005; Lv et al., 2016; Malig et al., 2016; Santus et al., 2012; Strickland et al., 2016; Xiao et al., 2016). One study did not provide overall estimates but reported results for the hot and cold seasons separately given the rather different effects (Ilabaca et al., 1999). The 17 studies were adjusted for seasonality, time trends, and meteorological factors, such as temperature and relative humidity, but only four studies were adjusted for influenza peaks (Table S1). To date, more than 425,000 pediatric pneumonia events have been investigated to assess its relationship to acute ambient air pollution in eight countries. Of these, six studies were conducted in the United States, six in Brazil, and one each in Chile, New Zealand and Australia, Italy, Spain and China (Table 1). Five studies investigated the association of air pollution with emergency visits due to pneumonia, nine considered hospital admissions due to pneumonia, and two explored mixed databases of hospital admissions and emergency visits. Only one study reported the results for emergency and hospital admission outcomes separately using the same database (Winquist et al., 2012). These studies defined the outcome by using the International Classification of Diseases (ICD) version 9 (codes 466, and 480–486) or ICD10 (codes J12-J18) (Table S2). Four studies reported the results from co-pollutant models (Barnett et al., 2005; Darrow et al., 2014; Farhat et al., 2005; Lv et al., 2016). The relative risks (by pollutant) estimated by individual studies are visualized through forest plots in Fig. 1. The degree of heterogeneity ($I^2$) in the current meta-analysis was large in pooled estimates for $PM_{10}$ (66.1%), $NO_2$ (71.1%), $O_3$ (75.2.0%) and CO (68.1%), and moderate for $PM_{2.5}$ (38.1%) and $SO_2$ (48.4%) (Fig. 1).

The daily mean concentrations of pollutants across all studies were 59.2 μg/m$^3$ for $PM_{10}$, 31.0 μg/m$^3$ for $PM_{2.5}$, 9.8 ppb for $SO_2$, 35.2 ppb for $O_3$ (eight-hour moving average), 61.7 ppb for $NO_2$, and 1900 ppb for CO (Table 2).

The main effect, ER per 10 μg/m$^3$ increase of pollutants, was 1.5% (95% CI: 0.6%–2.4%) for $PM_{10}$ and 1.8% (95% CI: 0.5%–3.1%) for $PM_{2.5}$. The corresponding values per 10 ppb increment of gaseous pollutants were 2.9% (95% CI: 0.4%–5.3%) for $SO_2$, 1.7% (95% CI: 0.5%–2.8%) for $O_3$, 1.4% (95% CI: 0.4%–2.4%) for $NO_2$, and 0.9% (95% CI: −0.0%–1.9%) for CO per 1000 ppb increment (Fig. 1). Results by subgroup were consistent with the overall associations (Fig. 2).

Subgroup analyses revealed that pooled estimates from studies originating from N-HIE countries were larger than in HIE countries for $NO_2$ ($RR_{N\_HIE}$ = 3.60 (95% CI: 0.80–6.40) vs $RR_{HIE}$ = 0.60 (95% CI: −0.20–1.40)). However, in case of $O_3$, an opposite pattern emerged ($RR_{N\_HIE}$ = 1.00 (95% CI: −0.50–2.60) vs $RR_{HIE}$ = 2.40 (95% CI: −1.00–3.80)). In addition, with the exception of $NO_2$ and $O_3$, the meta-regression did not reveal age specific effects (i.e. children under 5 versus general population) (Fig. 2). Sensitivity analyses demonstrated that all pollutants were positively associated with the outcome (Table S3, S4, S5, S6, S7 and S8). However, the size of the effect varied across studies, especially in the case of $SO_2$, $NO_2$ and CO (Table S5, S7 and S8). The funnel plots suggest some asymmetry of results for all pollutants (Fig. S2). The asymmetry of the results remained even when we excluded the studies with small numbers of cases and/or short observation periods (data not shown).

## 4. Discussion

Our analyses showed positive associations between all pollutants considered and pediatric hospital admissions due to pneumonia. With the exception of CO, all pollutants ($PM_{10}$, $PM_{2.5}$, $SO_2$, $NO_2$, $O_3$) were consistently associated with pediatric pneumonia

**Table 1**
Main characteristics of all time-series and case-crossover studies included in the meta-analysis.

| Record | Author | Year | Location | Period | Population | Study design | Data source of outcomes | Number of events[a] | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Ilbabaca | 1999 | Chile | 1995–1996 | 0–15 | Time-series | Hospital records (1 hospital) | 6344 | Emergency visit |
| 2 | Gouvenia | 2000 | Brazil | 1992–1994 | 28days - 5years | Time-series | Health Services Information database (150 hospitals) | 28,478 | Hospital admission |
| 3 | Barnett | 2005 | Australia + New Zealand | 1998–2001 | 0–14 | Case-crossover | Hospital record from State Government health Department | 4341[b] | Hospital admission |
| 4 | Farhat | 2005 | Brazil | 1996–1997 | 0–13 | Time-series | Children's Institute (1 hospital) | 508 | Emergency visit + Hospital admission |
| 5 | Santus | 2012 | Italia | 2007–2008 | 0–16 | Case-crossover | Emergency department (5 hospitals) | 1345 | Emergency visit |
| 6 | Winquist[c] | 2012 | US | 2001–2007 | 0–18 | Time-series | Hospital Association | 11,134 | Emergency visit, Hospital admission |
| 7 | Negrisoli | 2013 | Brazil | 2007–2008 | 0–10 | Time-series | DIITBUH[e] | 1797 | Hospital admission |
| 8 | Ostro | 2009 | US | 2000–2003 | 0–18 | Time-series | OSHPDH[f] | 3742 | Hospital admission |
| 9 | Darrow | 2014 | US | 1993–2010 | 0–4 | Time-series | Hospital record (41 hospital): 1993–2004; Georgia Hospital Association: 2005–2010 | 63,359 | Emergency visit |
| 10 | Pablo-Romero | 2015 | Spain | 2007–2011 | 0–14 | Time-series | DGHC[g] (3 hospitals) | 576 | Hospital admission |
| 11 | Souza | 2016 | Brazil | 2010–2012 | 0–10 | Time-series | SUS Department of Informatics | 234 | Hospital admission |
| 12 | Patto | 2016 | Brazil | 2011–2013 | 0–10 | Time-series | SUS Hospital Admission Authorizations | 1161 | Hospital admission |
| 13 | Xiao[d] | 2016 | US | 2002–2008 | 0–18 | Case-crossover | Georgia Hospital Association | 90,063 | Emergency visit |
| 14 | Strickland[d] | 2016 | US | 2002–2010 | 0–18 | Case-crossover | Geogia Hospital Association (150 hospitals) | 52,496 | Emergency visit |
| 15 | Lv | 2016 | China | 2016 | 0–15 | Case-crossover | Jian Qilu Hospital database | 379 | Hospital admission |
| 16 | Maglig | 2016 | US | 2005–2008 | 0–18 | Case-crossover | COSHPD[h] | 158,814 | Emergency visit + Hospital admission |
| 17 | Tuan | 2016 | Brazil | 2012 | 0–10 | Time-series | SUS Hospital Admission Authorizations (6 hospitals) | 539 | Hospital admission |

[a] For studies not providing the total number of events: total number of events was calculated as (daily mean number of event) × (number of days in period).
[b] Batnet: number of events was estimated from daily number of case per state × number of day.
[d] Both Xiao(2016) and Strickland(2016) provided estimate for $PM_{2.5}$ and ambient pollutant concentration. Because Xiao(2016) has short time period than its counterpart, therefore we used the results of Strickland for $PM_{2.5}$.
[c] Winquist(2012) provided risk ratio of associations for hospital admission and emergency visits separately.
[e] DIITBUH: Department of Information and Information Technology of the Brazilian Unified Health System.
[f] OSHPDH: Office of Statewide Health Planning and Development, Healthcare Quality and Analysis Division.
[g] DGHC: Directorate General for Health Care of the Andalusian Health Service.
[h] COSHPD: The California Office of Statewide Health Planning and Development.

hospitalization. Most studies used pollutants that are commonly monitored by fixed monitoring stations. Our study confirms that several markers of ambient air pollution are significantly associated with health problems. Components of PM, such as elemental carbon, organic carbon, nitrates and copper, iron, potassium, nickel, silicon, vanadium, and zinc have been linked to early-life pneumonia (Fuertes et al., 2014; Ostro et al., 2009). Future studies may investigate the role of these particular markers of air pollution.

Mehta et al. reported that a 10 $\mu g/m^3$ increment in long-term exposure to $PM_{2.5}$ was associated with a 12% (95% CI: 3%–30%) higher risk of lower respiratory diseases (ALRI) (combining pneumonia and bronchitis) in children (Mehta et al., 2013a). In our meta-analysis, we estimated that the short-term effect of $PM_{2.5}$ on pneumonia hospitalization was about 1.8% (95%CI: 0.5%–3.1%) for a 10 $\mu g/m^3$ increment of $PM_{2.5}$. The discrepancy might be primarily explained by the inherently different time window considered in the Mehta et al. study, which addressed the cumulative long-term effects of past exposures on outcomes in a cohort of children. Time-series analyses, in contrast, usually capture only the most immediate acute effects of a few days of exposure on pneumonia hospitalizations in the following day(s). It is well known in air pollution epidemiology that the cumulative long-term effects of pollution are of a different order of magnitude compared to acute effects. Indeed, it is a major argument for promoting long-lasting, clean-air strategies over short-term, emergency management of smog episodes (Kunzli et al., 2001). Although we could not conduct meta-analyses for PM coarse ($PM_{10}$-$PM_{2.5}$), two studies showed associations between PM coarse and hospitalization due to pneumonia, with ERs of 8.6% (CI, 0.6%–22.7%) during the warm season and 3.2% (95%CI, 0.5%–13.0%) during the cold season at lag 0–6 in Chile (Ilabaca et al., 1999) and 5.6% (95%CI: 1.0%–10.6%) at lag 0–3 in Hong Kong (Qiu et al., 2014). These findings indicate that the coarse fraction of PM affects lower tract respiratory disease in children. Previous *in vitro* studies have shown that about 50% of PM with diameter less than 4 μm penetrates into the lower tract in children (Brown et al., 2013). The deep deposition and slower-clearance, fine PM could have stronger effects on lung cells (Valavanidis et al., 2008). The smallest size fractions of PM (i.e. ultrafine particles or nanoparticles) might differ in physical and aerodynamic properties, thus toxic pathways and effects of these components may also differ (Frampton and Rich, 2016). Unfortunately, we could not find any study to estimate the association between pneumonia in

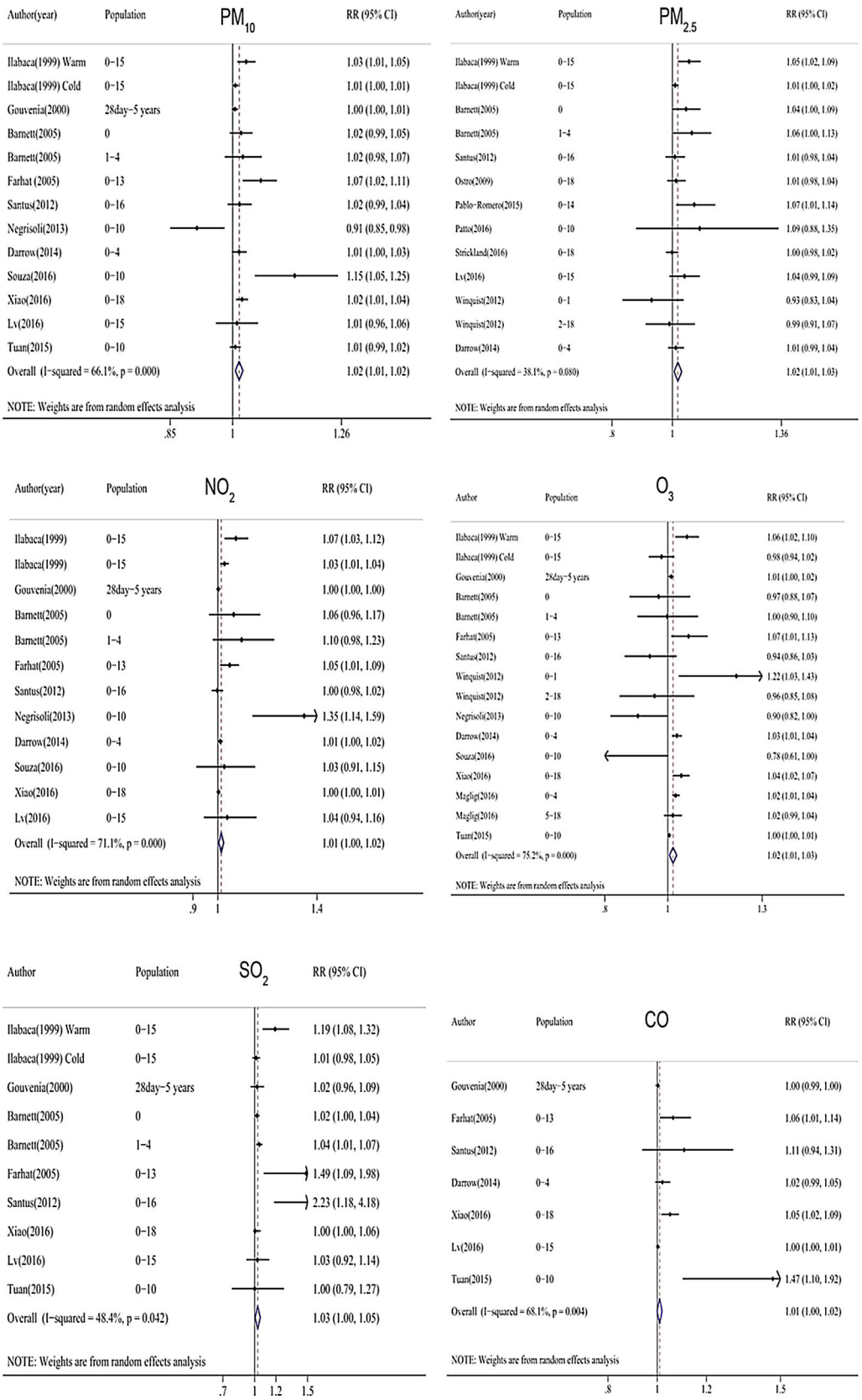


**Fig. 1.** Forest plot for the association between ambient air pollution and pneumonia hospitalization in children under 18 years old of $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$, $NO_2$, and CO. Relative risks (RRs) are for an increase of 10 $\mu g/m^3$ of $PM_{10}$ and $PM_{2.5}$, 10 ppb of $SO_2$, $NO_2$, $O_3$, and 1000 ppb of CO.
$I^2$ statistic indicates the proportion of total variability between effect estimates due to heterogeneity. $I^2$ ranges from 0 to 100% with 0–30%, 30%–50% and above 50% representing low, moderate, and high heterogeneity, respectively. The p-value is based on Q test.

**Table 2**
Descriptive statistics of pollutant concentrations as published in each study included in the review. Values were calculated from the daily mean concentrations of each study.

| | $PM_{10}$ (μg/m$^3$) | $PM_{2.5}$ (μg/m$^3$) | $SO_2$ (ppb) | $O_3$ (ppb) | $NO_2$ (ppb) | CO (ppb) |
|---|---|---|---|---|---|---|
| Daily mean (standard deviation) | 59.2(47.8) | 31.0(8.4) | 9.8 (8.1) | 35.2(13.3) | 61.7(16.7) | 1900(1600) |
| Range (Min-Max) | 17.6–175.0 | 9.4–96.0 | 1.2–26.4 | 13.8–62.9 | 9.2–198.4 | 500–49000 |
| Number of studies | 11 | 10 | 8 | 12 | 10 | 7 |
| Number of estimates | 13 | 13 | 10 | 16 | 12 | 7 |

children and $PM_1$, PM0.1 or other ultrafine particle fractions. Nonetheless, our results underscore the public health impact of particulate matter, consistent with the findings of others (Atkinson et al., 2014; Forouzanfar et al., 2015; Mehta et al., 2013b).

In this review, we could not find a clear effect of short-term exposure to CO on pediatric pneumonia. While the connection between CO and cardiovascular disease risk is very certain (Anoop S V Shah et al., 2016; Shah et al., 2013), its role on pneumonia has not been proven (United States Environmental Protection Agency, 2010). Indeed, several studies pointed out that CO at low concentrations is a protective factor against lower tract infection (Nobre et al., 2009; Tian et al., 2013). Thus, the role of CO on respiratory disease should be further investigated.

It is remarkable that associations between ambient air pollution and pediatric pneumonia were observed even in regions where the levels of pollution are quite low, for example, in Australia and New Zealand where daily means of $PM_{2.5}$ were $\leq$11 μg/m$^3$(Barnett et al., 2005) — far lower than the daily mean value recommended by the World Health Organization's air quality guideline (i.e. 25 μg/m$^3$). As shown in previous studies concentration-response functions are linear at low to moderate levels of pollution with some attenuation of these associations as concentrations get very high (Lippmann and Ito, 1995; Schwartz and Marcus, 1990). From the public health point of view, efforts to decrease air pollution can even be justified in low exposure settings.

Eight out of seventeen studies were carried out in Europe or North America. Six studies were carried out in Brazil. One study was conducted in China. Therefore, the comparison of results from high income economies (HIE) and not-high-income economies (N-HIE) (Fig. 2) suggest larger risks among children from lower socioeconomic groups. Children living in poverty might be particularly susceptible to the adverse respiratory health effects of air pollution. Children in low- and middle-income countries and in resource-poor settings may not only experience higher exposure to air pollution but also be exposed to additional risk factors for pneumonia, such as smoke from biomass burning or poor diets that may amplify the effects of ambient air pollution. In order to elucidate the worldwide effect of ambient air pollution on pneumonia infections, studies from N-HIE, such as those in Southeast Asia, the Middle East, or Africa are needed.

In this review, some studies reported mixed-pollutant effects for pneumonia outcomes. However, the maximum number of co-adjusted estimates was two, therefore we could not derive pooled estimates. The results from these reports call for further studies to disentangle the role of various markers of air pollution and to evaluate the possible independence of some pollutants; this would be relevant in assessing the burden of disease attributable to air pollution. For example, one study observed that more than 25% of the single-pollutant estimate of $PM_{10}$ could be explained by the co-varying $NO_2$ concentrations (Farhat et al., 2005).

The set of pollutants significantly associated with pneumonia raises the question about which one to use for assessing the burden attributable to air pollution. Pollutants such as PM, $NO_2$ and $SO_2$ are not independent but rather temporally correlated due to partly common sources, whereas $O_3$ is often not correlated. The global burden of disease study (GBD) considered PM and $O_3$; the former was found to be a leading cause of disability worldwide, whereas the burden associated with $O_3$ is substantially smaller. The burden associated with $NO_2$ — as an alternative marker to derive the health impact of ambient air pollution (Heroux et al., 2015) — is rather comparable to the one attributed to PM but, due to their correlation and shared sources, one cannot add up the related impact. The choice of pollution marker used in an impact assessment may depend on the context and question being addressed. In the context of traffic related policies, for example, $NO_2$ may provide a more comprehensive measure of impact than PM (Castro et al., 2017).

Although this review observed high heterogeneity in most of pollutants, the effects remained positive when we stratified the analysis by interaction factors, such as income level of country and age groups. The high heterogeneity might be due to differences of study locations. As seen in Table S9, results from meta-regression indicated strong effect modification by country location (N-HIE versus HIE countries) in models for $PM_{2.5}$, $NO_2$, and $O_3$. Moreover, though most of the asymmetry of the funnel plot was driven by a study with small daily case rates, some asymmetry still remained when considering larger studies only. Hence, the general heterogeneity drives the asymmetry in this meta-analysis.

### 4.1. Limitations

Our study has some limitations. First, our meta-analyses are based on observational studies, thus they may carry over uncontrolled time-varying biases if present in the source studies. We did not conduct a statistical assessment of publication biases because this test relies on assumptions unsuited to meta-analyses of observational studies (Egger et al., 1997). Though this is a meta-analysis of observational studies, individual studies have been extensively adjusted for possibly confounding variables, such as meteorological conditions, seasonality, and other time-varying factors (Table S1). Therefore, associations might be interpreted as causal. However, the lack of studies from not-high-income countries limits the generalizability of our results.

Second, ambient data from fixed monitoring stations represent the average ambient exposure conditions of the population rather than personal exposure. As shown by others, the variation in daily pollution measured at a fixed site captures the average variation of exposure of people living in the area. To the extent that spatial variation differs across the various pollutants, fixed site monitoring data may not equally represent ambient concentrations for the geographic regions where the hospitalized children live. For more homogenously distributed pollutants, such as $PM_{2.5}$, the pollution data may be representative of a larger region than in case of $NO_2$ or CO, where proximity to sources influences local pollution levels more strongly. However, even in the latter case, short-term temporal variations tend to be highly spatially correlated. Thus, despite possible difference in the absolute levels across the regions, estimates based on one or a few fixed site monitors provide a valid approximation of the association between daily levels of pollution and hospital admissions. Time-series data from monitoring stations located close to traffic hot spots may be less correlated with

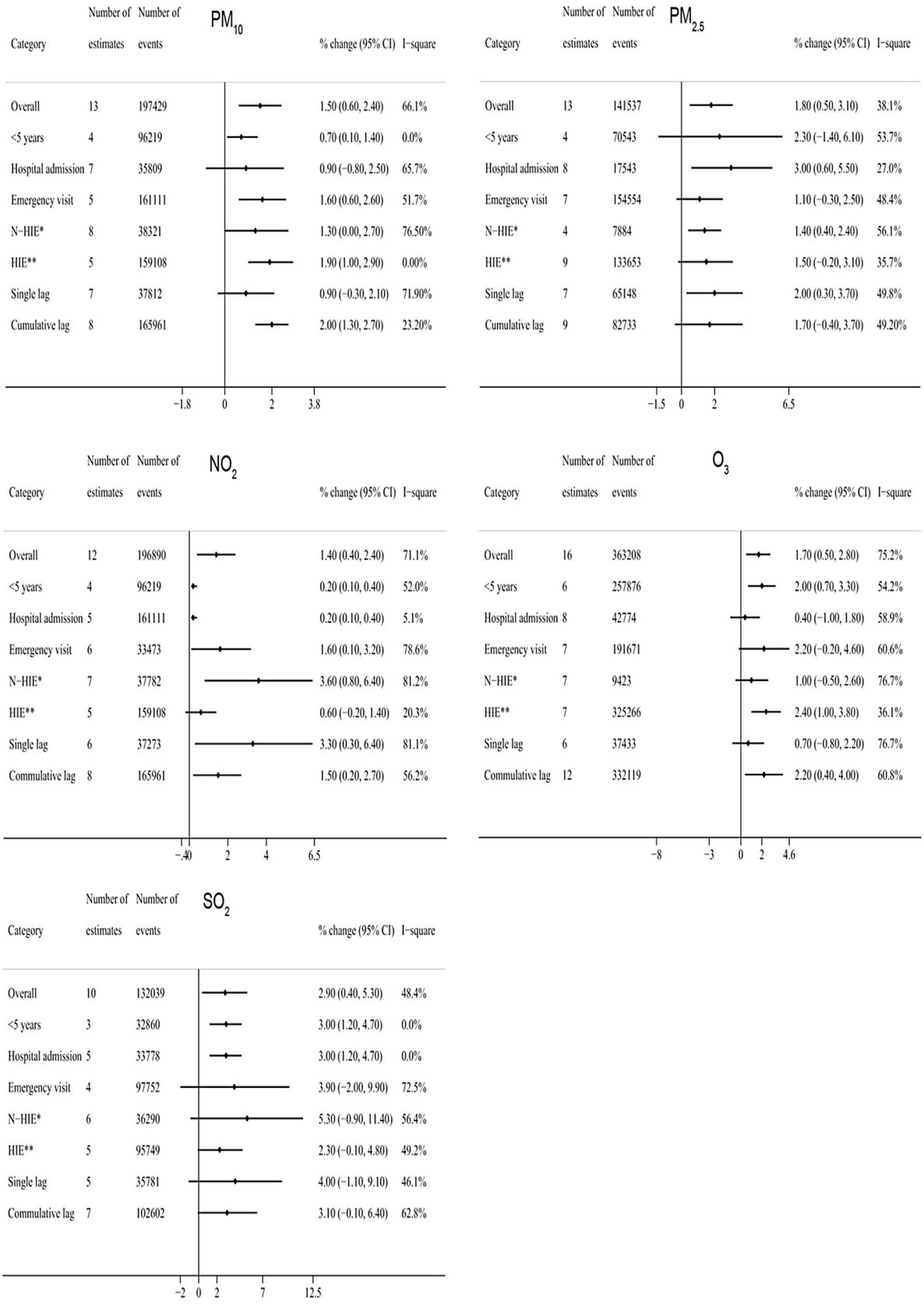


**Fig. 2.** Associations between hospitalization due to pneumonia and ambient air pollutants of $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$, and $NO_2$: stratified by age, outcome, income level of country and time of exposure (lag). Data for CO was insufficient to stratify analyses.

Percent changes are (% change) for an increase of 10 $\mu g/m^3$ of $PM_{10}$ and $PM_{2.5}$, 10 ppb of $SO_2$, $NO_2$, $O_3$, and 1000 ppb of CO.

*High-income economies (HIE): HIE are those with a Gross National Income (GNI) per capita of $12,476 or more n 2015.

**NOT high-income economies (N-HIE) are the following three categories: Low-income economies are those with a GNI per capita of $1025 or less in 2015; lower middle-income economies are those with a GNI per capita between $1026 and $4035 in 2015; upper middle-income economies are those with a GNI per capita between $4036 and $12,475 in 2015 https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups; Accessed: January 21, 2017.

temporal variations at less exposed sites, such as background stations. For this reason, many studies choose time-series data from background stations. While this issue remains a possible source of heterogeneity, it is unlikely to introduce systematic errors. Similarly, effects may differ between shorter and longer time series, given that controlling for seasonal influences may be less applicable in the former (Bhaskaran et al., 2013).

Third, in this analysis, several studies (Lv et al., 2016; Tuan et al., 2015) investigated associations with one-year time series data. Two studies from Brazil (Negrisoli and Nascimento, 2013; Souza and Nascimento, 2016) are based on small number of events, daily mean number of cases were 2.5 and 0.22, respectively. However, given the high statistical uncertainty of their results, they have only a minor influence on the meta-analytic estimates. Moreover, most of these studies adjusted for meteorological factors, such as temperature or humidity as well as seasonality (Table S1). But, none of them adjusted for influenza epidemics. As there is no causal link between such epidemics and short term variations in ambient air pollution, this could only lead to accidental confounding.

Finally, we did not access the primary data for each publication. Therefore the definition of pneumonia in this analysis solely relied on the case definition provided by the authors of the individual studies. However, the studies used information from hospital admissions, where pneumonia is reviewed and defined by the medical doctor, even for emergency visit cases. Studies used either the ICD9 (480–486) or ICD10 (J12-J18) code for pneumonia. Therefore, we believe the risk of selection bias to be very small.

## 5. Conclusions

Hospital admissions due to pneumonia are common among children and might contribute substantially to their fatality rate, particularly among children under five. Our meta-analysis confirms that short-term increases in ambient air pollution — as measured by the concentrations of $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$ and $NO_2$ — are associated with an increase in hospital admissions due to pneumonia. To better understand these associations and the related public health impact in the most polluted regions of the world, with differing sources of pollution, high incidence of pneumonia, and possible differences in underlying susceptibilities, studies are needed from not-high-income economies, such as those in Southeast Asia, the Middle East, and Africa.

## Funding and acknowledgment

NTTN and HA both hold Swiss Government Excellence Scholarship (ESKAS) for PhD in Epidemiology. They sincerely acknowledge the Swiss Government, the Swiss Tropical and Public Health Institute, and the Swiss School of Public Health (SSPH+) for their superb academic support. Furthermore, HA acknowledges the PhD Educational Platform in Health Sciences (PPHS) at the Faculty of Medicine, University of Basel, for a project stipend award. The funders had no role in the study design, data analysis, data interpretation or manuscript writing. The authors had full access to all data in the study and were responsible for the decision to submit for publication.

## Conflicts of interest

None.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.envpol.2017.07.063.

