

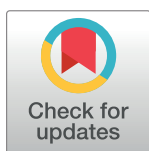
RESEARCH ARTICLE

Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis

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Abstract

Background

Several observational studies have suggested that outdoor air pollution may induce or aggravate asthma. However, epidemiological results are inconclusive due to the presence of numerous moderators which influence this association. The goal of this study was to assess the relationship between outdoor air pollutants and moderate or severe asthma exacerbations in children and adults through a systematic review and multilevel meta-analysis.

Material and methods

We searched studies published in English on PubMed, Scopus, and Google Scholar between January 2000 and October 2016. Studies following a case-crossover design with records of emergency departments and/or hospital admissions as a surrogate of moderate or severe asthma exacerbations were selected. A multilevel meta-analysis was employed, taking into account the potential clustering effects within studies examining more than one lag. Odds ratios (ORs) and 95% confidence intervals were estimated. A subgroup analysis in children aged 0 to 18 years and a sensitivity analysis based on the quality of the included studies as defined in the Newcastle-Ottawa Scale were performed. Publication bias was evaluated through visual inspection of funnel plots and by a complementary search of grey literature. (Prospero Registration number CRD42015032323).

Results

Database searches retrieved 208 records, and finally 22 studies were selected for quantitative analysis. All pollutants except SO₂ and PM₁₀ showed a significant association with asthma exacerbations (NO₂: 1.024; 95% CI: 1.005, 1.043, SO₂: 1.039; 95% CI: 0.988, 1.094), PM₁₀: 1.024; 95% CI: 0.995, 1.053, PM_{2.5}: 1.028; 95% CI: 1.009, 1.047, CO: 1.045; 95% CI:

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Citation: Orellano P, Quaranta N, Reynoso J, Balbi B, Vasquez J (2017) Effect of outdoor air pollution on asthma exacerbations in children and adults: Systematic review and multilevel meta-analysis. PLoS ONE 12(3): e0174050. <https://doi.org/10.1371/journal.pone.0174050>

Editor: Qinghua Sun, The Ohio State University, UNITED STATES

Received: September 5, 2016

Accepted: March 2, 2017

Published: March 20, 2017

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study did not receive any specific funding, but was supported by the research budget of the Universidad Tecnológica Nacional, Facultad Regional San Nicolás. PO is supported by the Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), and NQ by the Comisión de Investigaciones Científicas (CIC).

Competing interests: The authors have declared that no competing interests exist.

1.005, 1.086, O_3 : 1.032; 95% CI: 1.005, 1.060. In children, the association was significant for NO_2 , SO_2 and $PM_{2.5}$.

Conclusion

This meta-analysis provides evidence of the association between selected air pollutants and asthma exacerbations for different lags.

Introduction

Asthma can be defined as a chronic inflammatory disorder of the airways associated with bronchial hyper-responsiveness, reversible airflow limitation and recurrent symptoms of wheezing, chest tightness, and cough [1]. Worldwide, asthma accounts for nearly 1% of all disability adjusted life years (DALYs) lost [2]. According to recent estimates, as many as 623 million people are currently living with some level of asthma-related symptoms [3], while 250,000 deaths can be attributed to this disease each year [4]. Economic losses due to asthma are estimated to be the highest among patients with chronic diseases due to significant healthcare utilization. Hospitalization and medications are the most important associated direct costs, while work and school absenteeism account for the greatest percentage of indirect costs [5]. On the other hand, asthma exacerbations are common in asthmatic patients [6], and the main goal of asthma treatment is the prevention of exacerbations and fixed airflow limitation [7].

Asthma exacerbations can be classified as mild, moderate, and severe, with the latter two generally requiring an emergency department visit and likely hospitalization [8]. In children, several risk factors for asthma exacerbations have been identified, including poor asthma control, individual susceptibility, viral infections, allergen exposure, environmental tobacco smoke (ETS) exposure, and outdoor air pollution [9].

