



Multifactorial airborne exposures and respiratory hospital admissions — The example of Santiago de Chile



Ulrich Franck^{a,*}, Arne Marian Leitte^a, Peter Suppan^b

^a Core Facility Studies, Helmholtz Centre for Environmental Research — UFZ, Leipzig, Germany

^b Institute of Meteorology and Climate Research (IMK-IFU), Karlsruhe Institute of Technology (KIT), Garmisch-Partenkirchen, Germany

HIGHLIGHTS

- We assessed effects of multiple airborne exposures on respiratory hospital admissions of the population of Santiago de Chile.
- We found significant adverse effects for CO, NO₂, PM10 and PM2.5, but not O₃.
- Effect strength and lag time depend on the type of pollutant.
- Different airborne pollutants account for varying adverse effects.

ARTICLE INFO

Article history:

Received 16 May 2014

Received in revised form 18 July 2014

Accepted 25 August 2014

Available online xxxx

Keywords:

Respiratory health effects

Hospital admissions

Airborne pollutants

Multiple exposures

ABSTRACT

Our results provide evidence for respiratory effects of combined exposure to airborne pollutants in Santiago de Chile. Different pollutants account for varying adverse effects. Ozone was not found to be significantly associated with respiratory morbidity.

Background: High concentrations of various air pollutants have been associated with hospitalization due to development and exacerbation of respiratory diseases. The findings of different studies vary in effect strength and are sometimes inconsistent.

Objectives: We aimed to assess associations between airborne exposures by particulate matter as well as gaseous air pollutants and hospital admissions due to respiratory disease groups under the special orographic and meteorological conditions of Santiago de Chile.

Methods: The study was performed in the metropolitan area of Santiago de Chile during 2004–2007. We applied a time-stratified case-crossover analysis taking temporal variation, meteorological conditions and autocorrelation into account. We computed associations between daily ambient concentrations of carbon monoxide (CO), nitrogen dioxide (NO₂), particulate matter (PM10 and PM2.5 — particulate matter with aerodynamic diameters less than 10 or 2.5 µm, respectively) or ozone (O₃) and hospital admissions for respiratory illnesses.

Results: We found for CO, NO₂, PM10 and PM2.5 adverse relationships to respiratory admissions while effect strength and lag depended on the pollutant and on the disease group. By trend, in 1-pollutant models most adverse pollutants were CO and PM10 followed by PM2.5, while in 2-pollutant models effects of NO₂ persisted in most cases whereas other effects weakened and significant effects remain for PM2.5, only. In addition the strongest effects seemed to be immediate or with a delay of up to one day, but effects were found until day 7, too. Adverse effects of ozone could not be detected.

Conclusions: Taking case numbers and effect strength of all cardiovascular diseases into account, mitigation measures should address all pollutants especially CO, NO₂, and PM10.

© 2014 Elsevier B.V. All rights reserved.

* Corresponding author at: Core Facility “Studies”, Helmholtz Centre for Environmental Research — UFZ, Permoserstrasse 15, 04318 Leipzig, Germany. Tel.: +49 341 2351540; fax: +49 341 235451540.

E-mail addresses: ulrich.franck@ufz.de (U. Franck), arne.leitte@googlemail.com (A.M. Leitte), peter.suppan@kit.edu (P. Suppan).

1. Introduction and aim of the study

A preceding study investigated the air pollution related cardiovascular hospital admissions in the city of Santiago de Chile (Franck et al., 2014). This present study is based on the same time period and exposure data but aimed at respiratory morbidity.

1.1. Results on respiratory health effects of particulate matter, CO, NO₂, and O₃ vary between studies

A number of studies have shown the detrimental effects of single common airborne pollutants on respiratory hospital admissions, doctor's house calls and emergency calls (Atkinson et al., 2012; Brunekreef, 2007; Hoek et al., 2013; Leitte et al., 2011, 2012). Increased health risks were also found for the conditions of Santiago de Chile (Bell et al., 2006; Cakmak et al., 2011, 2009b; Franck et al., 2014; Segual et al., 2012; Vera and Cifuentes, 2008; Vera et al., 2007).

Effect strengths for particulate matter vary between studies. Typically an increase of concentrations of ambient particulate matter (PM₁₀, PM_{2.5}) by 10 µg/m³ was found to be associated with a 3% to 6% increase of respiratory admissions and emergency calls by 3–12% per day (Chardon et al., 2007; Dominici et al., 2006; Fung et al., 2006; Jayaraman and Nidhi, 2008; Lippmann et al., 2000; Oftedal et al., 2003; Stieb et al., 2009; Tramuto et al., 2011). But, a small number of authors found considerable lower effect strengths (Jayaraman and Nidhi, 2008; Son et al., 2013). The different studies also found different time lags for respiratory health effects. Often, but not always a significant risk increase was found already for the day of exposure. The effects persisted some days up to around one week. The present study therefore wants to contribute to this discussion investigating strengths and lags of adverse effects of PM exposure on respiratory health in the city of Santiago de Chile.

Nitrogen dioxide is another urban pollutant known to be associated with detrimental respiratory effects. For doctor's house calls no significant risk increase could be shown (Chardon et al., 2007). But, the risk for hospital admissions was found to be increased by 4% up to 11% per 10 µg NO₂/m³ (Ackermann-Lieblich, 2011; Brunekreef, 2007; Jayaraman and Nidhi, 2008; Lee et al., 2007; Oftedal et al., 2003; Peel et al., 2005; Simpson et al., 2005; Spix et al., 1998; Stieb et al., 2009; Tramuto et al., 2011; Yang and Chen, 2007). Because NO₂ is a typical urban pollutant in Santiago de Chile related to traffic as an important source of various pollutants this study aimed also on effect strengths and lags of NO₂ associated hospital admissions.

Especially effects of O₃ were not consistent between studies. Some studies found significant numbers of respiratory hospital admissions (Chen et al., 2005; Jayaraman and Nidhi, 2008; Lee et al., 2007; Simpson et al., 2005; Spix et al., 1998; Yang and Chen, 2007) whereas other studies found no effect or a statistically protecting effect on respiratory morbidity (Fung et al., 2007; Oftedal et al., 2003). Such a statistically protecting effect was also shown for cardiovascular hospital admissions in Santiago de Chile (Franck et al., 2014).

