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

Nguyen Thi Trang Nhung\textsuperscript{a,b,c}, Christian Schindler\textsuperscript{a,b}, Tran Minh Dien\textsuperscript{d}, Nicole Probst-Hensch\textsuperscript{a,b}, Laura Perez\textsuperscript{a,b,1}, Nino Künzli\textsuperscript{a,b}

\textsuperscript{a} Swiss Tropical and Public Health Institute, Basel, Switzerland
\textsuperscript{b} University of Basel, Basel, Switzerland
\textsuperscript{c} Hanoi University of Public Health, Hanoi, Viet Nam
\textsuperscript{d} Vietnam National Children’s Hospital, Hanoi, Viet Nam

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 g/m\textsuperscript{3}) in the 7-day-average level of NO\textsubscript{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\textsubscript{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 g/m\textsuperscript{3} increase of PM with aerodynamic diameter < 2.5 \mu m (PM\textsubscript{2.5}) in children, age 1–4; and a 6.0% increase of asthma hospitalization per 5.1 ppb increase of 24-h NO\textsubscript{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.

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
0160-4120/ © 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
Northeast region (Ministry of Natural Resources and Environment, industry, and construction activities. Besides that coal mining in Quang

The main sources of air pollution in Vietnam are traffic, industry, and construction activities. Besides that coal mining in Quang

sulfur dioxide (SO2), and PM10 concentrations were frequently above

respiratory infections have not been studied in Northern Vietnam. Thus,

et al., 2015; Hanieh et al., 2015), and ambient air pollution (Le et al.,

et al., 2009), termination of breast feeding in early infancy (Anders

2007). Nonetheless, these associations and the related impact on lower

et al., 2015). 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 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 NO2, ozone (O3), sulfur dioxide (SO2), and PM10 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/m3 for PM10, and of 36.1 μg/m3 for PM2.5 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 PM2.5 by using MODIS satellite data has shown that monthly mean values of PM2.5 ranged from 50 μg/m3 to 100 μg/m3 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/km2 (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/km2 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 (21°02′56.05″N, 105°05′25.85″E) and the Lang Ha station (21°01′13.47″E, 105°04′24.10″E). Data were averaged by station and calendar day to provide 24-h means of PM10, PM2.5 and PM1 (air borne particulates with an aerodynamic diameter < 1 μm), NO2, nitrogen oxides (NOx), SO2, 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 O3, 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/m3. Since Lang ha station used ppb as a unit for measuring SO2, we converted these concentrations from ppb into μg/m3 by using the WHO conversion factor, 1 ppb = 2.62 μg/m3 at 25 Degree Celsius and 1013 mb (Danish Centre For Environment And Energy, n.d.).

We imputed missing daily concentration data of PM10 and SO2 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 PM1 and PM2.5 were only monitored in Nguyen Van Cu station, we used PM10 data from Lang Ha station along with data for other pollutants to impute the missing data for PM1 and PM2.5.

Daily averages of SO2 and PM10 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 °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 1600 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...
The outcomes selected in this paper were daily counts of pneumonia (International Classification Diseases 10th revision (ICD10 code J12-118), 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 function plots (PACF) of the residuals were used to determine the appropriate degrees of freedom of the spline function to minimize residual

\[ \text{risk ratio (RR)} \]


