Review

Ly M.T. Luong, Peter D. Sly, Phong K. Thai and Dung Phung*

Impact of ambient air pollution and wheeze-associated disorders in children in Southeast Asia: a systematic review and meta-analysis

https://doi.org/10.1515/reveh-2018-0079
Received November 21, 2018; accepted January 9, 2019; previously published online February 12, 2019

Abstract: Several systematic reviews have been conducted so far to examine the effect of air pollution on respiratory diseases, but there has not been a corresponding meta-analysis to estimate the effect sizes for wheeze-associated diseases/disorders, which is one of the leading causes of emergency department visits and hospitalizations for children worldwide. The aim of this review is to systematically evaluate the relationship between air pollution and risk of wheeze-associated disorders in children in Southeast Asia. We searched the relevant computerized databases (PubMed, EMBASE, Web of Science, Scopus and Cochrane library) for indexed publications up to July 2018. Finally, eight studies were qualified for performing a random-effect meta-analysis to compute the pooled effect sizes. The results show that each increase of 10 μg/m^3 in concentrations of $PM_{2.5}$, PM_1 was associated with 1–2% increase in risk of wheeze-associated disorders. Positive associations were found for PM_{10}, SO_2, NO_2, NO_x but no association was found for CO and O_3. We confirmed the strong effect of fine particulate matters on respiratory health and recommend an updated meta-analysis should be done when more studies are available.

Keywords: environment; health effect; paediatrics; respiratory; Southeast Asian nations.

***Corresponding author: Dung Phung,** Centre for Environment and Population Health, School of Medicine, Griffith University, Gold Coast, Queensland, Australia, E-mail: d.phung@griffith.edu.au
Ly M.T. Luong: Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia; Children's Health and Environment Program, The University of Queensland, Brisbane, Queensland, Australia; and Faculty of Environmental Sciences, VNU University of Science, Hanoi, Vietnam
Peter D. Sly: Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia; and Children's Health and Environment Program, The University of Queensland, Brisbane, Queensland, Australia
Phong K. Thai: Queensland Alliance for Environmental Health Science (QAEHS), The University of Queensland, Brisbane, Queensland, Australia

Introduction

Most countries in Southeast Asia are experiencing high levels of air pollution, especially in urban areas where the annual mean levels often exceed World Health Organization (WHO) limits 5–10 fold (1). Air pollution levels are at WHO target 3 ($PM_{2.5}$ 25–35 μg/m^3; PM_{10} 50–70 μg/m^3) in Vietnam, the Philippines and Myanmar and are at target 2 ($PM_{2.5}$ 15–25 μg/m^3; PM_{10} 30–50 μg/m^3) in Thailand and Indonesia compared to the WHO's air quality guideline for annual PM_{10} and $PM_{2.5}$ are 20 and 10 μg/m^3, respectively (2–4). In Vietnam, the air quality index levels was at 101–200 (unhealthy level for sensitive groups like children and elderly adults) on 40% and 60% of total monitoring days in Hanoi in 2013 and 2014 (5). Six cities in Myanmar have PM_{10} levels from 120 to 140 μg/m^3, $PM_{2.5}$ from 44 to 78 μg/m^3, ranked in top 3% of the most polluted cities in the world (6). Similarly, high concentration of particles and SO_2 pose serious environmental problems in Bangkok (7). In Southeast Asia, air pollution caused by forest fires and agricultural burning is also of concern, especially for Indonesia, Malaysia and Singapore (8, 9).

With such high level of air pollution, the effects of ambient air pollutants on the health of Southeast Asian populations are likely to be significant. There is a large body of evidence in the literature on the adverse effects of air pollutants on the respiratory system, especially in children and infants. These health effects vary from increased respiratory mortality (10–12) to respiratory morbidity including increased risk of inflammation such as asthma (13–15), allergic symptoms (16), acute respiratory (17–20), pneumonia and acute bronchitis (20–23), or decreased lung function (24, 25).

Ambient air pollution has been associated with increased respiratory morbidity and mortality, however, few studies have been carried out in Southeast Asia, where people are exposed to much higher levels of air pollution and might experience the greatest burden of diseases due to wheeze-associated diseases/disorders (26). Several systematic reviews have been conducted to examine the

effect of air pollution on respiratory diseases in children, but there has not been a corresponding meta-analysis to estimate the effect sizes for wheeze-associated diseases/disorders in Southeast Asian countries (27, 28). Wheezing is a high-pitched whistling sound made while breathing out and may be a symptom of a serious lung disease such as acute lower respiratory infection, asthma or other wheeze-associated disorders. Taken together, wheeze-associated diseases/disorders are the largest single cause of mortality and one of the leading causes of emergency department visits and hospitalizations for children worldwide (29–31).

The aim of this review is to systematically evaluate the impact of ambient air pollution on and the risk of wheeze-associated disorders in children (0–18 years old) in Southeast Asia.

Material and methods

Literature search strategy

This systematic review followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the recommendations of the meta-analysis of Observational Studies in Epidemiology (MOOSE) group (32, 33). A literature search of relevant computerized databases (PubMed, EMBASE, Web of Science, Scopus and Cochrane library) was performed on 24 July 2018. The search strategy comprised the relevant keywords of exposure (outdoor air pollutants), health outcome (wheeze-associated disorders), outcome measurements (health outcome) and population (Southeast Asia nations) (please see the search queries with relevant keywords in Supplementary material Table 1).

Selection criteria

The flow of studies through the review process is shown in Figure 1. Studies were included in this systematic review if they met the following criteria:

- Analytic studies quantitatively examined the association between air pollutants and health outcome of wheeze-associated disorders
- The subjects of the study are children up to 18 years old of age
- Provided quantitative results for the effects based on one of the following calculations: regression coefficient, percentage change, excess rate (ER), risk ratio (RR) and odds ratio (OR), standard error (SE) or and confidence interval (CI) of the effect size.
- Published in full-text in English.

Each study had to contain an outcome measure related to wheeze-associated disorders such as hospital admission, emergency room visit, prevalence, incidence, mortality for any symptom of wheeze-associated disorders. Exposure to air pollution was based on at least one air pollutant (PM_{10}, $PM_{2.5}$, PM_1, SO_2, NO_2, CO, O_3) (see Supplementary material Table 1).

Studies were excluded if they were:

- from the gray literature (unpublished or published in non-commercial form)
- not original research papers (e.g. commentary, communication, review)
- not studies in Southeast Asian countries
- not related to ambient air pollution (e.g. indoor, workplace, experiment, projected studies).

The selection of studies was carried out using a tier approach with sequential steps (Figure 1).

The initial search, after removing duplicates, was reviewed by the first reviewer (L.L.) on the basis of the title and abstract to check the inclusion and exclusion criteria. In order to avoid bias, eligible studies were assessed independently via Covidence (an online software for primary screening and data extraction developed by the Cochrane Community) by the first and second reviewers (L.L. and P.T.) to examine the full text of articles against the inclusion criteria. All selected studies and unsolved conflicts between the two reviewers were then discussed with the third reviewer (D.P.) for final decisions before extracting data by both L.L. and P.T.

Quality assessment

To evaluate the quality of the selected studies, a criteria for quality assessment was modified from the criteria recommended by the BioMed Central for study assessment (34, 35) (see Supplementary material Table 2). The criteria comprise: (i) Sources of the information; (ii) Study design; (iii) Study results; and (iv) Study discussion.

A score scheme of 20 items corresponding to four assessment criteria was developed to evaluate each study. The quality score of each study could range from 1 to 30 (see Supplementary material Table 2).

Data extraction

The data extracted from each included study comprised: Citation information (first author last name and publication year, location in which the study was performed); Study setting (study design and time-span, age of population); Exposure (pollutant, mean concentration, unit of increment, and controlled variables); Outcome (health outcome/diagnosis, total events, day lags of the effect, outcome variables).