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# Supplemental material:

**Short-term association between ambient air pollution and pneumonia in children: A systematic review and meta-analysis of time-series and case-crossover studies**

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## Contents



**Figures:**



**Tables:**

## A. Search strategy

Searching databases
We systematically reviewed all published peer reviewed scientific journals, which are indexed in PubMed and Web of Science up to January, 3 2017
Search query for PubMed:

1: pneumonia OR pneumococcal OR streptococcus pneumoniae
2: ozone OR Ozone
3: sulphur dioxide OR Sulphur dioxide
5: carbon monoxide OR Carbon Monoxide
6: Nitrogen Dioxide OR nitrogen dioxide
7: particulate matter OR Particulate Matter
8: air pollution OR Air pollution
9: Hospital* OR emergency visit
10: 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
11: 10 AND 1 AND 9

Search query for Web of Science:
1: Pneumonia* OR respiratory
2: hospital* OR emergency visit
3: Ozone OR Carbon Monoxide OR Sulfur Dioxide OR Nitrogen Dioxide OR Particulate Matter OR PM10 OR PM2.5
4: 1 AND 2 AND 3

**B. PRISMA diagram**

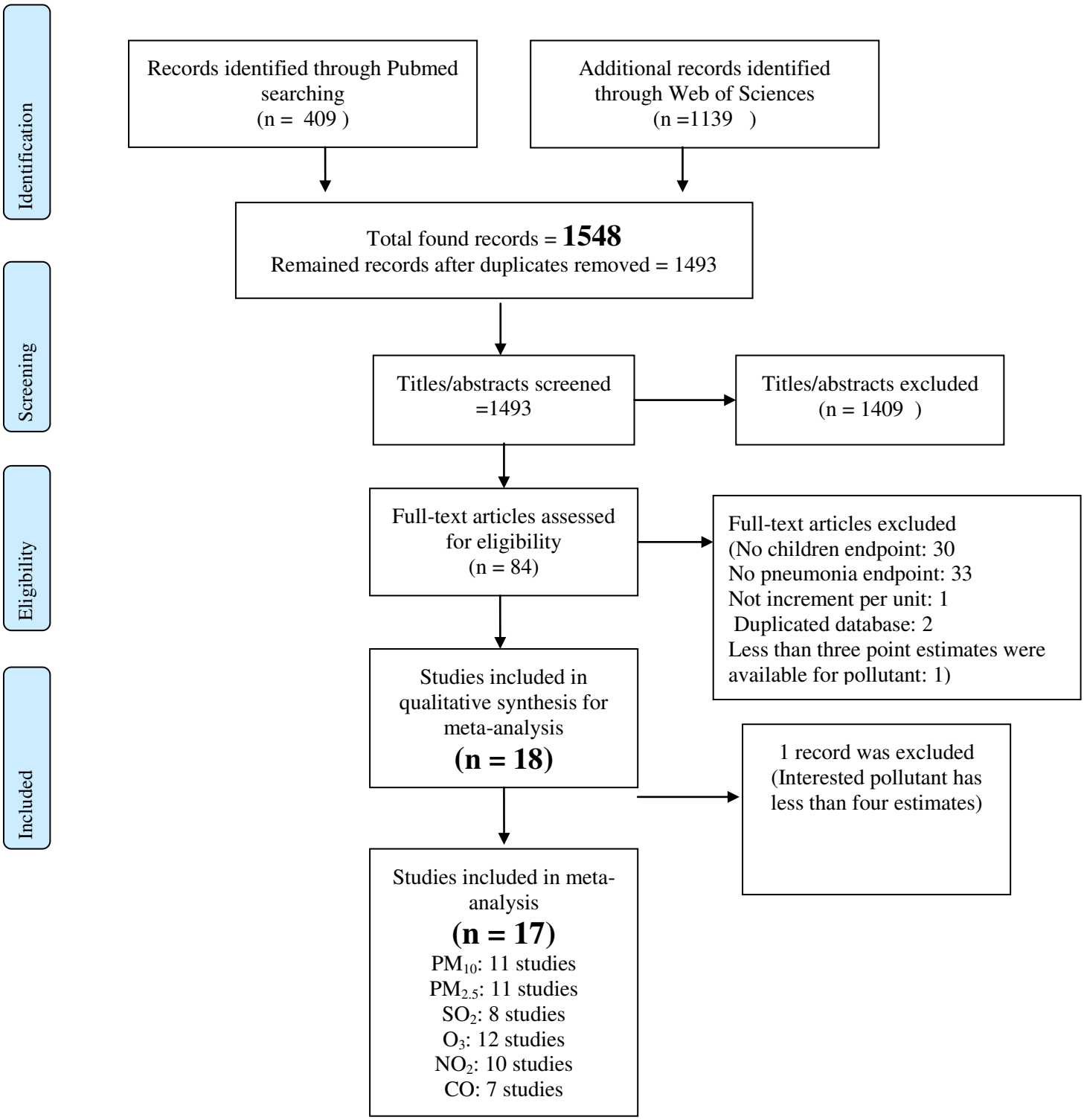


Figure S1 PRISMA diagram

Table S1: Characteristic of study quality

| Author | Year | Generalizability | Daily pollutant level | Number of Events | Time stratified cases for case-crossover analysis | Single pollutant | Multiple pollutants | Adjusted for time trend | Adjusted for temperature | Adjusted for seasonality | Adjusted for humidity | Adjusted for influenza | Number of monitoring station[$] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ilbabaca | 1999 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | 4 ($PM_{10}$+$PM_{2.5}$+ $SO_2$+$NO_2$+$O_3$) |
| Gouvenia | 2000 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | 12($PM_{10}$)<br>13($SO_2$)<br>5($O_3$)<br>4($NO_2$+CO) |
| Barnett | 2005 | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | × | 9($PM_{2.5}$)<br>28($PM_{10}$)<br>26($NO_2$)<br>37(CO)<br>17($SO_2$)<br>11($O_3$) |
| Farhat | 2005 | ✓ | ✓ | ✓ | n/a | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | 13 ($SO_2$+$PM_{10}$)<br>6($NO_2$)<br>8(CO) |
| Santus | 2012 | ✓ | ✓ | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | 3($O_3$+$PM_{10}$)<br>1($SO_2$+$PM_{2.5}$)<br>8($NO_2$)<br>5(CO) |
| Winquist | 2012 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | 2($PM_{2.5}$+$O_3$) |
| Negrisoli | 2013 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | 1($NO_2$+$PM_{10}$+$O_3$) |
| Ostro | 2009 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | not report |
| Darrow | 2014 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | not report |
| Pablo-Romero | 2015 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | not report |
| Souza | 2016 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | not report |
| Patto | 2016 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | n/a |
| Xiao | 2016 | ✓ | ✓ | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | n/a |
| Strickland | 2016 | ✓ | ✓ | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | n/a |
| Lv | 2016 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | × | not report |
| Maglig | 2016 | ✓ | ✓ | ✓ | ✓ | ✓ | × | ✓ | ✓ | ✓ | ✓ | ✓ | |
| Tuan | 2016 | ✓ | ✓ | ✓ | n/a | ✓ | × | ✓ | ✓ | ✓ | ✓ | × | Not report |

[$]: Number of station for each interested pollutant. n/a: not applicable

B. Extended results

Table S2: Summary of characteristics of all studies included in the meta-analysis, presented by pollutant

| | | | | PM10 (24h mean) µg/m3 | | | PM2.5 (24h mean) µg/m3 | | | SO2(24h mean) ppb | | | NO2 (24h mean) ppb | | | CO (24h mean) ppb | | | O3 (8h average) ppb | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Outcome | Definition | Income level | *Average concentration* | Cumulative lag | Single lag | *Average concentration* | Cumulative lag | Single lag | *Average concentration* | Cumulative lag | Single lag | *Average concentration* | Cumulative lag | Single lag | *Average concentration* | Cumulative lag | Single lag | *Average concentration* | Cumulative lag | Single lag |
| Ilbabaca | Pneumonia | ICD9: 480-486 | HIE | *80.3: (warm) 123.9 (cold)* | 0-6 | **2**, 3 | *34.3 (warm) 71.3 (cold)* | 0-6 | **2**, 3 | *5.7 (warm) 12.1 (cold)* | **0-6** | **2**, 3 | *51.6 (warm) 85.2 (cold)* | **0-6** | **2**, 3 | - | | | *33.3 (warm) 13.8 (cold)* | **0-6** | **2**, 3 |
| Gouvenia | Pneumonia | ICD9: 480-486 | N-HIE[2] | *64.9* | | 0 | - | | | *7.0* | | 1 | *198.4* | | 0 | *490 0* | | 0 | *36.5* | | 0 |
| Barnett | Pneumonia + acute bronchitis | ICD9: 480-486; ICD10: J12-J17, J18.0, J18.1,J18.8 ,J18.9, J20, J21 | HIE[1] | *17.6* | 0-1 | | *9.4* | 0-1 | | *7.4* | 0-1 | | *9.2* | 0-1 | | - | | | *23.2* | 0-1 | |
| Farhat | Pneumonia | ICD9: 480-486 | N-HIE[2] | *62.6* | 0-5 | | - | | | *9.0* | 0-5 | | *66.6* | 0-2 | | *320 0* | 0-1 | | *41.5* | 0-6 | |
| Santus | Pneumonia | Review by medical doctor | HIE[1] | *47.08* | 0-2 | | *32.8* | 0-2 | | *1.6* | 0-2 | | *116.8* | 0-2 | | *130 0* | 0-2 | | *42.7* | 0-2 | |
| Winquist | Pneumonia | ICD9 480-486 | HIE[1] | - | | | *14.4* | 0-4 | | - | | | - | | | - | | | *36.3* | 0-4 | |
| Negrisoli | Pneumonia | ICD10: J12-J18 | N-HIE[2] | *34.4* | | **0**, 1, 2, | - | | | - | | | *25.6* | | **0**, 1, 2, | - | | | *18.6* | | **0**, 1, |

| | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 3,4,5 | | | | | | | | 3,4,5 | | | | | | 2,3,4,5 |
| Ostro | Pneumonia | ICD9: 480-486 | HIE[1] | - | | | *19.4* | | **0**,1,2,3 | - | | | - | | | - | | | - | |
| Darrow | Pneumonia | ICD9: 480-486 | HIE[1] | *22.2* | 0-2 | | *14.1* | 0-2 | | - | | | *45.8* | 0-2 | | *900* | 0-2 | | *45.9* | 0-2 | |
| Pablo-Romero | Pneumonia | ICD9: 480-486 | HIE[1] | - | | | *17.3* | | 5 | - | | | - | | | - | | | - | | |
| Souza | Pneumonia | ICD10 J12-J18.9 | N-HIE[2] | *35.7* | | **0**, 1, 2, 3,4, 5 | - | | | - | | | *30.1* | | **0**, 1, 2, 3,4, 5 | - | | | *39* | | **0**, 1, 2, 3,4,5 |
| Patto | Pneumonia | ICD10 J12-J18.9 | N-HIE[2] | | | | *18.7* | | **0**,1,2, 3,4,5 | - | | | - | | | - | | | - | | |
| Xiao | Pneumonia | ICD9 480-489 | HIE[1] | *22.5* | 0-3 | | - | | | *18.0* | 0-3 | | *19.7* | 0-3 | | *500* | 0-3 | | *42.1* | 0-3 | |
| Strickland | Pneumonia | ICD9 480-489 | HIE[1] | - | | | *12.9* | | **0**,1 | - | | | | - | | | | | - | | |
| Lv | Pneumonia | Diagnosis by doctors | N-HIE[2] | *175* | | | *96* | | **0**,1,2, 3,4,5 | *26.4* | | **0**,1, 2,3, 4,5 | *29.4* | | **0**,1, 2,3, 4,5 | *1200* | | **0**,1, 2,3, 4,5 | - | | |
| Maglig | Pneumonia | ICD9: 480-486 | HIE[1] | - | | | - | | | - | | | - | | | - | | | *62.9* | 0-3 | |
| Tuan | Pneumonia | ICD10 : J12-J19.8 | N-HIE[2] | *23* | | 0,1, 2,3, 4,5 | - | | | *3.1* | | 0,1, 2,3, 4,5 | - | | 0.9 | | 3,4 | | *47.2* | | 2,3 |

[1]High-income economies (HIE): HIE are those with a Gross National Income (GNI) per capita of $12,476 or more in 2015

[2]NOT high-income economies (N-HIE) are the following three categories: Low-income economies are those with a GNI per capita of $1,025 or less in 2015; lower middle-income economies are those with a GNI per capita between $1,026 and $4,035 in 2015; upper middle-income economies are those with a GNI per capita between $4,036 and $12,475 in 2015 (https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups; Accessed: January 21, 2017.

## Appendix C: Leave-one-study-out sensitivity analysis and Funnel plot

Table S3: Leave-one-study-out sensitivity analysis for $PM_{10}$

| Study left out | Relative risk (95%CI) | $I^2$ | $P_Q$ |
|---|---|---|---|
| Ilabaca(1999) | 1.016(1.004-1.028) | 66.8% | 0.001 |
| Gouvenia(2000) | 1.018(1.006-1.029) | 66.6% | <0.001 |
| Barnett(2005) | 1.015(1.005-1.025) | 70.9% | <0.001 |
| Farhat(2005) | 1.013(1.004-1.021) | 60.1% | 0.004 |
| Santus(2012 | 1.015(1.006-1.025) | 68.7% | <0.001 |
| Negrisoli(2013) | 1.016(1.008-1.024) | 59.1% | 0.005 |
| Darrow(2014) | 1.015(1.005-1.025) | 68.5% | <0.001 |
| Sousa(2016) | 1.014(1.005-1.022) | 60.5% | 0.003 |
| Xiao(2016) | 1.014(1.004-1.024) | 65.7% | 0.001 |
| Lv(2016) | 1.015(1.006-1.025) | 68.9% | <0.001 |
| Tuan(2016) | 1.017(1.006-1.027) | 68.6% | <0.001 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S4: Leave-one-study-out sensitivity analysis for $PM_{2.5}$

| Study left out | Relative risk (95%CI) | $I^2$ | $P_Q$ |
|---|---|---|---|
| Ilabaca(1999) | 1.017(1.001-1.032) | 28.9% | 0.170 |
| Barnet(2005) | 1.014(1.002-1.026) | 32.1% | 0.143 |
| Santus(2012) | 1.020(1.006-1.034) | 43.0% | 0.056 |
| Winquist(2012) | 1.020(1.007-1.032) | 39.5% | 0.085 |
| Ostro(2009) | 1.019(1.005-1.034) | 43.2% | 0.055 |
| Darrow(2014) | 1.020(1.005-1.034) | 43.2% | 0.055 |
| Paplo-Romero(2015) | 1.015(1.003-1.027) | 31.4% | 0.140 |
| Patto(2016) | 1.018(1.005-1.031) | 42.0% | 0.062 |
| Strickland(2016) | 1.022(1.008-1.036) | 36.2% | 0.101 |
| Lv(2016) | 1.017(1.004-1.030) | 39.6% | 0.077 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S5: Leave-one-study-out sensitivity analysis for $SO_2$

| Study left out | Relative risk (95%CI) | $I^2$ | $P_Q$ |
|---|---|---|---|
| Illabaca(1999) | 1.024(1.002-1.046) | 30.2% | 0.187 |
| Gouvenia (2000) | 1.030(1.003-1.057) | 54.1% | 0.026 |
| Barnett(2005) | 1.034(0.992-1.077) | 54.1% | 0.033 |
| Farhat(2005) | 1.026(1.005-1.047) | 40.1% | 0.100 |
| Santus(2012) | 1.028(1.005-1.050) | 46.6% | 0.060 |
| Xiao(2016) | 1.036(1.007-1.064) | 47.2% | 0.056 |
| Lv(2016) | 1.029(1.003-1.055) | 54.1% | 0.026 |
| Tuan(2016) | 1.029(1.004-1.055) | 54.0% | 0.026 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S6: Leave-one-study-out sensitivity analysis for $O_3$

| Study left out | Relative risk (95%CI) | $I^2$ | $P_Q$ |
|---|---|---|---|
| Ilabaca(1999) | 1.016(1.004-1.028) | 74.4% | <0.001 |
| Gouvenia (2000) | 1.017(1.001-1.032) | 76.4% | 0.001 |
| Barnet(2005) | 1.018(1.006-1.030) | 78.3% | <0.001 |
| Farhat(2005) | 1.015(1.004-1.027) | 75.2% | <0.001 |
| Santus(2012) | 1.018(1.006-1.030) | 76.0% | <0.001 |
| Winquist(2012) | 1.017(1.005-1.028) | 76.6% | <0.001 |
| Negrisoli (2013) | 1.018(1.007-1.030) | 74.9% | 0.001 |
| Darrow(2014) | 1.015(1.003-1.027) | 73.2% | <0.001 |
| Souza(2016) | 1.018(1.006-1.029) | 74.7% | <0.001 |
| Xiao(2016) | 1.014(1.002-1.026) | 73.7% | <0.001 |
| Maglig(2016) | 1.015(1.001-1.029) | 73.9% | <0.001 |
| Tuan(2016) | 1.018(1.003-1.033) | 66.0% | <0.001 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S7: Leave-one-study-out sensitivity analysis for $NO_2$

| **Study left out** | **Relative risk (95%CI)** | **$I^2$** | **$P_Q$** |
|---|---|---|---|
| Illabaca(1999) | 1.007(0.999-1.016) | 58.4% | 0.010 |
| Gouvenia (2000) | 1.022(1.007-1.036) | 67.5% | 0.001 |
| Barnett (2005) | 1.013(1.003-1.022) | 73.9% | <0.001 |
| Farhat (2005) | 1.011(1.002-1.021) | 69.3% | <0.001 |
| Santus(2012) | 1.016(1.006-1.027) | 73.6% | <0.001 |
| Negrisoli (2013) | 1.012(1.003-1.021) | 65.6% | <0.001 |
| Darrow(2014) | 1.017(1.004-1.029) | 72.0% | <0.001 |
| Souza(2016) | 1.014(1.004-1.024) | 73.7% | <0.001 |
| Xiao(2016) | 1.021(1.007-1.034) | 73.7% | <0.001 |
| Maglig(2016) | 1.014(1.004-1.024) | 73.5% | <0.001 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S8: Leave-one-study-out sensitivity analysis for CO

| **Study left out** | **Relative risk (95%CI)** | **$I^2$** | **$P_Q$** |
|---|---|---|---|
| Gouvenia (2000)[8] | 1.034(1.001-1.066) | 73.5% | 0.002 |
| Farhat (2005)[9] | 1.007(0.998-1.017) | 67.2% | 0.009 |
| Santus(2012) | 1.009(0.999-1.019) | 71.5% | 0.004 |
| Darrow(2014) | 1.008(0.998-1.019) | 71.3% | 0.004 |
| Xiao(2016) | 1.005(0.997-1.013) | 56.4% | 0.043 |
| Lv(2016) | 1.043(1.002-1.066) | 72.1% | 0.003 |
| Tuan(2016) | 1.008(0.999-1.016) | 64.0% | 0.016 |

$P_Q$: the test of the heterogeneity statistics. P-value >0.05 means that the individual studies is not heterogeneity.
$I^2$ ranges from 0-30%, 30%-50% and above 50% where they represent low, moderate, and high heterogeneity, respectively

Table S9: Coefficients and 95% confident intervals of covariates used in the meta-regression.

| Pollutants | Covariates | Coefficient | 95%CI of Coefficient | | p-value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| $PM_{10}$ | Children under 5 vs general population[$] | -0.005 | -0.012 | 0.001 | 0.112 |
| | Non- HIE* vs HIE | -0.001 | -0.005 | 0.003 | 0.654 |
| $PM_{2.5}$ | Children under 5 vs general population[$] | -0.008 | -0.017 | 0.002 | 0.111 |
| | Non- HIE* vs HIE | 0.024 | 0.013 | 0.034 | P<0.001 |
| $SO_2$ | Children under 5 vs general population[$] | -0.213 | -0.525 | 0.099 | 0.182 |
| | Non- HIE* vs HIE | -0.109 | -0.447 | 0.228 | 0.526 |
| $O_3$ | Children under 5 vs general population[$] | 0.007 | 0.005 | 0.008 | P<0.001 |
| | Non- HIE* vs HIE | -0.016 | -0.017 | -0.015 | P<0.001 |
| $NO_2$ | Children under 5 vs general population[$] | -0.008 | -0.009 | -0.007 | P<0.001 |
| | Non- HIE* vs HIE | 0.007 | 0.005 | 0.008 | P< 0.001 |

* HIE: High Income Economic. N-HIE: Non-High Income Economic; studies were categorised as "children under 5" if the study investigated the association of ambient air pollution and hospital admission in children up to 5 years of age in separate model; studies providing estimates only for "children ages from 0 to 18" or " 0-13" were assigned to the category of the "general population"

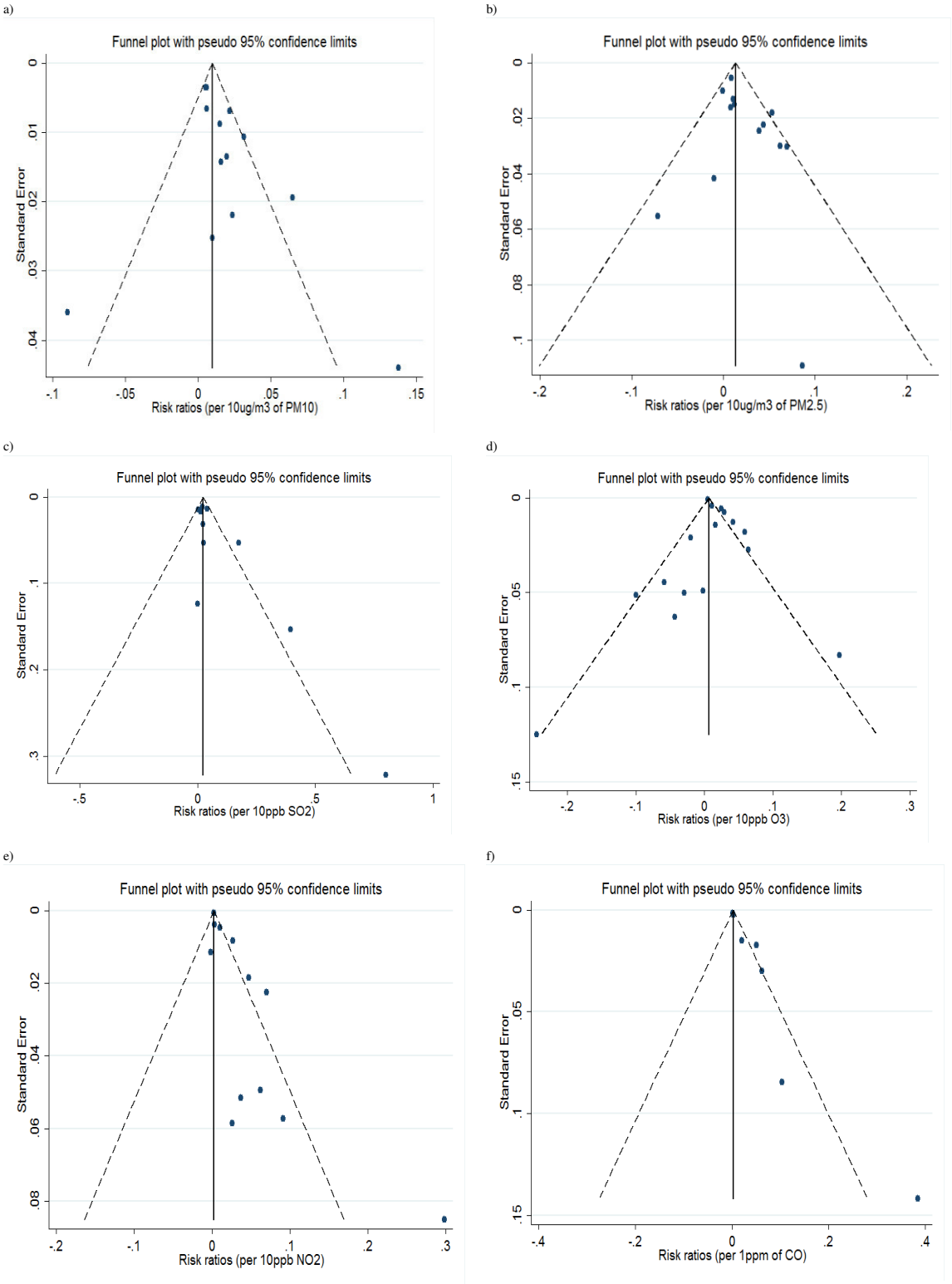


**Figure S2**: Funnel plot for the published relative risks of pneumonia hospitalization associated with a 10 $\mu g/m^3$ increment in a) $PM_{10}$, b) $PM_{2.5}$, c) $SO_2$, d) $O_3$, e) $NO_2$ , and f) CO

Center lines of the funnel plots represent a fixed effect

# CHAPTER 5: ASSOCIATION BETWEEN AMBIENT AIR POLLUTION AND PNEUMONIA IN VIETNAM

The article was published as:

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NHUNG, N. T. T., SCHINDLER, C., DIEN, T. M., PROBST-HENSCH, N., PEREZ, L. & KÜNZLI, N. 2018. Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: An eight-year time series study. *Environment International,* 110**,** 139-148.

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Environment International 110 (2018) 139–148

Contents lists available at ScienceDirect

Environment International

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

# Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: An eight-year time series study

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ARTICLE INFO

*Keywords:*
Ambient air pollution
Children
Pneumonia
Bronchitis
Asthma
Time-series analysis

ABSTRACT

*Background:* Lower respiratory diseases are the most frequent causes of hospital admission in children worldwide, particularly in developing countries. Daily levels of air pollution are associated with lower respiratory diseases, as documented in many time–series studies. However, investigations in low-and-middle-income countries, such as Vietnam, remain sparse.

*Objective:* This study investigated the short-term association of ambient air pollution with daily counts of hospital admissions due to pneumonia, bronchitis and asthma among children aged 0–17 in Hanoi, Vietnam. We explored the impact of age, gender and season on these associations.

*Methods:* Daily ambient air pollution concentrations and hospital admission counts were extracted from electronic databases received from authorities in Hanoi for the years 2007–2014. The associations between outdoor air pollution levels and hospital admissions were estimated for time lags of zero up to seven days using Quasi-Poisson regression models, adjusted for seasonal variations, meteorological variables, holidays, influenza epidemics and day of week.

*Results:* All ambient air pollutants were positively associated with pneumonia hospitalizations. Significant associations were found for most pollutants except for ozone and sulfur dioxide in children aged 0–17. Increments of an interquartile range (21.9 μg/m$^3$) in the 7-day-average level of $NO_2$ were associated with a 6.1% (95%CI 2.5% to 9.8%) increase in pneumonia hospitalizations. These associations remained stable in two-pollutant models. All pollutants other than CO were positively associated with hospitalizations for bronchitis and asthma. Associations were stronger in infants than in children aged 1–5.

*Conclusion:* Strong associations between hospital admissions for lower respiratory infections and daily levels of air pollution confirm the need to adopt sustainable clean air policies in Vietnam to protect children's health.

## 1. Introduction

A child's respiratory system is susceptible to the adverse health effects of air pollution. Children have higher breathing rates than adults (Ginsberg et al., 2005). As children grow, long-term exposure to air pollution may lead to deviations from normal growth patterns (Thurston et al., 2017). Additionally, children may spend more time outdoors engaging in physical activity and thereby inhaling higher doses of air pollutants (Gilliland, 2009).

The association between air pollution and hospitalization for acute respiratory infection (ARI) has been investigated worldwide (Barnett et al., 2005; Darrow et al., 2014; Qiu et al., 2014; Winquist et al., 2012). These studies demonstrated that daily levels of common markers of ambient air pollution such as nitrogen dioxide ($NO_2$) and particulate matter (PM) are associated with ARI. For example, Barnett et al. (2005) reported a 2.4% increase of daily hospital admissions due to pneumonia and bronchitis for a 3.8 μg/m$^3$ increase of PM with aerodynamic diameter < 2.5 μm ($PM_{2.5}$) in children, age 1–4; and a 6.0% increase of asthma hospitalization per 5.1 ppb increase of 24-h $NO_2$ in children 5–14 in New Zealand and Australia, respectively. However, evidence from Vietnam is sparse. Only one study conducted in Ho Chi Minh (HCM) (Southern Vietnam) has examined this relationship. Le et al.

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http://dx.doi.org/10.1016/j.envint.2017.10.024
Received 3 June 2017; Received in revised form 26 October 2017; Accepted 28 October 2017
Available online 08 November 2017

(2012) showed positive associations between ARI and both $NO_2$ and PM with aerodynamic diameter < 10 μm ($PM_{10}$) during the dry season 2003–2005, but the results were not statistically significant given the rather short series and limited statistical power (Bhaskaran et al., 2013).