<table>
<thead>
<tr>
<th>Outcome by age group</th>
<th>Number of admissions</th>
<th>Daily Mean (SD)</th>
<th>Daily mean (SD) in warm season (April–October)</th>
<th>Daily mean (SD) in cold season (November–February)</th>
<th>Number of admissions</th>
<th>Daily Mean (SD)</th>
<th>Daily mean (SD) in warm season (April–October)</th>
<th>Daily mean (SD) in cold season (November–March)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia (ICD10: J12-J18)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>25,016</td>
<td>8.5(4.7)</td>
<td>8.3(4.3)</td>
<td>8.9(5.1)</td>
<td>18,908</td>
<td>9.2(5.0)</td>
<td>8.7(4.05)</td>
<td>10.25(5.5)</td>
</tr>
<tr>
<td>1–5 years</td>
<td>14,576</td>
<td>5.0(3.1)</td>
<td>5.1(3.1)</td>
<td>4.9(3.2)</td>
<td>11,421</td>
<td>5.6(3.3)</td>
<td>5.6(3.2)</td>
<td>5.7(3.4)</td>
</tr>
<tr>
<td>All age 0–17</td>
<td>40,733</td>
<td>14.0(6.8)</td>
<td>13.7(6.3)</td>
<td>14.2(7.4)</td>
<td>31,233</td>
<td>15.0(7.1)</td>
<td>14.6(6.6)</td>
<td>16.3(7.8)</td>
</tr>
<tr>
<td>Bronchitis and asthma (ICD10: J20, J21, J45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>9195</td>
<td>3.1(2.4)</td>
<td>3.1(2.4)</td>
<td>3.1(2.4)</td>
<td>7471</td>
<td>3.2(2.5)</td>
<td>3.5(2.4)</td>
<td>3.9(2.5)</td>
</tr>
<tr>
<td>1–5 years</td>
<td>6799</td>
<td>2.3(1.8)</td>
<td>2.4(1.9)</td>
<td>2.3(1.9)</td>
<td>5649</td>
<td>2.8(1.9)</td>
<td>2.8(2.0)</td>
<td>2.8(1.9)</td>
</tr>
<tr>
<td>All age 0–17</td>
<td>17,118</td>
<td>5.9(3.6)</td>
<td>5.9(3.6)</td>
<td>5.9(3.6)</td>
<td>13,994</td>
<td>6.9(3.6)</td>
<td>6.6(3.7)</td>
<td>7.2(3.5)</td>
</tr>
</tbody>
</table>

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 PM10 and SO2 measurements are available for the period 2007–2014 while PM1, NO2, NO, SO2, CO and O3 measurements are available for 2009–2014.

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 PM10, NO2, and CO were 93.0 μg/m3, 49.0 μg/m3, and 2656.0 μg/m3, respectively. Generally, concentrations were higher in the cold season, except for O3 (Table 2). Daily means of PM1 were strongly correlated with daily means of PM10 ( spearman rank correlation coefficient, \( r = 0.7 \)) and of PM2.5 ( \( r = 0.9 \)). In contrast, the temporal correlations between PM and gaseous pollutants were lower (0.06 ≤ |r| ≤ 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
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 SO2 and O3. The strongest effect estimate was observed for NO2 (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 NO2 of one IQR (i.e., 21.9 μg/m3).

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 NO2 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 2
Overall and seasonal distribution of daily pollutant concentrations and meteorological data (mean (sd), minimum, maximum and interquartile ranges), Hanoi.