The number of recent studies which addressed effects of CO on hospital admission is significantly lower than for the other pollutants. Additionally, the findings of former studies were not congruent. Increased exposure to CO was found to be associated with respiratory morbidity with risk increases of up to 12% per 1 mg/m³ CO and similar lags as for PM exposure. But, risk increases and lags vary from study to study (Chen et al., 2005; Peel et al., 2005; Stieb et al., 2009; Tramuto et al., 2011). In contrast to other studies, Tramuto et al. found the effects of CO during the warm seasons, only (Tramuto et al., 2011). Therefore, the present study intended to contribute to the findings on respiratory health effects of CO.

Ozone is a pollutant linked to the intensity of sun radiation. Hence, it plays a dominant role during summer and in southern countries. O₃ exposure is accused to produce detrimental respiratory effects. But, especially effects of this pollutant were not consistent between studies. Some studies found significant numbers of respiratory hospital admissions (Chen et al., 2005; Jayaraman and Nidhi, 2008; Lee et al., 2007; Simpson et al., 2005; Spix et al., 1998; Yang and Chen, 2007) whereas other studies found no effect or a statistically protecting effect on respiratory morbidity (Fung et al., 2007; Oftedal et al., 2003). Such a statistically protecting effect was also shown for cardiovascular hospital admissions in Santiago de Chile (Franck et al., 2014). Hence, the present

study wanted to verify or falsify the protecting effects of ozone on respiratory diseases.

Adverse respiratory effects of airborne pollutants may generally be caused by a mixture of pollutants and not always by a dominating pollutant or a simple superposition of the effects of single pollutants (Mauderly and Samet, 2009). The present study therefore also focused on the stability of the respiratory effects of the airborne pollutants within 2-pollutant models.

1.2. The distinctive feature of airborne outdoor exposure in Santiago de Chile

Santiago de Chile is surrounded by Andean Mountains in the east and the Cordillera of the Coast. The specific atmospheric and geographic conditions cause high contamination levels due to relatively high anthropogenic and natural emissions. Depending on season, the main contamination is due to primary emissions: particulate matter, sulfur dioxide (SO₂), nitrogen dioxide (NO₂) and carbon monoxide (CO) (Cakmak et al., 2009b; Moreno et al., 2010; Kavouras et al., 2001). High emission levels, high solar radiation in the summer and the specific orographic conditions resulted in high levels of combined exposure of the 6 million inhabitants of Chile's capital. A more detailed description of air pollution situation in Santiago de Chile is given in Cakmak et al. (2009b), Elshorbany et al. (2009), Franck et al. (2014) and Suppan et al. (2012).

Different types of natural and anthropogenic sources emit different airborne pollutants. Identification of most adverse pollutants and mixtures of pollutions may help to develop the optimal mitigation strategies for the protection of the health of Santiago's inhabitants. Thus, this study aimed on identification of harmful pollutants for development or exacerbation of respiratory diseases. Additionally, the study focused on the persistency of the exposure by one pollutant taking a second one into account. The study also intended to contribute to the findings about air pollution associated respiratory morbidity which are partially inconsistent (see paragraph 1.2). In addition, this article compares the findings regarding respiratory hospital admissions with the findings on cardiovascular hospital admissions (Franck et al., 2014).

2. Material and methods

2.1. Study area and period

Around 88.7% of Chile's population lives in cities. In the city of Santiago (área urbana) are living around 5.39 Mio inhabitants (census 2002) which is more than one third of the total population of the country. The city lies in the center of the Santiago Basin, a large bowl-shaped valley between the Andes and the Cordillera de la Costa mountain ranges; the distance from the Pacific Ocean is 100 km (Gramsch et al., 2006). The geographic location in the Santiago Basin strongly limits ventilation and dispersion of air pollutants. During summer, central Chile is generally influenced by subtropical anticyclone in the south-eastern pacific in Santiago (Schmitz, 2005). These conditions with high temperatures and clear sky, favor the formation of ozone through the photochemical oxidation of carbon monoxide and volatile organic compounds (VOC) in the presence of high concentrations of nitrogen oxides. Daily variation of exposure concentrations is high which results in significant numbers of days on which the Chilean National Ambient Air Quality Standard (NAAQS) mean of 80 ppb maximum hourly and the NAAQS average of 61 ppb maximum over 8 h were exceeded (Bell et al., 2008; Segual et al., 2012). This limit was exceeded also during the study period from January 1, 2004 until December 31, 2007 (Franck et al., 2014).

2.2. Health data

Effects on respiratory morbidity of air pollutants were determined based on daily numbers of respiratory hospital admissions. The

data were kindly provided by the Departamento de Estadísticas e Información de Salud (DEIS) of the Ministerio de Salud de Chile. All cases of hospital admissions (in total 75,303) which are registered by the Fondo Nacional de Salud de Chile (FONASA) and the Instituciones de Salud Previsional (ISAPRES) were analyzed. Each single case was listed per day. The cases were annotated with detailed ICD-10 codes. The respiratory cases were filtered and the case numbers per day were summarized. The resulting time series have been checked carefully for unrealistic outliers, which have not been found. For the analyses of lagged effects, the total numbers of hospital admissions per day have been related to the exposure concentrations of the same day and up to seven days prior the admissions. In addition to the total case numbers of respiratory admissions this study used the case numbers of admissions due to pneumonia.

2.3. Air pollution data

Averages of concentrations measured by seven of eight monitoring stations of the atmospheric pollution monitoring Network at Santiago de Chile were used for the estimation of the exposure of Santiago's inhabitants. All stations were equipped with devices measuring PM₁₀, PM_{2.5}, NO₂, CO, and O₃. Only data of the Las Condes station were not taken into account. This station has to be excluded because it was not characteristic for the exposure of the population of Santiago (a detailed description of the reasons and a map with the location of the stations are given in Franck et al. (2014)). Seasonal monitors were not included. Concentration data existed for more than 90% of the days for O₃ until more than 97% of the days for PM.

2.4. Meteorological data

Meteorological data (wind speed, direction, temperature, humidity) were provided by a local monitoring network (Suppan et al., 2012) and weather underground (www.wunderground.com). Table 1 and Supplementary Fig. S1 show the variations of air temperature, relative humidity, and wind speed during the study period.