Several studies have confirmed that air pollution from ozone (O_3), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter (PM) may induce or aggravate asthma [10]. A large number of observational studies have been conducted to assess the effect of air pollutants in asthma prevalence, incidence, and exacerbations. According to a number of published meta-analysis [11,12,13,14], these pollutants in the atmosphere are associated with higher incidence, prevalence, hospitalizations, or worsening of symptoms of asthma. Regarding the short-term effects of air pollutants in terms of exacerbations or worsening of symptoms, three studies have found an association with PM, NO_2 , SO_2 , carbon monoxide (CO) and O_3 [15,16,17]. In one of these studies analyzing data from Asia, the association was not significant in people aged 15–64 years [17].

The present study provides complementary results to these previous meta-analyses, with two main methodological differences. First, our study has estimated a pooled association measure considering all lag times between air pollution increase and asthma exacerbations for each individual study, using a multilevel analysis. In contrast, previous meta-analyses either used only one lag for study, selecting them through predetermined rules of choice, or made subgroup analysis of specific lags. Second, our meta-analysis selected only studies following case-crossover designs, while previous meta-analyses included all time-series designs. The pros and cons of these choices are examined in the discussion section. Thus, the goal of this study was to assess the association between the increase in concentration of outdoor air pollutants and moderate or severe asthma exacerbations in children and adults, through a systematic review, multilevel meta-analysis, and meta-regression of case-crossover studies, pooling all the lag times and taking into account potential moderators.

Materials and methods

We prepared this article according to the PRISMA guidelines for systematic reviews and meta-analysis [18] (S1 Table). The protocol for this study was registered in PROSPERO (<http://www.crd.york.ac.uk/PROSPERO/>) under registration number CRD42015032323 before the formal screening of search results (S1 File). A pilot of the study was previously carried out to adjust the search strategy.

Search strategy and sources

We searched studies published in English in PubMed, Scopus, and Google Scholar between January 2000 and October 2016. The searched studies should explore the relationship between outdoor air pollution and acute exacerbations of asthma in children and adults through a case-crossover observational design. Moderate and severe exacerbations were represented as visits to emergency departments or hospitalizations by this cause. A combination of the following terms combined using Boolean connectors was used: “asthma”, “wheeze”, “pollut*”, “contamin*”, “hospitaliz*”, “admission*”, “emergenc*”, “attack*”, “case crossover”. A detailed description of the search strategy in PubMed, Scopus, and Google Scholar is shown in the supplementary material (S2 Table). In addition, we have manually searched in reference lists from other systematic reviews in order to find additional studies.

Study selection

Two reviewers (PO and JR) independently screened all records retrieved from database searches in three stages. First they searched the assessment of titles, second the assessment of abstracts, and finally they screened the assessment of full-text articles. Any disagreement was resolved by consensus with the help of a third reviewer (BB). The inclusion criteria for the retrieved articles were: (1) studies following a case-crossover design; (2) assessment of outdoor air pollution represented by NO₂, SO₂, PM₁₀, PM_{2.5}, CO and O₃; (3) studies working with records of emergency departments or hospital admissions as a surrogate of moderate or severe asthma exacerbations; (4) studies reporting odds ratio (OR) and 95% confidence intervals (95%CI) as the measure of association; and (5) articles published as a full-text document.

Data extraction

Data were extracted by means of a data extraction form developed in Microsoft Excel®. These data included: (1) first author and year of publication; (2) participant’s age and gender; (3) OR and 95% confidence intervals (95%CI); (4) the lags, understood as the time distance between the increase of the selected pollutant and the date of the asthma exacerbation. Other variables considered were latitude and elevation of the study sites. These variables were used in the meta-regression analysis. In the case of multicity studies, a separate OR was extracted for each city. When this information was not available, the data was considered as missing.

Risk of bias and quality assessment

Two reviewers (PO and JR) independently evaluated the methodological quality of each selected study, in order to determine the risk of bias. The Newcastle–Ottawa scale (NOS) for case-control studies was used as a measure of the quality of individual studies [19]. In this scale, there are three dimensions: selection of the study group, comparability of the groups, and exposure ascertainment. A total of seven questions are raised, with a minimum of zero and a maximum of nine stars. Study quality is then graded as poor (1–3 stars), intermediate (4–6 stars), or high (7–9 stars). An explanation of each question adapted for this study is

presented in the supporting material (S3 Table). The potential risk of publication bias was evaluated by visual examination of funnel plots asymmetry [20]. In addition, a grey literature search was performed in order to identify studies from conference proceedings and other sources that may have had null results and were not published as articles in journals. The sources for the grey literature search were Google Scholar, Scopus, Biomed Central (<http://www.biomedcentral.com>) and NLM Gateway (<https://gateway.nlm.nih.gov/gw/Cmd>).

