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

Nguyen Thi Trang Nhung[a,b,c,*], Christian Schindler[a,b], Tran Minh Dien[d], Nicole Probst-Hensch[a,b], Laura Perez[a,b,1], Nino Künzli[a,b]

[a] Swiss Tropical and Public Health Institute, Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Hanoi University of Public Health, Hanoi, Viet Nam
[d] Vietnam National Children's Hospital, Hanoi, Viet Nam

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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.

* Corresponding author at: Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, P.O. Box, CH4002, Basel, Switzerland.
E-mail address: nhung.nguyen@swisstph.ch (N.T.T. Nhung).
[1] Laura Perez worked at the Swiss Tropical and Public Health Institute until June 2016. Present address of Laura Perez is Holeestrasse 149, 4054 Basel, Switzerland.

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(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 χ^2 test).

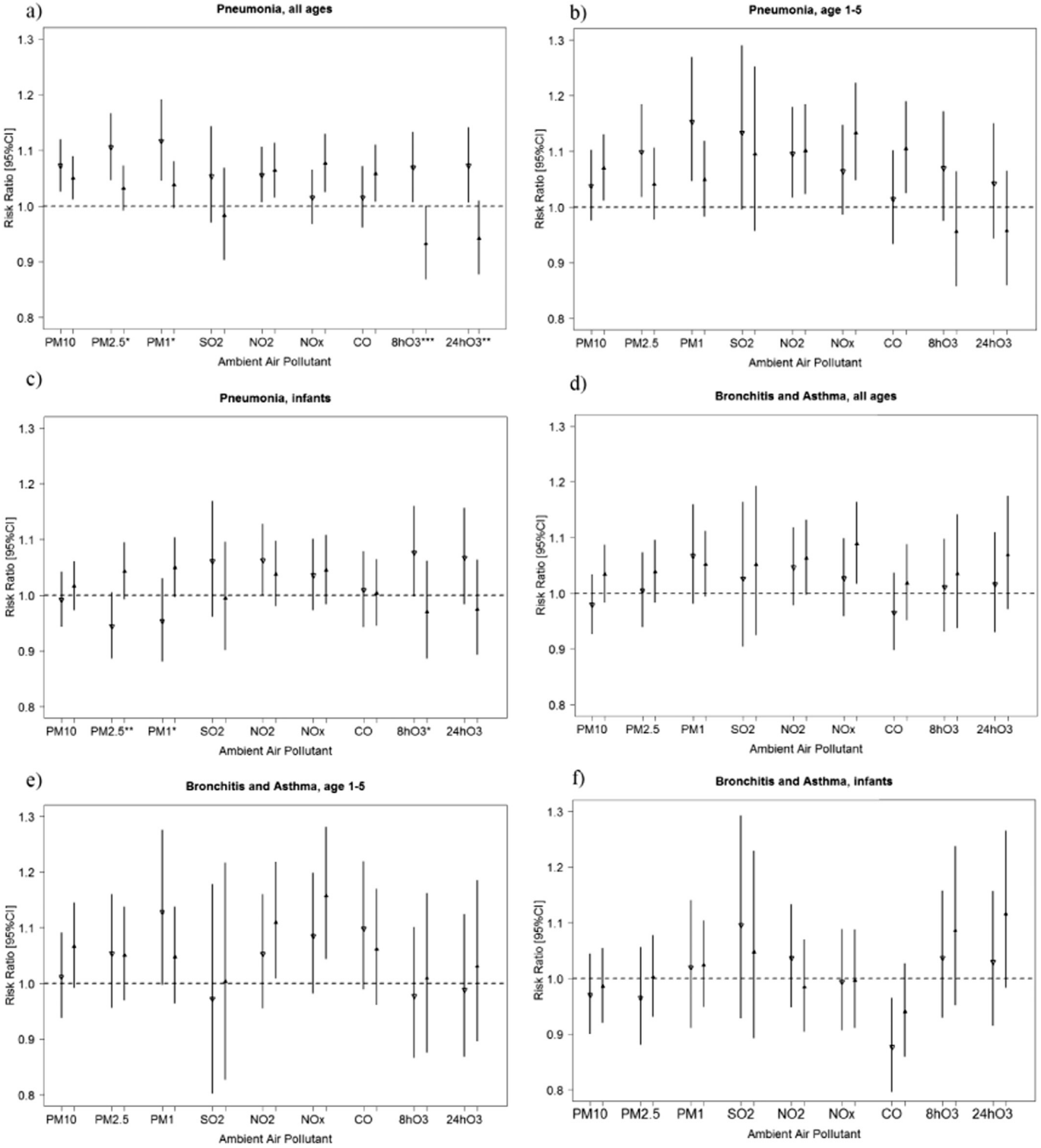

Fig. 1. Season –specific risk ratios per interquartile range increase in the seven-day moving average ambient air pollutant concentrations (lag 0–6) for a) Pneumonia, all ages, b) Pneumonia, age 1–5, c) Pneumonia, infants, d) Bronchitis and asthma, all ages, e) Bronchitis and asthma, age 1–5, f) Bronchitis 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-