The burden of ARIs such as bronchitis and pneumonia is very large among Vietnamese children. Pneumonia accounted for 11% of the total burden of diseases in children under 15 year of age in 2008 (Nhung et al., 2014), and for 11% of total deaths among children under five (data from 2014) (Nguyen et al., 2016). Pneumonia infection is the most common cause of hospital admission in Hanoi children, accounting for 54.1% of all respiratory disease-related admissions during 2007–2014(Nguyen et al., 2017). Bronchitis ranked at the second position with 19.1% of hospital admissions for respiratory diseases. Pneumonia and bronchitis were also the leading causes of prolonged hospitalization and death at the hospital during our study period. In addition, once a child develops pneumonia, proper treatment with a full course of antibiotics is vital. As a consequence, the treatment cost becomes a health economic burden for patients. The average of treatment cost for an outpatient case of pneumonia was US$71 and for severe pneumonia was US$ 235 in Pakistan (Hussain et al., 2006). The estimated treatment cost for suspected pneumonia was about US$31 in Vietnam and up to 63% of these costs were accounted for by drugs (Anh et al., 2010).

A number of risks for lower respiratory diseases have been documented in Vietnam, including environmental tobacco smoke (Suzuki et al., 2009), termination of breast feeding in early infancy (Anders et al., 2015; Hanieh et al., 2015), and ambient air pollution (Le et al., 2012). Nonetheless, these associations and the related impact on lower respiratory infections have not been studied in Northern Vietnam. Thus, it is difficult to predict the benefit of clean air policies on respiratory health in children — such as those documented in a Swiss landmark study (Bayer-Oglesby et al., 2005) — or to compare the cost-effectiveness of clean air strategies versus the provision of antibiotics.

Hanoi is a polluted city in Vietnam. The proportion of days with Air Quality Index levels at 101–200 (unhealthy level for sensitive group) ranged from 40% to 60% of total monitoring days between 2013 and 2014, according to a report from the Ministry of Natural Resources and Environment, 2014 (Ministry of Natural Resources and Environment, 2014). The report also pointed out that daily mean $NO_2$, ozone ($O_3$), sulfur dioxide ($SO_2$), and $PM_{10}$ concentrations were frequently above the World Health Organization (WHO) suggested levels. An earlier study using ground sampling measurements in Hanoi reported an annual mean of 87.1 μg/m$^3$ for $PM_{10}$, and of 36.1 μg/m$^3$ for $PM_{2.5}$ during August 1998 to July 1999(Hien et al., 2002). This study also demonstrated that wind speed, temperature and relative humidity were closely related to air pollution concentration. A recent study estimating $PM_{2.5}$ by using MODIS satellite data has shown that monthly mean values of $PM_{2.5}$ ranged from 50 μg/m$^3$ to 100 μg/m$^3$ in the Northeast region of Vietnam during the period 2009–2012(Nguyen et al., 2015). The main sources of air pollution in Vietnam are traffic vehicle exhaust, industry, and construction activities. Besides that coal mining in Quang Ninh, cement production in Hai Phong, a steel factory in Thai Nguyen and agricultural activities in Hanoi are the other local emissions in the Northeast region (Ministry of Natural Resources and Environment, 2014).

Hanoi had about 7.3 million inhabitants in 2014 with an average population density of about 2213 people/km$^2$ (Hanoi Population and Family Planning Branch, 2014). Children accounted for 28% of the total population in Hanoi. Details regarding population density and geography are presented on the map of Fig. A1. The intake fraction (an approach to quantify the link between the pollutant emissions and population exposure) of the Hanoi population may be high, as Hanoi has both high population density and vehicle volume. For example, the population density in Hoan Kiem district (central district of Hanoi) reached 38,250 people/km$^2$ in 2014 (Hanoi Population and Family Planning Branch, 2014). Therefore, the objective of this work is to investigate the short-term effects of exposure to ambient air pollution on hospital admissions due to pneumonia, bronchitis and asthma symptoms in Hanoi children under 18 years of age.

## 2. Materials and methods

### 2.1. Data source

Data on hourly means of air pollutants was obtained from two fixed monitoring stations, the Nguyen Van Cu station (2102′56.05″N, 105,052′58.59″E) and the Lang Ha station (2101′13.47″N, 105,048′24.10″E). Data were averaged by station and calendar day to provide 24-h means of $PM_{10}$, $PM_{2.5}$ and $PM_1$ (air borne particulates with an aerodynamic diameter < 1 μm), $NO_2$, nitrogen oxides ($NO_x$), $SO_2$, and carbon monoxide (CO). The daily means of the pollutants were accepted in the study if > 16 out of 24 hourly measurements were available. For $O_3$, we calculated two measures, the eight-hour maximum (the highest moving eight-hour average) and the 24-h maximum (the highest hourly mean on a given day). For these measures to be accepted, 18 out of 24 hourly measurements were required. All indicators were expressed in μg/m$^3$. Since Lang ha station used ppb as a unit for measuring $SO_2$, we converted these concentrations from ppb into μg/m$^3$ by using the WHO conversion factor, 1 ppb = 2.62 μg/m$^3$ at 25 Degree Celsius and 1013 mb (Danish Centre For Environment And Energy, n.d.).

We imputed missing daily concentration data of $PM_{10}$ and $SO_2$ in different steps. First we generated values for one-day gaps by taking the mean value of the neighboring days. To impute missing data in longer gaps, we used a regression model incorporating daily concentration data of the same pollutant from the other stations, of other pollutants from the same station, as well as daily temperature, relative humidity and wind speed. In addition, these models contained sine and cosine functions of time with a period of one year. We also considered interactions between the different variables. After these imputations, we filled any remaining one-day gaps as described in step one. Since $PM_1$ and $PM_{2.5}$ were only monitored in Nguyen Van Cu station, we used $PM_{10}$ data from Lang Ha station along with data for other pollutants to impute the missing data for $PM_1$ and $PM_{2.5}$.

Daily averages of $SO_2$ and $PM_{10}$ were generated from measurements taken from Lang Ha station (from January 2007 to May 2009) and from Nguyen Van Cu station (from June 2009 to December 2014). For other pollutants, we used data from Nguyen Van Cu station (June 2009 to December 2014).

Meteorological data were also collected for the same period from four meteorological stations, namely Lang, Ba Vi, Son Tay, and Ha Dong, and included 24-h temperature means (in $^0$C), relative humidity (in percent) and wind speed (m/s). Daily means of temperature, humidity, and wind speed were calculated by averaging values across the four stations.

Hospital admission records from January 1, 2007 to December 30, 2014 were retrieved from the computerized database of the Vietnam National Children's Hospital, Hanoi, Vietnam. In this paper, a hospital admission is defined as a hospital stay for at least one night. Readmissions within 24 h after discharge were considered as continuation of the previous hospitalization. With 1660 beds, the hospital covered the majority of all hospital admissions due to severe illnesses in Hanoi. Before being referred to a children's hospital, most children first undergo a health check at an out-patient department of the hospital. Only children with severe illness are admitted to the hospital, while the others receive prescriptive medication and are treated as outpatients. Patients with life-threatening diseases such as severe breathlessness, liver and heart failure are often directly brought to the emergency department, from where they are transferred to a specific department on the next day. A detailed description of this database, quality control and quality assurance procedures was published elsewhere (Nguyen

**Table 1**
Total and age-group specific number of hospital admissions due to pneumonia and bronchitis and asthma, Hanoi, 2007–2014[a] and 2009–2014[a].

| | 2007–2014[a] | | | | 2009–2014[a] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | By season | | | | By season | |
| Outcome by age group | Number of admissions | Daily Mean (SD) | Daily mean (SD) in warm season (April–October) | Daily mean (SD) in cold season (November–February) | Number | Daily Mean (SD) | Daily mean (SD) in warm season (April–October) | Daily mean (SD) in cold season (November–March) |
| Pneumonia (ICD10: J12-J18) | | | | | | | | |
| < 1 year | 25,016 | 8.5(4.7) | 8.3(4.3) | 8.9(5.1) | 18,908 | 9.2(5.0) | 8.7(4.0.5) | 10.2(5.5) |
| 1–5 years | 14,576 | 5.0(3.1) | 5.1(3.1) | 4.9(3.2) | 11,421 | 5.6(3.3) | 5.6(3.2) | 5.7(3.4) |
| All age 0–17 | 40,733 | 14.0(6.8) | 13.7(6.3) | 14.2(7.4) | 31,233 | 15.3(7.1) | 14.6(6.6) | 16.3(7.8) |
| Bronchitis and asthma (ICD10: J20, J21, J45) | | | | | | | | |
| < 1 year | 9195 | 3.1(2.4) | 3.1(2.4) | 3.2(2.4) | 7471 | 3.7(2.5) | 3.5(2.4) | 3.9(2.5) |
| 1–5 years | 6799 | 2.3(1.8) | 2.4(1.9) | 2.3(1.9) | 5649 | 2.8(1.9) | 2.8(2.0) | 2.8(1.9) |
| All age 0–17 | 17,118 | 5.9(3.6) | 5.8(3.6) | 5.9(3.6) | 13,994 | 6.9(3.6) | 6.6(3.7) | 7.2(3.5) |

Hospital admission is defined as a stay at the hospital for at least one night. Abbreviation: SD: Standard Deviation. ICD10: International Classification Diseases 10th revision.
[a] Daily $PM_{10}$ and $SO_2$ measurements are available for the period 2007–2014 while $PM_{2.5}$, $PM_1$, $NO_x$, $NO_2$, $SO_2$, CO and $O_3$ measurements are available for 2009–2014.

et al., 2017). The outcomes selected in this paper were daily counts of pneumonia (International Classification Diseases 10th revision (ICD10) code J12-J18), bronchitis and asthma (ICD10 code: J20, J21, J45). Since electronic data from hospital registrations were anonymous, no informed consent was required; the study underwent an ethical review by the Vietnam National Children's Hospital's ethical committee (approval number NHP-RICH-15-009, May 2015).

### 2.2. Data analysis

To explore the association between ambient air pollution and daily counts of hospital admissions for pneumonia, bronchitis, and asthma, we used generalized additive quasi-Poisson regression models with a log-link function and adjustment for over-dispersion (i.e. variability exceeding the one of a conventional Poisson regression model), adjusting for potential confounders. Thin plate spline functions, a special form of penalized splines, were used to capture time trends and seasonal variations. At first, core models were built. Partial autocorrelation function plots (PACF) of the residuals were used to determine the appropriate degrees of freedom of the spline function to minimize residual serial correlation (Roger D. Peng et al., 2006). If it was not possible to sufficiently remove partial autocorrelation at lag one, we added an autoregressive term to the model. In addition, we included in the models the potential confounders that are daily mean temperature, relative humidity, wind speed (m/s), and categorical variables for day of the week, holidays, and influenza epidemics. Day of week is treated as a categorical variable with values ranging from 0 (Sunday) to 6 (Saturday).We adjusted for meteorological factors averaged over the same day and the day before (i.e., lags 0 to 1) and over the five days preceding this period (i.e., lags 2 to 6) and interaction terms between them. The best averaging period for meteorological factors was chosen based on Generalized Cross-Validation (GCV) values which measure models fit. Holidays included in the models were defined as government holidays. A day was considered as belonging to a period of influenza epidemic if the number of influenza cases (ICD10 code J11) over a three-day period, including the preceding day and the consecutive day, was above the 95th percentile of daily influenza cases. Secondly, air pollutant concentrations were added after having derived the core models. We estimated associations between the two-day moving average (lags 0–1), three-day moving average (lags 0–2) and the seven-day moving average (lag0–6) pollutant concentration and hospital admissions. For better comparison with lag one estimates provided by some studies, those were derived as well. To facilitate comparisons across pollutants, results are reported as risk ratios (RR) of hospital admissions with 95% confidence intervals (CI) for a one interquartile range (IQR) increment in the level of the respective pollutant variable. Analyses were performed for infants, children aged 1–5, and children of all ages (0–17 years). Ultimately, the effects on children aged 6–17 years were not reported, as the number of hospital admissions in this age group was very small (Nguyen et al., 2017). Statistical significance was defined as two-tailed $p$-value $< 0.05$.

We estimated pollutant effects separately for the warm season (April–October) and for the cold season (November–March) using an interaction term, since a previous study from Vietnam showed a higher association in the cold season (Le et al., 2012). Analyses were also stratified by gender to evaluate potential effect modification. The statistical significance of the differences in the two gender-specific estimates was assessed using a $Chi^2$-test.

We also derived two-pollutant models combining all pollutants ($PM_{10}$, $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, CO and $O_3$). Variance inflation factor (VIF) was used to evaluate the multicollinearity in the models. All pairs of pollutants had VIF-values maximum of 7.6, thus clearly below the threshold of 10 indicating strong multicollinearity (Kutner et al., 2004). In the sensitivity analysis, we a) conducted analyses with natural cubic spline functions with seven knots per year to capture trends and seasonal variations, three degrees of freedom (df) for temperature and four df for relative humidity on the day of admissions like in a previous study in Vietnam (Le et al., 2012); and b) varied the level of smoothness of the trend function (i.e., with 5 to 9 degrees of freedom per year). All results of sensitivity analyses are presented as supplementary material. All statistical analyses were conducted using R (version 2.15.3, http://www.r-project.org), using the “mgcv”, “spline” and “gam” packages.

## 3. Results

Descriptive statistics for daily hospital admissions are presented in Table 1, while Table 2 presents daily pollutant concentrations, meteorological variables and hospital admission data. We examined 40,733 hospital admissions for pneumonia (i.e., about 14 cases per day) and 17,118 hospital admissions for bronchitis and asthma (5.9 cases per day). Daily hospital admission counts were similar in the cold and warm seasons (Table 1).

The daily mean concentrations of $PM_{10}$, $NO_2$, and CO were 93.0 μg/$m^3$, 49.0 μg/$m^3$ and 2656.0 μg/$m^3$, respectively. Generally, concentrations were higher in the cold season, except for $O_3$ (Table 2). Daily means of $PM_1$ were strongly correlated with daily means of $PM_{10}$ (spearman rank correlation coefficient, $r = 0.7$) and of $PM_{2.5}$ ($r = 0.9$). In contrast, the temporal correlations between PM and gaseous pollutants were low ($0.06 \leq |r| \leq 0.48$), both in the cold and warm seasons (Table A1). Daily mean temperature and relative humidity in Hanoi were 24 °C and 82%, respectively.

Table 3 summarizes the risk ratio (RR) of hospital admissions for

**Table 2**
Overall and seasonal distribution of daily pollutant concentrations and meteorological data (mean (sd), minimum, maximum and interquartile ranges), Hanoi.

| | Mean(SD) | Median | Minimum - Maximum | Interquartile range | Missing day(%) | Season mean | |
|---|---|---|---|---|---|---|---|
| | | | | | | Warm (April–October) | Cold (November–March) |
| Pollutants | | | | | | | |
| 24 h $PM_{10}$ ($\mu g/m^3$) | 93.0(59.0) | 77.6 | 6.1–403.5 | 66.5 | 5.8% | 85.9 | 103.5 |
| 24 h $PM_{2.5}$ ($\mu g/m^3$) | 56.1(33.3) | 48.0 | 6.0–213.0 | 39.4 | 7.7% | 47.4 | 70.0 |
| 24 h $PM_1$ ($\mu g/m^3$) | 43.7(29.1) | 35.6 | 6.1–186.9 | 33.8 | 8.1% | 33.2 | 60.3 |
| 24 h $SO_2$ ($\mu g/m^3$) | 32.4(33.7) | 17.0 | 1.0–149.7 | 40.6 | 6.5% | 27.7 | 39.2 |
| 24 h $NO_2$ ($\mu g/m^3$) | 49.0(18.0) | 47.2 | 1.9–122.2 | 21.9 | 3.3% | 45.3 | 54.4 |
| 24 h NOx ($\mu g/m^3$) | 86.4(27.9) | 84.4 | 1.9–227.5 | 36.7 | 3.1% | 80.6 | 95.1 |
| 24 h CO ($\mu g/m^3$) | 2656.1(721.5) | 2649.4 | 51.7–5152.4 | 986.3 | 3.1% | 2626.8 | 2700.2 |
| 8 h-moving average $O_3$ ($\mu g/m^3$) | 92.9(75.1) | 69.8 | 3.0–431.5 | 85.2 | 21.4% | 96.8 | 85.4 |
| 24 h-maximum $O_3$ ($\mu g/m^3$) | 121.1(91.2) | 93.2 | 3.6–554.9 | 109.4 | 21.4% | 124.0 | 115.7 |
| Meteorological | | | | | | | |
| Temperature (°C) | 23.9(5.3) | 25.2 | 7–34 | | 0.0% | 27.4 | 18.8 |
| Relative humidity (%) | 82.4(7.7) | 83.2 | 50.3–98 | | 0.0% | 82.9 | 81.6 |
| Wind speed(m/s) | 1.3(0.5) | 1.15 | 0.2–4.5 | | 0.0% | 1.3 | 1.2 |

Daily $PM_{10}$ and $SO_2$ measurements are available from January 2007 to December 2014 from two stations, namely Lang Ha and Nguyen Van Cu. Other pollutant measurements are available from June 2009 to December 2014 from one station, namely Nguyen Van Cu. Abbreviation: SD: Standard Deviation.

pneumonia per IQR of the seven-day (lag 0–6) mean concentration of the pollutants. Among children under 18 years of age, hospital admissions for pneumonia were positively associated with all pollutants. Statistically significant associations were observed for all pollutants, except $SO_2$ and $O_3$. The strongest effect estimate was observed for $NO_2$ (RR = 1.061, 95%CI 1.025–1.098). That means with an average daily number of pneumonia admissions of about 15, the risk ratio of 1.061 corresponds to about one additional case for a short term increment in $NO_2$ of one IQR (i.e., 21.9 $\mu g/m^3$).

In general, RRs for pneumonia hospitalization were higher among children aged 1–5 as compared to infants. For instance, the RR for an IQR increase in $NO_2$ was highest among children aged 1–5 (RR = 1.100, 95%CI 1.041–1.162) and clearly lower in infants (RR = 1.050, 95%CI 1.005–1.097). Similar patterns were also found for lag 0–1, lag 0–3 and lag 1 (Tables A2, A3 and A4 in the supplementary material). Pneumonia related hospitalizations were more strongly associated with lag 0–3 and lag 0–6 pollutant means than with lag 0–1 mean. RRs per IQR ranged from 1.014 to 1.041 for lag 0–1, from 1.022 to 1.061 for lag 0–3, and from 1.019 to 1.061 for lag 0–6 means for all pollutants in children under 18 years.

**Table 3**
Adjusted risk ratios (RR) with 95% confidence intervals (CI) for an interquartile range increase (see Table 2) in the 7-day moving average (lag 0–6) of ambient air pollution concentrations and hospital admissions due to pneumonia and bronchitis/asthma in children of all ages and by age group, Hanoi.

| Outcome by pollutant | All ages(0–17) | | | 1–5 Years of age | | | < 1 Year of age | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| Pneumonia | | | | | | | | | |
| $PM_{10}$ | 1.058*** | 1.028 | 1.090 | 1.056* | 1.012 | 1.102 | 1.007 | 0.974 | 1.042 |
| $PM_{2.5}$ | 1.053** | 1.019 | 1.088 | 1.063* | 1.011 | 1.117 | 1.010 | 0.970 | 1.052 |
| $PM_1$ | 1.057** | 1.020 | 1.095 | 1.077** | 1.018 | 1.139 | 1.029 | 0.984 | 1.076 |
| $SO_2$ | 1.019 | 0.948 | 1.096 | 1.110 | 0.986 | 1.250 | 1.034 | 0.948 | 1.129 |
| $NO_2$ | 1.061*** | 1.025 | 1.098 | 1.100*** | 1.041 | 1.162 | 1.050* | 1.005 | 1.097 |
| $NO_x$ | 1.046* | 1.009 | 1.085 | 1.101*** | 1.040 | 1.166 | 1.041 | 0.995 | 1.088 |
| CO | 1.040* | 1.001 | 1.080 | 1.066* | 1.005 | 1.130 | 1.006 | 0.960 | 1.054 |
| 8 h average $O_3$ | 1.024 | 0.973 | 1.077 | 1.030 | 0.953 | 1.114 | 1.029 | 0.964 | 1.098 |
| 24 h maximum $O_3$ | 1.022 | 0.969 | 1.077 | 1.010 | 0.931 | 1.095 | 1.022 | 0.956 | 1.092 |
| Bronchitis and asthma | | | | | | | | | |
| $PM_{10}$ | 1.008 | 0.971 | 1.047 | 1.032 | 0.987 | 1.080 | 0.977 | 0.927 | 1.030 |
| $PM_{2.5}$ | 1.025 | 0.981 | 1.071 | 1.051 | 0.986 | 1.121 | 0.989 | 0.931 | 1.050 |
| $PM_1$ | 1.058* | 1.008 | 1.111 | 1.072 | 0.998 | 1.151 | 1.027 | 0.961 | 1.097 |
| $SO_2$ | 1.038 | 0.927 | 1.163 | 0.988 | 0.832 | 1.173 | 1.070 | 0.925 | 1.237 |
| $NO_2$ | 1.055* | 1.004 | 1.108 | 1.079* | 1.004 | 1.160 | 1.009 | 0.945 | 1.077 |
| $NO_x$ | 1.056* | 1.004 | 1.111 | 1.116** | 1.035 | 1.203 | 0.994 | 0.929 | 1.063 |
| CO | 0.991 | 0.942 | 1.044 | 1.077 | 0.999 | 1.162 | 0.908** | 0.848 | 0.973 |
| 8 h average $O_3$ | 1.013 | 0.943 | 1.087 | 0.985 | 0.889 | 1.090 | 1.043 | 0.949 | 1.147 |
| 24 h maximum $O_3$ | 1.032 | 0.960 | 1.110 | 1.003 | 0.903 | 1.114 | 1.057 | 0.960 | 1.164 |

Number of admissions and interquartile range units presented in Table 2.
Risk ratios (RR) estimated from Quasi-Poisson regression models, adjusting for secular trends and seasonal variation, day of the week, holiday, influenza epidemic, and meteorological factors including temperature, relative humidity, and wind speed average. Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007–2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8 h average $O_3$, 24 h maximum $O_3$ to the period 2009–2014.

*** $p < 0.001$.
** $p < 0.01$.
* $p < 0.05$ (Wald $\chi^2$ test).

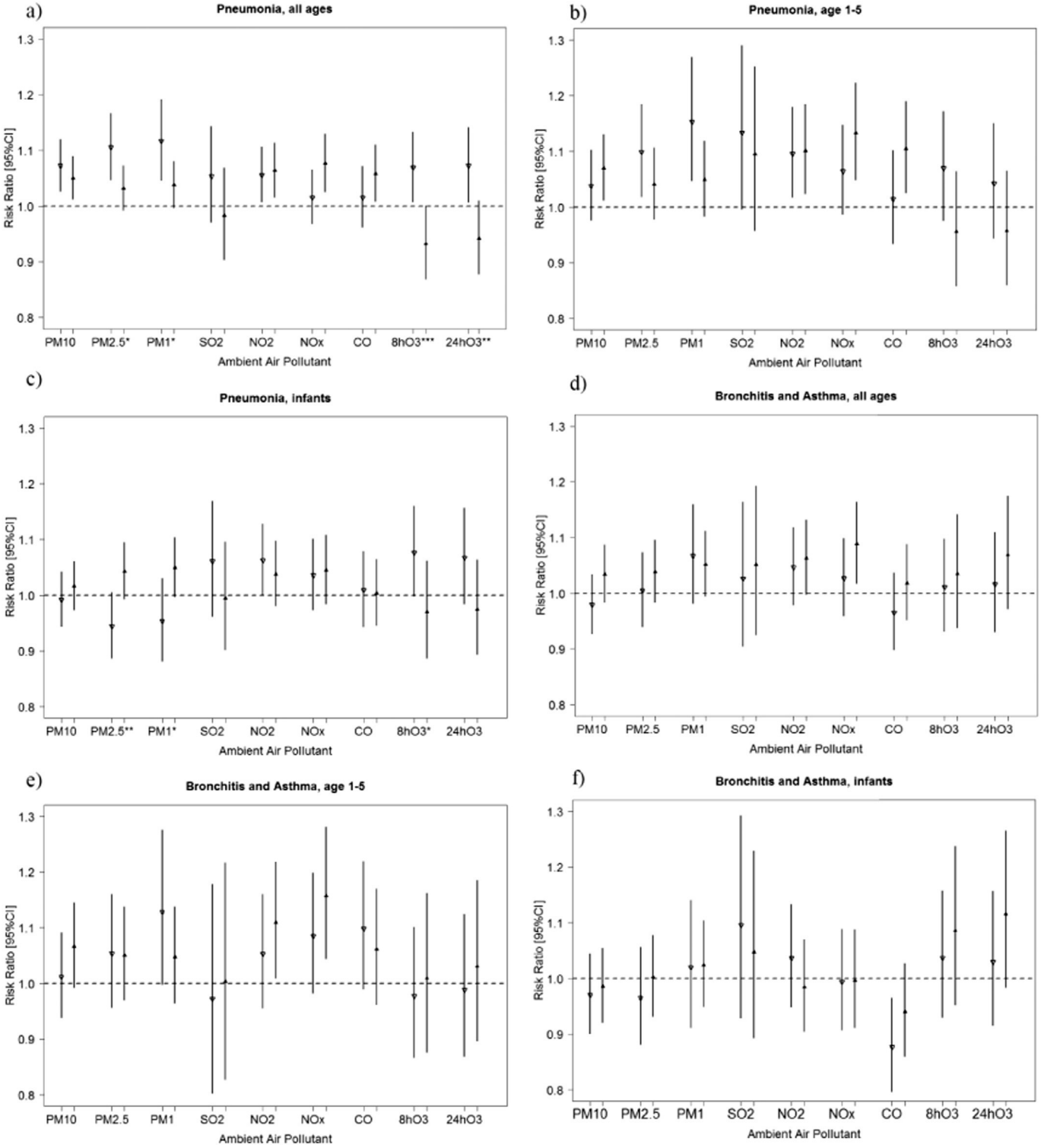


**Fig. 1.** Season –specific risk ratios per interquartile range increase in the seven-day moving average ambient air pollutant concentrations (lag 0–6) for a) Pneumonia, all ages, b) Pneumonia, age 1–5, c) Pneumonia, infants, d) Bronchitis and asthma, all ages, e) Bronchitis and asthma, age 1–5, f) Bronchitis and asthma, in infants Hanoi.
Triangle point down: warm season (April–October), filled triangle point-up: cold season (November – March), Bar: 95% confidence intervals, $*p < 0.05$; $**p < 0.01$, $***p < 0.001$. Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007–2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8 h average $O_3$, 24 h maximum $O_3$ to the period 2009–2014.