Sensitivity analysis

We performed a sensitivity analysis based on the quality of the included studies as defined in the NOS. Studies classified with 6 or more stars (intermediate-high quality) were selected for the sensitivity analysis.

Statistical analysis

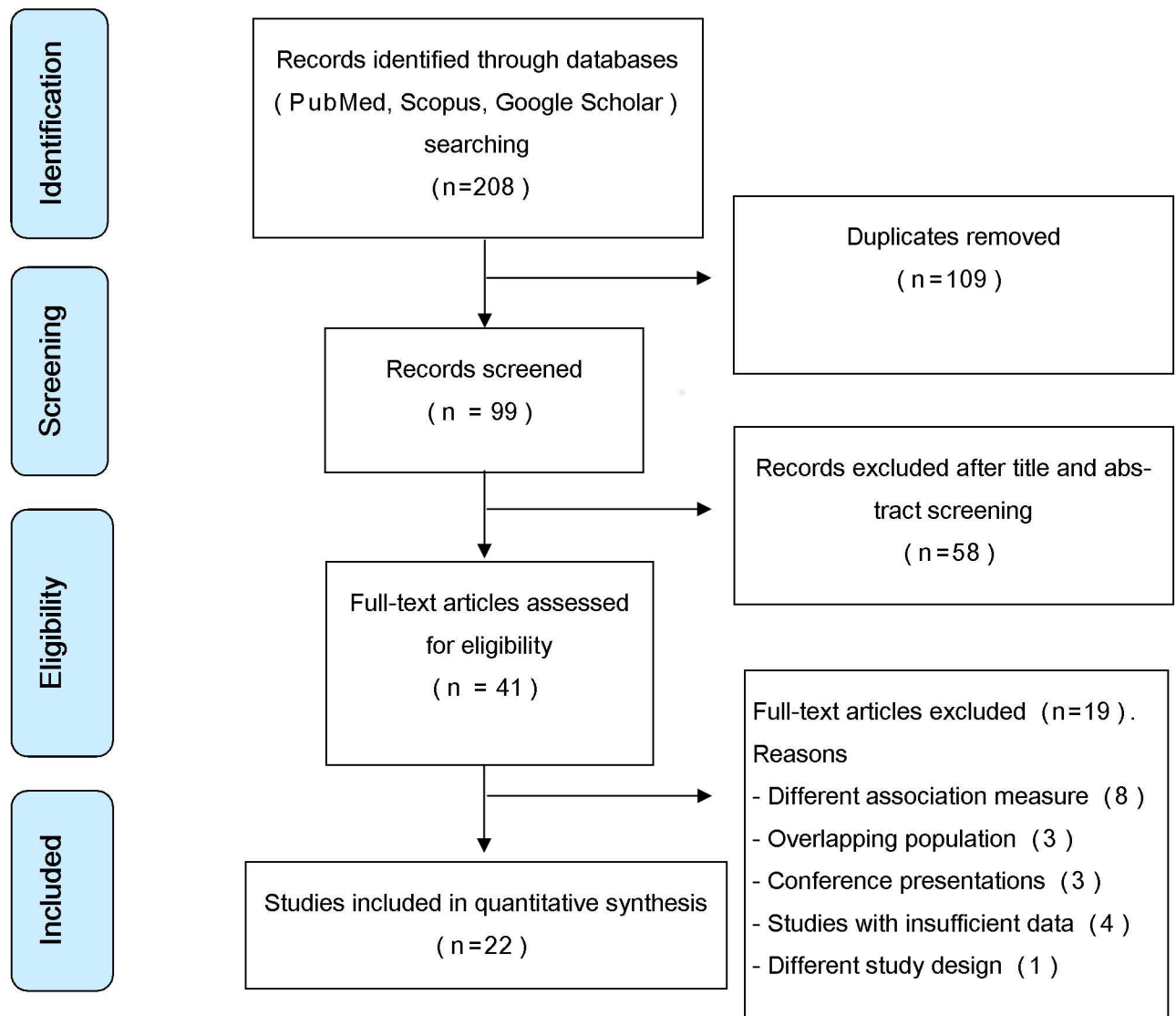
The ORs and 95% CIs derived from single-pollutant models were retrieved and weighted based on the inverse of the variance method, assuming that observations with lower variances should be given more weight in the analysis. Where necessary, the coefficient estimates were recalculated to reflect a 10- $\mu\text{g}/\text{m}^3$ increase in PM_{10} and $\text{PM}_{2.5}$, a 10 ppb increase in NO_2 , SO_2 , and O_3 , and a 1 ppm increase in CO, assuming a linear relationship within the considered range. The majority of studies contributed with more than one lag between the increases in pollutant concentration up to the date of the asthma exacerbation. Accordingly, we used two or more effect sizes from each study, one for each lag. Thus, a multilevel meta-analytic model was employed, taking into account the potential clustering effects within studies examining more than one lag at a time. Other meta-analyses considered only one lag per study using a preset rule. On the contrary, the multilevel meta-analysis allows for the hierarchical structure of the data, in which lags are nested within studies. The multilevel model was then extended using a multilevel meta-regression model to test the modifying effect of the lag and other moderators, i.e. the latitude and elevation. The heterogeneity was measured with the Q_E -test for residual heterogeneity, which tests whether the variability in the observed effect sizes that is not accounted for by the moderators is larger than one would expect based on sampling variability [21]. A subgroup analysis in children aged 0 to 18 years was also performed, to evaluate the possible association in this age group. All analyses were performed using the “metafor” package (version 1.9–4) [21] in the statistical software R, version 3.2.2 (<https://www.r-project.org/>) [22]. The latitude and elevation of the cities were obtained through packages “ggmap” [23] and “weatherr” [24] from the same software.