Data synthesis

We performed a random-effect meta-analysis to compute the pooled effect sizes of ambient air pollutants on wheeze-associated disorders using the data obtained from the higher-quality studies (score >20, 75% of the total maximum score). As indicated in Supplementary material Table 3, the higher-quality studies were published in peer review journals, had higher scores in study design (cohort/panel or time series/case-crossover study) and validation of results answering the research questions with presented measurements such as

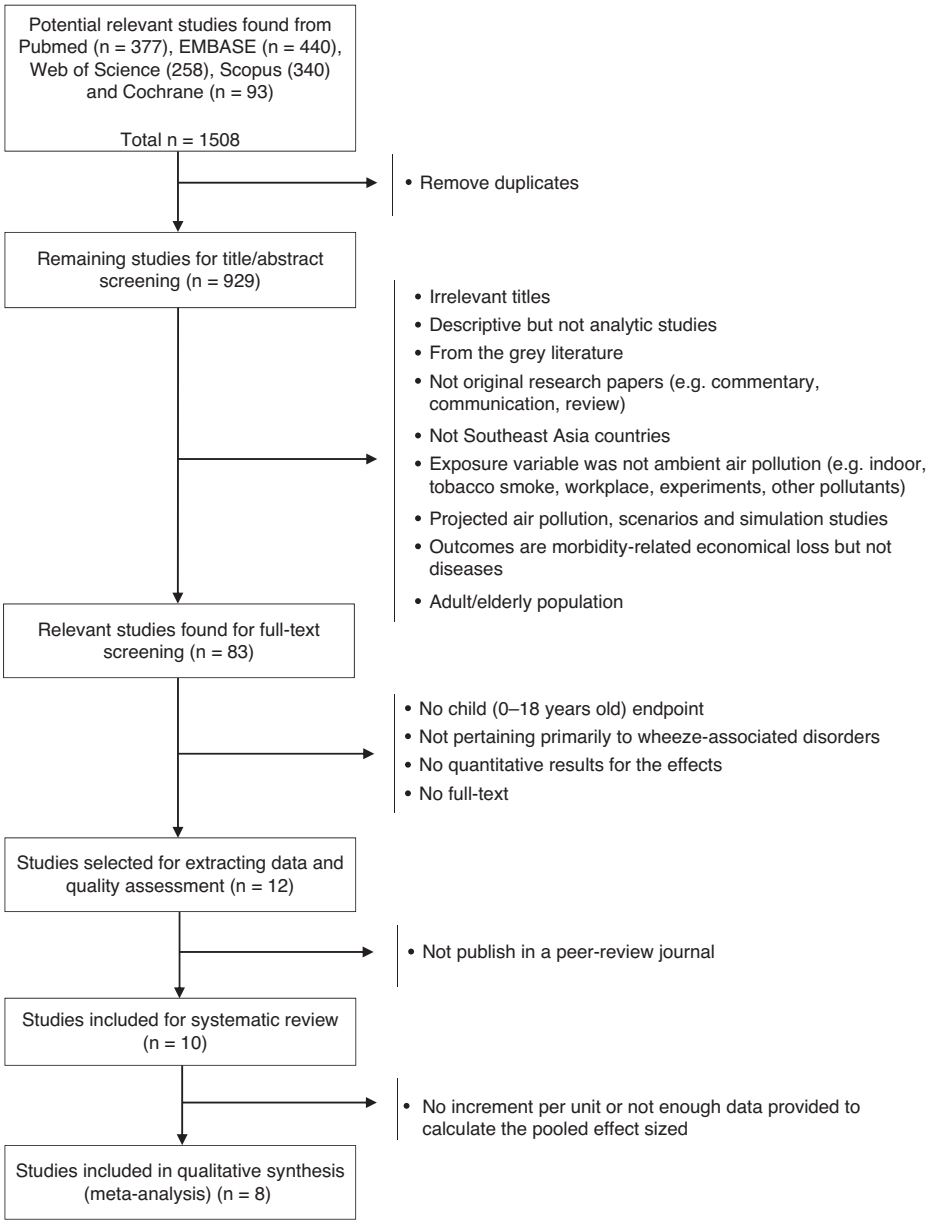

Figure 1: Flow diagram for inclusion and exclusion of studies.

ER/OR/RR per units of increment and 95% CI. The lower-quality studies (score <20) were included in a sensitivity analysis to determine influence on the pooled effects.

Before computing pooled effect size for each pollutant, effect estimates from studies reported in form of ER were converted to RR by formula: RR = 1 + ER and OR was considered the same as RR. If the studies reported effect estimate per U unit of pollutant, the RR_{10} for each increase of 10 unit of pollutant was calculated by:

$$RR_{10} = RR^{\frac{10}{U}}$$

where U is the units of increment used in the original study.

For studies used mg/m^3, ppm, ppb for the unit of measurement or unit of increment, all estimate RR_{10} were converted to μg/m^3.

For studies where values were not presented in the article or in supplementary documents, we contacted the authors for additional information. Each single city in a multi-city study and each sub-group defined by age, diagnosis, health outcome or season was included one by one as an independent study. The pooled effect sizes were computed for every single lag and cumulative lag provided in individual studies for each air pollutant separately if at least three individual estimates were available (27, 36).

To explore the heterogeneity between studies in the pooled analyses we used the coefficient of inconsistency (I^2) recommended by Higgins et al. (37) which can provide the percentage of total variation among studies due to heterogeneity (37). The heterogeneity degree ranges from 0 to 100% where they represent a result of low (<25%), moderate (25–75%) and high (>75%) heterogeneity. Because studies were performed in different populations which may produce

Table 1: Summaries of 10 studies included in the systematic review.

Study citation information and setting				Exposure					Outcome				
												Outcome variable	
Authors (year)	Location	Study design time-span	Population (years old)	Pollutant	Mean concentration	Unit of increment	Unit of measurement	Controlled variables	Health outcome/ diagnosis	Total events[a]	Lag (days)	ER/OR/RR (95% CI)	RR_{10} (95% CI)
Chew et al. (1999)	Singapore	Time series 1990–1994	3–12					Wind speed, temperature DOW	Admission and ER visit	30,312		ER (SD)	RR (95% CI)
				TSP	51.2	20	µg/m³				1	5.80 (1.46)	1.029 (1.015–1.043)
				SO_2	38.1	20	µg/m³		Asthma		1	2.90 (0.81)	1.014 (1.006–1.022)
				NO_2	18.9	15	µg/m³				1	0.76 (0.43)	1.005 (0.999–1.010)
Vichit-Vadakan et al. (2001)	Thailand	Panel study 1996	8–12					Temperature, humidity,	Incidence rate	28		OR (95% CI)	OR (95% CI)
				PM_{10}	104	45	µg/m³	DOW,	Lower		0–4	1.29 (1.16–1.43)	1.058 (1.034–1.083)
				$PM_{2.5}$	56	26	µg/m³	age, sex, education, respiratory condition, air condition	respiratory infection		0–4	1.11 (0.96–1.29)	1.041 (0.984–1.103)
Aekplakorn et al. (2003)	Thailand	Cohort 1997–1998	6–14					Time, temperature,	Incidence rate	231		OR (95% CI)	OR (95% CI)
											0	1.00 (0.93–1.07)	1.00 (0.93–1.07)
				PM_{10}	34.3	10	µg/m³	wind speed,	Lower		0	1.02 (0.93–1.10)	1.02 (0.93–1.10)
				$PM_{2.5}$	25.31	10	µg/m³	relative	respiratory		0	1.00 (0.94–1.06)	1.00 (0.94–1.06)
				SO_2	18.59	10	µg/m³	humidity	infection		1	0.90 (0.83–0.97)	0.90 (0.83–0.97)
				SO_2	18.59	10	µg/m³				2	0.96 (0.90–1.02)	0.96 (0.90–1.02)
				SO_2	18.59	10	µg/m³				3	0.98 (0.92–1.04)	0.98 (0.92–1.04)
				SO_2	18.59	10	µg/m³				0–3	0.91 (0.83–1.00)	0.91 (0.83–1.00)
				SO_2	18.59	10	µg/m³				0–4	0.90 (0.81–1.00)	0.90 (0.81–1.00)
				SO_2	18.59	10	µg/m³				0–5	0.89 (0.80–1.00)	0.89 (0.80–1.00)
				SO_2	18.59	10	µg/m³						
Hong et al. (2004)	Indonesia	Cross-sectional 2001	0–12	(1) Area 1				Age, number of	Prevalence rate	27	NA	OR (95% CI)	OR (95% CI)
												1.18 (0.46–3.01)	1.022 (0.904–1.154)
				PM_{10}	102.9	76.8	µg/m³	children				1.18 (0.46–3.01)	NA
				NO_2	16.8	0	µg/m³	in the	Wheezing			1.18 (0.46–3.01)	1.001 (0.997–1.004)
				CO	4.4	2.8	mg/m³	household, income, floor area, cooking fuel, household smoking	asthma				
			0–12										
				(2) Area 2						25			
				PM_{10}	73.7	47.6	µg/m³					0.85 (0.35–2.08)	0.966 (0.802–1.166)
				NO_2	24.6	7.8	µg/m³					0.85 (0.35–2.08)	0.812 (0.260–2.557)
				CO	2.9	1.3	mg/m³					0.85 (0.35–2.08)	0.999 (0.992–1.006)

Table 1 (continued)