Daily counts of hospital admissions due to bronchitis and asthma were positively associated with all pollutants, except CO, and in all ages (lag 0–6 results), although RRs were statistically significant only for $PM_1$, $NO_2$, and $NO_x$. Associations were strongest with $PM_1$ (among all children) (RR = 1.058; 95%CI 1.008–1.111) and $NO_x$ (RR = 1.056, 95%CI: 1.004–1.111). $PM_{10}$ and $O_3$ were also positively associated with hospital admissions for bronchitis and asthma in infants, although statistical significance was not reached. In contrast, the non-significant inverse association of CO with hospital admissions due to bronchitis and asthma seen in all age groups reached statistical significance among infants (RR = 0.908, 95%CI 0.848–0.973) (Table 3). Tables A2 and A3 provide risk ratios for bronchitis and asthma associated with the two-

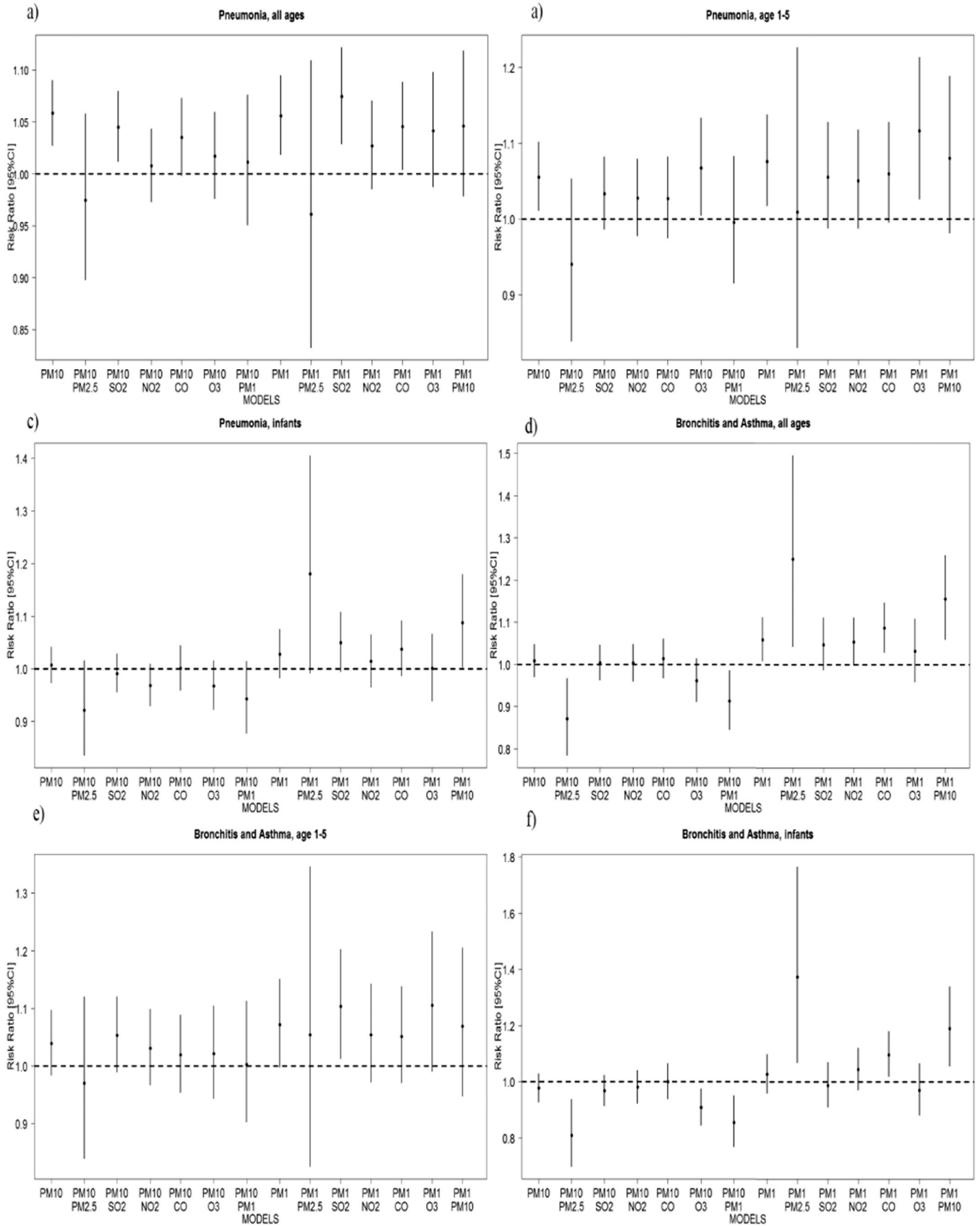


**Fig. 2.** Estimated risk ratios (with 95% confidence intervals) per one interquartile range of $PM_{10}$ and $PM_1$, respectively, from single pollutants models (left most estimate) and two-pollutant models with adjustment for $PM_{10}$, $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, CO and 8 h average $O_3$, for a) Pneumonia, all ages, b) Pneumonia age 1–5; c) Pneumonia, infants; d) Bronchitis and asthma, all ages, e) Bronchitis and asthma, age 1–5, and f) Bronchitis and asthma, infants, Hanoi.
Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007–2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, CO, 8 h average $O_3$ to the period 2009–2014.

day (lag 0–1) and three-day (lag 0–2) moving pollutant averages, and Table A4 provides the estimate for lag 1. Associations were strongest for lag 0–3 for hospital admissions due to bronchitis and asthma.

Fig. 1 presents results for cold (November–March) and warm seasons (April–October). Associations with pneumonia hospitalizations were higher in the warm season than in the cold season for all pollutants except $NO_2$, $NO_x$, and CO. Associations between ozone and pneumonia were positive overall, but negative in the cold season. For bronchitis and asthma, risk ratios were positive and higher in the cold season.

Two-pollutant models are presented in Fig. 2 and Table A5. Pneumonia related estimates for $NO_2$ were not only the largest (per IQR), but also the most stable one across all two-pollutant models. In contrast, effects of $PM_{10}$, $PM_{2.5}$ and $PM_1$ all dropped and lost statistical significance after inclusion of $NO_2$. Pneumonia (all ages) effect estimates of $PM_{10}$ were also substantially reduced after inclusion of $O_3$ but remained stable in the age group 1–5 year. Results for $PM_1$ were somewhat less sensitive to the inclusion of other pollutants, except the highly correlated $PM_{2.5}$, across all age groups and outcomes. Results for bronchitis and asthma and $O_3$ were also insensitive to the inclusion of other pollutants (Table A5). The associations between CO and hospitalization for bronchitis and asthma remained negative after adjustment for other pollutants but moved closer to the null.

Associations between ambient air pollutants and hospitalization of children aged 0–5 are shown in Fig. 3. All associations were positive, except in the case of CO. We found no evidence of gender differences (all $p$-values $> 0.05$).

Fig. A2 shows the results of sensitivity analyses for lag 0–6 of ambient air pollution concentrations using the same modeling approach as in the HCM study. All associations were very similar to those provided by our own models for lag 0–6. Fig. A3 illustrates the lag 0–6 risk ratio per IQR from the models with varying degrees of freedom per year. Effect estimates for PM on pneumonia (all ages) were sensitive to the degrees of freedom (df) chosen per year. For instance, effects of $PM_{10}$ increased gradually, with the df peaking at eight df (Fig. A3).

## 4. Discussion

This is the largest population-based study on the acute effects of ambient air pollution on children's health in Vietnam, to date. Associations with pneumonia-related admissions were strongest and rather similar for $NO_2$ and the three measures of PM. We did not find statistically significant associations between $O_3$ and hospitalization for either pneumonia or bronchitis and asthma. Results did not substantially change when using natural spline models for temperature and humidity at the date of hospital admissions, as in the models of the HCM city study (Fig. A2). The results are generally consistent with other studies showing hospital admissions for ARI associated with markers of primary traffic pollutants such as $NO_2$ or CO (Barnett et al., 2005; Darrow et al., 2014; Karr et al., 2009; Le et al., 2012; Ostro et al., 2009; Winquist et al., 2012), however, a clear source attribution cannot be made given the similar results seen for PM.

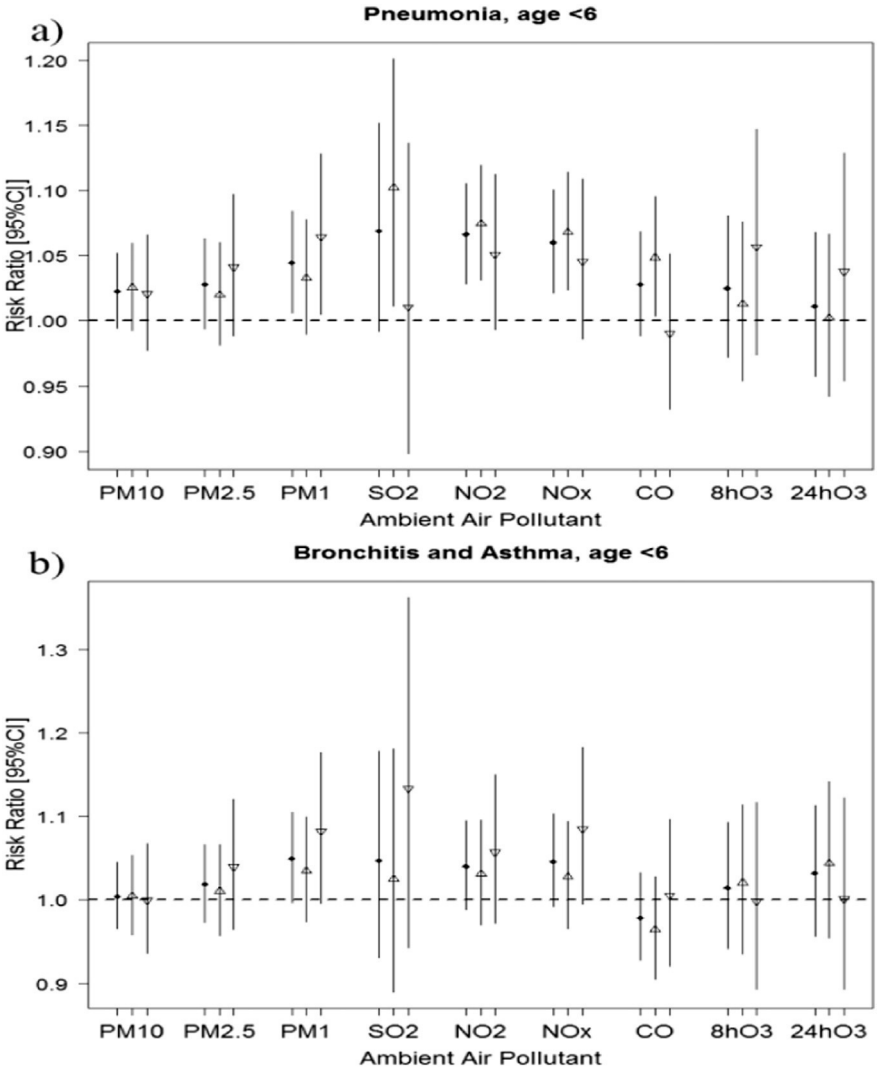


**Fig. 3.** Gender-specific risk ratios (with 95%-confidence intervals) per interquartile range of ambient air pollutants for a) Pneumonia in children age < 6 and b) Bronchitis and asthma at age < 6, Hanoi.
Filled Diamond: all children, triangle upward: males, triangle downward: females.
Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007–2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8 h average $O_3$, 24 h maximum $O_3$ to the period 2009–2014.

In our study, outdoor air pollution levels were relatively high compared to WHO standards, especially during the cold season. Daily $PM_{10}$ concentrations exceeded the WHO guideline values (24-h mean = 50 μg/m$^3$) on 2138 days (77.6%), while daily $PM_{2.5}$ concentrations exceeded recommended levels on 1618 days (85.7%). Notably, daily mean $NO_2$ levels recorded between 2009 and 2014 ranged from 1.9 μg/m$^3$ to 122.2 μg/m$^3$.

Time-series of daily $PM_1$ as a marker of exposure to very small particles are far less frequently available, as $PM_1$ is not regulated (Frampton and Rich, 2016; Stafoggia et al., 2016). Thus, it is a rather unique feature of our study to demonstrate positive associations between $PM_1$ and ARI among Hanoi children. Indeed, $PM_1$ showed the strongest associations of all pollutants in the case of hospitalizations due to pneumonia among the 1–5 year age group, and for bronchitis and asthma in all age groups. This may be an indication that smaller size PMs induce stronger inflammatory responses, particularly the ultrafine particles that can penetrate deeply into lung alveoli or be transported to other organs (Frampton and Rich, 2016; Oberdörster et al., 1994). Lanzinger et al. (2016) find a significant association of hospital admission for respiratory disease with ultrafine particles in the size range from 20 to 100 nm in Augsburge and Dresden (Germany), but not in other regions in Central Europe. Zwozdziak et al. (2016) reported a decrease in lung function parameters with increasing exposure of indoor $PM_1$ in school children. However, to our knowledge, no previous study has investigated the association between outdoor $PM_1$ and ARI in children.

Risk ratios tended to be lower among infants compared to those seen among children aged 1–5. Some previous studies observed a similar pattern (Barnett et al., 2005; Darrow et al., 2014). One explanation of this finding may be that older children spend more time outside, thereby increasing personal exposure. In Vietnam, infants are mostly kept indoors until the first birthday. Cumulative lifetime exposure is also larger for older children, which may be relevant if long-term exposure further amplifies susceptibility to acute effects of air pollution. Another reason for smaller effects in infants could be the relative protection from ARI due to breast feeding (maintained breast feeding rate above 50% from 2010 to 2015)(UNICEF, 2016). However, our findings for infants cannot be easily compared with other studies, given that the association between ARI in infants and ambient air pollution is still not well documented. Some studies even excluded this group from time series analyses (Lanzinger et al., 2016).

Surprisingly, CO was negatively related to bronchitis and asthma admissions of infants. These negative and statistically significant associations were stronger after adjusting for daily $PM_{2.5}$ concentrations. However, we observed positive associations of CO with pneumonia-related admissions. In line with our findings, a study conducted in Hong Kong reported that a 1 ppm (~1000 μg/m$^3$) increase of CO was associated with a 5.7% (95%CI 2.1–9.2) decrease in lower respiratory infections throughout the population, with smaller effect estimates in children compared to adults (Tian et al., 2013). In contrast, Santus et al. (2012) reported a 5.9% and 9.4% increase of asthma and pneumonia hospitalizations, respectively, per 1000 μg/m$^3$ of ambient CO concentrations in children under 16. Similarly, Barnett et al. (2005) reported positive associations between CO and pneumonia and acute bronchitis in infants and children 1–4 years of age in Australia and New Zealand. Whether toxic or beneficial effects prevail after CO exposure at ambient concentrations remains unclear (United States Environmental Protection Agency, 2010). Indeed, some toxicological studies reported anti-inflammatory effects of exogenous CO because CO could kill bacteria (Nobre et al., 2009; Otterbein et al., 2005). Interestingly, in this study, CO showed negative associations only for bronchitis and asthma. The diagnosis of asthma at young ages is rather uncertain and infections may play a dominant role in the youngest children, coded as “asthma”. Therefore our findings would be in line with hypothesis of an anti-inflammatory role of CO. However, the significantly positive associations of CO with pneumonia-related hospitalization would not support this argument. We could not identify specific sources of bias to explain the negative CO associations found in this study. In experimental studies, exposure was usually only two hours per day, whereas our analyses used 24-h means. We conclude that the association between CO and respiratory diseases needs further investigation.

We found seasonal variations in the association between ambient air pollution and ARI in this study. Our study identified stronger short-term associations of $PM_{10}$, $NO_2$, and $NO_x$ in children under six years during the cold season (November – March), which is consistent with previous results from Vietnam (Le et al., 2012). In contrast to significant positive findings in the warm season, we observed no relevant association of $O_3$ with pneumonia during the cold season, particularly after adjusting for other pollutants (despite small differences of $O_3$ concentrations during the two seasons). As in the study from Australia (Barnett et al., 2005), the difference in season-specific effect estimates may reflect differences in the exposure-relevant behavior of children in the warm versus the cold season. In Hanoi, children spend more time outside during the warm season, especially in the afternoon when photochemical pollutant concentrations are the highest. The observed seasonal difference in hospital admissions is larger than what one expects based on the difference in air pollution alone. The latter is though only one out of many determinants of hospital admissions.

Normally, the time from onset of illness to hospitalization of Vietnam children ranges from 1 to 6 days, therefore, we focused on the associations within this time window of exposure (i.e., lag 0–6). In fact, the lag 0–6 risk ratios for pneumonia hospitalization were stronger than risk ratios for lag 0–1 or lag 0–2. These results are consistent with other studies where longer averaging times of exposure tended to show stronger associations. Indeed, following respiratory syncytial virus infection, the development of clinical signs severe enough to lead to hospitalizations may take a few days (Karr et al., 2007).

About 85% of children in our study population are from 0 to 5 years of age (Nguyen et al., 2017). Of these, a larger proportion of children are infants. So, the findings in this study mainly reflect the effects of air pollutants in children under 6 years of age. In Hanoi, several hospitals have a Paediatric Department such as the Bach Mai hospital. However the numbers of beds for children and the numbers of paediatric doctors are limited in these hospitals. Therefore most children with conditions requiring hospitalization are admitted to the Vietnam National Children's Hospital. Unfortunately, the hospital is usually overloaded, so young children are prioritized. Children above 6 years of age are preferably transferred to other hospitals. Taking asthma as an example, older children are frequently admitted to the respiratory departments of general hospitals (e.g. Bach Mai or Hanoi hospital of Lung diseases and Tuberculosis). Therefore, to investigate the effects of air pollution among older children (e.g. 6–17 year-olds), analyses of data from general hospitals would be useful.

The results of two pollutant models are shown in Fig. 2 and Table A5. Temporal correlations among the PMs were high, but low to moderate in all other cases (Table A5). Two-pollutant models could be used to evaluate the possible role of single pollutants. However, as shown in Table A5, the two-pollutant models did not reveal consistent patterns across all outcomes. One general observation was the tendency of $PM_{10}$ estimates to shrink in two-pollutant models. $PM_1$ estimates decreased for pneumonia with adjustment for $PM_{2.5}$, while becoming stronger for asthma and bronchitis. Instead estimates for $PM_{2.5}$ were less sensitive and occasionally increased with co-adjustment. The finding of the very stable coefficients seen for $NO_2$ across all two-pollutant models is remarkable in case of pneumonia whereas it was less so for bronchitis and asthma. In particular, co-pollutant models combining $NO_2$ with PM revealed rather independent effects for $NO_2$ whereas those for PM were substantially explained by $NO_2$ rather than PM per se. Thus, in case of Hanoi, we conclude that $NO_2$ concentrations capture pneumonia relevant air pollution better than $PM_{10}$, $PM_{2.5}$ or $PM_1$. Whether $NO_2$ estimates reflect effects of $NO_2$ per se or some unmeasured other marker of air pollution cannot be answered with our

data. These rather stable $NO_2$ findings for pneumonia are though a clear argument for the use of $NO_2$ as a marker of ambient air pollution in health impact assessments for pneumonia in Hanoi, following the recommendation of the WHO (Heroux et al., 2015).

This study has some limitations. First, because the Vietnam National Children's Hospital is the tertiary hospital, children with severe diseases might make up a larger proportion than in other hospitals. In addition, outpatients were excluded from our study. As seen in a study conducted in the United States, the strengths of the association with air pollution might vary between the type of health care visits, a possible marker of severity (Winquist et al., 2012). We do not know how these factors and selection patterns affect the size of the risk ratios, but if severe cases are more strongly associated with air pollution, our estimates would tend to be larger than for a population-based sample of "average cases". Second, the definition of outcomes in this study eventually relies on the diagnosis and ICD10 coding at the time of discharge where misclassification of the type of respiratory disease might happen, particularly in the youngest age group. For example, there are many controversies on diagnosing "asthma" in small children. Hence, some diagnostic labeling should be interpreted with caution. Nonetheless, the findings are consistent across outcomes, except CO, which has been discussed above. Third, our time series analysis relies on pollution data ($PM_1$, $PM_{2.5}$, CO, and $O_3$) from only one fixed-site monitoring station. Ideally, one would use several monitoring stations to reduce exposure misclassification. On the other hand, if exposure misclassification is mostly characterized by Berkson error (Wacholder, 1995), effect estimates may show little bias even with only one reference monitoring station. Otherwise, unless temporal variation in ambient pollutant levels observed at the reference station is smaller than the variation experienced by the average population, effects will likely be underestimated (Zmirou et al., 1998). Fourth, the daily number of admissions due to bronchitis and asthma was rather small. Thus, statistical power to analyze this data was limited, thereby reducing the reliability of results.

## 5. Conclusion

In summary, this study has shown strong and consistent associations between children's hospital admissions for acute respiratory diseases and ambient air pollutant concentrations in Hanoi, Vietnam. Associations were strongest with $NO_2$ for both pneumonia, and bronchitis and asthma hospital admissions of children under 18 years old. Given that exposure affects large populations, even modest improvements of ambient air quality would result in noticeable reductions of the burden of respiratory diseases and related hospital admissions among children. Thus, the adoption of the WHO clean air targets (Kutlar Joss et al., 2017) and related clean air strategies should be enforced to protect the health of Vietnamese children and to reduce the costs to the health care system.

## Acknowledgments

NTTN was supported by the Swiss Government Excellence Scholarships (ESKAS) with a PhD fellowship at Swiss Tropical and Public Health Institute. The funder had no role in study design, data analyses, data interpretation or writing of the paper. The authors had full access to all data in the study and take full responsibility for the publication decision. We thank the Center of Environmental Monitoring -Vietnam Environmental Administration, National Hydro-Meteorological Service, and Lang Meteorological station for providing air quality data, and the Vietnam National Children's Hospital for providing hospital data.

## Declaration of competing financial interests

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2017.10.024.

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**Supplementary**

# Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: An eight-year time series study

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**Table:**



**Figure:**

Table A1: Temporal spearman rank correlation coefficients among daily mean concentrations of ambient air pollutants during the year and by seasons

| | $PM_{10}$ | $PM_{2.5}$ | $PM_1$ | $SO_2$ | $NO_2$ | $NO_x$ | CO | 8h moving average of $O_3$ | Maximum of 24h $O_3$ |
|---|---|---|---|---|---|---|---|---|---|
| **Overall year** | | | | | | | | | |
| $PM_{10}$ | 1 | | | | | | | | |
| $PM_{25}$ | 0.90 | 1 | | | | | | | |
| $PM_1$ | 0.70 | 0.91 | 1 | | | | | | |
| $SO_2$ | 0.13 | 0.31 | 0.44 | 1 | | | | | |
| $NO_2$ | 0.32 | 0.42 | 0.48 | 0.52 | 1 | | | | |
| $NO_x$ | 0.24 | 0.32 | 0.31 | 0.38 | 0.81 | 1 | | | |
| CO | 0.26 | 0.27 | 0.19 | 0.07 | 0.42 | 0.61 | 1 | | |
| 8h moving average of $O_3$ | 0.11 | 0.10 | 0.16 | 0.17 | 0.12 | -0.17 | 0.02 | 1 | |
| Maximum of 24h $O_3$ | 0.12 | 0.11 | 0.16 | 0.18 | 0.14 | -0.14 | 0.06 | 0.98 | 1 |
| **Warm season (April to October)** | | | | | | | | | |
| $PM_{10}$ | 1 | | | | | | | | |
| $PM_{25}$ | 0.91 | 1 | | | | | | | |
| $PM_1$ | 0.67 | 0.88 | 1 | | | | | | |
| $SO_2$ | -0.03 | 0.10 | 0.24 | 1 | | | | | |
| $NO_2$ | 0.17 | 0.26 | 0.34 | 0.50 | 1 | | | | |
| $NO_x$ | 0.15 | 0.17 | 0.15 | 0.37 | 0.75 | 1 | | | |
| CO | 0.21 | 0.22 | 0.12 | -0.06 | 0.28 | 0.55 | 1 | | |
| 8h moving average of $O_3$ | 0.02 | 0.04 | 0.17 | 0.13 | 0.08 | -0.19 | -0.01 | 1 | |
| Maximum of 24h $O_3$ | 0.02 | 0.05 | 0.17 | 0.13 | 0.10 | -0.16 | 0.04 | 0.98 | 1 |
| **Cold season (November to March)** | | | | | | | | | |
| $PM_{10}$ | 1 | | | | | | | | |
| $PM_{25}$ | 0.96 | 1 | | | | | | | |
| $PM_1$ | 0.91 | 0.98 | 1 | | | | | | |
| $SO_2$ | 0.35 | 0.45 | 0.46 | 1 | | | | | |
| $NO_2$ | 0.54 | 0.54 | 0.53 | 0.49 | 1 | | | | |
| $NO_x$ | 0.39 | 0.41 | 0.39 | 0.33 | 0.84 | 1 | | | |
| CO | 0.31 | 0.35 | 0.35 | 0.29 | 0.56 | 0.68 | 1 | | |
| 8h moving average of $O_3$ | 0.36 | 0.31 | 0.29 | 0.43 | 0.28 | -0.06 | 0.13 | 1 | |
| Maximum of 24h $O_3$ | 0.37 | 0.32 | 0.30 | 0.85 | 0.30 | -0.03 | 0.17 | 0.97 | 1 |

Table A2: Adjusted risk ratios (RR) for an interquartile range increase in the two-day moving average of ambient air pollution concentrations and hospital admissions due to pneumonia and bronchitis/asthma in children of all ages and by age group, Hanoi

| Outcome by pollutant | All ages (0-17) | | | 1-5 Years of Age | | | <1 Year of Age | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| Pneumonia | | | | | | | | | |
| $PM_{10}$ | 1.039 | 1.015 | 1.064 | 1.026 | 0.991 | 1.063 | 1.014 | 0.986 | 1.042 |
| $PM_{2.5}$ | 1.041 | 1.014 | 1.070 | 1.044 | 1.002 | 1.088 | 1.015 | 0.982 | 1.049 |
| $PM_1$ | 1.040 | 1.010 | 1.070 | 1.048 | 1.002 | 1.097 | 1.024 | 0.988 | 1.061 |
| $SO_2$ | 1.040 | 0.985 | 1.098 | 1.101 | 1.008 | 1.202 | 1.027 | 0.961 | 1.098 |
| $NO_2$ | 1.036 | 1.011 | 1.062 | 1.045 | 1.006 | 1.087 | 1.034 | 1.003 | 1.066 |
| $NO_x$ | 1.026 | 1.001 | 1.053 | 1.058 | 1.016 | 1.101 | 1.015 | 0.983 | 1.047 |
| CO | 1.020 | 0.995 | 1.046 | 1.027 | 0.988 | 1.068 | 1.006 | 0.975 | 1.038 |
| 8h average $O_3$ | 1.014 | 0.981 | 1.047 | 1.009 | 0.961 | 1.060 | 1.040 | 0.999 | 1.083 |
| 24h maximum $O_3$ | 1.015 | 0.982 | 1.048 | 0.994 | 0.945 | 1.045 | 1.048 | 1.007 | 1.090 |
| Bronchitis and Asthma | | | | | | | | | |
| $PM_{10}$ | 1.021 | 0.990 | 1.053 | 1.032 | 0.987 | 1.080 | 1.009 | 0.968 | 1.053 |
| $PM_{2.5}$ | 1.018 | 0.982 | 1.055 | 1.027 | 0.975 | 1.083 | 1.004 | 0.957 | 1.054 |
| $PM_1$ | 1.022 | 0.983 | 1.062 | 1.022 | 0.964 | 1.083 | 1.013 | 0.961 | 1.067 |
| $SO_2$ | 1.102 | 1.013 | 1.198 | 1.045 | 0.924 | 1.182 | 1.141 | 1.019 | 1.277 |
| $NO_2$ | 1.007 | 0.973 | 1.042 | 1.004 | 0.954 | 1.056 | 1.004 | 0.960 | 1.051 |
| $NO_x$ | 1.017 | 0.981 | 1.053 | 1.039 | 0.985 | 1.095 | 0.989 | 0.943 | 1.037 |
| CO | 0.993 | 0.960 | 1.027 | 1.026 | 0.975 | 1.079 | 0.961 | 0.918 | 1.006 |
| 8h average $O_3$ | 0.998 | 0.954 | 1.044 | 0.999 | 0.934 | 1.067 | 1.023 | 0.965 | 1.085 |
| 24h maximum $O_3$ | 1.001 | 0.957 | 1.047 | 1.009 | 0.943 | 1.079 | 1.019 | 0.961 | 1.080 |

Interquartile range: $PM_{10}$: 66.5µg/$m^3$, $PM_{2.5}$ = 39.4 µg/$m^3$; $PM_1$ = 33.8 µg/$m^3$, $SO_2$ = 40.6 µg/$m^3$, $NO_2$ = 21.9 µg/$m^3$, $NO_x$ = 36.7 µg/$m^3$, CO = 986.3 µg/$m^3$, $8hO_3$ = 85.2 µg/$m^3$, $24hO_3$ = 109.4 µg/$m^3$ Abbreviation: RR: Risk ratio; CI: Confidence Interval

Risk ratios estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday, influenza epidemic, meteorological factors including temperature, relative humidity, wind speed average.

Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8h average $O_3$, 24h maximum $O_3$ to the period 2009-2014.