Results

Characteristics and quality of studies

Database searches retrieved 208 records. After removing duplicates, title and abstract screen on 99 records were completed by reviewers, and 41 articles were selected for full-text eligibility assessment. Nineteen studies were excluded due to different reasons (Fig 1). Finally, 22 studies were selected for quantitative analysis (Fig 1), representing 267,413 visits to emergency departments, emergency calls, or hospitalizations due to asthma exacerbations in all age groups.

Of these studies, 12 analyzed only children and one analyzed only adults. The outcomes were hospitalizations (seven), emergency department visits (10), both (four) or emergency telephone calls (one). Studies were carried out in 12 countries. 10 were classified as high-income countries, and two were classified as upper-middle-income countries according to the World Bank classification [25]. The elevation of the cities where the studies were carried out were between eight and 1,134 meters over the sea level, and absolute latitudes were between



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-

Fig 1. PRISMA flowchart of the study identification and selection process.

<https://doi.org/10.1371/journal.pone.0174050.g001>

25° and 54°, while tropical climate zones were not represented. A general description of each included study can be seen in [Table 1](#).

The lags considered included single-day lags (0 to 6 days) and cumulative lags (1 to 6 days moving average) before the date of the event. The majority of studies assessed the effect of more than one pollutant (16 studies), while eight studies considered two or multiple pollutant models in addition to single pollutant models. All studies employed generalized linear model (GLM) techniques to estimate the regressions, but two studies also used a generalized additive model (GAM). The other variables considered for adjusting the regressions were temperature, relative humidity, dew point, barometric pressure, wind speed, global radiation, cloudiness,

Table 1. Characteristics of the included studies.