Study citation information and setting				Exposure					Outcome				
												Outcome variable	
Authors (year)	Location	Study design time-span	Population (years old)	Pollutant	Mean concentration	Unit of increment	Unit of measurement	Controlled variables	Health outcome/ diagnosis	Total events[a]	Lag (days)	ER/OR/RR (95% CI)	RR_{10} (95% CI)
Langkulsen et al. (2006)	Thailand	Cross-sectional 2004	10–15	(1) Area 1 PM_{10}	65	18	µg/m³	Control area	prevalence rate	40	NA	OR (95% CI) 2.44 (1.21–4.93)	OR (95% CI) 1.641 (1.112–2.426)
			10–15	(2) Area 2 PM_{10}	67.5	20.5	µg/m³		NSRD and PCP	55		2.6 (1.38–4.91)	1.594 (1.170–2.172)
			10–15	(3) Area 3 PM_{10}	52.2	5.2	µg/m³			33		1.57 (0.76–3.25)	2.381 (0.590–9.647)
Vichit-Vadakan et al. (2008)	Thailand	Time series 1999–2003	<5	PM_{10}	52.1	10	µg/m³	Temperature, relative humidity, day of week, public holidays	Mortality Lower respiratory infection	1826[a]	0–1	ER (95% CI) 7.7 (–3.6 to 20.3)	RR (95% CI) 1.077 (0.964–1.203)
Mehta et al. (2013)	Vietnam	Case-crossover 2003–2005	<5	(1) Overall:				Rainfall, temperature, humidity, season	Hospital admission Acute lower respiratory infection	15,717		ER (95% CI)	RR (95% CI)
				PM_{10}	73.19	10	µg/m³				1–6	–1.1 (–2.31 to 0.12)	0.989 (0.977–1.001)
				O_3	75.03	10	µg/m³				1–6	–1.96 (–3.25 to 0.64)	0.980 (0.968–1.006)
				NO_2	22.1	10	µg/m³				1–6	–1.08 (–5.14 to 3.17)	0.989 (0.949–1.032)
				SO_2	21.58	10	µg/m³				1–6	2.61 (–1.49 to 6.87)	1.026 (0.985–1.069)
			<5	(2) Dry season						6269			
				PM_{10}	83.64	10	µg/m³				1–6	1.25 (–0.55 to 3.09)	1.013 (0.995–1.031)
				O_3	91.84	10	µg/m³				1–6	–0.79 (–2.67 to 1.13)	0.992 (0.973–1.011)
				NO_2	23.06	10	µg/m³				1–6	8.5 (0.8–16.79)	1.085 (1.008–1.168)
				SO_2	26.37	10	µg/m³				1–6	5.85 (0.44–11.55)	1.059 (1.004–1.116)
			<5	(3) Rainy season						9421			
				PM_{10}	63.1	10	µg/m³				1–6	–3.11 (–4.76 to –1.42)	0.969 (0.952–0.986)
				O_3	59	10	µg/m³				1–6	–2.98 (–4.78 to –1.14)	0.970 (0.952–0.989)
				NO_2	21.2	10	µg/m³				1–6	–5.15 (–9.94 to –0.1)	0.949 (0.901–0.999)
				SO_2	15	10	µg/m³				1–6	–2.3 (–8.25 to 4.41)	0.977 (0.918–1.044)

Table 1 (continued)

Study citation information and setting				Exposure					Outcome				
												Outcome variable	
Authors (year)	Location	Study design time-span	Population (years old)	Pollutant	Mean concentration	Unit of increment	Unit of measurement	Controlled variables	Health outcome/ diagnosis	Total events[a]	Lag (days)	ER/OR/RR (95% CI)	RR_{10} (95% CI)
Rahman et al. (2017)	Malaysia	Case-crossover 2006–2010	0–14	(1)				Age, gender, sex, nationality, race, diagnose, subtypes	Hospital admission			OR (95% CI)	OR (95% CI)
				PM_{10}	35–65	10	µg/m³		Acute bronchiolitis	5779	0	1.115 (1.093–1.138)	1.115 (1.093–1.138)
				CO	0–2439	10	µg/m³				0	0.894 (0.247–3.234)	0.894 (0.247–3.234)
				O_3	80–150	10	µg/m³				0	0.990 (0.978–1.002)	0.990 (0.978–1.002)
				NO_2[e]	0–103.4	10	µg/m³				0	1.007 (0.983–1.031)	1.007 (0.983–1.031)
			0–14	(2)					Asthma	5582	0	0.990 (0.989–0.992)	0.990 (0.989–0.992)
				PM_{10}	35–65	10	µg/m³				0	0.925 (0.862–0.992)	0.925 (0.862–0.992)
				CO	0–2439	10	µg/m³				0	1.000 (0.999–1.000)	1.000 (0.999–1.000)
				O_3	80–150	10	µg/m³				0	0.990 (0.989–0.992)	0.990 (0.989–0.992)
				NO_2	0–103.4	10	µg/m³				0	1.037 (1.034–1.040)	1.037 (1.034–1.040)
			0–14	(3)					Acute bronchitis	287	0	0.708 (0.543–0.923)	0.708 (0.543–0.923)
				PM_{10}	35–65	10	µg/m³				0	1.002 (1.000–1.004)	1.002 (1.000–1.004)
				CO	0–2439	10	µg/m³				0	1.012 (1.008–1.017	1.012 (1.008–1.017
				O_3	80–150	10	µg/m³						
				NO_2	0–103.4	10	µg/m³						
			0–14	(4)									
				PM_{10}	35–65	10	µg/m³		Unspecified	26	0	1.055 (1.051–1.059)	1.055 (1.051–1.059)
				CO	0–2439	10	µg/m³		Acute lower		0	0.726 (0.533–0.989)	0.726 (0.533–0.989)
				O_3	80–150	10	µg/m³		respiratory		0	0.998 (0.995–1.001)	0.998 (0.995–1.001)
				NO_2	0–103.4	10	µg/m³		infection		0	1.004 (0.999–1.010)	1.004 (0.999–1.010)
Nhung et al. (2018)	Vietnam	Time series 2007–2014	<1	(1)				DOW, holidays, daily mean temperature, relative humidity, wind speed, influenza epidemics	Hospital admission Bronchitis and asthma	9195		RR (95% CI)	RR (95% CI)
				PM_{10}	93	66.5	µg/m³				0–6	0.977 (0.927–1.030)	0.997 (0.989–1.004)
				$PM_{2.5}$	56.1	39.4	µg/m³				0–6	0.989 (0.931–1.050)	0.997 (0.982–1.012)
				PM_1	43.7	33.8	µg/m³				0–6	1.027 (0.961–1.097)	1.008 (0.988–1.028)
				SO_2	32.4	40.6	µg/m³				0–6	1.070 (0.925–1.237)	1.008 (0.988–1.028)
				NO_2	49	21.9	µg/m³				0–6	1.009 (0.945–1.077)	1.004 (0.974–1.034)
				NO_x	86.4	36.7	µg/m³				0–6	0.994 (0.929–1.063)	0.998 (0.980–1.017)
				CO	2656.1	986.3	µg/m³				0–6	0.908 (0.848–0.973)	0.999 (0.998–1.000)
				$8hO_3$	92.9	85.2	µg/m³				0–6	1.043 (0.949–1.147)	1.005 (0.994–1.016)
				$24hO_3$	121.1	109.4	µg/m³				0–6	1.057 (0.960–1.164)	1.005 (0.996–1.014)
			1–5	(2)						6799			
				PM_{10}	93	66.5	µg/m³				0–6	1.032 (0.897–1.080)	1.005 (0.984–1.012)
				$PM_{2.5}$	56.1	39.4	µg/m³				0–6	1.051 (0.986–1.121)	1.013 (0.996–1.029)
				PM_1	43.7	33.8	µg/m³				0–6	1.072 (0.998–1.151)	1.021 (0.999–1.042)
				SO_2	32.4	40.6	µg/m³				0–6	0.988 (0.832–1.173)	0.997 (0.956–1.040)
				NO_2	49	21.9	µg/m³				0–6	1.079 (1.004–1.160)	1.035 (1.002–1.070)
				NO_x	86.4	36.7	µg/m³				0–6	1.116 (1.035–1.203)	1.030 (1.009–1.052)
				CO	2656.1	986.3	µg/m³				0–6	1.077 (0.999–1.162)	1.001 (1.000–1.002)

Table 1 (continued)