Table A3: Adjusted risk ratios (RR) for an interquartile range increase in the three-day moving average of ambient air pollution concentrations and hospital admissions due to pneumonia and bronchitis/asthma in children of all ages and by age group, Hanoi

| Outcome by pollutant | All ages (0-17) | | | 1-5 Years of Age | | | <1 Year of Age | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| Pneumonia | | | | | | | | | |
| $PM_{10}$ | 1.058 | 1.028 | 1.090 | 1.056 | 1.012 | 1.102 | 1.007 | 0.974 | 1.042 |
| $PM_{2.5}$ | 1.053 | 1.019 | 1.088 | 1.063 | 1.011 | 1.117 | 1.010 | 0.970 | 1.052 |
| $PM_1$ | 1.057 | 1.020 | 1.095 | 1.077 | 1.018 | 1.139 | 1.029 | 0.984 | 1.076 |
| $SO_2$ | 1.019 | 0.948 | 1.096 | 1.110 | 0.986 | 1.250 | 1.034 | 0.948 | 1.129 |
| $NO_2$ | 1.061 | 1.025 | 1.098 | 1.100 | 1.041 | 1.162 | 1.050 | 1.005 | 1.097 |
| $NO_x$ | 1.046 | 1.009 | 1.085 | 1.101 | 1.040 | 1.166 | 1.041 | 0.995 | 1.088 |
| CO | 1.040 | 1.001 | 1.080 | 1.066 | 1.005 | 1.130 | 1.006 | 0.960 | 1.054 |
| 8h average $O_3$ | 1.024 | 0.973 | 1.077 | 1.030 | 0.953 | 1.114 | 1.029 | 0.964 | 1.098 |
| 24h maximum $O_3$ | 1.022 | 0.969 | 1.077 | 1.010 | 0.931 | 1.095 | 1.022 | 0.956 | 1.092 |
| Bronchitis and Asthma | | | | | | | | | |
| $PM_{10}$ | 1.008 | 0.971 | 1.047 | 1.034 | 0.986 | 1.085 | 0.977 | 0.927 | 1.030 |
| $PM_{2.5}$ | 1.025 | 0.981 | 1.071 | 1.028 | 0.972 | 1.088 | 0.989 | 0.931 | 1.050 |
| $PM_1$ | 1.058 | 1.008 | 1.111 | 1.024 | 0.962 | 1.090 | 1.027 | 0.961 | 1.097 |
| $SO_2$ | 1.038 | 0.927 | 1.163 | 1.029 | 0.903 | 1.172 | 1.070 | 0.925 | 1.237 |
| $NO_2$ | 1.055 | 1.004 | 1.108 | 1.027 | 0.970 | 1.087 | 1.009 | 0.945 | 1.077 |
| $NO_x$ | 1.056 | 1.004 | 1.111 | 1.066 | 1.005 | 1.132 | 0.994 | 0.929 | 1.063 |
| CO | 0.991 | 0.942 | 1.044 | 1.034 | 0.976 | 1.096 | 0.908 | 0.848 | 0.973 |
| 8h average $O_3$ | 1.013 | 0.943 | 1.087 | 1.020 | 0.950 | 1.096 | 1.043 | 0.949 | 1.147 |
| 24h maximum $O_3$ | 1.032 | 0.960 | 1.110 | 1.031 | 0.958 | 1.109 | 1.057 | 0.960 | 1.164 |

Interquartile range: $PM_{10}$ = 66.5µg/$m^3$, $PM_{2.5}$ = 39.4 µg/$m^3$; $PM_1$ = 33.8 µg/$m^3$, $SO_2$ = 40.6 µg/$m^3$, $NO_2$ = 21.9 µg/$m^3$, $NO_x$ = 36.7 µg/$m^3$, CO = 986.3 µg/$m^3$, $8hO_3$ = 85.2 µg/$m^3$, $24hO_3$ = 109.4 µg/$m^3$

Abbreviation: RR: Risk ratio; CI: Confidence Interval

Risk ratios estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday, influenza epidemic, meteorological factors including temperature, relative humidity, wind speed average.

Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8h average $O_3$, 24h maximum $O_3$ to the period 2009-2014.

Table A4: Adjusted risk ratios for an interquartile range increase in daily mean of ambient air pollution concentrations at day 1 (pollution level at one day before admission) and hospital admissions due to pneumonia and bronchitis and asthma in children of all ages and by age group, Hanoi

| Outcome by pollutant | All ages (0-17) | | | 1-5 Years of Age | | | <1 Year of Age | | |
|---|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| Pneumonia | | | | | | | | | |
| $PM_{10}$ | 1.024 | 1.004 | 1.046 | 1.024 | 0.993 | 1.057 | 1.001 | 0.977 | 1.026 |
| $PM_{2.5}$ | 1.033 | 1.009 | 1.058 | 1.039 | 1.002 | 1.078 | 1.009 | 0.980 | 1.039 |
| $PM_1$ | 1.031 | 1.005 | 1.057 | 1.042 | 1.002 | 1.085 | 1.013 | 0.981 | 1.045 |
| $SO_2$ | 1.031 | 0.984 | 1.081 | 1.091 | 1.011 | 1.178 | 1.021 | 0.965 | 1.082 |
| $NO_2$ | 1.014 | 0.993 | 1.036 | 1.026 | 0.992 | 1.061 | 1.014 | 0.987 | 1.041 |
| $NO_x$ | 1.014 | 0.992 | 1.036 | 1.044 | 1.008 | 1.080 | 1.003 | 0.976 | 1.030 |
| CO | 1.011 | 0.989 | 1.033 | 1.020 | 0.987 | 1.055 | 0.999 | 0.972 | 1.026 |
| 8h average $O_3$ | 1.022 | 0.993 | 1.051 | 1.037 | 0.993 | 1.082 | 1.031 | 0.996 | 1.068 |
| 24h maximum $O_3$ | 1.024 | 0.996 | 1.053 | 1.031 | 0.987 | 1.076 | 1.037 | 1.002 | 1.073 |
| Bronchitis and Asthma | | | | | | | | | |
| $PM_{10}$ | 1.007 | 0.980 | 1.035 | 1.009 | 0.969 | 1.051 | 0.998 | 0.961 | 1.036 |
| $PM_{2.5}$ | 1.008 | 0.977 | 1.041 | 0.999 | 0.953 | 1.047 | 1.006 | 0.964 | 1.050 |
| $PM_1$ | 1.017 | 0.983 | 1.053 | 0.994 | 0.944 | 1.047 | 1.024 | 0.978 | 1.072 |
| $SO_2$ | 1.081 | 1.005 | 1.163 | 1.023 | 0.919 | 1.139 | 1.041 | 0.946 | 1.145 |
| $NO_2$ | 1.002 | 0.973 | 1.032 | 0.994 | 0.951 | 1.039 | 1.003 | 0.964 | 1.044 |
| $NO_x$ | 1.000 | 0.970 | 1.031 | 1.018 | 0.973 | 1.065 | 0.978 | 0.939 | 1.019 |
| CO | 0.987 | 0.958 | 1.016 | 1.003 | 0.961 | 1.048 | 0.966 | 0.928 | 1.005 |
| 8h average $O_3$ | 1.005 | 0.966 | 1.045 | 1.000 | 0.943 | 1.060 | 1.027 | 0.975 | 1.080 |
| 24h maximum $O_3$ | 1.005 | 0.967 | 1.044 | 1.005 | 0.948 | 1.067 | 1.022 | 0.972 | 1.075 |

Interquartile range: $PM_{10}$=66.5µg/$m^3$, $PM_{2.5}$ = 39.4 µg/$m^3$; $PM_1$ = 33.8 µg/$m^3$, $SO_2$ = 40.6 µg/$m^3$, $NO_2$ = 21.9 µg/$m^3$, $NO_x$ = 36.7 µg/$m^3$, CO = 986.3 µg/$m^3$, $8hO_3$ = 85.2 µg/$m^3$, $24hO_3$ = 109.4 µg/$m^3$

Abbreviation: RR: Risk ratio; CI: Confidence Interval

Risk ratios estimated from a Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday, influenza epidemic, meteorological factors including temperature, relative humidity, wind speed average.

Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8h average $O_3$, 24h maximum $O_3$ to the period 2009-2014.

Table A5: Adjusted risk ratios per interquartile range increase in the 7-day moving average (lag 0-6) from single pollutant models and two-pollutant models controlling for other pollutants without interaction for pneumonia, all ages; Pneumonia, age 1-5; pneumonia in infants; Bronchitis and Asthma, all ages, Bronchitis and Asthma, age 1-5, and Bronchitis and Asthma, infants, Hanoi.

| Pollutant in the model | Pneumonia ,all ages | | | Pneumonia, 1-5 | | | Pneumonia, infants | | | Bronchitis and Asthma, all ages | | | Bronchitis and Asthma, age 1-5 | | | Bronchitis and Asthma, infants | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | | RR | 95%CI | |
| | | Lower | Upper | | Lower | Upper | | Lower | Upper | | Lower | Upper | | Lower | Upper | | Lower | Upper |
| **PM10** | | | | | | | | | | | | | | | | | | |
| $PM_{10}$ & $PM_{2.5}$ | 0.975 | 0.898 | 1.058 | 0.940 | 0.839 | 1.053 | 0.921 | 0.835 | 1.015 | 0.871 | 0.784 | 0.967 | 0.970 | 0.840 | 1.121 | 0.809 | 0.697 | 0.938 |
| $PM_{10}$ & $PM_1$ | 1.011 | 0.951 | 1.076 | 0.996 | 0.916 | 1.083 | 0.943 | 0.877 | 1.014 | 0.913 | 0.845 | 0.985 | 1.002 | 0.903 | 1.113 | 0.855 | 0.768 | 0.951 |
| $PM_{10}$ & $SO_2$ | 1.045 | 1.012 | 1.080 | 1.034 | 0.987 | 1.082 | 0.991 | 0.955 | 1.028 | 1.004 | 0.962 | 1.047 | 1.053 | 0.990 | 1.121 | 0.968 | 0.914 | 1.024 |
| $PM_{10}$ & $NO_2$ | 1.008 | 0.973 | 1.043 | 1.028 | 0.978 | 1.080 | 0.968 | 0.929 | 1.008 | 1.003 | 0.961 | 1.048 | 1.031 | 0.967 | 1.099 | 0.981 | 0.924 | 1.041 |
| $PM_{10}$ & CO | 1.035 | 0.998 | 1.073 | 1.027 | 0.975 | 1.082 | 1.001 | 0.958 | 1.045 | 1.013 | 0.968 | 1.061 | 1.019 | 0.955 | 1.088 | 1.001 | 0.940 | 1.066 |
| $PM_{10}$ & $O_3$ | 1.017 | 0.976 | 1.059 | 1.067 | 1.005 | 1.133 | 0.967 | 0.922 | 1.015 | 0.961 | 0.911 | 1.014 | 1.021 | 0.944 | 1.104 | 0.908 | 0.845 | 0.976 |
| **$PM_{2.5}$** | | | | | | | | | | | | | | | | | | |
| $PM_{2.5}$ & $PM_{10}$ | 1.078 | 0.993 | 1.172 | 1.127 | 1.000 | 1.271 | 1.095 | 0.989 | 1.212 | 1.174 | 1.051 | 1.311 | 1.083 | 0.929 | 1.262 | 1.214 | 1.041 | 1.416 |
| $PM_{2.5}$ & $PM_1$ | 1.096 | 0.958 | 1.254 | 1.064 | 0.889 | 1.272 | 0.875 | 0.744 | 1.029 | 0.853 | 0.722 | 1.008 | 1.016 | 0.812 | 1.272 | 0.755 | 0.598 | 0.953 |
| $PM_{2.5}$ & $SO_2$ | 1.067 | 1.025 | 1.110 | 1.040 | 0.980 | 1.104 | 1.023 | 0.974 | 1.074 | 1.015 | 0.962 | 1.071 | 1.087 | 1.007 | 1.174 | 0.952 | 0.885 | 1.024 |
| $PM_{2.5}$ & $NO_2$ | 1.014 | 0.978 | 1.051 | 1.041 | 0.987 | 1.098 | 0.986 | 0.944 | 1.030 | 1.022 | 0.976 | 1.071 | 1.042 | 0.971 | 1.118 | 1.004 | 0.942 | 1.070 |
| $PM_{2.5}$ & CO | 1.044 | 1.006 | 1.084 | 1.049 | 0.992 | 1.110 | 1.016 | 0.971 | 1.064 | 1.049 | 0.999 | 1.101 | 1.034 | 0.963 | 1.110 | 1.049 | 0.982 | 1.122 |
| $PM_{2.5}$ & $O_3$ | 1.024 | 0.979 | 1.070 | 1.095 | 1.022 | 1.174 | 0.979 | 0.927 | 1.033 | 0.986 | 0.928 | 1.048 | 1.056 | 0.964 | 1.156 | 0.926 | 0.855 | 1.004 |
| **$PM_1$** | | | | | | | | | | | | | | | | | | |
| $PM_1$ & $PM_{10}$ | 1.046 | 0.979 | 1.118 | 1.080 | 0.982 | 1.189 | 1.088 | 1.003 | 1.179 | 1.155 | 1.059 | 1.259 | 1.069 | 0.948 | 1.205 | 1.190 | 1.056 | 1.340 |
| $PM_1$ & $PM_{2.5}$ | 0.961 | 0.833 | 1.109 | 1.009 | 0.830 | 1.227 | 1.181 | 0.992 | 1.406 | 1.249 | 1.043 | 1.496 | 1.054 | 0.825 | 1.346 | 1.374 | 1.069 | 1.767 |
| $PM_1$ & $SO_2$ | 1.074 | 1.029 | 1.122 | 1.056 | 0.988 | 1.128 | 1.050 | 0.995 | 1.108 | 1.047 | 0.986 | 1.111 | 1.104 | 1.013 | 1.202 | 0.987 | 0.910 | 1.069 |
| $PM_1$ & $NO_2$ | 1.027 | 0.986 | 1.070 | 1.051 | 0.988 | 1.118 | 1.014 | 0.964 | 1.065 | 1.053 | 0.998 | 1.111 | 1.054 | 0.972 | 1.142 | 1.044 | 0.971 | 1.122 |
| $PM_1$ & CO | 1.046 | 1.004 | 1.089 | 1.060 | 0.996 | 1.128 | 1.038 | 0.987 | 1.092 | 1.086 | 1.029 | 1.146 | 1.051 | 0.971 | 1.138 | 1.097 | 1.020 | 1.180 |
| $PM_1$ & $O_3$ | 1.041 | 0.988 | 1.098 | 1.116 | 1.026 | 1.214 | 1.000 | 0.939 | 1.066 | 1.031 | 0.959 | 1.108 | 1.105 | 0.991 | 1.233 | 0.969 | 0.883 | 1.065 |
| **$SO_2$** | | | | | | | | | | | | | | | | | | |
| $SO_2$ & $PM_{10}$ | 0.991 | 0.918 | 1.070 | 1.094 | 0.966 | 1.239 | 1.055 | 0.962 | 1.157 | 1.020 | 0.905 | 1.150 | 0.904 | 0.754 | 1.085 | 1.102 | 0.945 | 1.285 |
| $SO_2$ & $PM_{2.5}$ | 0.834 | 0.703 | 0.991 | 1.065 | 0.819 | 1.384 | 0.773 | 0.622 | 0.961 | 1.088 | 0.853 | 1.387 | 0.757 | 0.535 | 1.072 | 1.395 | 1.002 | 1.943 |
| $SO_2$ & $PM_1$ | 0.823 | 0.691 | 0.979 | 1.036 | 0.794 | 1.351 | 0.734 | 0.589 | 0.915 | 1.021 | 0.799 | 1.305 | 0.747 | 0.525 | 1.061 | 1.288 | 0.923 | 1.798 |
| $SO_2$ & $NO_2$ | 0.836 | 0.710 | 0.984 | 1.057 | 0.824 | 1.355 | 0.694 | 0.564 | 0.854 | 1.093 | 0.871 | 1.370 | 0.893 | 0.639 | 1.249 | 1.272 | 0.933 | 1.733 |

| | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $SO_2$ & CO | 0.879 | 0.753 | 1.026 | 1.067 | 0.840 | 1.356 | 0.762 | 0.625 | 0.928 | 1.231 | 0.988 | 1.533 | 0.912 | 0.665 | 1.251 | 1.527 | 1.131 | 2.061 |
| $SO_2$ & $O_3$ | 0.830 | 0.672 | 1.026 | 1.342 | 0.971 | 1.856 | 0.908 | 0.704 | 1.170 | 1.343 | 1.003 | 1.800 | 1.625 | 1.053 | 2.508 | 1.081 | 0.730 | 1.600 |
| **$NO_2$** | | | | | | | | | | | | | | | | | | |
| $NO_2$ & $PM_{10}$ | 1.061 | 1.017 | 1.107 | 1.092 | 1.024 | 1.164 | 1.055 | 1.004 | 1.109 | 1.037 | 0.980 | 1.097 | 1.038 | 0.954 | 1.131 | 1.004 | 0.930 | 1.083 |
| $NO_2$ & $PM_{2.5}$ | 1.055 | 1.011 | 1.101 | 1.083 | 1.016 | 1.154 | 1.046 | 0.994 | 1.100 | 1.024 | 0.968 | 1.084 | 1.035 | 0.949 | 1.128 | 0.988 | 0.916 | 1.066 |
| $NO_2$ & $PM_1$ | 1.051 | 1.007 | 1.098 | 1.084 | 1.016 | 1.156 | 1.035 | 0.984 | 1.090 | 1.016 | 0.959 | 1.076 | 1.032 | 0.946 | 1.127 | 0.977 | 0.905 | 1.055 |
| $NO_2$ & $SO_2$ | 1.049 | 1.007 | 1.093 | 1.064 | 0.998 | 1.133 | 1.058 | 1.005 | 1.114 | 1.015 | 0.959 | 1.075 | 1.073 | 0.986 | 1.168 | 0.948 | 0.877 | 1.024 |
| $NO_2$ & CO | 1.053 | 1.009 | 1.099 | 1.093 | 1.020 | 1.171 | 1.044 | 0.989 | 1.102 | 1.071 | 1.008 | 1.138 | 1.034 | 0.945 | 1.131 | 1.074 | 0.991 | 1.165 |
| $NO_2$ & $O_3$ | 1.051 | 1.003 | 1.102 | 1.073 | 0.996 | 1.156 | 1.064 | 1.003 | 1.129 | 1.039 | 0.972 | 1.110 | 1.106 | 1.004 | 1.219 | 0.977 | 0.894 | 1.067 |
| **CO** | | | | | | | | | | | | | | | | | | |
| CO & $PM_{10}$ | 1.024 | 0.980 | 1.071 | 1.046 | 0.977 | 1.120 | 0.983 | 0.930 | 1.038 | 0.954 | 0.899 | 1.013 | 1.036 | 0.950 | 1.131 | 0.873 | 0.807 | 0.946 |
| CO & $PM_{2.5}$ | 1.019 | 0.974 | 1.065 | 1.032 | 0.963 | 1.106 | 0.977 | 0.925 | 1.032 | 0.935 | 0.881 | 0.993 | 1.033 | 0.945 | 1.129 | 0.848 | 0.783 | 0.919 |
| CO & $PM_1$ | 1.023 | 0.978 | 1.070 | 1.038 | 0.969 | 1.113 | 0.971 | 0.919 | 1.026 | 0.931 | 0.877 | 0.988 | 1.033 | 0.945 | 1.130 | 0.842 | 0.778 | 0.912 |
| CO & $SO_2$ | 1.060 | 1.016 | 1.106 | 1.049 | 0.981 | 1.121 | 1.036 | 0.982 | 1.092 | 0.967 | 0.912 | 1.025 | 1.070 | 0.983 | 1.166 | 0.870 | 0.804 | 0.941 |
| CO & $NO_2$ | 1.011 | 0.963 | 1.061 | 1.010 | 0.935 | 1.091 | 1.006 | 0.947 | 1.068 | 0.965 | 0.904 | 1.032 | 1.064 | 0.964 | 1.175 | 0.885 | 0.811 | 0.966 |
| CO & $O_3$ | 1.037 | 0.987 | 1.089 | 1.013 | 0.936 | 1.096 | 1.015 | 0.956 | 1.079 | 0.989 | 0.925 | 1.058 | 1.102 | 0.999 | 1.216 | 0.904 | 0.829 | 0.987 |
| **$O_3$** | | | | | | | | | | | | | | | | | | |
| $O_3$ & $PM_{10}$ | 1.044 | 0.987 | 1.104 | 1.035 | 0.950 | 1.128 | 1.061 | 0.991 | 1.136 | 0.992 | 0.918 | 1.071 | 0.945 | 0.843 | 1.059 | 1.046 | 0.944 | 1.158 |
| $O_3$ & $PM_{2.5}$ | 1.040 | 0.982 | 1.101 | 1.022 | 0.937 | 1.115 | 1.062 | 0.991 | 1.139 | 0.988 | 0.913 | 1.068 | 0.928 | 0.826 | 1.042 | 1.051 | 0.947 | 1.166 |
| $O_3$ & $PM_1$ | 1.041 | 0.983 | 1.103 | 1.030 | 0.942 | 1.126 | 1.063 | 0.991 | 1.141 | 0.990 | 0.914 | 1.071 | 0.925 | 0.822 | 1.040 | 1.057 | 0.952 | 1.173 |
| $O_3$ & $SO_2$ | 1.033 | 0.977 | 1.092 | 1.016 | 0.930 | 1.110 | 1.038 | 0.968 | 1.114 | 0.976 | 0.902 | 1.056 | 0.919 | 0.817 | 1.034 | 1.026 | 0.925 | 1.138 |
| $O_3$ & $NO_2$ | 1.008 | 0.956 | 1.062 | 1.009 | 0.930 | 1.094 | 1.008 | 0.942 | 1.079 | 0.999 | 0.928 | 1.076 | 0.955 | 0.859 | 1.062 | 1.050 | 0.952 | 1.159 |
| $O_3$ & CO | 1.016 | 0.965 | 1.070 | 1.028 | 0.950 | 1.112 | 1.024 | 0.958 | 1.094 | 1.011 | 0.941 | 1.087 | 0.964 | 0.870 | 1.068 | 1.058 | 0.961 | 1.164 |

Risk ratios estimated from Quasi-Poison regression models, adjusting for time trends and seasonal variations, day of week, holiday, influenza epidemic, meteorological factors including temperature, relative humidity, wind speed average.

Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, , CO, 8h average $O_3$ to the period 2009-2014.

Abbreviation: RR: Risk ratio; CI: Confidence Interval

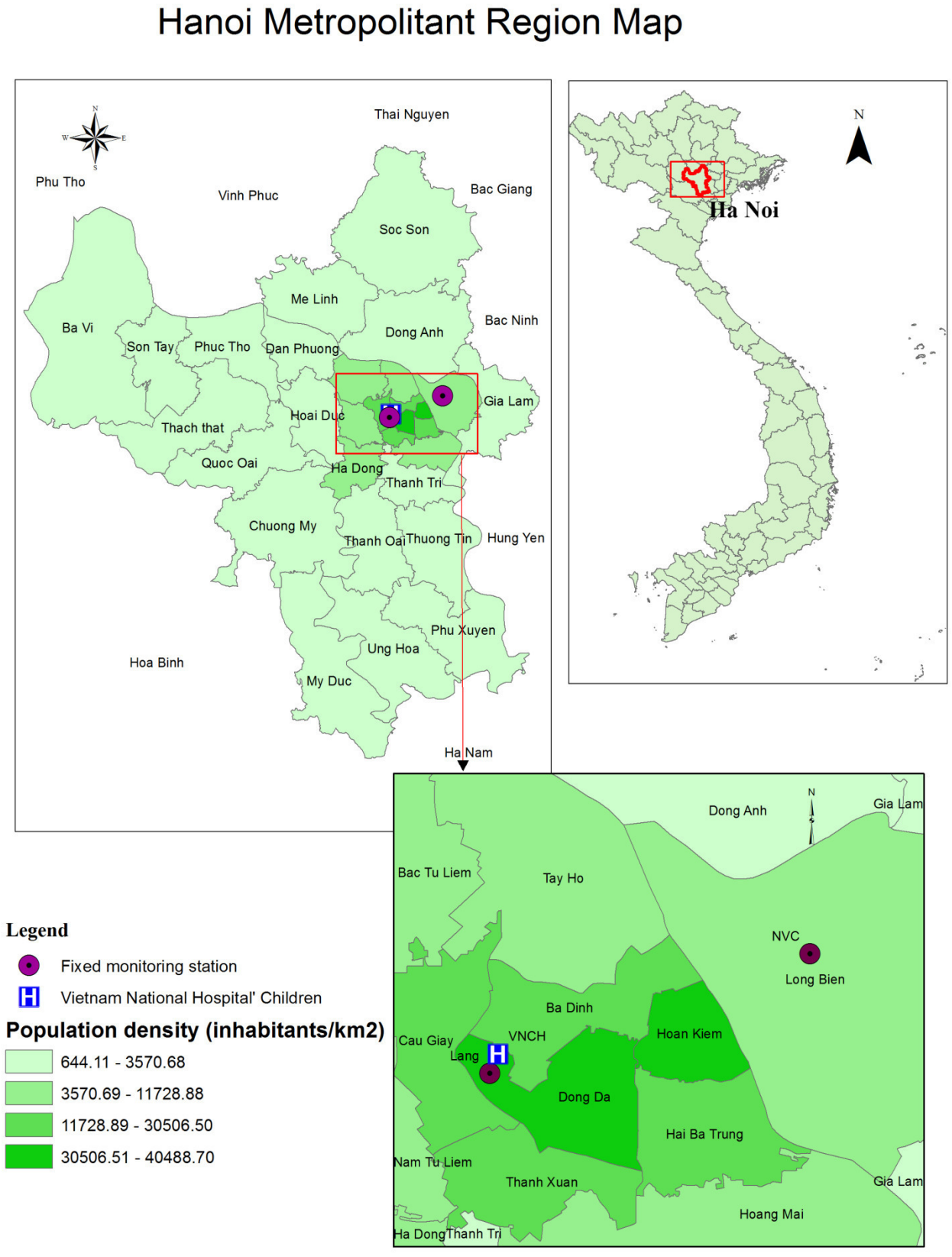



**Figure A1:** Map of Hanoi Metropolitan Region. Vietnam National Children's Hospital and two fixed site monitoring stations

Abbreviation: NVC Nguyen Van Cu monitoring station ; VNCH: Vietnam National Children's Hospital.

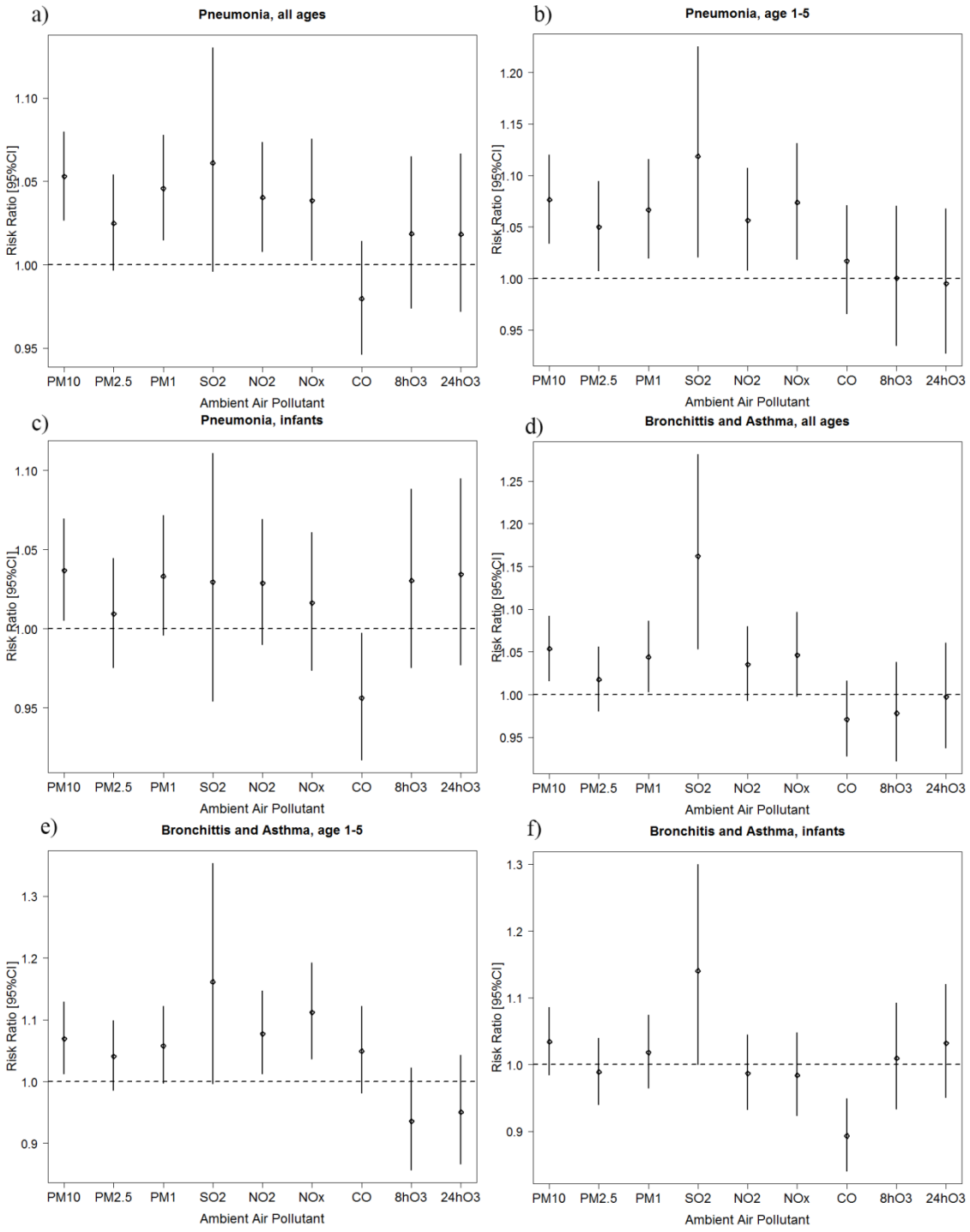
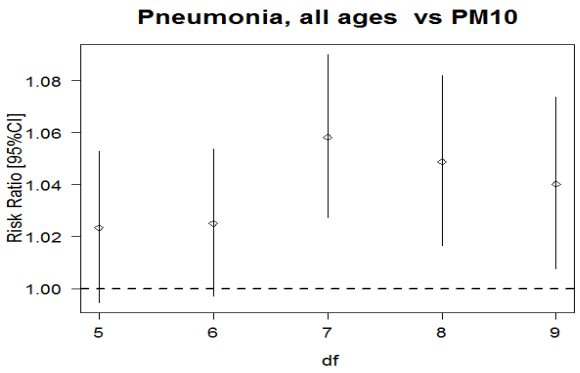
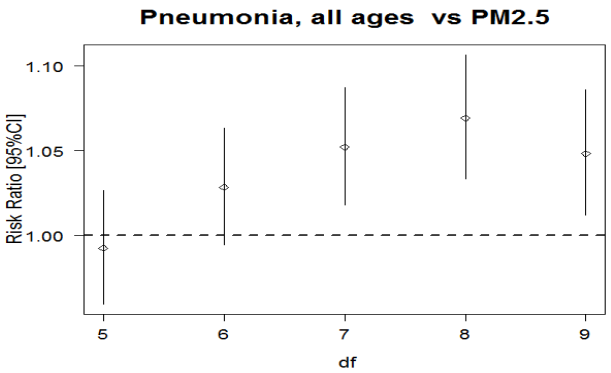


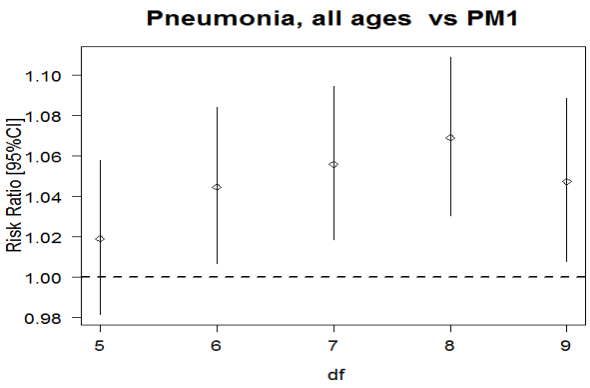

**Figure A2**: Risk ratios per one interquartile range (lag 0-6) using models with 7knot per year, natural cubic spline with df =3 for temperature and df=4 for humidity for a) Pneumonia, all ages, b) Pneumonia, age 1-5; c) Pneumonia, infants; d) Bronchitis and Asthma, all ages, e) Bronchitis and Asthma, age 1-5 and f) Bronchitis and Asthma, infants, Hanoi.