First author, year	Country	Country classification	N	Ages (years)	Pollutants	NOS scale	Ref.
Alman, 2016	USA	High-income	1,136	0–≥ 65	PM _{2.5}	5	[26]
Canova, 2012	UK	High-income	234	18–≥ 75	PM ₁₀	7	[27]
Chen, 2013	Taiwan	High-income	1,912	5–15	PM _{2.5} , O ₃	6	[28]
Ding, 2016	China	Upper-middle-income	2,507	0–18	NO ₂ , SO ₂ , PM ₁₀ , PM _{2.5} , CO, O ₃	5	[29]
Glad, 2012	USA	High-income	6,979	0–≥ 75	PM _{2.5}	6	[30]
Gleason, 2014	USA	High-income	21,854	3–17	PM _{2.5} , O ₃	6	[31]
Grineski, 2011	USA	High-income	3,504	1–≥ 65	NO ₂ , PM _{2.5}	6	[32]
Iskandar, 2012	Denmark	High-income	8,226	0–18	NO ₂ , PM ₁₀ , PM _{2.5}	5	[33]
Laurent, 2008	France	High-income	4,677	0–≥ 65	NO ₂ , SO ₂ , PM ₁₀ , O ₃	5	[34]
Lavigne, 2012	Canada	High-income	3,728	2–≥ 60	NO ₂ , SO ₂ , PM _{2.5} , CO, O ₃	6	[35]
Lewin, 2013	Canada	High-income	429	0–4	SO ₂ , PM _{2.5}	5	[36]
Li, 2011	USA	High-income	7,063	2–18	NO ₂ , SO ₂ , PM _{2.5} , CO	6	[37]
Lin, 2003	Canada	High-income	7,319	6–12	NO ₂ , SO ₂ , CO, O ₃	5	[38]
Pereira, 2010	Australia	High-income	603	0–19	NO ₂ , CO	5	[39]
Sacks, 2014	USA	High-income	121,621	0–≥ 65	O ₃	6	[40]
Santus, 2012	Italy	High-income	3,579	0–≥ 75	NO ₂ , SO ₂ , PM ₁₀ , PM _{2.5} , CO, O ₃	5	[41]
Smargiassi, 2009	Canada	High-income	1,842	2–4	SO ₂	6	[42]
Sunyer, 2002	Spain	High-income	4,635	14–≥ 80	NO ₂ , SO ₂ , PM ₁₀ , CO, O ₃	8	[43]
Tecer, 2008	Turkey	Upper-middle-income	2,779	0–14	PM ₁₀ , PM _{2.5}	5	[44]
Ueda 2010	Japan	High-income	3,427	0–12	NO ₂ , SO ₂ , PM ₁₀	5	[45]
Villeneuve 2007	Canada	High-income	57,912	2–≥ 75	NO ₂ , SO ₂ , PM ₁₀ , PM _{2.5} , O ₃	6	[46]
Yamazaki 2015	Japan	High-income	1,447	0–14	NO ₂ , PM ₁₀ , PM _{2.5} , O ₃	5	[47]

NO₂: nitrogen dioxide, SO₂: sulfur dioxide, O₃: ozone, CO: carbon monoxide, PM₁₀: particulate matter < 10 µm, PM_{2.5}: particulate matter < 2.5 µm, N: number of emergency department visits, hospitalizations or participants, NOS scale: Newcastle-Ottawa scale.

<https://doi.org/10.1371/journal.pone.0174050.t001>

and one study took into account the influenza and soybean asthma outbreaks, while four studies failed to consider the adjustment for other variables.

According to the NOS, 20 studies were classified as intermediate quality, and the remaining two studies were classified as high quality. The two main problems related to studies' quality were the adequate case definition and the ascertainment of exposure, because in most articles there was no independent validation and the residential address of cases was not verified.

Data preprocessing, heterogeneity, and publication bias

In quantitative analysis, the 22 studies contributed with 345 effect sizes corresponding to NO₂ (68), SO₂ (60), PM₁₀ (44), PM_{2.5} (68), CO (50) and O₃ (55) were included.

Based on the results of the meta-regression, the lag significantly affected the relationship between the increases in pollutant concentrations and severe asthma exacerbations for the NO₂ and the O₃ (Table 2). For SO₂, PM₁₀, PM_{2.5} and CO, the lag had no influence on the associations. Other moderators that influenced these associations were the elevation over the sea level for the PM₁₀ and the latitude for the PM₁₀, PM_{2.5} and CO (Table 2). The Q_E for each pollutant showed a significant heterogeneity for the SO₂, PM₁₀, PM_{2.5}, and O₃, which could possibly indicate that other moderators not considered in the models are influencing the association between these pollutants and the occurrence of asthma exacerbations (Table 2).

An asymmetry in data points can be observed for NO₂, PM₁₀, and CO, where the absence of negative outcomes produced by less precise studies suggested potential publication biases (Fig 2).

Table 2. Multilevel meta-regression analysis.