Study citation information and setting				Exposure					Outcome				
												Outcome variable	
Authors (year)	Location	Study design time-span	Population (years old)	Pollutant	Mean concentration	Unit of increment	Unit of measurement	Controlled variables	Health outcome/ diagnosis	Total events[a]	Lag (days)	ER/OR/RR (95% CI)	RR_{10} (95% CI)
				$8hO_3$	92.9	85.2	µg/m³				0–6	0.985 (0.889–1.090)	0.998 (0.986–1.010)
				$24hO_3$	121.1	109.4	µg/m³				0–6	1.003 (0.903–1.114)	1.000 (0.991–1.010)
			0–17	(3)						17,118			
				PM_{10}	93	66.5	µg/m³				0–6	1.008 (0.971–1.047)	1.001 (0.996–1.007)
				$PM_{2.5}$	56.1	39.4	µg/m³				0–6	1.025 (0.981–1.071)	1.006 (0.995–1.018)
				PM_1	43.7	33.8	µg/m³				0–6	1.058 (1.008–1.111)	1.017 (1.002–1.032)
				SO_2	32.4	40.6	µg/m³				0–6	1.038 (0.927–1.163)	1.009 (0.982–1.038)
				NO_2	49	21.9	µg/m³				0–6	1.055 (1.004–1.108)	1.025 (1.002–1.048)
				NO_x	86.4	36.7	µg/m³				0–6	1.056 (1.004–1.111)	1.015 (1.001–1.029)
				CO	2656.1	986.3	µg/m³				0–6	0.991 (0.942–1.044)	1.000 (0.999–1.000)
				$8hO_3$	92.9	85.2	µg/m³				0–6	1.013 (0.943–1.087)	1.002 (0.993–1.010)
				$24hO_3$	121.1	109.4	µg/m³				0–6	1.032 (0.960–1.110)	1.003 (0.996–1.010)
Luong et al. (2018)	Vietnam	Time series 2010–2014	0–5	(1) Full year				Temperature, relative humidity, DOW, times, season	Wheeze associated disorder hospital admission (Acute bronchiolitis, unspecified acute lower respiratory infection, asthma, status asthmaticus)	6902		RR (95% CI)	RR (95% CI)
					46.9	10	µg/m³				0–5	0.994 (0.976–1.011)	0.994 (0.976–1.011)
				$24hO_3$	46.9	10	µg/m³				0	0.997 (0.982–1.013)	0.997 (0.982–1.013)
				$24hO_3$	46.9	10	µg/m³				1	1.005 (0.988–1.021)	1.005 (0.988–1.021)
				$24hO_3$	46.9	10	µg/m³				2	0.994 (0.978–1.011)	0.994 (0.978–1.011)
				$24hO_3$	46.9	10	µg/m³				3	1.002 (0.986–1.019)	1.002 (0.986–1.019)
				$24hO_3$	46.9	10	µg/m³				4	0.991 (0.974–1.008)	0.991 (0.974–1.008)
				$24hO_3$	46.9	10	µg/m³				5	1.005 (0.990–1.019)	1.005 (0.990–1.019)
				$24hO_3$									
			0–5	(2) Winter									
				$24hO_3$	42.4	10	µg/m³			1694	0–5	0.998 (0.939–1.059)	0.998 (0.939–1.059)
				$24hO_3$	42.4	10	µg/m³				0	0.980 (0.933–1.029)	0.980 (0.933–1.029)
				$24hO_3$	42.4	10	µg/m³				1	1.016 (0.967–1.067)	1.016 (0.967–1.067)
				$24hO_3$	42.4	10	µg/m³				2	0.992 (0.944–1.041)	0.992 (0.944–1.041)
				$24hO_3$	42.4	10	µg/m³				3	1.023 (0.975–1.074)	1.023 (0.975–1.074)
				$24hO_3$	42.4	10	µg/m³				4	0.985 (0.938–1.033)	0.985 (0.938–1.033)
				$24hO_3$	42.4	10	µg/m³				5	1.003 (0.959–1.048)	1.003 (0.959–1.048)

Table 1 (continued)

Study citation information and setting				Exposure						Outcome			Outcome variable	
Authors (year)	Location	Study design time-span	Population (years old)	Pollutant	Mean concentration	Unit of increment	Unit of measurement	Controlled variables		Health outcome/ diagnosis	Total events[a]	Lag (days)	ER/OR/RR (95% CI)	RR_{10} (95% CI)
			0–5 (3) Summer	$24hO_3$	52	10	µg/m³				1293	0–5	0.973 (0.941–1.006)	0.973 (0.941–1.006)
				$24hO_3$	52	10	µg/m³					0	1.003 (0.976–1.031)	1.003 (0.976–1.031)
				$24hO_3$	52	10	µg/m³					1	0.993 (0.962–1.024)	0.993 (0.962–1.024)
				$24hO_3$	52	10	µg/m³					2	1.004 (0.973–1.035)	1.004 (0.973–1.035)
				$24hO_3$	52	10	µg/m³					3	0.992 (0.961–1.024)	0.992 (0.961–1.024)
				$24hO_3$	52	10	µg/m³					4	0.989 (0.958–1.021)	0.989 (0.958–1.021)
				$24hO_3$	52	10	µg/m³					5	0.992 (0.965–1.021)	0.992 (0.965–1.021)

CI, confidence interval; DOW, day of week; ER, excess rate; OR, odd ratio; RR, risk ratio.
[a]Total events was calculated as (daily mean number of event) × (number of days in period) for studies do not provide the total number of events.

considerable heterogeneity of findings, we applied random-effects approach (38) to estimate the pooled effect sizes with consideration of variation in both within and between studies. We used funnel plot techniques, Begg's rank test and Egger's regression test to visually explore the present of publication bias (39, 40).

We conducted several sensitivity analyses. First, we repeated the analysis by leaving out each included study one by one to test its contribution to the pooled effect sizes. Second, the pooled effect sizes were computed for only the shortest single lag or cumulative lag, if no single lag estimates were provided in individual studies. Third, to test if the lower quality score studies (score <20) influenced the pooled estimates, we tried to add the cross-sectional studies to the meta-analysis by assuming the units of increment in those studies as the difference in mean concentration of air pollutant between study and control area. Fourth, to evaluate the influence of study design, we estimated the pooled effect sizes for the studies with time-series and case-crossover design only. Finally, we excluded small studies (events <0.3% of total events) in meta-analysis if find they may introduce bias to our analysis. We used the z-test to examine the difference between two pooled effects from main and sensitivity analyses.

All statistical analyses were conducted by using STATA 12 (STATA Corporation, College Station, TX, USA).

Results

Twelve studies were selected for extracting data and quality assessment. Ten studies were of sufficient quality for inclusion in the systematic review with their main characteristics summarized in Table 1.

Based on the data in Table 1, nearly 84,000 pediatric wheeze-associated disorders events have been investigated to assess the impact of ambient air pollution in five countries. Of these, four studies were conducted in Thailand (7, 41–43), three in Vietnam (44–46), and one each in Singapore, Indonesia and Malaysia (8, 9, 47).

Eight studies reported the effects of PM_{10} (7, 8, 41–44, 46, 47), three reported the effects of $PM_{2.5}$ (41, 43, 46), four studies reported the effects of SO_2 (9, 43, 44, 46), five studies reported the effects of NO_2 (8, 9, 44, 46, 47), three reported the effects of CO (8, 46, 47) and four reported the effects of O_3 (44–47). Only one study reported the effects of TSP, PM_1 and NO_x but Nhung et al. (46) presented three estimates for PM_1 and NO_x while only one estimate for TSP was given by Chew et al. (9), therefore the effects of TSP were analyzed further. The daily mean concentrations of pollutants across all studies were 68.2 µg/m³ for PM_{10}, 45.8 µg/m³ for $PM_{2.5}$, 27.7 µg/m³ for SO_2, 33.5 µg/m³ for NO_2 and 2479 µg/m³ for CO and 81.1 µg/m³ for O_3 (Table 2).

Most studies controlled the potential confounding effects of temperature, humidity and day of week (DOW) (5–7 studies) but only one study adjusted for rainfall and influenza epidemics (Table 1).

Table 2: Descriptive statistics of air pollutant concentrations calculated from the daily mean values published in each included study in the systematic review.

Air pollutant, μg/m³	Daily mean (SD)	Range		Number of studies	Number of estimates
		Min	Max		
PM_{10}	68.2 (23.2)	34.3	104.0	8	11
$PM_{2.5}$	45.8 (17.7)	25.3	56.1	3	3
PM_1	43.7 (0)	43.7	43.7	1	1
SO_2	27.7 (9.1)	18.6	38.1	4	4
NO_2	33.5 (34.0)	0.0	103.4	5	6
NO_x	86.4 (0)	86.4	86.4	1	3
CO	2479.0 (1584.8)	0.0	4400.0	3	4
O_3	81.1 (40.6)	42.4	150.0	4	7

Four studies investigated the association of air pollution with hospital admissions for wheeze-associated disorders, four explored rate the ratio of incidence or prevalence and the rest considered emergency room visits or mortality (Table 1). Five studies defined the outcome using the International Classification of Diseases (ICD) version 9 or 10 (9, 42, 44–46), one based on the hospital admission data (47) and four used questionnaires for wheezing symptoms (7, 8, 41, 43).