2.5. Statistical analysis

Various methods in environmental epidemiology are able to analyze the influence of pollutants on health. This study intended to quantify relationships between daily variations of the concentrations of common airborne pollutants and daily hospital admissions due to respiratory diseases in Santiago de Chile. A number of authors demonstrated that case-crossover and time series methods give similar results (Basu et al., 2005; Lu and Zeger, 2007; Tong et al., 2012). In the present study we applied a time stratified case-crossover analysis (CCO) using daily numbers of respiratory hospital admissions and daily mean values of the concentrations of airborne pollutants.

The CCO was introduced by Maclure (1991) for the investigation of transient effects on the risk of events while controlling for seasonality and other long-term modifiers. An extensive description of the approaches is given in Barnett and Dobson (2010). One important advantage of the CCO is that each subject is their own control, and so any fixed characteristics (e.g. gender, smoking status and social status) are ab initio controlled for (Barnett and Dobson, 2010). More details of the use of CCO were also given in Franck et al. (2014).

A time stratified method was used to choose control and event days because it has been shown that it reduces bias (Janes et al., 2005). The control days lie in a stratum of 28 days, which is in agreement to other studies (Guo et al., 2009; Dimitrova et al., 2012). By choosing a stratum of 28 days seasonal patterns in concentrations of air pollutants and numbers of hospitalizations are removed. Confounding by day of the week (Janes et al., 2005) was avoided including a match by the day of the week additionally to the strata matching.

Table 1

Descriptive statistics of meteorological data during the study period (based on daily mean values from weather underground – www.wunderground.com).

	Air temperature (°C)	Relative humidity (%)	Wind speed (m/s)
Mean	14.1	65.7	6.0
Min	2	33	0
10th percentile	7	46	2
25th percentile	11	55	3
Median	14	66	6
75th percentile	18	77	8
90th percentile	21	85	11
Max	25	96	32

To ensure the detection of the majority of short-term effects, we investigated the relationships using lags from 0 to 7 days.

Many epidemiological time series studies show that meteorological parameters are modifiers of health effects. This fact was also shown for the effects of outdoor air pollution in Santiago de Chile (Bell et al., 2008; Muggeo and Hajat, 2009). Therefore, all models were controlled by including variables of outdoor air temperature and relative air humidity. Seasonal variations within pollution concentrations, numbers of hospital admission, temperature, and relative humidity were controlled for.

The risks are given by odds ratios (ORs) for an interquartile range increase (IQR – the difference between the fourth and the first quartile) of the concentrations of the air pollutant. A conditional logistic regression is used to calculate the OR for cases compared with controls for the unit increase in exposure concentrations. The risk assessments were carried out using the software R (R Development Core Team, 2008; Barnett and J., 2010). The time series study is based on exposure, climate, and health data of 1461 days; between 1.1.2004 and 31.12.2007. A more detailed description is given in Franck et al. (2014).

3. Results

3.1. Air pollution during the study period

During the study period, yearly mean values of concentrations were high especially for PM₁₀ and PM_{2.5} (Table 2). For only around 25% of the days, the daily mean concentration of PM₁₀ was below the European daily limit value of 50 µg/m³. Also the yearly mean concentrations of the 2008/50/EC guideline were exceeded for PM₁₀ and PM_{2.5} (Table 2).

Daily mean concentrations of pollutants were correlated (Table 3). Concentrations of O₃ showed negative correlation coefficients to the concentrations of the other investigated pollutants.

3.2. Respiratory hospital admissions

During the study period 95,597 patients were admitted to hospital due to respiratory diseases (Table 4). These numbers included 12,875 cases of COPD and 44,430 cases of pneumonia showing that pneumonia was the most relevant disease with respect of hospitalization.

The effect strengths depend on the pollutant. 1-Pollutant models show that increases of CO and NO₂ concentrations were most adversely related to respiratory morbidity (Fig. 1). PM₁₀ was also found to be a pollutant which detrimentally affects numbers of hospital admissions. Significant adverse effects for the air pollutants were found for the day of exposure or lagged with highest effects of pollutants one day after exposure increase. O₃ did not adversely affect the numbers of respiratory hospital admissions (Fig. S2 in the Supplementary material).

The effect strengths depend on the type of disease. Similar health effects were found for pneumonia but the effect of NO₂ seemed to be less adverse (Fig. 2). None of the investigated pollutants was adversely

associated with health effects on COPD (Fig. S3 in the Supplementary material).

2-Pollutant models allowed evaluating the stability of effects. In 2-pollutant models the most consistent effects on all respiratory hospitalizations were found for NO₂ (Fig. 3) whereas the effects of CO and particulate matter disappear while controlling for the other pollutants except for O₃ (Figs. S4, S5, S6 in the Supplementary material). Effects on pneumonia only persisted for exposure to CO if controlling for O₃, and NO₂ if controlling for PM (Figs. S7 and S8 in the Supplementary material). In 2-pollutant models, all investigated pollutants did not significantly affect the number of hospital admissions due to COPD (Figs. S9, S10, S11, S12 in the Supplementary material).

4. Discussion

4.1. Pollutant concentrations in Santiago de Chile

Urban traffic and industry are important sources of the investigated air pollutants in Santiago de Chile (Cakmak et al., 2009a; Moreno et al., 2009; Suppan et al., 2012). Pollutant concentrations, except O₃, were positively correlated (Table 3). Especially, the correlation between PM10 and PM2.5 concentrations was high because PM2.5 is a part of PM10. Yearly mean concentrations of PM10 and PM2.5 were high in comparison to limit respectively target values of the European Commission (40 µg/m³ and 25 µg/m³). Lower mixing layer heights and temperature inversions were especially found during winter time (Seidel et al., 2010) whereas high concentrations of O₃ are related to strong sun radiation which occurs more frequently during summer month. This can explain the negative correlation coefficients of O₃ with the other investigated air pollutants. Remarkable daily variations of pollutant concentrations allowed that assessments based on time series with daily variations detected short-term respiratory health effects of these pollutants (Table 2).