Pollutant	Q _E (P-value)	Moderator	P-value
NO ₂	0.33	Lag	<0.01
		Latitude	0.80
		Elevation	0.14
SO ₂	0.02	Lag	0.36
		Latitude	0.51
		Elevation	0.16
PM ₁₀	<0.01	Lag	0.4
		Latitude	<0.01
		Elevation	<0.01
PM _{2.5}	<0.01	Lag	0.76
		Latitude	0.01
		Elevation	0.81
CO	0.85	Lag	0.39
		Latitude	0.01
		Elevation	0.55
O ₃	0.03	Lag	<0.01
		Latitude	0.22
		Elevation	0.54

NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide; PM₁₀: particulate matter < 10 µm; PM_{2.5}: particulate matter < 2.5 µm; Q_E: test for residual heterogeneity.

<https://doi.org/10.1371/journal.pone.0174050.t002>

The plots show the observed outcomes (Log odds ratios) on the horizontal axis against their corresponding standard errors for nitrogen dioxide (NO₂), sulfur dioxide (SO₂), ozone (O₃), carbon monoxide (CO), particulate matter < 10 µm (PM₁₀) and particulate matter < 2.5 µm (PM_{2.5}). The search of grey literature identified seven additional studies not included in our analysis; five were conference abstracts [48–52] and two were articles published in local languages (Italian and Korean) [53,54]. In none of these studies the association of pollutants with asthma exacerbations was negative, null or non-significant.

Association between pollutants and asthma exacerbations

The only pollutants that did not show a significant association with asthma exacerbations within the considered lags were SO₂ (OR: 1.039; 95% CI: 0.988,1.094) and PM₁₀ (OR: 1.024; 95% CI: 0.995,1.053), while this association was significant for NO₂ (OR: 1.024; 95% CI: 1.005,1.043), PM_{2.5} (OR: 1.028; 95% CI: 1.009,1.047), CO (OR: 1.045; 95% CI: 1.005,1.086), and O₃ (OR: 1.032; 95% CI: 1.005,1.060). Figures in [S2 File](#) show forest plots with adjusted ORs and their 95%CI for the associations between pollutants and asthma exacerbations, as reported in each original article. In the subgroup analysis of children aged 0 to 18 years, the association was significant for NO₂ (OR: 1.040; 95% CI: 1.001,1.081), SO₂ (OR: 1.047; 95% CI: 1.009,1.086), and PM_{2.5} (OR: 1.022; 95% CI: 1.000,1.045). A subgroup analysis of adults was not performed as only one study was focused exclusively on this age group, while few studies reported results of adults separately from those of children.

Sensitivity analysis

For the sensitivity analysis, 11 studies with a NOS scale ≥ 6 (intermediate-high quality) were selected, representing 113 effect sizes. According to these analyses, the association was