Eight studies with quality score higher than 20 were included to perform a meta-analysis. All of these studies provided at least one estimate (overall or single lag) for the effects, of which two studies provided results for the seasons separately (44, 45). The pooled effect sizes of risk ratios (by pollutants) are presented in Figure 2. The degree of heterogeneity (I^2) in the current meta-analysis was large in pooled estimates for PM_{10} (99.6%), CO (85%), NO_2 (94.2%) and moderate for $PM_{2.5}$ (57.5%), SO_2 (61.7%), CO (74.1%) and NO_x (56.3%) and O_3 (49.6%), and low for PM_1 (0.0%) and O_3 (22.0%) (Figure 2A–C).

The pooled effect, RR per 10 μg/m³ increase of pollutants, was 1.020 (95% CI: 0.999–1.041) for PM_{10}, 1.010 (95% CI: 1.001–1.020) for $PM_{2.5}$, 1.007 (95% CI: 1.007–1.028) for PM_1 (Figure 2A), 0.999 (95% CI: 0.985–1.014) for SO_2, 1.008 (95% CI: 0.998–1.018) for NO_2, 1.013 (95% CI: 0.997–1.029) for NO_x (Figure 2B) and 1.000 (95% CI: 0.999–1.002) for CO; 0.999 (95% CI: 0.998–1.001) for O_3 (Figure 2C).

The index of heterogeneity (I^2) ranges from 0 to 100% where they represent low, moderate and high heterogeneity, respectively. The p-value is based on the Q test.

Most of sensitivity analyses demonstrated that there was no notable change in the pooled effect size when changing the included studies (see Supplementary material Table 3–10).

For PM_{10}, the association changed from non-significant to significant in sensitivity analysis 1 (leave-one-study-out) and 3 (lower quality score studies were included) (see Supplementary material Table 3).

For SO_2, the association changed from negative to significantly positive in sensitivity analysis 2 (only shortest single lag or cumulative lag) and 5 (small studies were excluded) (see Supplementary material Table 6, Supplementary material Figure 1).

The small number of included studies (less than 8) was not adequate to properly assess a funnel plot or more advanced regression-based assessments. Thus, we did not evaluate publication bias (48).

Discussion

This is the first meta-analysis to assess the effects of air pollution on wheeze-associated disorders among children in Southeast Asia and to provide effect size estimates. We found positive associations between PMs and wheeze-associated disorders. Our study confirmed that fine particulate matter ($PM_{2.5}$, PM_1) were significantly associated with wheeze-associated disorders among children. $PM_{2.5}$, PM_1 are health-damaging particles not only because of their chemical components but because they can penetrate deep inside the lungs to aggravate existing asthma or to contribute to the development of chronic bronchitis (20, 49–51). Our meta-analyses showed wheeze-associated disorders were most strongly associated with PM_1, which was consistent with the limited literature available on fine particles (46, 52, 53). Earlier evidence indicated that the small particles can reach bronchioles and penetrate up to the primary, secondary terminal bronchi, and alveoli in the lung which may trigger mucous secretions in airways, reduce air flow and then cause wheezing (54, 55). Although

previous studies reported significant effects of PM_{10} on respiratory diseases in children (27, 52, 56), the effects on wheeze-associated disorders was not clear. We found significant associations in some sensitivity analyses but those results were based on removing a large study or including lower quality score studies into meta-analysis so we concluded that further studies were needed to clarify this association.

We did not observe a significant association between SO_2 and wheeze-associated disorders in the main results, however, most of the negative effect for SO_2 were from one small study (231 events) which might

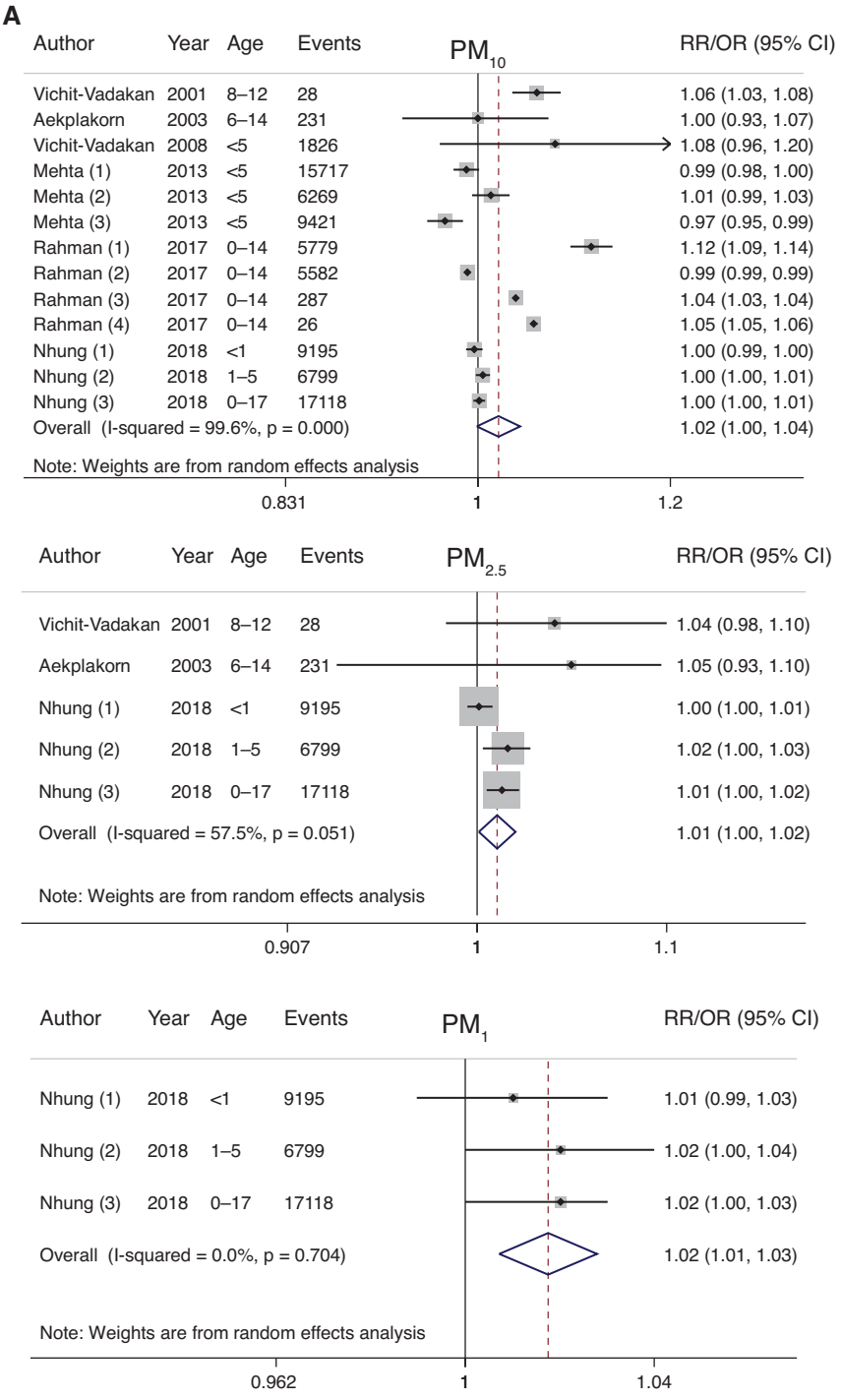

Figure 2: Forest plot for the association between ambient air pollution and wheeze-associated disorder in children in Southeast Asia. Risk ratios/odd ratios (RRs/ORs) are for an increase of 10 μg/m³ of air pollutant (PM_{10}, $PM_{2.5}$, PM_1, SO_2, NO_2, NO_x, CO and O_3).