4.2. Health effects

4.2.1. Particulate matter

Schwela (2000) gave a résumé of recent reviews of the World Health Organization and other papers including a number of review articles. The author stated that adverse effects of PM exposure were the most robust in 2-pollutant models, that the effects are linear over a wide concentration range (≥ 100 µg PM10/m³) and that no threshold has been recorded below which no effect occurs. The present study found diminishing effect levels of some pollutants if controlling other air pollutants for PM10 and PM2.5. Janssen et al. stated from their assessment that both particle metrics, PM10 and PM2.5, are significantly associated with daily mortality (Janssen et al., 2013). Hoek et al. (2013) described in their review significant heterogeneity in PM2.5 effect estimates across mortality and morbidity studies, likely related to variations in particle composition, differences of infiltration of particles indoors, population characteristics and methodological differences in exposure assessment and confounder control (Hoek et al., 2013). Recent studies often are attributing stronger effects to PM2.5 than PM10 (Chardon et al., 2007; Stafoggia et al., 2013) but sometimes

Table 3

Pearson correlation coefficients of daily mean concentrations of air pollutants (station Las Condes not included).

	CO	NO ₂	O ₃	PM10	PM2.5
CO	1.00	0.94	−0.72	0.82	0.88
NO ₂	0.94	1.00	−0.68	0.84	0.87
O ₃	−0.72	−0.68	1.00	−0.37	−0.52
PM10	0.82	0.84	−0.37	1.00	0.94
PM2.5	0.88	0.87	−0.52	0.94	1.00

All correlations are significant on a 5% level.

similar or lower effects (Barnett et al., 2005; Chen et al., 2005). In the present study, there was a tendency to stronger effects of PM10 than PM2.5. A few other publications also described stronger effects of PM10 than PM2.5 (Lipsett et al., 2006; Vera et al., 2007). The harmfulness of particulate matter was found to be related to the chemical composition (Breyse et al., 2013; Dominici et al., 2007; Lodovici and Bigagli, 2011). Janssen et al. concluded from their analysis that particle composition and especially the content of black carbon were playing an important role in the air pollutant associated pathogenesis (Franco Suglia et al., 2008; Janssen et al., 2011, 2014). Because of the lack of more detailed data on airborne particulates, the present study could not differ for the composition of particulate matter. The present study could also not differ for cases with preexisting conditions with a supposed higher vulnerability.

4.2.2. Ozone

As already a number of other studies (Goldberg et al., 2013; Le et al., 2012; Linn et al., 2000; Luginaah et al., 2005; Oftedal et al., 2003; Sauerzapf et al., 2009; Vaneckova and Bambrick, 2013; Zauli Sajani et al., 2011), this study also could not find consistent evidence for detrimental respiratory health effects of O₃. Lin et al. stated geographic differences in the associations between ozone levels and respiratory hospital admissions among children in the United States of America (Lin et al., 2008). When region-specific results were combined, no state-wide association was apparent. Medina-Ramon et al. found increased hospitalization rates but confirmed in a large sample of cities and PM10 is associated with respiratory hospital admissions and provided evidence that the effect of O₃ was modified by city characteristics (Medina-Ramon et al., 2006). For Santiago de Chile, Vera and Cifuentes found a moderate effect of O₃ on hospital admissions only due to acute respiratory infections that were 2.2 (0.0–4.6)% but not for other respiratory diagnoses (Vera and Cifuentes, 2008). A study using the same database as the present study could not show detrimental effects of O₃ on cardiovascular hospital admissions (Franck et al., 2014). Wong et al. discussed temperature as a modifying factor and found adverse association between ozone and hospital admissions at higher daily mean temperatures, only (Wong et al., 2010). The present study took temperature as a confounding variable into account but detrimental effects of ozone could not be found. Lippmann et al. found that spatial inhomogeneity of air pollutant concentrations may hide negative associations with human health (Lippmann et al., 2000). Generally, odds for respiratory symptoms may be increased by O₃ exposure but result in application of appropriate medicaments and not hospitalization (Altug et al.,

Table 2

Descriptive statistics of concentrations of air pollutants during the study period (all values in µg/m³; except CO in mg/m³) in comparison to the European limit values (station Las Condes not included).

Pollutant	Mean	Median	25th percentile	75th percentile	Variance	2008/50/EG	
						Limit value	Averaging time
CO	0.8	0.57	0.3	1.3	0.7	10	8 h
NO ₂	34.0	24.0	15.4	44.6	678.6	40	1 year
O ₃	14.9	16.7	8.4	20.8	45.1	120	8 h
PM10	72.2	62.8	49.2	88.4	1161.0	40	1 year
PM2.5	33.7	27.6	20.8	41.7	335.0	25	1 year

Table 4

Case numbers of diseases of the respiratory system.

Disease	Total sum	Daily mean	Daily median	Daily min	Daily max	25th percentile	75th percentile
All respiratory diseases	95,597 (100%)	65.43	60	10	42	82	95,597
COPD	12,875 (13.5%)	8.81	8	0	5	12	12,875
Pneumonia	44,430 (46.5%)	30.41	24	2	16	39	44,430

2014; Lewis et al., 2013). Therefore, we assume that unidentified factors and/or the negative correlation between concentrations of O₃ and the other investigated pollutants may mask rather small adverse health effects of ozone.

4.2.3. NO₂

A number of studies described effects of NO₂ on respiratory morbidity (Braga et al., 2001; Faustini et al., 2013; Llorca et al., 2005; Luginaah et al., 2005; Tramuto et al., 2011). In Brazil, Braga et al. found decreasing effect strengths of NO₂ in 2-pollutant models if controlling for particulate matter (Braga et al., 2001). In the present study, both, NO₂ and articulate matter were the pollutants with the most distinct effects on respiratory hospitalization. Effects of NO₂ on respiratory diseases remained significant controlling in 2-pollutant models for CO, PM10, and O₃. The numbers of respiratory hospital admissions were found to be increased for more than one day indicating a considerable total effect of this pollutant. Some other studies also stated strong and longer lasting effects of NO₂ than for the other investigated pollutants (Faustini et al., 2013; Luginaah et al., 2005). Tao et al. (2014) also found increased risks for respiratory hospital admissions due to exposure to NO₂ lagged 1–4 days and strongest effects for this pollutant, PM10 and SO₂ (which was not investigated has lower concentrations in Santiago de Chile).

4.2.4. CO

Generally, epidemiological studies on effects of CO on respiratory morbidity resulted in different findings (Tian et al., 2013). Some authors described significant increases of numbers of hospital admissions (Luginaah et al., 2005; Zanobetti and Schwartz, 2006). Other authors

found small but significant effects of CO on respiratory hospitalizations (Fusco et al., 2001; Hinwood et al., 2006; Sauerzapf et al., 2009), could also not see significant effects (Fung et al., 2006), or detected protecting effects of CO for respiratory tract infections at lower concentration levels (Tian et al., 2013).