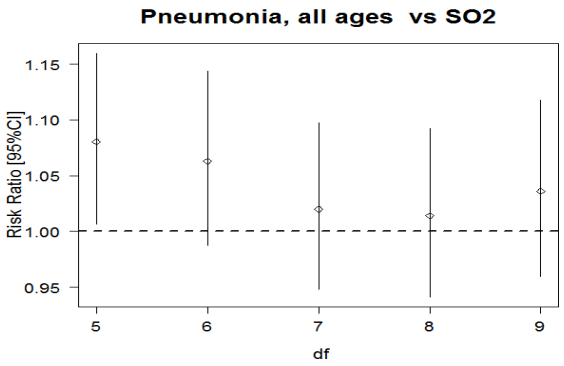
Bar: 95% confidence intervals.

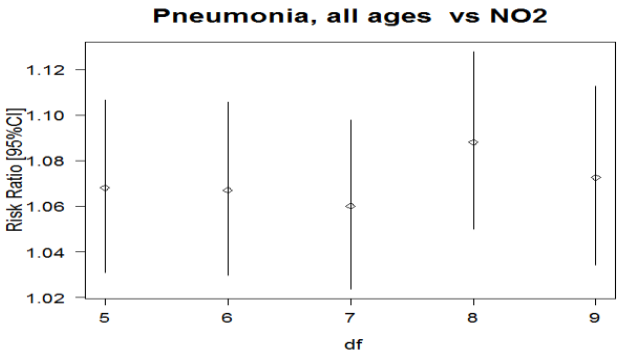
Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8h average $O_3$, 24h maximum $O_3$ to the period 2009-2014

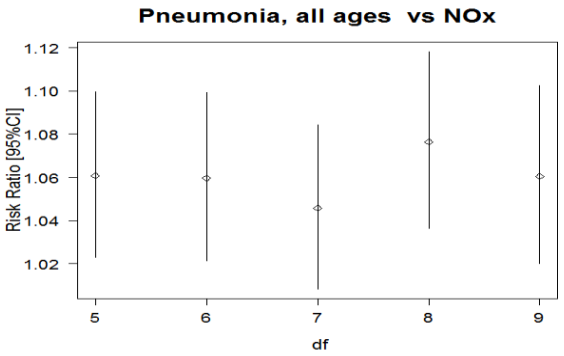

Pneumonia, all ages vs PM10
Risk Ratio [95%CI]
1.00
1.02
1.04
1.06
1.08
5
6
7
8
9
df

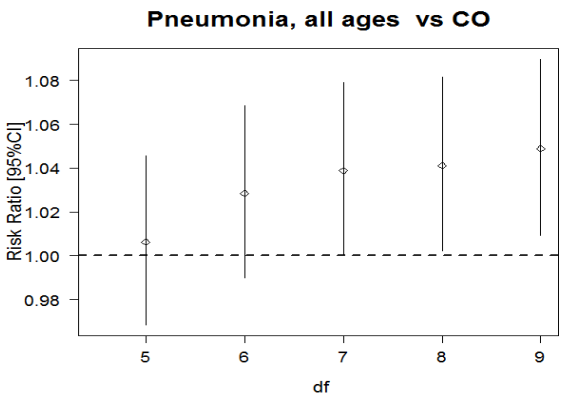

Pneumonia, all ages vs PM2.5
Risk Ratio [95%CI]
1.00
1.05
1.10
5
6
7
8
9
df

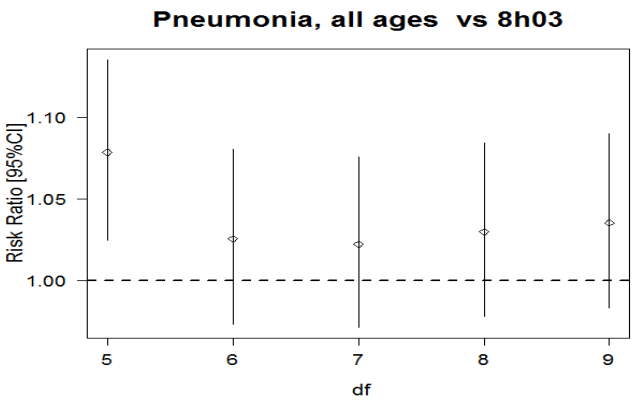

Pneumonia, all ages vs PM1
Risk Ratio [95%CI]
0.98
1.00
1.02
1.04
1.06
1.08
1.10
5
6
7
8
9
df

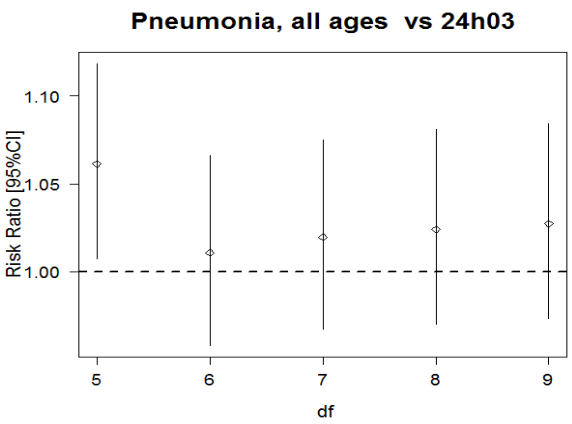

Pneumonia, all ages vs SO2
Risk Ratio [95%CI]
0.95
1.00
1.05
1.10
1.15
5
6
7
8
9
df

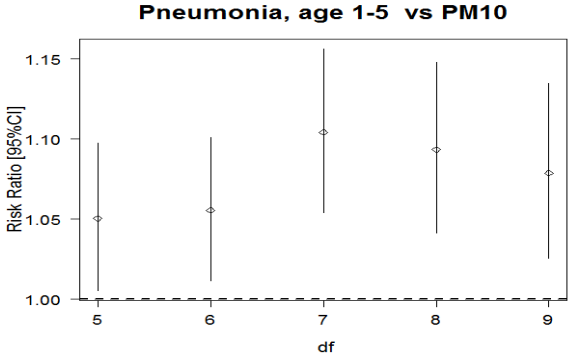

Pneumonia, all ages vs NO2
Risk Ratio [95%CI]
1.02
1.04
1.06
1.08
1.10
1.12
5
6
7
8
9
df

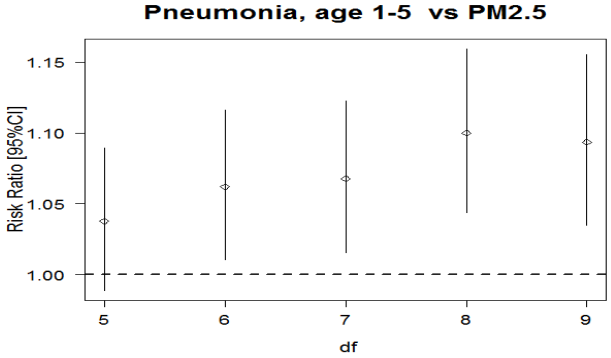

Pneumonia, all ages vs NOx
Risk Ratio [95%CI]
1.02
1.04
1.06
1.08
1.10
1.12
5
6
7
8
9
df

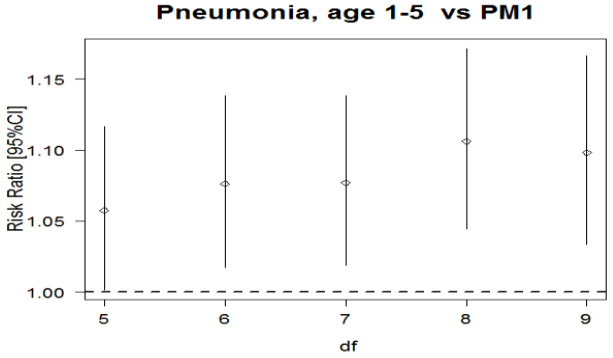

Pneumonia, all ages vs CO
Risk Ratio [95%CI]
1.08
1.06
1.04
1.02
1.00
0.98
5
6
7
8
9
df

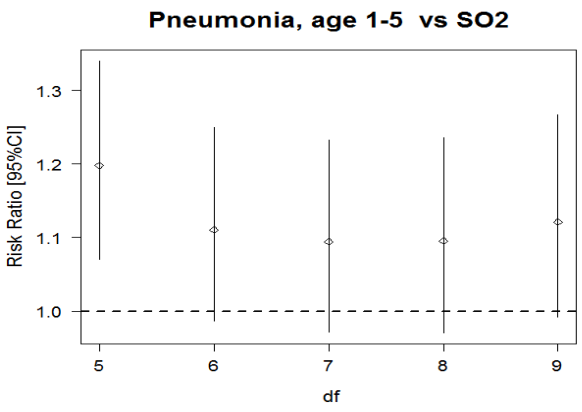

Pneumonia, all ages vs 8h03
Risk Ratio [95%CI]
1.10
1.05
1.00
5
6
7
8
9
df

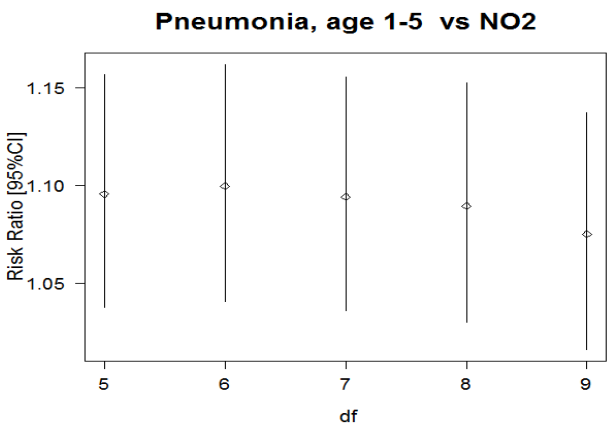

Pneumonia, all ages vs 24h03
Risk Ratio [95%CI]
1.10
1.05
1.00
5
6
7
8
9
df

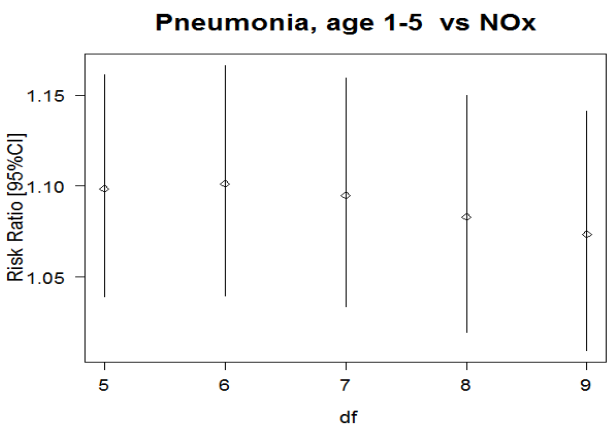

Pneumonia, age 1-5 vs PM10
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df

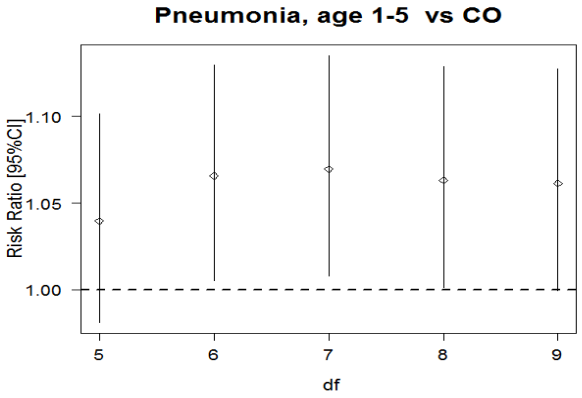

Pneumonia, age 1-5 vs PM2.5
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df

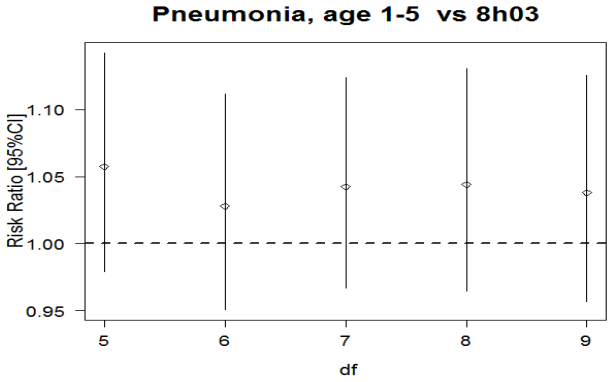

Pneumonia, age 1-5 vs PM1
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df

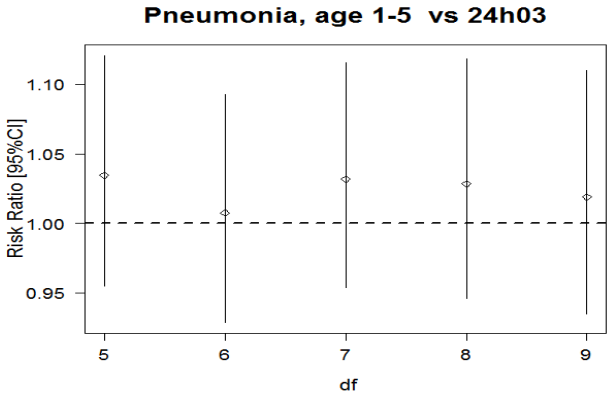

Pneumonia, age 1-5 vs SO2
Risk Ratio [95%CI]
1.0
1.1
1.2
1.3
5
6
7
8
9
df

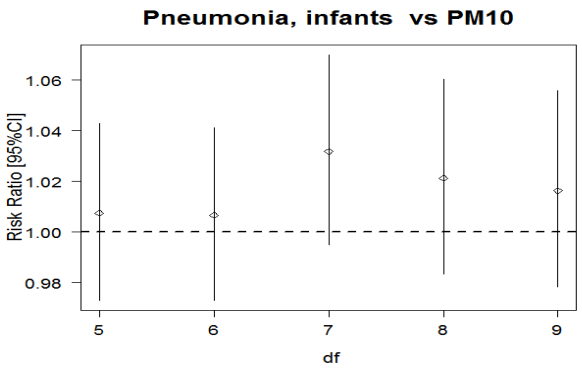

Pneumonia, age 1-5 vs NO2
Risk Ratio [95%CI]
1.05
1.10
1.15
5
6
7
8
9
df

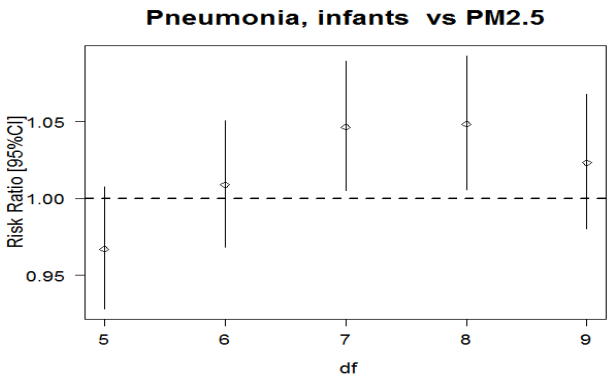

Pneumonia, age 1-5 vs NOx
Risk Ratio [95%CI]
1.05
1.10
1.15
5
6
7
8
9
df

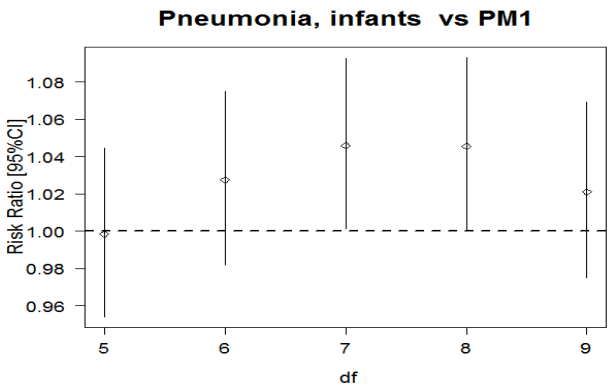

Pneumonia, age 1-5 vs CO
Risk Ratio [95%CI]
1.00
1.05
1.10
5
6
7
8
9
df

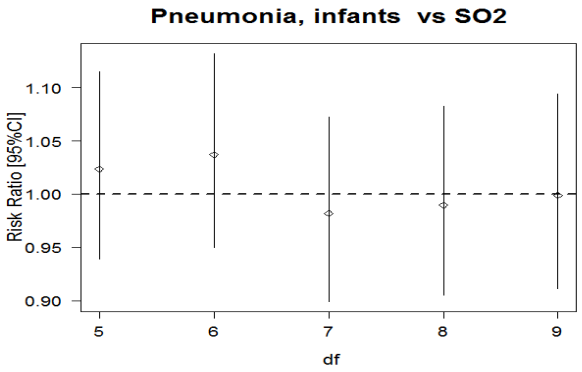

Pneumonia, age 1-5 vs 8h03
Risk Ratio [95%CI]
0.95
1.00
1.05
1.10
5
6
7
8
9
df

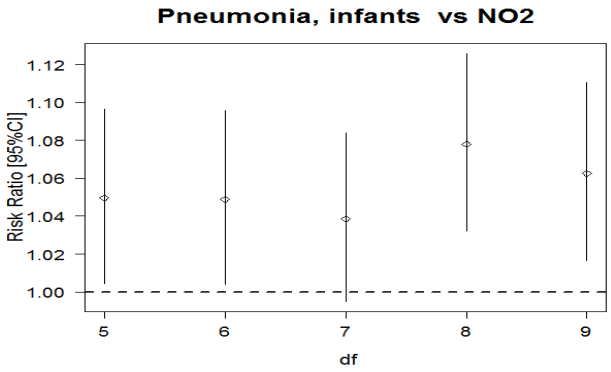

Pneumonia, age 1-5 vs 24h03
Risk Ratio [95%CI]
0.95
1.00
1.05
1.10
5
6
7
8
9
df


Pneumonia, infants vs PM10
Risk Ratio [95%CI]
1.06
1.04
1.02
1.00
0.98
5
6
7
8
9
df


Pneumonia, infants vs PM2.5
Risk Ratio [95%CI]
1.05
1.00
0.95
5
6
7
8
9
df


Pneumonia, infants vs PM1
Risk Ratio [95%CI]
1.08
1.06
1.04
1.02
1.00
0.98
0.96
5
6
7
8
9
df


Pneumonia, infants vs SO2
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
0.90
5
6
7
8
9
df


Pneumonia, infants vs NO2
Risk Ratio [95%CI]
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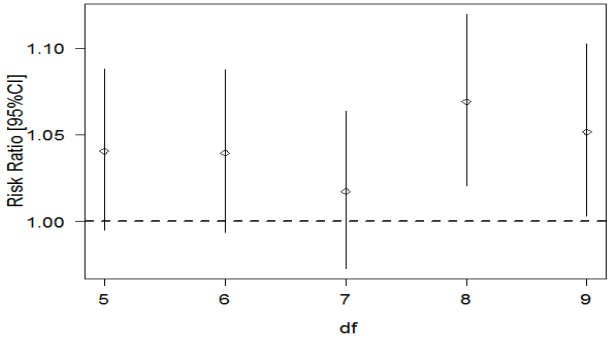
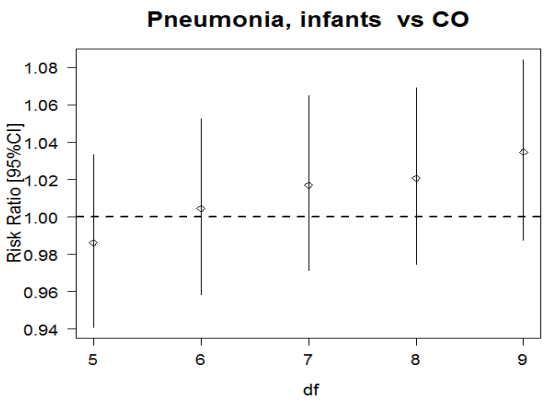
1.10
1.08
1.06
1.04
1.02
1.00
5
6
7
8
9
df


Pneumonia, infants vs NOx
Risk Ratio [95%CI]
1.10
1.05
1.00
5
6
7
8
9
df


Pneumonia, infants vs CO
Risk Ratio [95%CI]
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1.04
1.02
1.00
0.98
0.96
0.94
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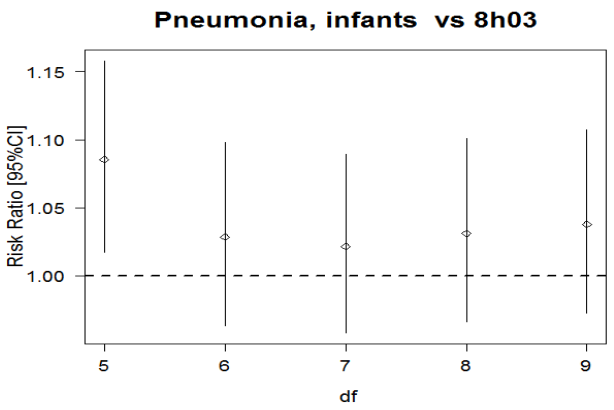
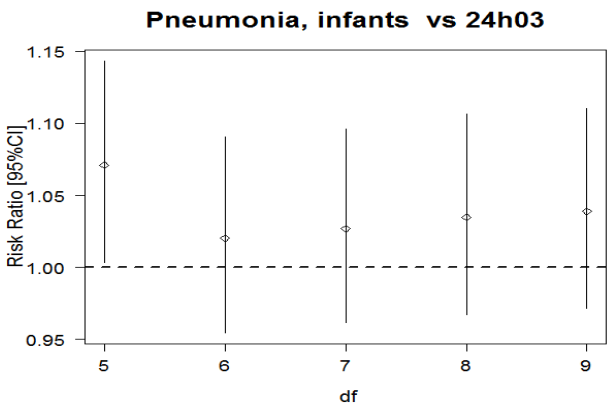
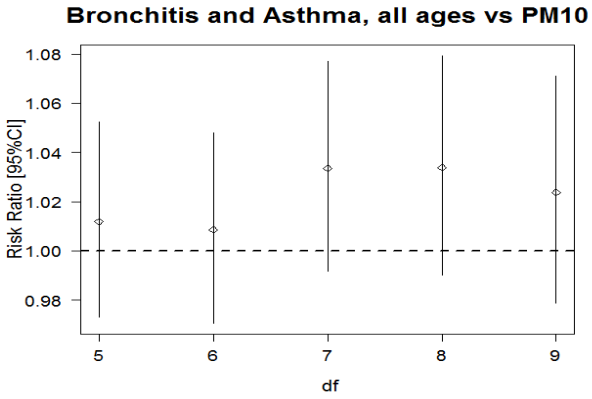
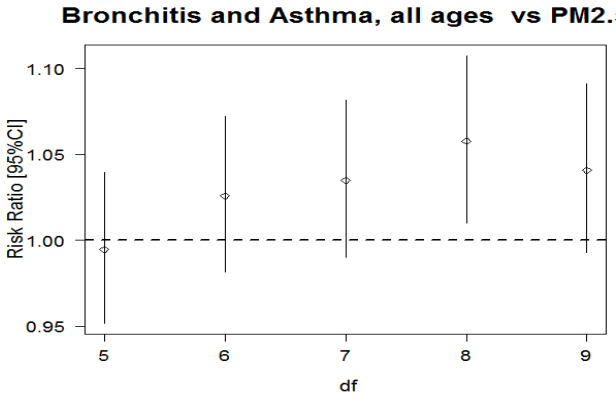
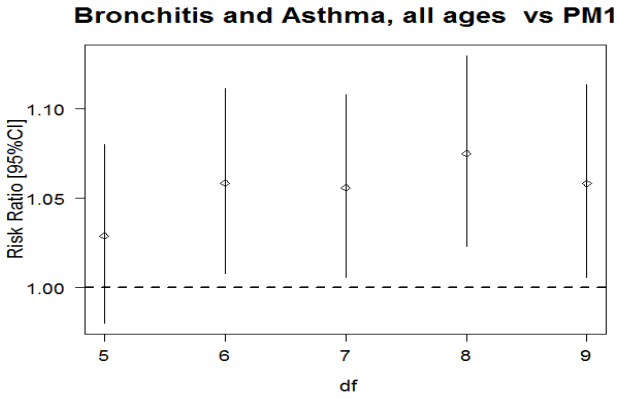
6
7
8
9
df

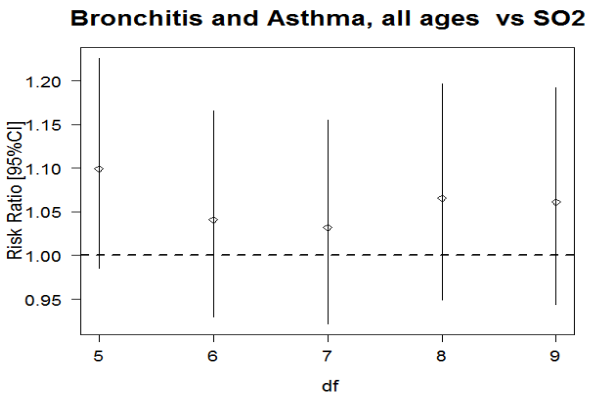

Pneumonia, infants vs 8h03
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df