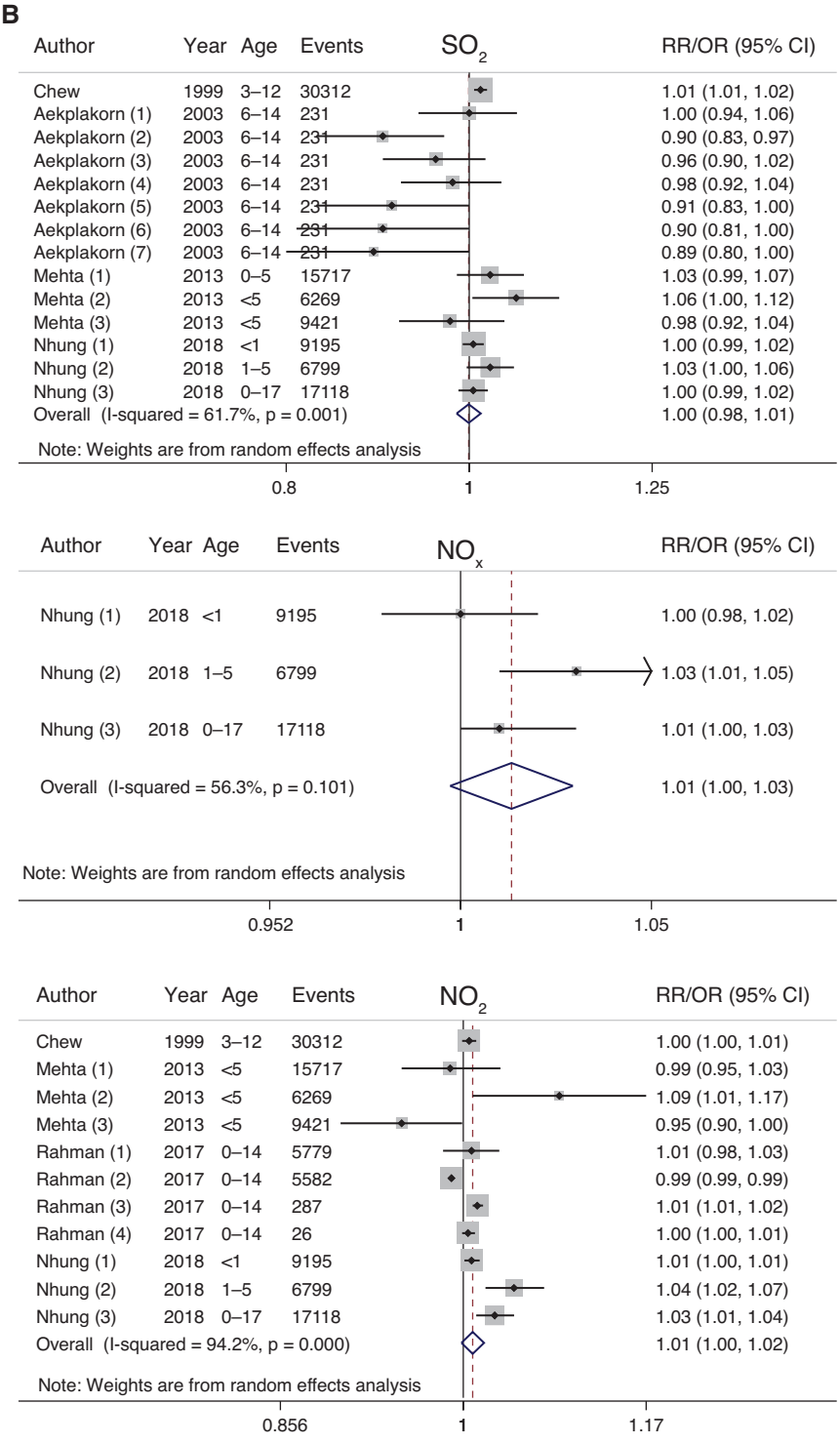

Figure 2: (Continued)

have introduced bias into our analysis (43). A sensitivity analysis conducted by excluding that small study identified a significant effect of SO_2 (RR = 1.012. 95% CI: 1.004–1.020). SO_2 inflames the respiratory tract to cause coughing, mucus secretion, aggravation of asthma and chronic bronchitis and makes children more sensitive to infections of the respiratory system (57). There is evidence from recent studies reporting the association between ambient SO_2 levels and hospital admissions or emergency department visits for respiratory outcomes such as asthma-related symptoms, allergy exacerbation or respiratory infections (57, 58).

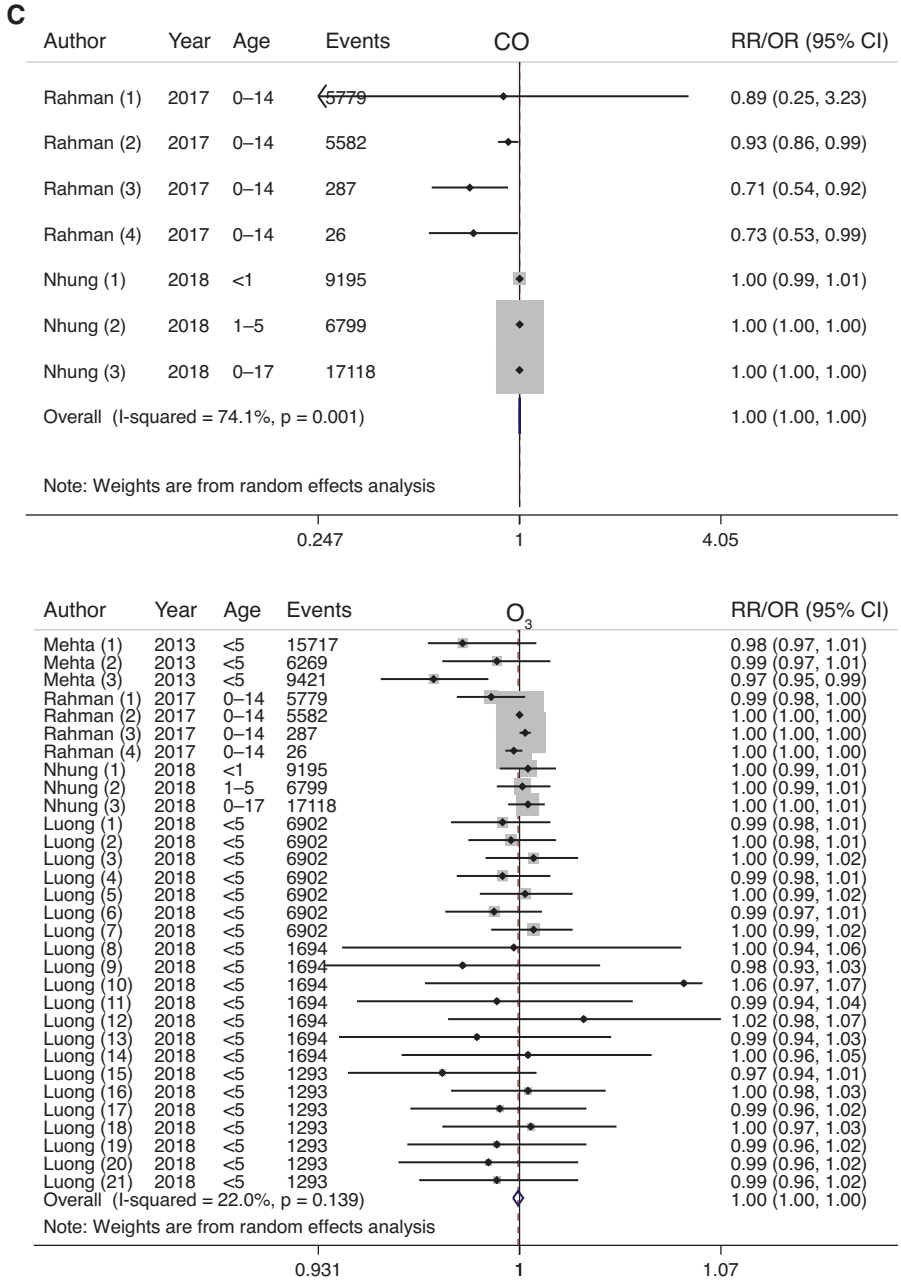

Figure 2: (Continued)

We found positive associations between oxides of nitrogen (NO_2 and NO_x) and wheeze-associated disorders. Oxides of nitrogen contribute to the formation of O_3 and photochemical smog and have significant impacts on human health, especially asthma, bronchial symptoms, lung inflammation and reduced lung function (58, 59). At low level of exposure, NO_2 can irritate the throat and lung, causing shortness of breath, cough, fatigue or nausea (59, 60). Epidemiologic studies have shown that exposure to NO_2 can increase airway inflammation in healthy children, as well as increase symptoms of bronchitis in asthmatics (59, 61). Positive associations between exposures to NO_2 and increased emergency department visits and hospitalizations for wheezing among children have been also reported in previous studies (61–63).

While the connection between CO, O_3 and risk of respiratory admission in children has been reported in previous studies (64–68), their effects on wheeze-associated disorders has not been proven among children in Southeast Asia (44–47). In our review, there was no apparent association found for CO and O_3, with a percent change of close to zero. Indeed, CO at low concentrations was

reported elsewhere as a protective factor against lower tract infection and not all studies in the literature found a positive association between O_3 and hospital admission for asthma (69–72). Thus, the role of CO and O_3 on respiratory disease should be further investigated.