Despite of the known toxicological effects of CO, our assessments did not find evidence for a strong detrimental impact of this pollutant if considering the simultaneous exposure to other airborne pollutants. In 2-pollutant models of the present study adverse effects of CO only persisted if controlling for O₃ and disappeared if controlling for the other air pollutants. Weather conditions also modify effects of CO (Vanos et al., 2014). The high correlation coefficients with the concentrations of other pollutants may additionally have masked small detrimental effects of CO.

4.3. Strengths and limitations of the study

A main advantage of the study was the almost complete inclusion of the whole population of the city and nearly all hospital admissions. Complete data of public (FONASA) as well as private health insurance systems (ISAPRES) served as a basis of the epidemiological assessments. A general limitation of the most epidemiological studies addressing effects of air pollutants is the lack of indoor pollution data and the missing information about movement of people in the city which will also influence the inhaled dose. The considered number of airborne pollutants was limited. Many studies found evidence for adverse effects of ultrafine particles on morbidity and mortality. By trend, exposure to such particles may be stronger associated to cardiovascular than respiratory morbidity (Leitte et al., 2011). Because of lack of data, the present study

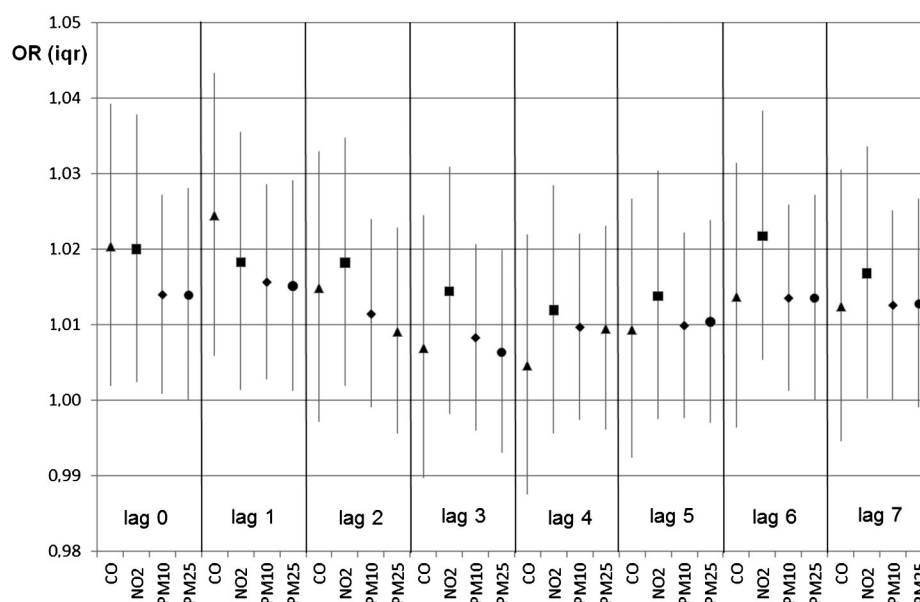


Fig. 1. Odds ratios for the associations between hospital admissions due to respiratory diseases for an interquartile range increase of exposures to CO, NO₂, PM10, and PM2.5 (1-pollutant models; lines indicate a significance level of 95%).

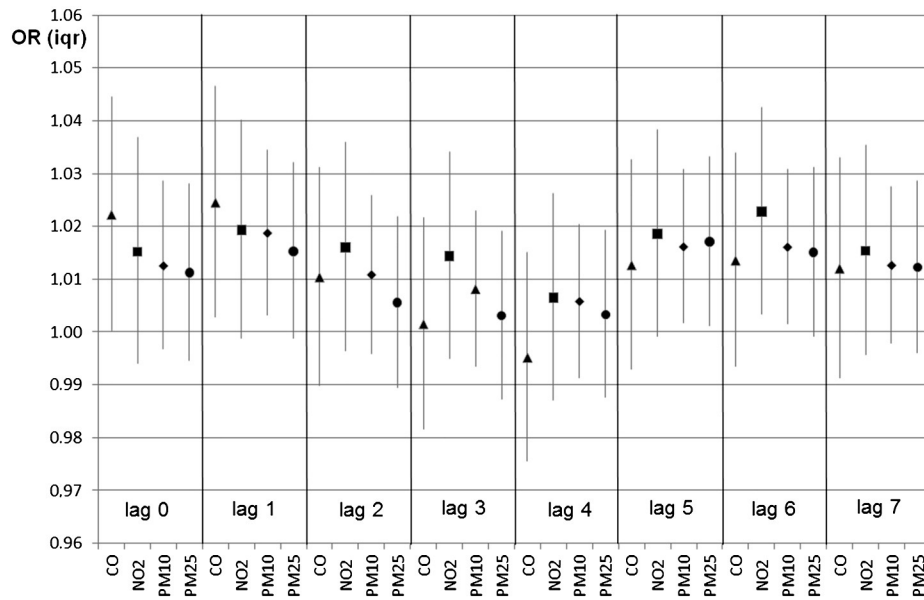


Fig. 2. Odds ratios for the associations between hospital admissions due to pneumonia for an interquartile range increase of exposures to CO, NO₂, PM₁₀, and PM_{2.5} (1-pollutant models; lines indicate a significance level of 95%).

could not consider chemical composition of particles which determines reactivity of particles and can therefore result in varying effect strength (Janssen et al., 2014; Leitte et al., 2012). A more detailed discussion of these limitations is given in the paper which investigated cardiovascular morbidity considering the same study area and period (Franck et al., 2014).

5. Conclusions

NO₂, particulate matter (PM₁₀, PM_{2.5}) and O₃ are dominant air pollutants in Santiago de Chile. NO₂ and PM are adversely associated with respiratory health even if their effects were controlled for other air pollutants. The lack of evidence for detrimental respiratory effects of ozone is controversial and effects of O₃ need to be further

investigated. With all due caution, the results may indicate that mitigation measures should preferentially address other pollutants and not ozone which is strongly associated with sun radiation.

Nevertheless, traffic and industry are playing an important role as sources for all the pollutants under investigation in this study. Therefore, mitigation measures in these fields will result in an improved state of public health even if our models show most adverse effects for only some of the investigated pollutants.

This study confirmed the prognosis that the reduction of urban air pollution in Santiago will significantly contribute to the protection of human health in the capital of Chile (Cifuentes et al., 2001) not only with respect to cardiovascular (Franck et al., 2014) but also respiratory diseases.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.scitotenv.2014.08.093>.