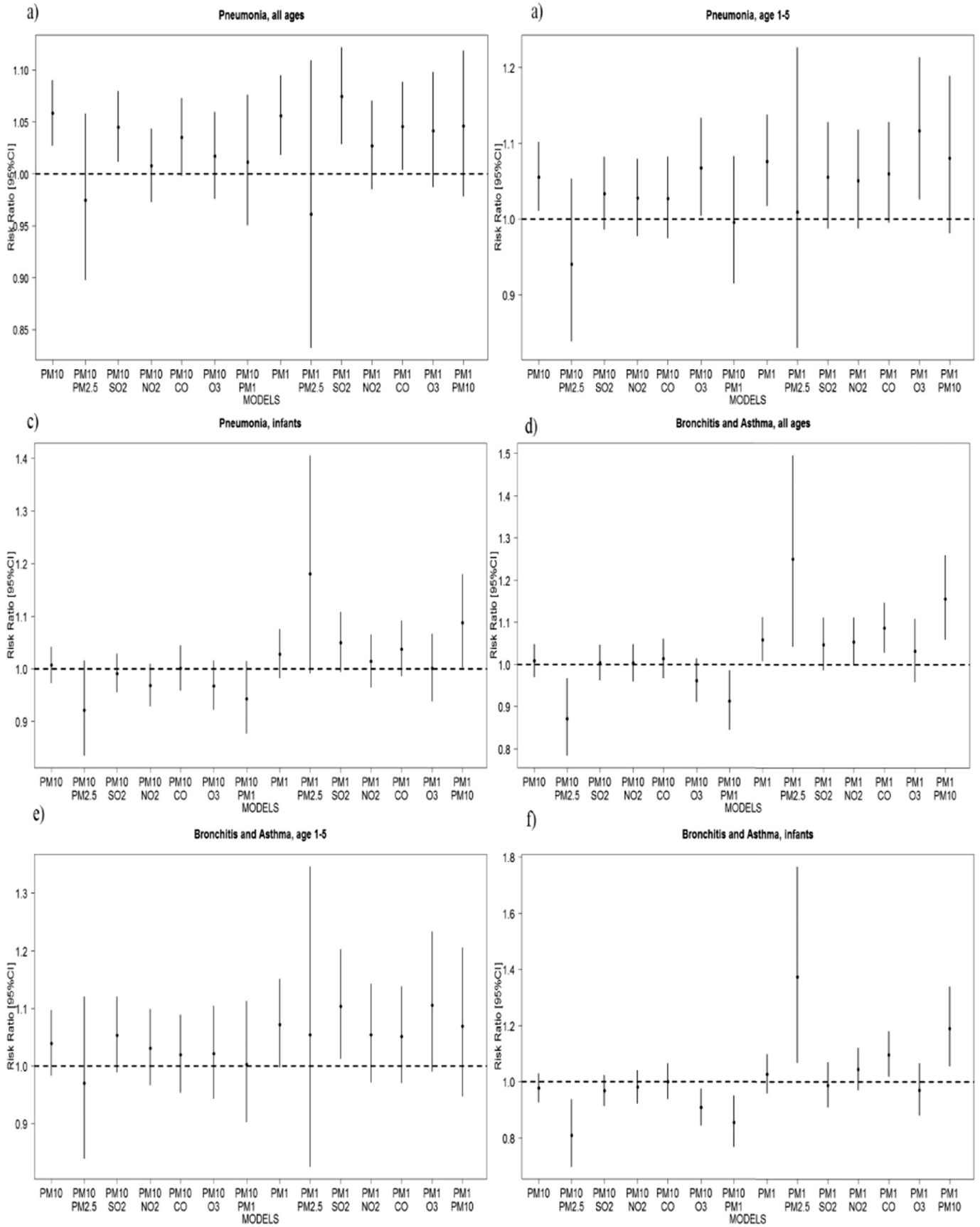

Fig. 2. Estimated risk ratios (with 95% confidence intervals) per one interquartile range of PM_{10} and PM_1, respectively, from single pollutants models (left most estimate) and two-pollutant models with adjustment for PM_{10}, $PM_{2.5}$, PM_1, SO_2, NO_2, CO and 8 h average O_3, for a) Pneumonia, 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.

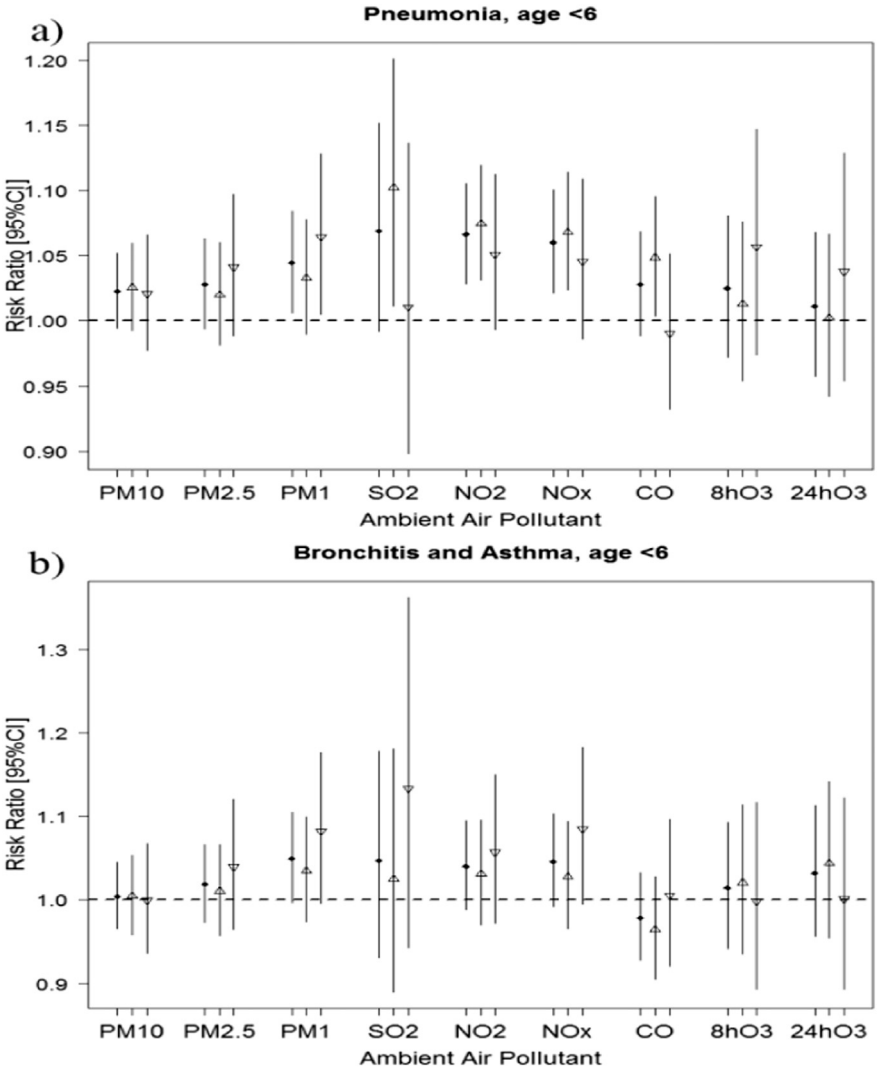

Fig. 3. Gender-specific risk ratios (with 95%-confidence intervals) per interquartile range of ambient air pollutants for a) Pneumonia in children age < 6 and b) Bronchitis and asthma at age < 6, Hanoi.
Filled Diamond: all children, triangle upward: males, triangle downward: females.
Risk ratios of PM_{10} 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.

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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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