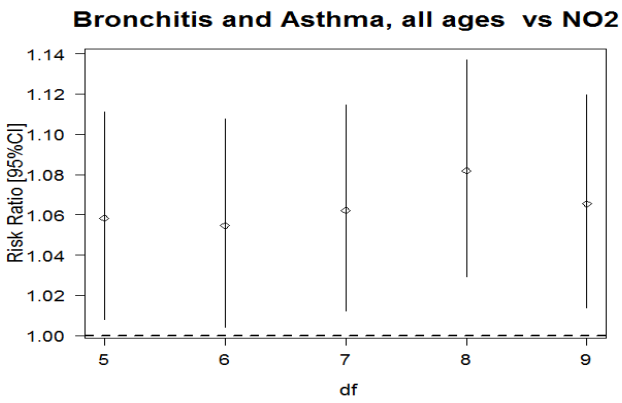

Pneumonia, infants vs 24h03
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
0.95
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs PM10
Risk Ratio [95%CI]
1.08
1.06
1.04
1.02
1.00
0.98
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs PM2.5
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs PM1
Risk Ratio [95%CI]
1.10
1.05
1.00
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs SO2
Risk Ratio [95%CI]
1.20
1.15
1.10
1.05
1.00
0.95
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs NO2
Risk Ratio [95%CI]
1.14
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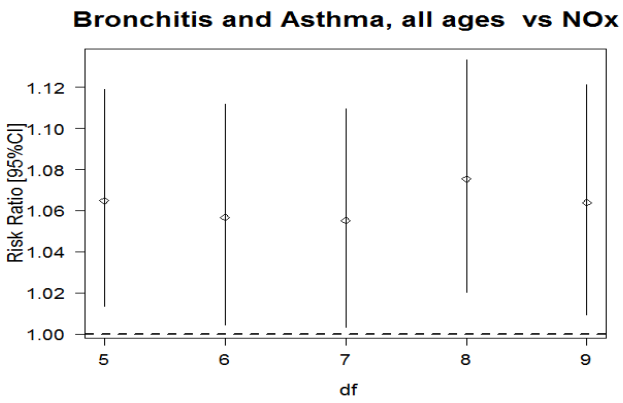
1.10
1.08
1.06
1.04
1.02
1.00
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs NOx
Risk Ratio [95%CI]
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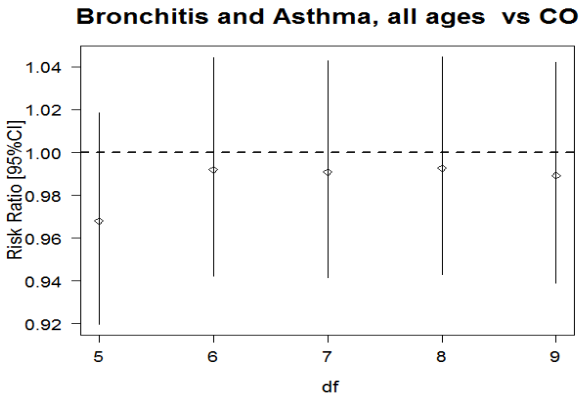
1.10
1.08
1.06
1.04
1.02
1.00
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs CO
Risk Ratio [95%CI]
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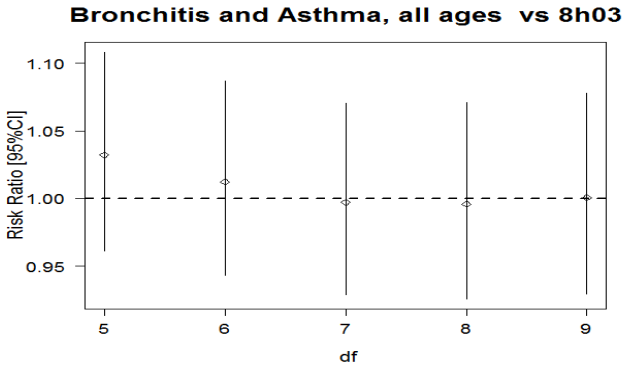
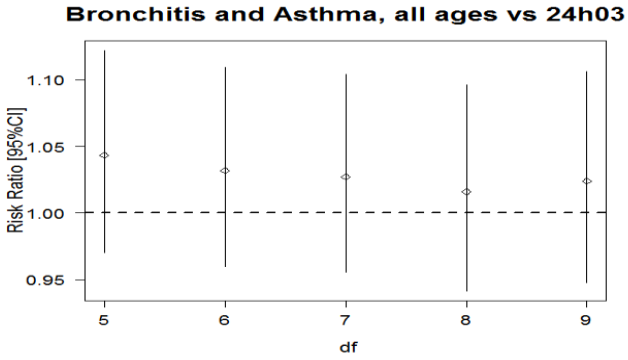
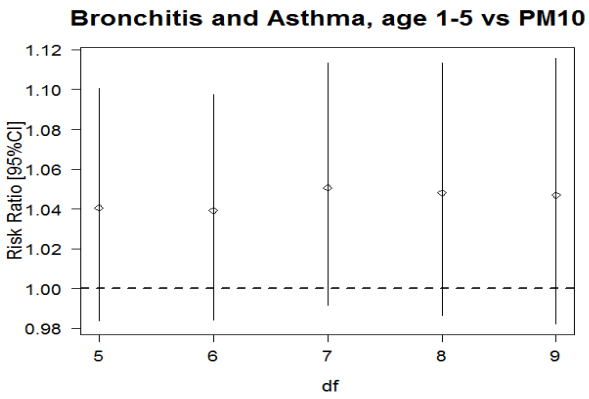
1.02
1.00
0.98
0.96
0.94
0.92
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs 8h03
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
5
6
7
8
9
df


Bronchitis and Asthma, all ages vs 24h03
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
5
6
7
8
9
df


Bronchitis and Asthma, age 1-5 vs PM10
Risk Ratio [95%CI]
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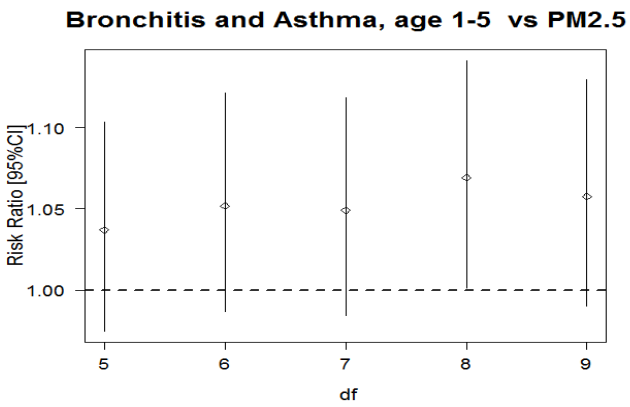
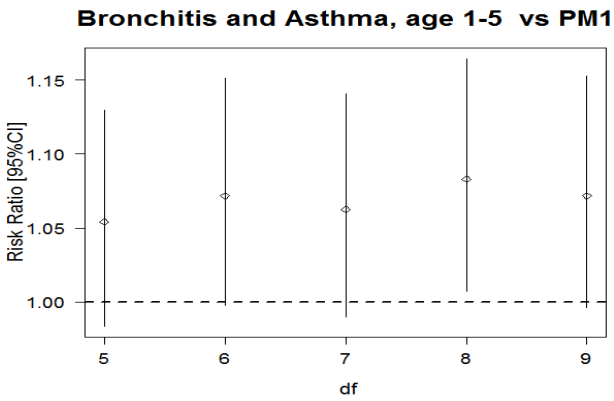
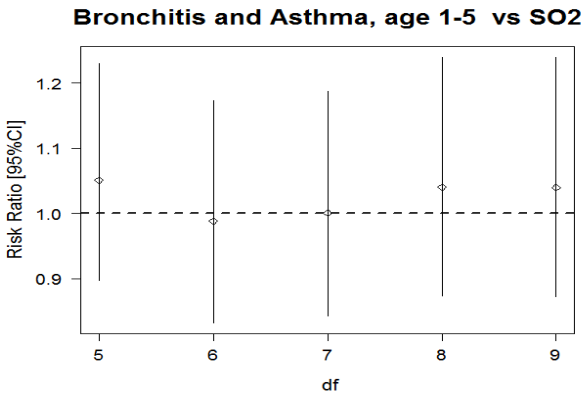
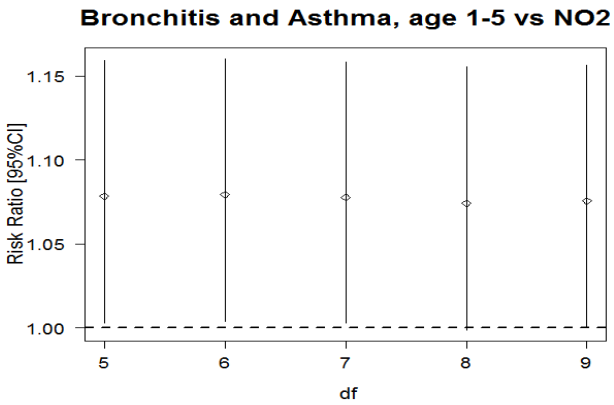
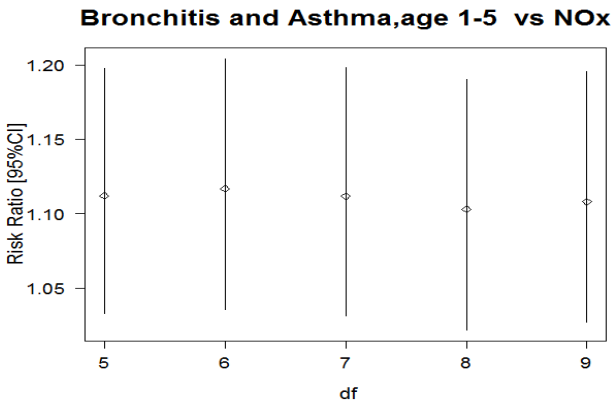
1.08
1.06
1.04
1.02
1.00
0.98
5
6
7
8
9
df

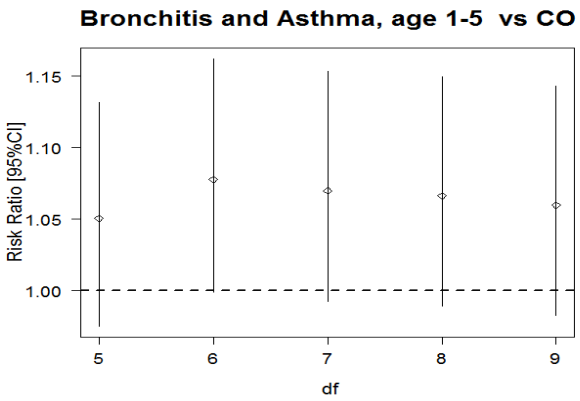

Bronchitis and Asthma, age 1-5 vs PM2.5
Risk Ratio [95%CI]
1.10
1.05
1.00
5
6
7
8
9
df

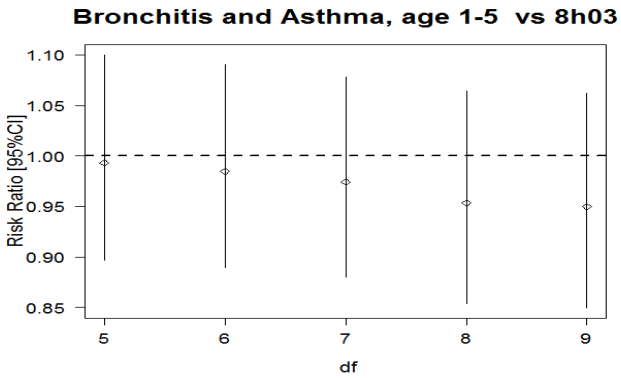

Bronchitis and Asthma, age 1-5 vs PM1
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df

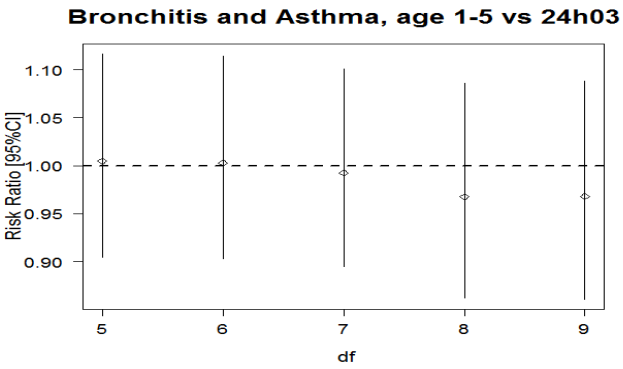

Bronchitis and Asthma, age 1-5 vs SO2
Risk Ratio [95%CI]
1.2
1.1
1.0
0.9
5
6
7
8
9
df


Bronchitis and Asthma, age 1-5 vs NO2
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df


Bronchitis and Asthma,age 1-5 vs NOx
Risk Ratio [95%CI]
1.20
1.15
1.10
1.05
5
6
7
8
9
df


Bronchitis and Asthma, age 1-5 vs CO
Risk Ratio [95%CI]
1.15
1.10
1.05
1.00
5
6
7
8
9
df


Bronchitis and Asthma, age 1-5 vs 8h03
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
0.90
0.85
5
6
7
8
9
df


Bronchitis and Asthma, age 1-5 vs 24h03
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
0.90
5
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7
8
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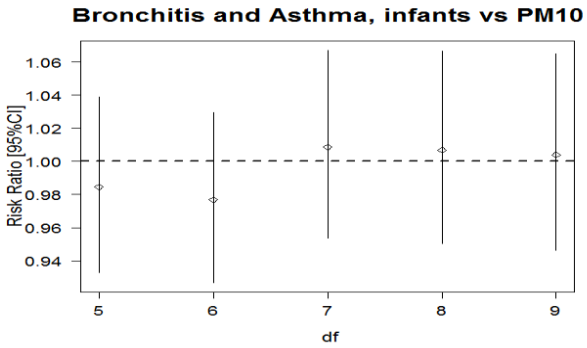
df


Bronchitis and Asthma, infants vs PM10
Risk Ratio [95%CI]
1.06
1.04
1.02
1.00
0.98
0.96
0.94
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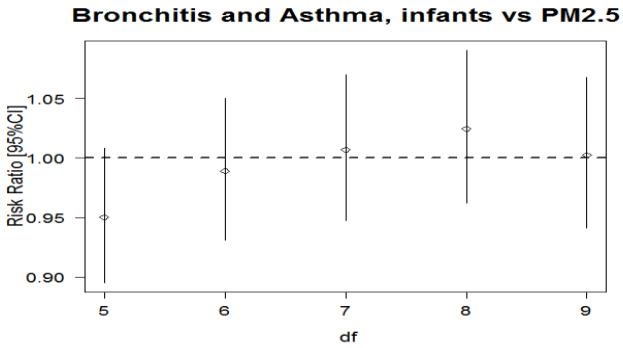
9
df


Bronchitis and Asthma, infants vs PM2.5
Risk Ratio [95%CI]
1.05
1.00
0.95
0.90
5
6
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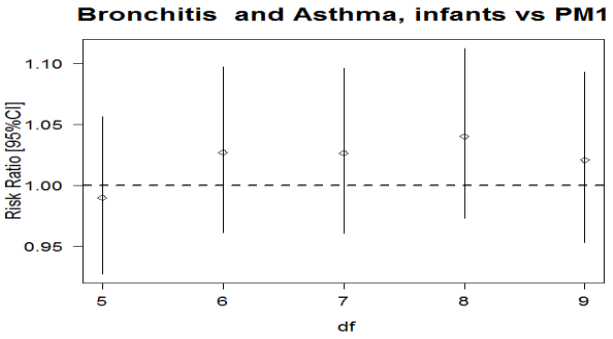
df


Bronchitis and Asthma, infants vs PM1
Risk Ratio [95%CI]
1.10
1.05
1.00
0.95
5
6
7
8
9
df

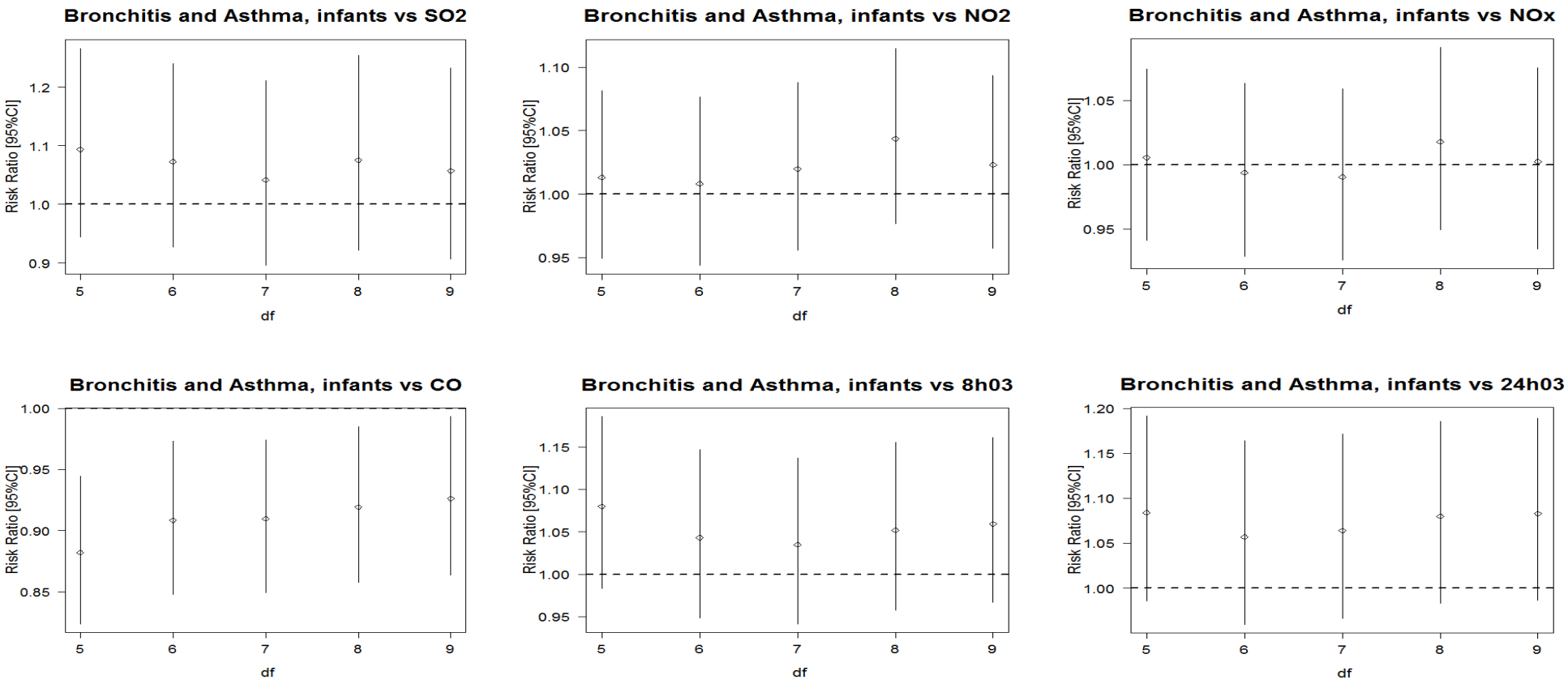



**Figure A3**: Estimated risk ratio per IQR increase in seven day moving average pollutant concentration (lag 0-6) for models with different degrees of freedom (knots) per year included in the cubic thin plate spline function used to capture time trends and seasonal variations.
Risk ratios of $PM_{10}$ and $SO_2$ refer to the period 2007-2014, risk ratios of $PM_{2.5}$, $PM_1$, $SO_2$, $NO_2$, $NO_x$, CO, 8h average $O_3$, 24h maximum $O_3$ to the period 2009-2014

## CHAPTER 6: GENERAL DISCUSSION

The present study documents the increasing trend of hospital admission rates in the Hanoi paediatric unit during the period 2007–2014. Pneumonia is the leading cause of hospitalization and death among children with respiratory diseases. Among Hanoi children, air pollution is a risk factor of hospitalization due to pneumonia; short term variations in $PM_{10}$, $PM_{2.5}$, $PM_1$ and $NO_2$ (but not in $SO_2$) were associated with hospital admissions for pneumonia. The strongest effects of air pollution were observed for children aged 0-5 years. Also, season was found a modify factor of the associations between ambient air pollution and hospitalization for pneumonia among Hanoi children.

In the following sections, the findings will be discussed in terms of the key messages derived from hospital data, ambient air quality data for Hanoi and the short-term effects of ambient air pollution on hospital admissions due to pneumonia among Hanoi children. The discussion section will also present other relevant potential modifiers of the effects identified in this work.

### 6.1 Key messages from childhood hospitalization data

As a first step, this work provides specific rates of emergency and hospital admissions, based on data from the largest tertiary hospital in the North of Vietnam. This information can be useful for future health assessment studies. For instance, age-gender specific rates are useful for estimating the burden of disease for a range of health conditions, both in Vietnam and globally. In addition, this data can help to identify Vietnamese childhood disease patterns, thereby contributing to developing and evaluating health prevention programs in Vietnam.

The Government of Vietnam made significant efforts to reduce under-five childhood mortality by two thirds by 2015, in accordance with the fourth millennium development goal (Vietnam Ministry of Health, 2015b). Since 1990, a series of national intervention programs has been implemented to improve children's health. These were the Acute Respiratory Infection programme, the Control of Diarrhoea programme, the Integrated Management of Childhood Illness (IMCI) programme, the Programme for Immunization and the National Action Plan for Child Survival (2012-2015) (Vietnam Ministry of Health, 2016). These programmes explicitly provided training curricula for health care workers, upgraded the health facilities and

distributed vaccines to children. As a result, immunization coverage rates reached more than 90% in 2015 (Vietnam Ministry of Health, 2015a, Vietnam Ministry of Health, 2017). Infant mortality fell from 58/1000 live births in 1990 to 23.2/1000 live births in 2012 (Vietnam Ministry of Health, 2016). The current study found an overall rise in hospital admissions over the last years, particularly of children under five years of age. This finding might reflect changes in thresholds for admission or in the health-care seeking behaviours of parents. This data also reflects the utilization of the curative treatment system in Vietnam. Therefore, the finding might reflect the efforts of the Government of Vietnam towards improving access to health care. However, it also suggests that the government should sustain and further strengthen measures to achieve the third sustainable development goal (SDG3 on Good Health and Well-being) when disease episodes are escalating.

The Government of Vietnam has shown a strong commitment to protecting children's rights (The National Assembly, 2004). As part of this commitment, the Social Health Insurance Scheme (SHIS) extends to all children under six years of age in Vietnam (Tran Van Tien et al., 2011). The SHIS scheme mainly covers curative services provided by health facilities (Anh et al., 2010, Tran Van Tien et al., 2011). This increase of hospital admissions has created financial pressure on the SHIS (Tran Van Tien et al., 2011). This pressure could be alleviated if certain health conditions were increasingly treated in smaller health facilities. As discussed in chapter three, respiratory diseases can be cured at grassroots level health premises and in district general hospitals. An increase of admissions to tertiary hospitals for such diseases reflects the increasing demand for admission to national level curative services. In other words, it sets the scene for health system overload at higher levels in Vietnam.

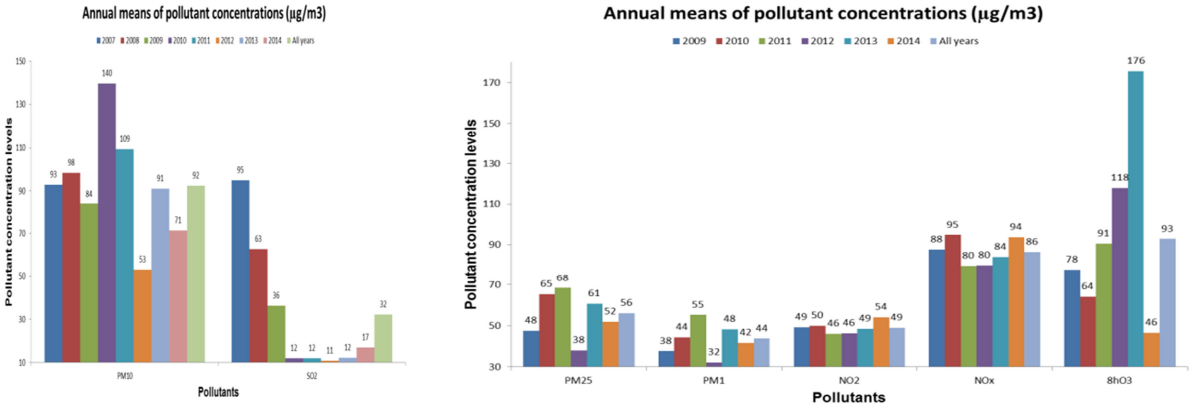
## 6.2 Air pollution in Vietnam

### 6.2.1 Ambient air quality concentrations in Hanoi

This study shows that air pollution levels in Hanoi exceed both the national ambient air quality standards and the WHO limit levels. Figure 6.1 compares annual means of pollutant concentrations across the years studied. The annual average value of $PM_{10}$ in Hanoi during 2007–2014 was 92µg/$m^3$, nearly twice the Vietnam ambient air quality standard (50µg/$m^3$) (Ministry of Natural Resources and Environment, 2014) and five times as high as the WHO guideline value (20µg/$m^3$)(World Health Organization, 2006). Similarly, the annual mean of $PM_{2.5}$ was 55µg/$m^3$, which is also

twice the Vietnam limit values (25 µg/m$^3$) and 5.5 times as high as the WHO guideline value (10 µg/m$^3$) (Figure 6.1). The annual level of $PM_{10}$ concentration in Hanoi in 2010 was seven times as high as the WHO guideline values. The concentration of $O_3$ in 2013 peaked at 176µg/m$^3$; was far higher than both the Vietnam and WHO standards.

a) b)




c)

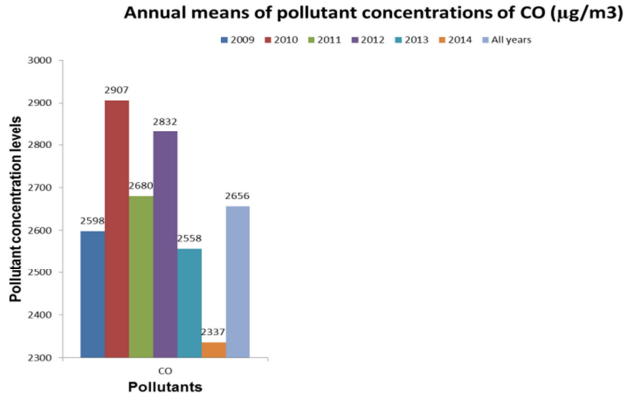



Figure 6.1: Annual means of concentration levels of a) $PM_{10}$ and $SO_2$ (2007–2014) b) $PM_{2.5}$, $PM_1$, $NO_2$, $NO_x$ and $O_3$ (2009–2014), and c) CO (2009–2014), Hanoi, Vietnam.

Table 6.1 compares the daily mean levels of $PM_{10}$, $SO_2$, $NO_2$ and $O_3$ in Ho Chi Minh city with those of Hanoi, two cities with ambient air quality standards. In general, the daily concentrations of almost all air pollutants in Hanoi rarely exceed Vietnam's ambient air quality standards. However, if comparing with the WHO standards,

concentration levels of all pollutants frequently exceed the limit values, except for those of $O_3$ (table 6.1).

Table 6.1: Mean of daily pollutant concentrations in Ho Chi Minh and Hanoi cities and ambient air quality standards of Vietnam and the World Health Organization guideline

| Pollutants ($\mu g/m^3$) | Daily pollutant concentration | | | Daily concentrations | |
|---|---|---|---|---|---|
| | Ho Chi Minh (2001-2003)[1] | Ho Chi Minh (2004-2007)[2] | Hanoi (2007-2014)[3] | Vietnam ambient air quality standards (TCVN)[+] | WHO guideline[++] |
| $PM_{10}$ | 73 | 74 | 93 | *150* | *50* |
| $PM_{2.5}$ | | | 56 | *50* | *25* |
| $SO_2$ | 22 | 30 | 32 | *125* | *20* |
| $NO_2$ | 22 | 19 | 49 | *100* | - |
| 8h mean $O_3$ | 75 | 40 | 93 | *120* | *100* |

[1] Concentrations were extracted from Le et al. (2012)

[2] Concentrations were extracted from Phung et al. (2016)

[3] Concentrations were extracted from the present study

All concentration measures were obtained from fixed monitoring stations

[+] Ambient air quality standard of Vietnam(Ministry of Natural Resources and Environment, 2014)

[++] Ambient air quality standard of the World Health Organization (World Health Organization, 2006)

- not available

Table 6.1 also indicates that while the $PM_{10}$ and $SO_2$ concentrations in Ho Chi Minh city increased slightly during years from 2001 to 2007, the concentration levels of $NO_2$ and $O_3$ declined during that time. Nonetheless, concentration levels of all pollutants in Ho Chi Minh were lower than those in Hanoi during 2007–2014.

### 6.2.2 Local emission sources of air pollution in Hanoi

The polluted atmosphere in Hanoi is mainly caused by vehicle emissions (Ministry of Natural Resources and Environment, 2014). The number of motorcycles in Hanoi has increased from 0.65 million in 2001 to 4.6 million in 2013 (Figure 6.2) (Vietnam Ministry of Transport, 2013). It was estimated that the annual average growth rate of cars in Vietnam was nearly 18% during 2008–2013 (Vietnam Ministry of Transport, 2013). Hanoi is one of the cities with the fastest growth in the number of private vehicles. Given the change in fuel formulas and the improvement of diesel filters in recent years, pollutant concentrations should have decreased. However, cars in Vietnam tend to use old combustion technology. Many vehicles including buses do not have pollution control devices. Moreover, as a consequence of more private vehicles, congestion occurs more frequently in Hanoi. As a result of these factors, pollutant markers of traffic pollution (i.e $NO_2$) in Hanoi have remained at high levels, as seen in Figure 6.1.