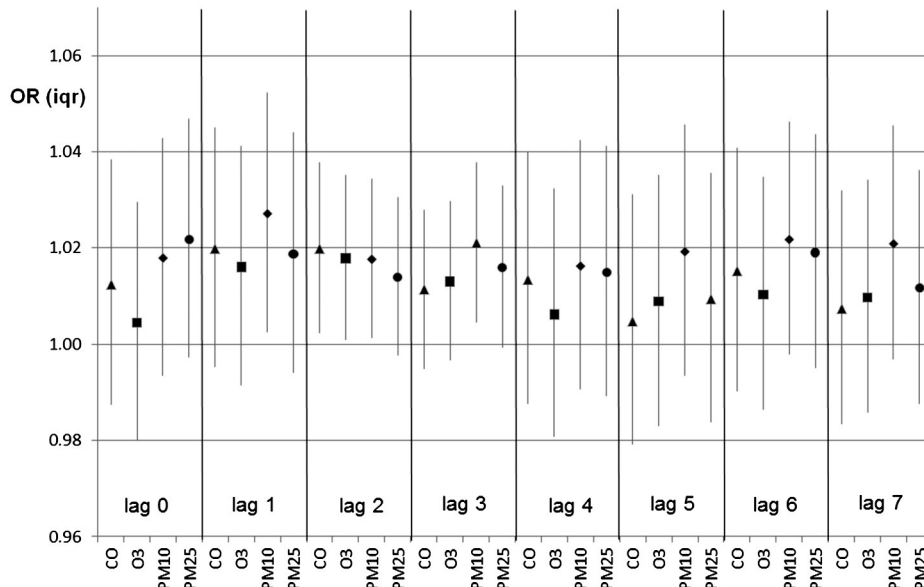


Fig. 3. Odds ratios for the associations between hospital admissions due to respiratory diseases for an interquartile range increase of exposure to NO₂ controlling for CO, O₃, PM₁₀, and PM_{2.5} (2-pollutant models; lines indicate a significance level of 95%).

Acknowledgments

The authors very appreciated the support of the Ministerio de Salud de Chile. The health data were kindly provided by the Departamento de Estadísticas e Información de Salud (DEIS). The study was funded by 'Initiative and Networking Fund' of the Helmholtz Association and was carried out within the framework of the Risk Habitat Megacity research initiative (<http://www.ufz.de/risk-habitat-megacity>).