Ambient air pollutants in Southeast Asia are emitted from a mixture of sources including power plants, industries, road vehicles and the burning of biomass from crop fields or forest, and the use of fossil fuels for domestic cooking. This means that the composition of air pollutants in Southeast Asian countries is diverse and could differ considerably from North America and Europe where the majority of previous studies have been performed.

Seven out of 10 studies included in this review were carried out in low-income countries whose children may suffer larger risks of respiratory admission (27, 73, 74). This is because children living in low- and middle-income countries might not only experience higher exposure to ambient air pollution but also be exposed to additional risk factors for respiratory diseases, wheeze-associated disorders, such as smoke from biomass burning at home, a large fraction of the population continues to use tobacco products in the home, or poor diets that may amplify the effects of ambient air pollution (28, 56, 75). Therefore, in Southeast Asia, ambient air pollution poses additional risks for wheeze-associated disorders among children who are already exposed to other pollution at home and still needs to be considered as an important public health issue.

Limitations

This study has some limitations. First, the results are based on a small number of studies, and they did not cover for all countries in Southeast Asia. This limitation calls for further studies in Southeast Asia to evaluate the effect of air pollution on children's health, which would help in an updated systematic review and meta-analysis. Second, some studies investigated associations in a very short period time of months or 1-year and were based on a very small number of events (7, 8, 41, 43). However, they have only a minor influence on the meta-analytic estimates according to their small weight contributing to the pooled effect (sensitivity analyses support this suggestion). Finally, our meta-analysis is based on different designs of observational studies from cross-sectional, cohort, panel to case-crossover and time-series. Therefore, individual studies may be influenced by uncontrolled time-varying biases which we could not examine (27, 39, 48).

Conclusion

The present systematic review and meta-analysis demonstrated a significant relationship between air pollutants and the elevated risk of wheeze-associated disorders among children in Southeast Asian countries. Our meta-analysis found that for each increase of 10 $\mu g/m^3$ in concentrations of $PM_{2.5}$, or PM_1 was associated with an increase of 1–2% risk of wheezing symptom outcome. Meanwhile, the effects of other air pollutants (PM_{10}, SO_2, NO_2, NO_x, CO and O_3) was not statistically significant. Our study contributes to the current literature to better understand the public health impact in the most polluted regions of the world. However, the number of studies conducted in Southeast Asia is still small and more studies are needed from this region.

Author statement

Research funding: L.L. is funded by an Australia Award Scholarship. P.D.S. is funded by a NHMRC Senior Principal Research Fellowship. D.P. is funded by research start-up fund provided by Griffith School of Medicine. P.T. was funded by a QUT VC Research Fellowship during part of this study.

Conflict of interest: Authors state no conflict of interest.

Informed consent: Informed consent is not applicable.

Ethical approval: This study was approved by UQ School of Medicine Low Risk Ethical Review Committee (#2016-SOMILRE-0155).

References

1. WHO. Air pollution levels rising in many of the world's poorest cities; 2016 [cited 2018/29/09]. Available from: http://www.who.int/en/news-room/detail/12-05-2016-air-pollution-levels-rising-in-many-of-the-world-s-poorest-cities.
2. AQICN. World Health Organization: 2014 Air Pollution Ranking; 2015 [cited 2018/29/09]. Available from: http://aqicn.org/faq/2015-05-16/world-health-organization-2014-air-pollution-ranking/.
3. World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide – Global update 2005 – Summary of risk assessment. Geneva: WHO; 2006.
4. WHO. WHO Global Urban Ambient Air Pollution Database (update 2016); 2016 [cited 2018/29/09]. Available from: http://www.who.int/phe/health_topics/outdoorair/databases/cities/en/.
5. MONRE. National State of Environment Report 2013 on Air quality. Vietnam Environment Administration; 2014.
6. WHO. Ambient (outdoor) air pollution database 2016; 2016 [cited 2018/29/09]. Available from: http://www.who.int/phe/health_topics/outdoorair/databases/who-aap-database-may2016.xlsx?ua=1.

7. Langkulsen U, Jinsart W, Karita K, Yano E. Respiratory symptoms and lung function in Bangkok school children. Eur J Public Health 2006;16(6):676–81.
8. Hong CY, Chia SE, Widjaja D, Saw SM, Lee J, Munoz C, et al. Prevalence of respiratory symptoms in children and air quality by village in rural Indonesia. J Occup Environ Med 2004;46(11):1174–9.
9. Chew F, Goh D, Ooi B, Saharom R, Hui J, Lee B. Association of ambient air-pollution levels with acute asthma exacerbation among children in Singapore. Allergy 1999;54(4):320–9.
10. Ritz B, Wilhelm M, Zhao Y. Air pollution and infant death in southern California, 1989–2000. Pediatrics 2006;118(2):493–502.
11. Dominici F, Peng RD, Zeger SL, White RH, Samet JM. Particulate air pollution and mortality in the United States: did the risks change from 1987 to 2000? Am J Epidemiol 2007;166(8):880–8.
12. Ye Y, Zulu E, Mutisya M, Orindi B, Emina J, Kyobutungi C. Seasonal pattern of pneumonia mortality among under-five children in Nairobi's informal settlements. Am J Trop Med Hyg 2009;81(5):770–5.
13. Delfino RJ, Staimer N, Gillen D, Tjoa T, Sioutas C, Fung K, et al. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. Environ Health Perspect 2006;114:1736–43.
14. Andersen ZJ, Wahlin P, Raaschou-Nielsen O, Scheike T, Loft S. Ambient particle source apportionment and daily hospital admissions among children and elderly in Copenhagen. J Expo Sci Environ Epidemiol 2007;17(7):625–36.
15. Weinmayr G, Romeo E, De Sario M, Weiland SK, Forastiere F. Short-term effects of PM10 and NO2 on respiratory health among children with asthma or asthma-like symptoms: a systematic review and meta-analysis. Environ Health Perspect 2010;118(4):449.
16. Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, et al. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. Am J Respir Crit Care Med 2002;166(8):1092–8.
17. Le TG, Ngo L, Mehta S, Do V, Thach T, Vu X, et al. Effects of short-term exposure to air pollution on hospital admissions of young children for acute lower respiratory infections in Ho Chi Minh City, Vietnam. Res Rep Health Eff Inst 2012(169):5–72; discussion 3–83.
18. Lin W, Huang W, Zhu T, Hu M, Brunekreef B, Zhang Y, et al. Acute respiratory inflammation in children and black carbon in ambient air before and during the 2008 Beijing Olympics. Environ Health Perspect 2011;119(10):1507.
19. O'Connor GT, Neas L, Vaughn B, Kattan M, Mitchell H, Crain EF, et al. Acute respiratory health effects of air pollution on children with asthma in US inner cities. J Allergy Clin Immunol 2008;121(5):1133–9.e1.
20. Ostro B, Roth L, Malig B, Marty M. The effects of fine particle components on respiratory hospital admissions in children. Environ Health Perspect 2009;117(3):475.
21. Karr C, Lumley T, Schreuder A, Davis R, Larson T, Ritz B, et al. Effects of subchronic and chronic exposure to ambient air pollutants on infant bronchiolitis. Am J Epidemiol 2007;165(5):553–60.
22. Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, et al. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. Environ Health Perspect 2006;114:277–81.
23. Sram RJ, Binkova B, Dostal M, Merkerova-Dostalova M, Libalova H, Milcova A, et al. Health impact of air pollution to children. Int J Hyg Environ Health 2013;216(5):533–40.
24. Gehring U, Gruzieva O, Agius RM, Beelen R, Custovic A, Cyrys J, et al. Air pollution exposure and lung function in children: the ESCAPE project. Environ Health Perspect (Online) 2013;121(11–12):1357.
25. Götschi T, Heinrich J, Sunyer J, Künzli N. Long-term effects of ambient air pollution on lung function: a review. Epidemiology 2008;19(5):690–701.
26. Health Effects Institute. Outdoor air pollution and health in the developing countries of Asia: a comprehensive review. Special report 18, HEI International Scientific Oversight Committee, 2010.
27. Nhung NTT, Amini H, Schindler C, Kutlar Joss M, Dien TM, Probst-Hensch N, et al. 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 2017;230:1000–8.
28. Mehta S, Shin H, Burnett R, North T, Cohen AJ. Ambient particulate air pollution and acute lower respiratory infections: a systematic review and implications for estimating the global burden of disease. Air Qual Atmos Health 2013;6(1):69–83.
29. World Health Organozation. Pneumonia – Fact sheet N°331: World Health Organization; 2015. Available from: http://www.who.int/mediacentre/factsheets/fs331/en/.
30. World Health Organozation. Asthma – Fact sheet N°307: World Health Organization; 2013 [updated 11/2013]. Available from: http://www.who.int/mediacentre/factsheets/fs307/en/.
31. GINA. Global strategy for asthma management and prevention. Global Intiative for Asthma, 2014. Available from: https://ginasthma.org/.
32. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. J Am Med Assoc 2000;283(15):2008–12.
33. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264–9.
34. Phung D, Thai PK, Guo Y, Morawska L, Rutherford S, Chu C. Ambient temperature and risk of cardiovascular hospitalization: an updated systematic review and meta-analysis. Sci Total Environ 2016;550:1084–102.
35. Berman NG, Parker RA. Meta-analysis: neither quick nor easy. BMC Med Res Methodol 2002;2(1):10.
36. Shah ASV, Lee KK, McAllister DA, Hunter A, Nair H, Whiteley W, et al. Short term exposure to air pollution and stroke: systematic review and meta-analysis. Br Med J 2016;354:i4851.
37. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. Br Med J 2003;327(7414):557.
38. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1(2):97–111.
39. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Br Med J 1997;315(7109):629–34.
40. Rothstein H, Sutton A, Borenstein M. Publication Bias in Meta-Analysis. Publication Bias in Meta-Analysis-Prevention, Assessment and Adjustment. Chichester: John Wiley & Sons; 2005.
41. Vichit-Vadakan N, Ostro BD, Chestnut LG, Mills DM, Aekplakorn W, Wangwongwatana S, et al. Air pollution and respiratory symptoms: results from three panel studies in Bangkok, Thailand. Environ Health Perspect 2001;109(Suppl 3):381.
42. Vichit-Vadakan N, Vajanapoom N, Ostro B. The Public Health and Air Pollution in Asia (PAPA) Project: estimating the mortality effects of particulate matter in Bangkok, Thailand. Environ Health Perspect 2008;116(9):1179.
43. Aekplakorn W, Loomis D, Vichit-Vadakan N, Shy C, Plungchuchon S. Acute effects of SO2 and particles from a power plant on