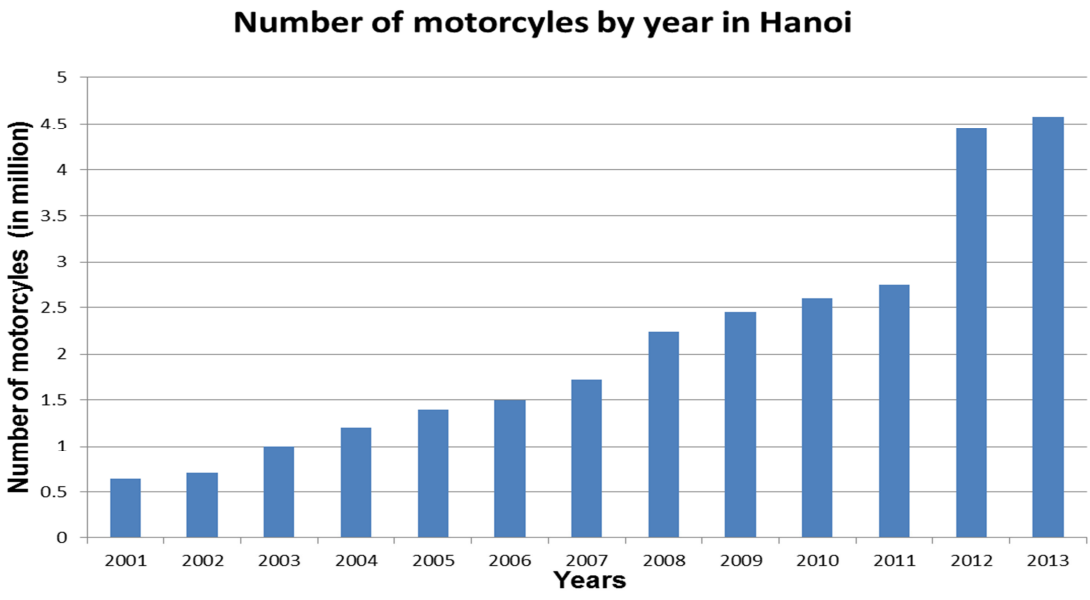



Figure 6.2: Numbers of motorcycles in Hanoi during 2001–2013

Data from Vietnam Ministry of Transport (2013)

Another important emission source in Hanoi is residential/commercial cooking (Ministry of Natural Resources and Environment, 2014). Hanoi had approximately 7.3 million inhabitants in 2014 (Hanoi Population and Family Planning Branch, 2014).

Hanoi citizens use various kinds of fuel for cooking, such as wood fuel and smoky coal briquettes. Coal particles, which are usually used to make coal briquettes, create high sulphur and heavy metal emissions (Hai and Oanh, 2013). Food stall and commercial activities are frequently located in densely populated areas, along the narrow roads of the inner city. Commercial cooking in Hanoi starts typically at 4:00 a.m. and ends at 11:00 p.m. The busiest time is between 6:00 p.m. to 9:00 p.m., when residential cooking is also more intensive. As a result, the period of highest pollution ranges from 4:00 p.m. to 9:00 p.m. in Hanoi (Ministry of Natural Resources and Environment, 2014).

In sum, residential/commercial cooking and diesel traffic contributes 16% and 10% of total $PM_{2.5}$, respectively, in Hanoi (Hai and Oanh, 2013).

### 6.2.3 Air quality standard values in Vietnam

Air quality standards have led state air pollution regulatory agencies to promulgate transportation control plans or industrial factories in order to reduce the high air pollution levels. The standards are also used for health impact assessment of air pollution. As presented in Table 6.3, Vietnam's values of ambient air quality standards comply poorly with WHO values, except for $NO_2$. As suggested by Kutlar Joss et al. (2017), the Government of Vietnam should harmonize the national air quality standards with the WHO guideline values, to support policies against air pollution. By doing so, the government can implement public health interventions aimed at protecting children's health and move toward achieving SDG3, and/or SDG7 (Sustainable Cities and Communities)

Table 6.2: Comparison of ambient air quality standards of Vietnam (QCVN 05:2013/BTNMT) and the World Health Organization (expressed in µg/$m^3$)

| Pollutants | Hourly mean | | 8-hour mean | | 24-hour mean | | Annual mean | |
|---|---|---|---|---|---|---|---|---|
| | QCVN[$] | WHO[@] | QCVN[$] | WHO[@] | QCVN[$] | WHO[@] | QCVN[$] | WHO[@] |
| $PM_{10}$ | - | | - | | 150 | 50 | 50 | 20 |
| $PM_{2.5}$ | - | | - | | 50 | 25 | 25 | 10 |
| $SO_2$ | 350 | | - | | 125 | 20 | 50 | - |
| $NO_2$ | 200 | 200 | - | | 100 | - | 40 | 40 |
| CO | 30000 | | 10000 | | - | - | - | - |
| $O_3$ | 200 | | 120 | 100 | - | - | - | - |

-: not available

[$] the World Health Organization air quality guideline

[®]Vietnam ambient air quality standard (QCVN 05:2013/BTNMT)

## 6.3 Comparing short-term effects of air pollution on pneumonia hospitalization of children

Figures 6.3 and 6.4 show comparisons of our findings with estimated effects from meta-analysis (so-called pooled estimates) and with the previous study in Ho Chi Minh city (Le et al., 2012). In order to compare effect estimates across studies, effect estimates in chapter five are recalculated for 10 µg/$m^3$ increments in $PM_{10}$, $PM_{2.5}$, $SO_2$, $O_3$, and for 1000 µg/$m^3$ increments in the case of CO.

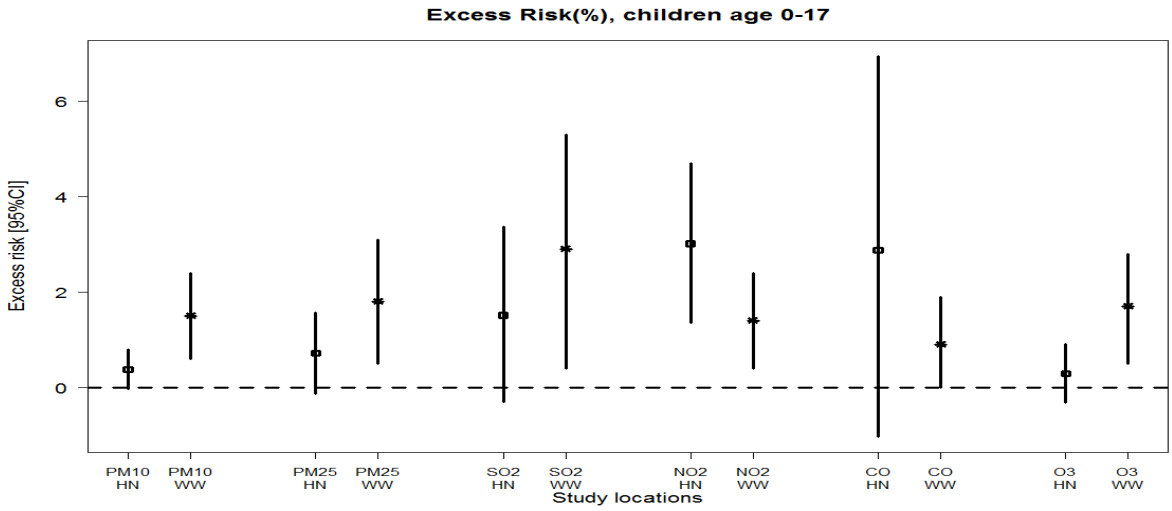



Figure 6.3: Association of ambient air pollutants with daily numbers of hospital admissions for pneumonia of Hanoi children (HN, **square**) and children worldwide (WW, **star**).

Excess risk (ER%) for pneumonia admissions (with 95% confidence interval) per 10 µg/m$^3$ increase in concentration levels of $PM_{10}$, $PM_{2.5}$, $SO_2$, $NO_2$ and $O_3$; and 1000 µg/m$^3$ increase in concentration levels of CO. The results were extracted from associations for lag 0-6

Excess risks among Hanoi children were re-analysed from the study presented in chapter 5. Pneumonia is outcome.

Excess risks for children globally were estimated using random effects meta-analysis presented in chapter 4. Pneumonia is outcome. This study pooled associations from the shortest lag structure in individual studies.

Abbreviation: HN-Hanoi, WW: worldwide

The findings for children aged 0–17 show that effect estimates in the present study are lower than the pooled estimate for most of the pollutants considered, except for $NO_2$ and CO. A 10 µg/m$^3$ increase in $PM_{10}$ in Hanoi was associated with an increase in hospitalizations for pneumonia in children by 0.37%, whereas the pooled estimate for children globally was 1.5%. Similarly, this study found that a 10 µg/m$^3$ increase in levels of $PM_{2.5}$ concentration was associated with a 0.7% increase in the total number of daily admissions for pneumonia, while the meta-analysis found a corresponding increase of 1.80% worldwide (figure 6.3). In contrast, estimated effects of $NO_2$ and CO in Hanoi are higher than the pooled estimates. The excess risk of pneumonia hospitalizations for children aged 0–17 years were 3.0% in this study and 1.4% in the meta-analysis, for $NO_2$ increases of 10 µg/m$^3$. Similarly, the

excess risk for a 1000 µg/m$^3$ increment in CO was 2.9% in this study and 0.1% in the meta-analysis.

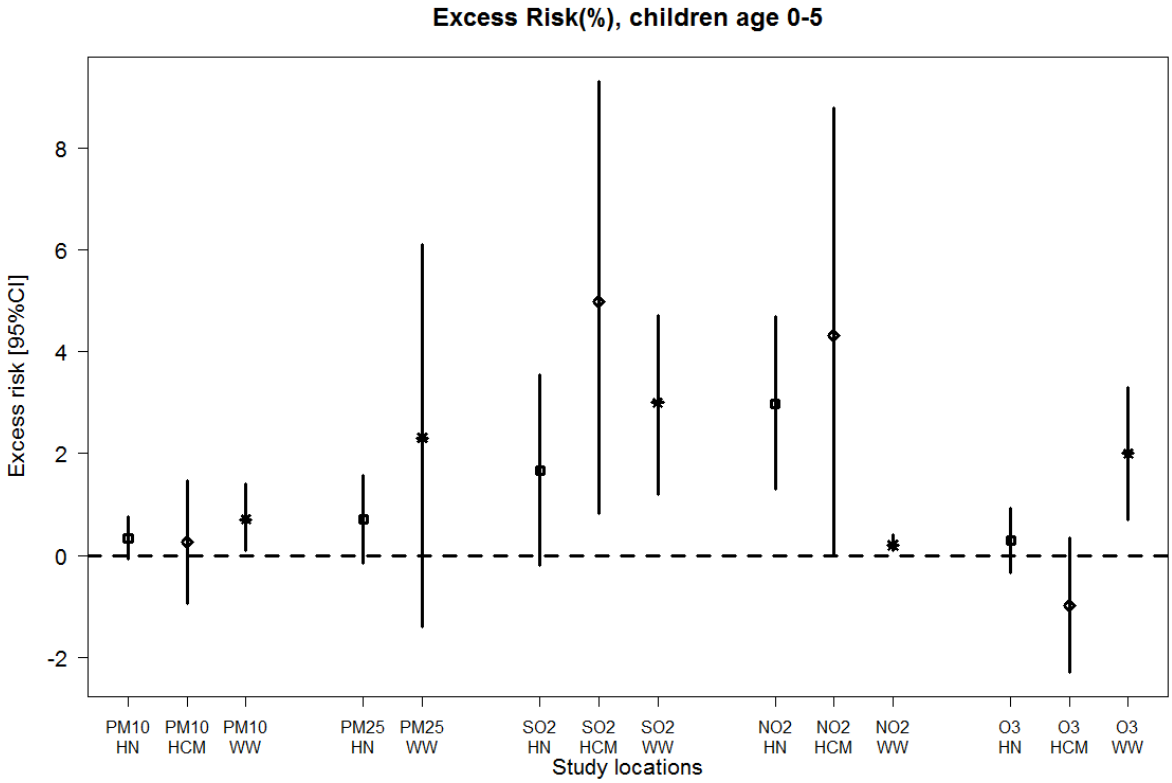



Figure 6.4: Association of ambient air pollutants with daily numbers of hospital admissions for children aged 0–5 in Hanoi (HN, **square**), Ho Chi Minh (HCM, **diamond**) and worldwide (WW, **star**).

Excess risk (ER%) for hospital admissions (with 95% confidence interval) per 10 µg/m$^3$ increase in concentration levels of $PM_{10}$, $PM_{2.5,}$ $SO_2$, $NO_2$ and $O_3$; and 1000 µg/m$^3$ increase in concentration levels of CO.

Excess risk among Hanoi children were re-analysed from the present study, pneumonia is an outcome (chapter 5). The results were extracted from associations for lag 0-6.

Excess risks in Ho Chi Minh children were studied by Le et al. (2012), acute lower respiratory disease is an outcome. The results were extracted from associations for lag 1-6. The study in Ho Chi Minh did not estimate effects of $PM_{2.5}$

Excess risks for children globally were estimated using random effects meta-analysis (chapter 4) with pneumonia as an outcome. This study pooled associations from the shortest lag structure in individual studies.

Abbreviation: HN-Hanoi, HCM: Ho Chi Minh, WW: worldwide

Figure 6.4 shows that point estimates for most pollutants across studies of children aged 0–5 differ, except for $PM_{10}$ (figure 6.4). The point estimates for a 10 µg/m$^3$ increase of $NO_2$ were 0.2% worldwide, 3.0% in Hanoi, and 4.3% in Ho Chi Minh.

However, the estimate for a 10 µg/$m^3$ increase of $SO_2$ in Hanoi was 1.7%, less than in Ho Chi Minh (5.0%) and worldwide (3.0%). The effects of $O_3$ on hospital admissions of Ho Chi Minh and Hanoi children, however, are less than the effect on children worldwide, with -0.98% in Ho Chi Minh and 0.29% in Hanoi, compared with 2.0% worldwide for each 10µg/$m^3$ increment of $O_3$. The increased estimates of $PM_{10}$ were similar across studies; both about 0.3% in Hanoi and Ho Chi Minh, and 0.7% worldwide. This evidence reconfirms the discussion in chapter 5, which states that pollutants from diesel exhaust (i.e. $NO_2$) are good predictors of pneumonia hospitalization in Vietnam.

Nonetheless, despite some variation across the studies, exposure to ambient air pollution was associated with hospital admissions for pneumonia in children.

## 6.4 Factors modifying the association between short-term exposure to ambient air pollution and hospital admissions due to pneumonia

The present study suggests that age is an important effect modifier, as estimated effects were higher for children aged 1–4 years than for infants. Some previous studies also support this conclusion. For instance, Darrow et al. (2014) found a 13.5 µg/$m^3$ (interquartile range) increment in $PM_{10}$ to be associated with an excess risk of 2.7% (95%CI: 0.1% to 5.6%) for children aged 1–4 years, while the corresponding estimate for infants was -0.3% (95%CI: -4.9 to 4.4%). Barnett et al. (2005) indicated that a 3.8 µg/$m^3$ (interquartile range) increase in the two-day moving average concentration of $PM_{2.5}$ accounted for a 2.4% increase in hospitalizations for pneumonia and acute bronchitis in children aged 1–4 and for a 1.7% increase in the hospitalization of infants. However, patterns among children above five years of age were still unclear. The results of our meta-regression (Table S6, supplementary document, chapter four) indicated that susceptibility to $NO_2$ was lower among children under five years than among the population of all children. The study also emphasized that evidence for $PM_{10}$ and $PM_{2.5}$ remained unclear. Similarly, Winquist et al. (2012) suggested that the effects of $O_3$ may be stronger for children aged 2–18 than for infants, although the effects of $PM_{2.5}$ were still uncertain. Since most analyses of effects on pneumonia have either been conducted among children of all ages or restricted to children under the age of five, evidence for associations among children aged 5–17 years is insufficient.

In our analyses, some of the observed associations showed seasonal patterns between pneumonia hospitalizations and $PM_{2.5}$, $PM_1$ and $O_3$. Although several previous studies also report different associations between air pollutants and pneumonia hospitalizations in winter and in summer, evidence of effect modification by season is not consistent. For instance, a study in Australia and New Zealand found higher $PM_{2.5}$ and $SO_2$ effects on pneumonia hospitalizations during the summer (Barnett et al., 2005). Similarly, $PM_{2.5}$ and $PM_1$ effects were higher for hospital admissions for pneumonia in the summer (April to October) for children of all ages in the present study. The higher summer season effects could be explained by different exposure patterns (e.g., children are likely to spend more time outdoors in the summer) or by the modifying effects of temperature (Barnett et al., 2005). In contrast, Ostro et al. (2009), who examined data in six California counties, found a higher effect of $PM_{2.5}$ on hospital admissions for pneumonia in the cool season among children <19 years of age (November to April). Similarly, Darrow et al. (2014) found stronger associations for $O_3$ and pneumonia hospitalizations during the cool season (November to February) in Atlanta, Georgia, USA. Higher effects in the cool season might be explained by the fact that these children tended to stay outside more on sunny days during the winter, whereas they were more likely to stay inside in the summer because of hot weather (Darrow et al., 2014).

We observed similar effects among boys and girls. To our knowledge, no study to date has investigated potential gender differences in the associations between childhood pneumonia hospitalizations and ambient air pollution. However, some studies have examined effect modification by sex among children for other health outcomes, such as change in lung function and hospitalizations for respiratory infections. Though these studies suggest that susceptibility to air pollution might differ between girls and boys, results are inconsistent. For example, Brunekreef et al. (1997) examined the change in forced expiratory volume in 1 second (FEV1) among 877 Dutch children living within 300 m of a motorway and reported stronger associations for girls. In contrast, Delfino et al. (2004) showed greater effects among boys in an analysis of the association between $PM_{2.5}$ and FEV1. Indeed, Lin et al. (2005) reported no differential effects of coarse particulate matter (PMc = $PM_{10}$-$PM_{2.5}$) on hospitalizations for respiratory diseases among girls and boys in Canada. Possible explanations for differences by sex in children are differences in anatomy

(lung size and growth), and life style behaviour (i.e. participation in sports) or exposure to dose (i.e. gas absorption) (Clougherty, 2010).

# CHAPTER 7: CONCLUSION AND OUTLOOK

## 7.1 Conclusion

This thesis work presented a pattern of emergency visits and hospital admission in Hanoi pediatrics in chapter three. The findings show the burden of childhood pneumonia in Vietnam has been increasing. Pneumonia has not only prolonged the length of hospital stays but also has increased the numbers of in-hospital deaths.

Exposure to high levels of air pollutants has been associated with increases in hospital admissions for pneumonia in several studies conducted in high income countries, and in our own study in Vietnam. Therefore, measures to abate air pollution should be part of prevention programmes aimed at improving children's health and reducing child mortality in Vietnam.

## 7.2 Outlook

Despite advancing knowledge of the effects of ambient air pollution on Vietnamese childhood, this work has some limitations that call for further research.

First, this analysis could not assess the potential effects of socio-economic class on the associations between air pollutants and hospital admissions for pneumonia. As seen in other studies, such as the one by Yap et al. (2013), children living in areas with a high living standard tend to experience weaker effects than those living in poor areas. However, unlike in developed countries, such as the United States, where poor children are likely to live in high-traffic areas (Gunier et al., 2003), poor children in Vietnam are more likely to live in rural areas where the air is less polluted. Thus, additional research needs to be carried out to explore this effect in Vietnam.

Second, the present study used one monitoring station only to represent daily levels of air pollutants for all of Hanoi. However, the agreement of data from fixed ambient air quality monitors and personal environmental exposures depends on the residential location, commuting transportation modes, and employment location (Cortese and Spengler, 1976). In addition, atmospheric concentrations of pollutants are usually highest near emission sources and decrease rapidly with increasing distance from the source. Moreover, Hanoi inhabitants' exposure to air pollution is also influenced by wind speed and wind direction (Hai and Kim Oanh, 2013, Hien et al., 2002, Huy and Kim Oanh, 2017). Therefore, individual exposures to air pollutants may differ substantially from the concentrations measured at fixed location

monitoring sites. Future research on the health effects of air pollution in Vietnam should use individualized exposure estimates, if possible.

Third, as discussed in chapter three and chapter five, most findings from this study relate to children under five, as the proportion of older children hospitalized in the Vietnam National Children's Hospital was small. The observed associations among older children are thus uncertain. We therefore suggest conducting studies of children aged 5 to17 to fill this gap.

Fourth, in the case of Vietnam, air pollution concentrations are higher than any limit values suggested by the Government of Vietnam or the WHO. Yet, air pollution is known to be associated with many health conditions present among the entire population, such as asthma and cardiovascular disease in adults (Thurston et al., 2017). In addition, constituents of air pollution in some provinces with dense industry, such as Quang Ninh (mining factories) and Hai Phong (power plants), might differ from those in Hanoi. Therefore, studies on the health effects of air pollution need more investment in Vietnam to support clean air policies.

Last, but not least, to date, most studies on the association between pneumonia hospitalizations and ambient air pollution were conducted in high-income countries, where both the incidence of pneumonia and ambient air pollution concentrations are low. Given that the majority of children infected with pneumonia are living in low-and middle-income countries, results showing the association between air pollution and disease in such settings provide vital information for public health action. We suggest replicating this study in other countries with settings similar to Vietnam.

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# Curriculum vitae

## Personal details

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## Education

| | |
|---|---|
| 09.2014-12.2017 | Doctor of Philosophy (PhD) in Epidemiology |
| | Swiss Tropical and Public Health Institute |
| | University of Basel, Switzerland |
| 09.2006-06.2007 | Master of Public Health Methodology |
| | School of Public Health, Université Libre De Bruxelles, Brussels, Belgium |
| 09.1996-06.2001 | Engineer of Mathematics- Applied Informatics |
| | Hanoi University of Science and Technology, Hanoi, Vietnam |
| | Thesis: E-commercial website |
| 09.1993-05.1996 | Huynh Thuc Khang High School, Nghe An, Vietnam |

## Employment history

| Time | Position title, Employer |
|---|---|
| 2014-2017: | PhD candidate, Swiss Tropical and Public Health Institute, Basel, Switzerland |
| 2002- 2014: | Lecturer, Researcher, Hanoi University of Public Health, Hanoi, Vietnam |

## Research experience

| Time | Name of projects (role ) |
|---|---|
| 2017 | Evaluation effects of ambient air pollution on hospital admissions for respiratory and cardiovascular diseases in Northern Vietnam (Principal Investigator). |
| | This research aimed to investigate the short-term effects of ambient air pollution on respiratory and cardiovascular hospital admissions in Northern Vietnam. |
| 2016 | Evaluation impact of tobacco tax in the Vietnam cigarette market (Data analyst) |
| | This study aimed to evaluate the impact of increasing the cigarette taxes on the its price in the retailer market in Vietnam |
| 2014-2017 | Estimate the Health Life (HALE) and burden of diseases in Vietnam (Researcher) |
| | This project aimed to estimate the healthy life expectancy and burden of diseases of Vietnam |
| 2014- 2017 | Evaluation effects of ambient air pollution on children health in Hanoi (PhD thesis) |
| | This study aimed to estimate the short-term of ambient air pollution on hospitalization in Hanoi children. |
| 2012-2013 | Southeast Asia Initiative on Tobacco Tax (SITT project) (Data analyst) |

| | |
|---|---|
| | This study aimed to investigate the cigarette price in the retailer market in Vietnam |
| 2007- 2012 | The Evidence Base for Health Policy in Viet Nam Project (VINE) (Principal Investigator) |
| | This project aimed to estimate the burden of diseases of Vietnam |
| 2007-2009 | Developing a tool measuring quality of life for the elderly in Vietnam |
| | This study aimed to adapt the World Health Organization Quality of Life (WHOQOL) to Vietnam context. |

**Teaching experience**

2005- 2017:

-Lecturer in Biostatistics and Data Analysis in Hanoi University of Public Health, Hanoi, Vietnam (1200 contact hours)

- Second -supervisors for Master of Public Health (6 students)
- Supervisor for Bachelor of Public Health (4 students)

**Award**

09.2017: PhD Programme of Health Science, University of Basel

Top-up stipend of 7,000 CHF for extending PhD work 2017-2018

09.2014: Swiss Government Excellence Scholarship for Foreign Scholar (ESKAS)

Stipend of 69'120 CHF for PhD fellowship in Switzerland (2014-2017)

09.2011: President's Emergency Plan For AIDS Relief

US$ 5000 for fellowship for Summer course in University of California, The United States of America

09.2006: The University Commission for Development

Stipend of €12'000 for Master degree fellowship in Belgium 2006-2007

**Presentation at Scientific meetings**

| **Date (location)** | **Title (Name of the conference)** |
|---|---|
| 22-23 November 2017 | Poster |
| Basel, Switzerland | Association between ambient air pollution and length of hospital stay in Hanoi children (Swiss Public Health Conference ) |
| 1-4 September 2016 | Poster |
| Rome, Italia | Association between particulate matter and hospitalization for pneumonia in Hanoi children (28$^{th}$ International Society of Environmental Epidemiology (poster presentation) |
| 11-13 May 2011 | Oral presentation |
| Danang, Vietnam | Burden of drowning in Children in Vietnam (World conference on drowning prevention) |
| 23-27 November 2010 | Oral presentation |
| Bali, Indonesia | Burden of disease and injury in Vietnam 2008 (42$^{nd}$ Asia Pacific Academic Consortium for Public Health) |

**Publication**

**Articles**

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**Nhung TT Nguyen**, Tran LK, Bui LN, et al. Estimation of Vietnam national burden of disease 2008. *Asia-Pacific journal of public health* 2014;26(5):527-35. doi: 10.1177/1010539513510556.

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Linh N Bui, **Nhung TT Nguyen**, Tran LK, et al. Risk factors of burden of disease: a comparative assessment study for evidence-based health policy making in Vietnam. *The Lancet* 2013;381:S23. doi: 10.1016/S0140-6736(13)61277-5 (Meeting abstract)

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**Nhung TT Nguyen**, Bui TT Quyen, Cuong V Pham. Burden of disease due to premature death in Chililab – Chi linh, Hai Duong. *Vietnam Journal of Public Health* 2012;24(24):24-31 (in Vietnamese).

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**Nhung TT Nguyen**, Long K Tran, Linh N Bui, et al. Preliminary findings on burden of disease and injury in Vietnam, 2006. *Viet Nam Journal of Public Health* 2009;20(20):4-10 (in Vietnamese).

Huong T Nguyen, Ha TH Le, **Nhung TT Nguyen**, et al. Preliminary finding of validity and reliability of quality of life in the Vietnamese elder. *Journal of Practical Medicine* 2009;675(9) (in Vietnamese)

**Report**

**Nguyen TT Nhung**, Bui Ngoc Linh, Tran Khanh Long, Theo Vos, Ngo Duc Anh, Nguyen Thanh Huong (2011). Comparative risk assessment for risk factors in Vietnam, *Medical Publishing House, Hanoi 2014.*

**Nguyen TT Nhung**, Bui Ngoc Linh, Tran Khanh Long, Theo Vos, Ngo Duc Anh, Nguyen Thanh Huong (2011). Burden of Disease and Injury in Vietnam 2008, *Medical Publishing House, Hanoi 2011.*

**Course accomplished during doctoral training**

| Title of lecture/workshop | Offered by | Time | ETCs |
|---|---|---|---|
| Chronic disease and molecular epidemiology | Swiss TPH | Autumn semester 2014 | 1 |
| Data Analysis in Epidemiology | Swiss TPH | Autumn semester 2014 | 2 |
| Epidemiological exposure assessment | Swiss TPH | Autumn semester 2014 | 1 |
| Epidemiology concept | Swiss TPH | Autumn semester 2014 | 3 |
| Statistical modelling | Swiss TPH | Autumn semester 2014 | 2 |
| Key Issues In International and Public health | Swiss TPH | Autumn semester 2014 | 2 |
| Programming with Stata | Swiss TPH | Autumn semester 2014 | 1 |
| GIS for Public Health | SSPH+, Basel | 11-13.11.2014 | 1.5 |
| Missing data in epidemiology: implications and analysis techniques | SSPH+ Basel | 27-29.04. 2015 | 1 |
| Systematic Reviews and Meta-Analysis: a Practical Approach | SSPH+, Bern | 18-20.05.2015 | 1 |
| Multilevel Modelling: Analysis of Clustered Data | SSPH+ Basel | 1-3.06.2015 | 1 |
| Flexible Parametric Survival Models | SSPH+ Bern | 21-23.01.2016 | 1.5 |
| Observational epidemiology workshop: advanced methods for data and exposure-response analyses | SSPH+ Basel | 5- 9.09.2016 | 2 |
| The Art of Fundraising (Transferable skills) | PPHS | 12 and 19.10.2016 | 12 hours |
| How to prepare a job application inside or outside of academia in Health Sciences (Transferable skills) | PPHS | 22 and 29.05.2017 | 1 |
| European Education Program in Epidemiology | | 2-7.07. 2017 | 3 |
| Walking in the Editors' Shoes: Journal editing and peer reviewing for young researchers in health sciences | | 14 and 28.11.2017 | 1 |
| Health systems | Swiss TPH | Autumn semester 2017 | 2 |
| **Total** | | | **26 credits** |