References

- Ackermann-Lieblich U. Respiratory and cardiovascular effects of NO₂ in epidemiological studies. In: Nriagu JO, editor. *Encyclopedia of Environmental Health*. Elsevier; 2011. p. 840–4.
- Altug H, Gaga EO, Dogeroglu T, Brunekreef B, Hoek G, Van Doorn W. Effects of ambient air pollution on respiratory tract complaints and airway inflammation in primary school children. *Sci Total Environ* 2014;479–480:201–9.
- Atkinson RW, Cohen A, Mehta S, Anderson HR. Systematic review and meta-analysis of epidemiological time-series studies on outdoor air pollution and health in Asia. *Air Qual Atmos Health* 2012;5:383–91.
- Barnett AG, J. DA. *Analysing seasonal health data*. Springer; 2010.
- Barnett AG, Dobson AJ. *Analysing Seasonal Health Data*. Springer; 2010.
- Barnett AG, Williams GM, Schwartz J, Neller AH, Best TL, Petroeschovsky AL, et al. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am J Respir Crit Care Med* 2005;171:1272–8.
- Basu R, Dominici F, Samet JM. Temperature and mortality among the elderly in the United States: a comparison of epidemiologic methods. *Epidemiology* 2005;16(1):58–66.
- Bell ML, Davis DL, Gouveia N, Borja-Aburto VH, Cifuentes LA. The avoidable health effects of air pollution in three Latin American cities: Santiago, Sao Paulo, and Mexico City. *Environ Res* 2006;100:431–40.
- Bell ML, O'Neill MS, Ranjit N, Borja-Aburto VH, Cifuentes LA, Gouveia NC. Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico. *Int J Epidemiol* 2008;37:796–804.
- Braga AL, Saldiva PH, Pereira LA, Menezes JJ, Conceicao GM, Lin CA, et al. Health effects of air pollution exposure on children and adolescents in Sao Paulo, Brazil. *Pediatr Pulmonol* 2001;31:106–13.
- Breyssse P, Delfino R, Dominici F, Elder AP, Frampton M, Froines J, et al. US EPA particulate matter research centers: summary of research results for 2005–2011. *Air Qual Atmos Health* 2013;6:333–55.
- Brunekreef B. Health effects of air pollution observed in cohort studies in Europe. *J Expo Sci Environ Epidemiol* 2007;17(Suppl. 2):S61–5.
- Cakmak S, Dales RE, Gultekin T, Vidal CB, Farnendaz M, Rubio MA, et al. Components of particulate air pollution and emergency department visits in Chile. *Arch Environ Occup Health* 2009a;64:148–55.
- Cakmak S, Dales RE, Vidal CB. Components of particulate air pollution and mortality in Chile. *Int J Occup Environ Health* 2009b;15:152–8.
- Cakmak S, Dales RE, Rubio MA, Vidal CB. The risk of dying on days of higher air pollution among the socially disadvantaged elderly. *Environ Res* 2011;111:388–93.
- Chardon B, Lefranc A, Granados D, Gremy I. Air pollution and doctors' house calls for respiratory diseases in the Greater Paris area (2000–3). *Occup Environ Med* 2007;64:320–4.
- Chen Y, Yang Q, Krewski D, Burnett RT, Shi Y, McGrail KM. The effect of coarse ambient particulate matter on first, second, and overall hospital admissions for respiratory disease among the elderly. *Inhal Toxicol* 2005;17:649–55.
- Cifuentes L, Borja-Aburto VH, Gouveia N, Thurston G, Davis DL. Assessing the health benefits of urban air pollution reductions associated with climate change mitigation (2000–2020): Santiago, Sao Paulo, Mexico City, and New York City. *Environ Health Perspect* 2001;109(Suppl. 3):419–25.
- Dimitrova R, Lurpionglukana N, Fernando HJS, Runger GC, Hyde P, Hedquist BC, et al. Relationship between particulate matter and childhood asthma - basis of a future warning system for central Phoenix. *Atmos Chem Phys* 2012;12(5):2479–90.
- Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, et al. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 2006;295:1127–34.
- Dominici F, Peng RD, Ebisu K, Zeger SL, Samet JM, Bell ML. Does the effect of PM10 on mortality depend on PM nickel and vanadium content? A reanalysis of the NMMAPS data. *Environ Health Perspect* 2007;115:1701–3.
- Elshorbagy YF, Kleffmann J, Kurtenbach R, Rubio M, Lissi E, Villena G, et al. Summertime photochemical ozone formation in Santiago, Chile. *Atmos Environ* 2009;43:6398–407.
- Faustini A, Stafoggia M, Colais P, Berti G, Bisanti L, Cadum E, et al. Air pollution and multiple acute respiratory outcomes. *Eur Respir J* 2013;42(2):304–13.
- Franck U, Leitte AM, Suppan P. Multiple exposures to airborne pollutants and hospital admissions due to diseases of the circulatory system in Santiago de Chile. *Sci Total Environ* 2014;468–469:746–56.
- Franco Suglia S, Gryparis A, Schwartz J, Wright RJ. Association between traffic-related black carbon exposure and lung function among urban women. *Environ Health Perspect* 2008;116:1333–7.
- Fung KY, Khan S, Krewski D, Chen Y. Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. *Inhal Toxicol* 2006;18:1005–11.
- Fung KY, Luginaah IN, Gorey KM. Impact of air pollution on hospital admissions in South-western Ontario, Canada: generating hypotheses in sentinel high-exposure places. *Environ Health* 2007;6:18.
- 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;17:1143–50.
- Goldberg MS, Burnett RT, Stieb DM, Brophy JM, Daskalopoulou SS, Valois MF, et al. Associations between ambient air pollution and daily mortality among elderly persons in Montreal, Quebec. *Sci Total Environ* 2013;463–464:931–42.
- Gramsch E, Cereceda-Balic F, Oyola P, von Baer D. Examination of pollution trends in Santiago de Chile with cluster analysis of PM10 and Ozone data. *Atmos Environ* 2006;40:5464–75.
- Guo Y, Jia Y, Pan X, Liu L, Wichmann HE. The association between fine particulate air pollution and hospital emergency room visits for cardiovascular diseases in Beijing, China. *Sci Total Environ* 2009;407(17):4826–30.
- Hinwood AL, De Klerk N, Rodriguez C, Jacoby P, Runnion T, Rye P, et al. The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992–1998: a case-crossover study. *Int J Environ Health Res* 2006;16:27–46.
- Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health* 2013;12:43.
- Janes H, Sheppard L, Lumley T. Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias. *Epidemiology* 2005;16:717–26.
- Janssen NA, Hoek G, Simic-Lawson M, Fischer P, van Bree L, ten Brink H, et al. Black carbon as an additional indicator of the adverse health effects of airborne particles compared with PM10 and PM2.5. *Environ Health Perspect* 2011;119:1691–9.
- Janssen NA, Fischer P, Marra M, Ameling C, Cassee FR. Short-term effects of PM2.5, PM10 and PM2.5–10 on daily mortality in The Netherlands. *Sci Total Environ* 2013;463–464:20–6.
- Janssen NA, Yang A, Strak M, Steenhof M, Hellack B, Gerlofs-Nijland ME, et al. Oxidative potential of particulate matter collected at sites with different source characteristics. *Sci Total Environ* 2014;472:572–81.
- Jayaraman G, Nidhi. Air pollution and associated respiratory morbidity in Delhi. *Health Care Manag Sci* 2008;11:132–8.
- Kavouras IG, Koutrakis P, Cereceda-Balic F, Oyola P. Source apportionment of PM10 and PM2.5 in five Chilean cities using factor analysis. *J Air Waste Manag Assoc* 2001;51:451–64.
- Le TG, Ngo L, Mehta S, Do VD, Thach TQ, Vu XD, 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;5–72. [discussion 73–83].
- Lee IM, Tsai SS, Chang CC, Ho CK, Yang CY. Air pollution and hospital admissions for chronic obstructive pulmonary disease in a tropical city: Kaohsiung, Taiwan. *Inhal Toxicol* 2007;19:393–8.
- Leitte AM, Schlink U, Herbarth O, Wiedensohler A, Pan XC, Hu M, et al. Size-segregated particle number concentrations and respiratory emergency room visits in Beijing, China. *Environ Health Perspect* 2011;119:508–13.
- Leitte AM, Schlink U, Herbarth O, Wiedensohler A, Pan XC, Hu M, et al. Associations between size-segregated particle number concentrations and respiratory mortality in Beijing, China. *Int J Environ Health Res* 2012;22:119–33.
- Lewis TC, Robins TG, Mentz GB, Zhang X, Mukherjee B, Lin X, et al. Air pollution and respiratory symptoms among children with asthma: vulnerability by corticosteroid use and residence area. *Sci Total Environ* 2013;448:48–55.
- Lin S, Bell EM, Liu W, Walker RJ, Kim NK, Hwang SA. Ambient ozone concentration and hospital admissions due to childhood respiratory diseases in New York State, 1991–2001. *Environ Res* 2008;108:42–7.
- Linn WS, Szlachet C, Gong Jr H, Kinney PL, Bernhane KT. Air pollution and daily hospital admissions in metropolitan Los Angeles. *Environ Health Perspect* 2000;108:427–34.
- Lippmann M, Ito K, Nadas A, Burnett RT. Association of particulate matter components with daily mortality and morbidity in urban populations. *Res Rep Health Eff Inst* 2000;5–72. [discussion 73–82].
- Lipsett MJ, Tsai FC, Roger L, Woo M, Ostro BD. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. *Environ Health Perspect* 2006;114:1215–20.
- Llorca J, Salas A, Prieto-Salceda D, Chinchon-Bengoechea V, Delgado-Rodriguez M. Nitrogen dioxide increases cardiorespiratory admissions in Torrelavega (Spain). *J Environ Health* 2005;68:30–5.
- Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. *J Toxicol* 2011;2011:487074.
- Lu Y, Zeger SL. On the equivalence of case-crossover and time series methods in environmental epidemiology. *Biostatistics* 2007;8:337–44.
- Luginaah IN, Fung KY, Gorey KM, Webster G, Wills C. Association of ambient air pollution with respiratory hospitalization in a government-designated "area of concern": the case of Windsor, Ontario. *Environ Health Perspect* 2005;113:290–6.
- Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol* 1991;133(2):144–53.
- Mauderly JL, Samet JM. Is there evidence for synergy among air pollutants in causing health effects? *Environ Health Perspect* 2009;117:1–6.
- Medina-Ramon M, Zanobetti A, Schwartz J. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 2006;163:579–88.
- Moreno T, Querol X, Alastuey A, Viana M, Gibbons W. Profiling transient daytime peaks in urban air pollutants: city centre traffic hotspot versus urban background concentrations. *J Environ Monit* 2009;11:1535–42.