respiratory symptoms of children, Thailand. Southeast Asian J Trop Med Public Health 2003;34(4):906–14.
44. Mehta S, Ngo LH, Van Dzung D, Cohen A, Thach TQ, Dan VX, et al. Air pollution and admissions for acute lower respiratory infections in young children of Ho Chi Minh City. Air Qual Atmos Health 2013;6(1):167–79.
45. Ly M. T. Luong, Dung Phung, Tran Ngoc Dang, Peter D. Sly, Lidia Morawska, Thai PK. Seasonal association between ambient ozone and hospital admission for respiratory diseases in Hanoi, Vietnam. PloS One 2018;13(9):e0203751.
46. Nhung NTT, Schindler C, Dien TM, Probst-Hensch N, Perez L, Künzli N. Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: an eight-year time series study. Environ Int 2018;110:139–48.
47. Rahman SRA, Ismail SS, Sahani M, Ramli MF, Latif MT. A case crossover analysis of primary air pollutants association on acute respiratory infection (ARI) among children in urban region of Klang valley, Malaysia. Ann Trop Med Parasitol 2017;10(1):44.
48. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol 2000;53(11):1119–29.
49. USEPA. Final Report: Integrated Science Assessment for Particulate Matter. Washington, DC: U.S. Environmental Protection Agency, EPA/600/R-08/139F; 2009 12/2008.
50. World Health Organization. WHO Air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide 2005. Available from: http://apps.who.int/iris/bitstream/10665/69477/1/WHO_SDE_PHE_OEH_06.02_eng.pdf.
51. Fuertes E, MacIntyre E, Agius R, Beelen R, Brunekreef B, Bucci S, et al. Associations between particulate matter elements and early-life pneumonia in seven birth cohorts: results from the ESCAPE and TRANSPHORM projects. Int J Hyg Environ Health 2014;217(8):819–29.
52. Luong LM, Phung D, Sly PD, Morawska L, Thai PK. The association between particulate air pollution and respiratory admissions among young children in Hanoi, Vietnam. Sci Total Environ 2017;578:249–55.
53. Halonen JI, Lanki T, Yli-Tuomi T, Kulmala M, Tiittanen P, Pekkanen J. Urban air pollution, and asthma and COPD hospital emergency room visits. Thorax 2008;63(7):635–41.
54. Kesavachandran C, Pangtey BS, Bihari V, Fareed M, Pathak MK, Srivastava AK, et al. Particulate matter concentration in ambient air and its effects on lung functions among residents in the National Capital Region, India. Environ Monit Assess 2013;185(2):1265–72.
55. Churg A, Brauer M, del Carmen Avila-Casado M, Fortoul TI, Wright JL. Chronic exposure to high levels of particulate air pollution and small airway remodeling. Environ Health Perspect 2003;111(5):714.
56. Nhung NTT, Schindler C, Dien TM, Probst-Hensch N, Perez L, Künzli N. Acute effects of ambient air pollution on lower respiratory infections in Hanoi children: an eight-year time series study. Environ Int 2018;110(Suppl C):139–48.
57. EPA. Integrated Science Assessment for Sulfur Oxides – Health Criteria; 2017. Available from: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=338596.
58. World Health Organization. Ambient (outdoor) air quality and health: World Health Organization; 2005. Available from: http://www.who.int/mediacentre/factsheets/fs313/en/.
59. EPA. Integrated Science Assessment for Oxides of Nitrogen – Health Criteria; 2016. Available from: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?
60. ATSDR. Agency for Toxic Substances and Disease Registry. ToxFAQs for nitrogen oxides. 2002. Available from: www.atsdr.cdc.gov/toxfaqs/tf.asp?id=396&tid=69.
61. USEPA. Final report: Integrated Science Assessment (ISA) for Sulfur Dioxide – Health Criteria. Washington, DC: U.S. Environmental Protection Agency, EPA/600/R-08/047F; 2008 07/2008.
62. Pikhart H, Bobak M, Kriz B, Danova J, Celko MA, Prikazsky V, et al. Outdoor air concentrations of nitrogen dioxide and sulfur dioxide and prevalence of wheezing in school children. Epidemiology 2000;11(2):153–60.
63. Pershagen G, Rylander E, Norberg S, Eriksson M, Nordvall SL. Air pollution involving nitrogen dioxide exposure and wheezing bronchitis in children. Int J Epidemiol 1995;24(6):1147–53.
64. Lin S, Liu X, Le LH, Hwang S-A. Chronic exposure to ambient ozone and asthma hospital admissions among children. Environ Health Perspect 2008;116(12):1725.
65. Yang Q, Chen Y, Shi Y, Burnett RT, McGrail KM, Krewski D. Association between ozone and respiratory admissions among children and the elderly in Vancouver, Canada. Inhal Toxicol 2003;15(13):1297–308.
66. Ghaffari HR, Aval HE, Alahabadi A, Mokammel A, Khamirchi R, Yousefzadeh S, et al. Asthma disease as cause of admission to hospitals due to exposure to ambient oxidants in Mashhad, Iran. Environ Sci Pollut Res 2017;24(35):27402–8.
67. Zhang S, Li G, Tian L, Guo Q, Pan X. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: a systematic review and meta-analysis. Environ Res 2016;148:15–23.
68. Evans KA, Halterman JS, Hopke PK, Fagnano M, Rich DQ. Increased ultrafine particles and carbon monoxide concentrations are associated with asthma exacerbation among urban children. Environ Res 2014;129:11–9.
69. Tian L, Qiu H, Pun VC, Lin H, Ge E, Chan JC, et al. Ambient carbon monoxide associated with reduced risk of hospital admissions for respiratory tract infections. Am J Respir Crit Care Med 2013;188(10):1240–5.
70. U.S. Environmental Protection Agency. Quantitative Risk and Exposure Assessment for Carbon Monoxide – Amended Carbon Monoxide (CO) Standards – Risk and Exposure Assessments from Current Review. North Carolina: Research Triangle Park; 2010.
71. Fusco D, Forastiere F, Michelozzi P, Spadea T, Ostro B, Arca M, et al. Air pollution and hospital admissions for respiratory conditions in Rome, Italy. Eur Respir J 2001;17(6):1143–50.
72. Schwartz J. Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am J Respir Crit Care Med 1994;150(3):648–55.
73. World Health Organization. 7 million premature deaths annually linked to air pollution: World Health Organization; 2014. Available from: http://www.who.int/mediacentre/news/releases/2014/air-pollution/en/.
74. Cohen AJ, Ross Anderson H, Ostro B, Pandey KD, Krzyzanowski M, Künzli N, et al. The global burden of disease due to outdoor air pollution. J Toxicol Environ Health 2005;68(13–14):1301–7.
75. Nguyen T, Tran T, Roberts C, Fox G, Graham S, Marais B. Risk factors for child pneumonia-focus on the Western Pacific Region. Paediatr Respir Rev 2017;21:95–101.

Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/reveh-2018-0079).