<table>
<thead>
<tr>
<th>Pollutants</th>
<th>Mean(SD)</th>
<th>Median</th>
<th>Minimum - Maximum</th>
<th>Interquartile range</th>
<th>Missing day(%)</th>
<th>Season mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Warm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(April–October)</td>
</tr>
<tr>
<td>24 h PM2.5 (μg/m³)</td>
<td>92.0(59.0)</td>
<td>77.6</td>
<td>6.1–402.5</td>
<td>66.5</td>
<td>5.8%</td>
<td>85.9</td>
</tr>
<tr>
<td>24 h PM1.0 (μg/m³)</td>
<td>56.1(33.3)</td>
<td>48.0</td>
<td>6.0–213.0</td>
<td>39.4</td>
<td>7.7%</td>
<td>47.4</td>
</tr>
<tr>
<td>24 h PM0.3 (μg/m³)</td>
<td>43.7(29.1)</td>
<td>35.6</td>
<td>6.1–186.9</td>
<td>33.8</td>
<td>8.1%</td>
<td>33.2</td>
</tr>
<tr>
<td>24 h SO2 (μg/m³)</td>
<td>32.4(33.7)</td>
<td>17.0</td>
<td>1.0–149.7</td>
<td>40.6</td>
<td>6.5%</td>
<td>27.7</td>
</tr>
<tr>
<td>24 h NO2 (μg/m³)</td>
<td>49.0(18.0)</td>
<td>47.2</td>
<td>1.9–122.2</td>
<td>21.9</td>
<td>3.3%</td>
<td>45.3</td>
</tr>
<tr>
<td>24 h NOx (μg/m³)</td>
<td>86.4(27.9)</td>
<td>84.4</td>
<td>1.9–227.5</td>
<td>36.7</td>
<td>3.1%</td>
<td>80.6</td>
</tr>
<tr>
<td>24 h CO (μg/m³)</td>
<td>2656.1(721.5)</td>
<td>2649.4</td>
<td>51.7–5152.4</td>
<td>986.3</td>
<td>3.1%</td>
<td>2626.8</td>
</tr>
<tr>
<td>8 h-moving average O3 (μg/m³)</td>
<td>92.9(75.1)</td>
<td>69.8</td>
<td>3.0–431.5</td>
<td>85.2</td>
<td>21.4%</td>
<td>96.8</td>
</tr>
<tr>
<td>24 h-maximum O3 (μg/m³)</td>
<td>121.1(91.2)</td>
<td>93.2</td>
<td>3.6–554.9</td>
<td>109.4</td>
<td>21.4%</td>
<td>124.0</td>
</tr>
<tr>
<td>Meteorological</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>23.9(3.3)</td>
<td>25.2</td>
<td>7–34</td>
<td>0.0%</td>
<td></td>
<td>27.4</td>
</tr>
<tr>
<td>Relative humidity (%)</td>
<td>82.4(7.7)</td>
<td>83.2</td>
<td>50.3–98</td>
<td>0.0%</td>
<td></td>
<td>82.9</td>
</tr>
<tr>
<td>Wind speed(m/s)</td>
<td>13.0(5.5)</td>
<td>11.5</td>
<td>0.2–4.5</td>
<td>0.0%</td>
<td></td>
<td>1.3</td>
</tr>
</tbody>
</table>

Daily PM1.0 and SO2 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.

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.

<table>
<thead>
<tr>
<th>Outcome by pollutant</th>
<th>All ages(0–17)</th>
<th>1–5 Years of age</th>
<th>&lt; 1 Year of age</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR 95%CI</td>
<td>RR 95%CI</td>
<td>RR 95%CI</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>Lower</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM0.5</td>
<td>1.058</td>
<td>1.028</td>
<td>1.090</td>
</tr>
<tr>
<td>PM2.5</td>
<td>1.053</td>
<td>1.019</td>
<td>1.088</td>
</tr>
<tr>
<td>PM1.0</td>
<td>1.057</td>
<td>1.020</td>
<td>1.095</td>
</tr>
<tr>
<td>SO2</td>
<td>1.019</td>
<td>0.948</td>
<td>1.096</td>
</tr>
<tr>
<td>NO2</td>
<td>1.061</td>
<td>1.025</td>
<td>1.098</td>
</tr>
<tr>
<td>NOx</td>
<td>1.046</td>
<td>1.009</td>
<td>1.085</td>
</tr>
<tr>
<td>CO</td>
<td>1.040</td>
<td>1.001</td>
<td>1.080</td>
</tr>
<tr>
<td>8 h average O3</td>
<td>1.024</td>
<td>0.973</td>
<td>1.077</td>
</tr>
<tr>
<td>24 h maximum O3</td>
<td>1.022</td>
<td>0.969</td>
<td>1.077</td>
</tr>
<tr>
<td>Bronchitis and asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM0.5</td>
<td>1.008</td>
<td>0.971</td>
<td>1.047</td>
</tr>
<tr>
<td>PM2.5</td>
<td>1.025</td>
<td>0.981</td>
<td>1.071</td>
</tr>
<tr>
<td>PM1.0</td>
<td>1.058</td>
<td>1.008</td>
<td>1.111</td>
</tr>
<tr>
<td>SO2</td>
<td>1.038</td>
<td>0.927</td>
<td>1.163</td>
</tr>
<tr>
<td>NO2</td>
<td>1.055</td>
<td>1.004</td>
<td>1.108</td>
</tr>
<tr>
<td>NOx</td>
<td>1.056</td>
<td>1.004</td>
<td>1.111</td>
</tr>
<tr>
<td>CO</td>
<td>0.991</td>
<td>0.942</td>
<td>1.044</td>
</tr>
<tr>
<td>8 h average O3</td>
<td>1.013</td>
<td>0.943</td>
<td>1.087</td>
</tr>
<tr>
<td>24 h maximum O3</td>
<td>1.032</td>
<td>0.960</td>
<td>1.110</td>
</tr>
</tbody>
</table>