- Moreno F, Gramsch E, Oyola P, Rubio MA. Modification in the soil and traffic-related sources of particle matter between 1998 and 2007 in Santiago de Chile. *J Air Waste Manag Assoc* 2010;60:1410–21.
- Muggeo VM, Hajat S. Modelling the non-linear multiple-lag effects of ambient temperature on mortality in Santiago and Palermo: a constrained segmented distributed lag approach. *Occup Environ Med* 2009;66:584–91.
- Oftedal B, Nafstad P, Magnus P, Bjorkly S, Skrondal A. Traffic related air pollution and acute hospital admission for respiratory diseases in Drammen, Norway 1995–2000. *Eur J Epidemiol* 2003;18:671–5.
- Peel JL, Tolbert PE, Klein M, Metzger KB, Flanders WD, Todd K, et al. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 2005;16:164–74.
- Development Core Team R. A language and environment for statistical computing; 2008 [from <http://www.R-project.org/>].
- Sauerzapf V, Jones AP, Cross J. Environmental factors and hospitalisation for chronic obstructive pulmonary disease in a rural county of England. *J Epidemiol Community Health* 2009;63:324–8.
- Schmitz R. Modelling of air pollution dispersion in Santiago de Chile. *Atmos Environ* 2005;39:2035–47.
- Schwela D. Air pollution and health in urban areas. *Rev Environ Health* 2000;15:13–42.
- Seguel RJ, Raúl GEM, Leiva MA. Ozone weekend effect in Santiago, Chile. *Environ Pollut* 2012;162:72–9.
- Seidel DJ, Ao CO, Li K. Estimating climatological planetary boundary layer heights from radiosonde observations: comparison of methods and uncertainty analysis. *J Geophys Res Atmos* 2010;115. [D16113].
- Simpson R, Williams G, Petroeschovsky A, Best T, Morgan G, Denison L, et al. The short-term effects of air pollution on hospital admissions in four Australian cities. *Aust N Z J Public Health* 2005;29:213–21.
- Son JY, Lee JT, Park YH, Bell ML. Short-term effects of air pollution on hospital admissions in Korea. *Epidemiology* 2013;24:545–54.
- Spix C, Anderson HR, Schwartz J, Vigotti MA, LeTertre A, Vonk JM, et al. Short-term effects of air pollution on hospital admissions of respiratory diseases in Europe: a quantitative summary of APHEA study results. *Air pollution and health: a European approach*. *Arch Environ Health* 1998;53:54–64.
- Stafoggia M, Samoli E, Alessandrini E, Cadum E, Ostro B, Berti G, et al. Short-term associations between fine and coarse particulate matter and hospitalizations in southern Europe: results from the MED-PARTICLES project. *Environ Health Perspect* 2013;121(9):1026–33.
- Stieb DM, Szyszkowicz M, Rowe BH, Leech JA. Air pollution and emergency department visits for cardiac and respiratory conditions: a multi-city time-series analysis. *Environ Health* 2009;8:25.
- Suppan P, Franck U, Schmitz R, Baier F. Air quality and health: a hazardous combination of environmental risks. In: Heinrichs D, Krellenberg K, Hansjürgens B, Martínez F, editors. *Risk habitat megacity*. Heidelberg, Dordrecht, London, New York: Springer; 2012. p. 229–50.
- Tao Y, Mi S, Zhou S, Wang S, Xie X. Air pollution and hospital admissions for respiratory diseases in Lanzhou, China. *Environ Pollut* 2014;185:196–201.
- 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;188:1240–5.
- Tong S, Wang XY, Guo Y. Assessing the Short-Term Effects of Heatwaves on Mortality and Morbidity in Brisbane, Australia: Comparison of Case-Crossover and Time Series Analyses. *PLoS One* 2012;7(5):e37500. <http://dx.doi.org/10.1371/journal.pone.0037500>.
- Tramuto F, Cusimano R, Cerame G, Vultaggio M, Calamusa G, Maida CM, et al. Urban air pollution and emergency room admissions for respiratory symptoms: a case-crossover study in Palermo, Italy. *Environ Health* 2011;10:31.
- Vaneckova P, Bambrick H. Cause-specific hospital admissions on hot days in Sydney, Australia. *PLoS One* 2013;8:e55459.
- Vanos JK, Hebborn C, Cakmak S. Risk assessment for cardiovascular and respiratory mortality due to air pollution and synoptic meteorology in 10 Canadian cities. *Environ Pollut* 2014;185:322–32.
- Vera J, Cifuentes L. Association of hospital admissions for cardiovascular causes and air pollution (PM10, PM25 and O3) in Santiago, Chile. *Epidemiology* 2008;19:S368.
- Vera J, Cifuentes LA, Strappa V. Association of particulate matter and hospital admissions in Santiago, Chile. *Epidemiology* 2007;18:S210–1.
- Wong CM, Vichit-Vadakan N, Vajanapoom N, Ostro B, Thach TQ, Chau PY, et al. Part 5. Public health and air pollution in Asia (PAPA): a combined analysis of four studies of air pollution and mortality. *Res Rep* 2010:377–418.
- Yang CY, Chen CJ. Air pollution and hospital admissions for chronic obstructive pulmonary disease in a subtropical city: Taipei, Taiwan. *J Toxicol Environ Health A* 2007;70:1214–9.
- Zanobetti A, Schwartz J. Air pollution and emergency admissions in Boston, MA. *J Epidemiol Community Health* 2006;60:890–5.
- Zauli Sajani S, Hanninen O, Marchesi S, Lauriola P. Comparison of different exposure settings in a case-crossover study on air pollution and daily mortality: counterintuitive results. *J Expo Sci Environ Epidemiol* 2011;21:385–94.