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 PM2.5, PM1.0, SO2, NO2, NOx, CO, 8 h average O3, 24 h maximum O3 to the period 2007–2014, risk ratios of PM2.5, PM1.0, SO2, NO2, NOx, 8 h average O3 to the period 2009–2014.

⁎⁎⁎ p < 0.001.
⁎⁎ p < 0.01.
⁎ p < 0.05 (Wald χ² test).
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\textsubscript{10} and PM\textsubscript{1}, respectively, from single pollutants models (left most estimate) and two-pollutant models with adjustment for PM\textsubscript{10}, PM\textsubscript{2.5}, SO\textsubscript{2}, NO\textsubscript{2}, CO and 8 h average O\textsubscript{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\textsubscript{10} and SO\textsubscript{2} refer to the period 2007–2014, risk ratios of PM\textsubscript{2.5}, PM\textsubscript{1}, SO\textsubscript{2}, NO\textsubscript{2}, CO, 8 h average O\textsubscript{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 NO2, NOx, 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 NO2 were not only the largest (per IQR), but also the most stable one across all two-pollutant models. In contrast, effects of PM10, PM2.5 and PM1 all dropped and lost statistical significance after inclusion of NO2. Pneumonia (all ages) effect estimates of PM10 were also substantially reduced after inclusion of O3 but remained stable in the age group 1–5 year. Results for PM1 were somewhat less sensitive to the inclusion of other pollutants, except the highly correlated PM2.5, across all age groups and outcomes. Results for bronchitis and asthma and O3 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 PM10 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 NO2 and the three measures of PM. We did not find statistically significant associations between O3 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 NO2 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.
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/m³) 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/m³ to 122.2 μg/m³.

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/m³) 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, Santos et al. (2012) reported a 5.9% and 9.4% increase of asthma and pneumonia hospitalizations, respectively, per 1000 μg/m³ 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_{2.5} 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 NO2 findings for pneumonia are though a clear argument for the use of NO2 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 (PM1, PM2.5, CO, and O3) 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 NO2 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.

References


Danish Centre For Environment And Energy (n.d.). Conversion between μg/m3 and ppb, (accessed 17 December 2015).


Gilliland, F.D., 2009. Outdoor air pollution, genetic susceptibility, and asthma management: opportunities for intervention to reduce the burden of asthma. Pediatrics 123(Suppl. 3), S168–173.


Karr, C., et al., 2007. E

Karr, C., et al., 2007. E


Stafoggia, M., et al., 2016. Desert dust outbreaks in Southern Europe: contribution to
daily PM10 concentrations and short-term associations with mortality and hospital
admissions. Environ. Health Perspect. 124, 413–419.
Suzuki, M., et al., 2009. Association of environmental tobacco smoking exposure with an
increased risk of hospital admissions for pneumonia in children under 5 years of age
Thurston, G.D., et al., 2017. A joint ERS/ATS policy statement: what constitutes an ad-
Tian, L., et al., 2013. Ambient carbon monoxide associated with reduced risk of hospital
admissions for respiratory tract infections. Am. J. Respir. Crit. Care Med. 188,
1240–1245.
Wacholder, S., 1995. When measurement errors correlate with truth: surprising e
ff
ct

differential misclassi
fi

ation. Epidemiology 6, 157–161.
Winquist, A., et al., 2012. Comparison of emergency department and hospital admissions
data for air pollution time-series studies. Environ. Health 11.
Epidemiology 9, 495–503.
Zwozdziak, A., et al., 2016. Influence of PM1 and PM2.5 on lung function parameters in