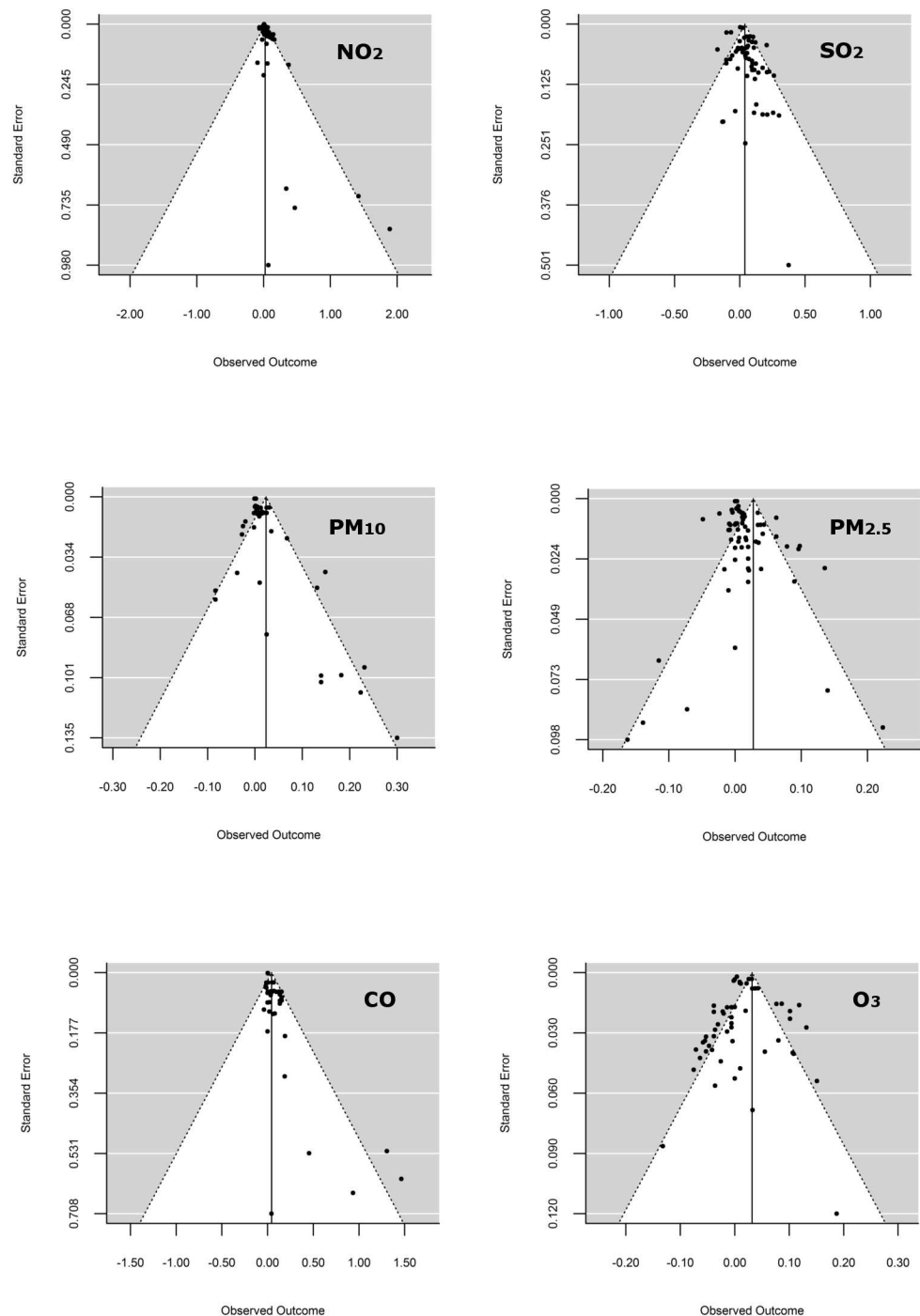


Fig 2. Funnel plot to explore publication bias for each pollutant. The figure shows the observed outcomes (Log odds ratios) on the horizontal axis against their corresponding standard errors.

<https://doi.org/10.1371/journal.pone.0174050.g002>

significant for NO₂ (OR: 1.009; 95% CI: 1.004,1.013), PM_{2.5} (OR: 1.023; 95% CI: 1.006,1.041) and O₃ (OR: 1.020; 95% CI: 1.013,1.027). Heterogeneity could be controlled after the sensitivity analysis for all pollutants (S4 Table). Publication bias in this subanalysis was not evaluated due to the more reduced sample size.

Discussion

This meta-analysis showed a significant association between the main pollutants, with the exception of SO_2 and PM_{10} , and moderate or severe exacerbations of asthma. Moreover, this approach allowed the simultaneous analysis of all lags considered in different studies, obtaining one pooled measure of association. In the subgroup analysis of children, the exacerbations were associated with NO_2 , SO_2 and $\text{PM}_{2.5}$. In the sensitivity analysis, where only studies with a NOS scale ≥ 6 were selected, the association was significant for NO_2 , $\text{PM}_{2.5}$ and O_3 . The most important outdoor air pollutants are PM, O_3 , SO_2 , NO_2 , CO and Lead (Pb) [55]. The main anthropogenic sources of PM are traffic and transportation, electricity generation and other combustion processes [56]. With respect to gases, the main sources of SO_2 in the developed world are primary emissions during energy production or industrial processes [57], while NO_2 and CO are principally emitted from fossil fuel combustion in urban environments [58]. Ozone is a secondary pollutant formed by photochemical reactions between sunlight and pollutant precursors, such as nitrogen oxides and volatile organic compounds [59]. Increased pollution exposures have been associated with increased numbers of hospital admissions and emergency-room visits, mainly due to exacerbations of chronic obstructive pulmonary disease (COPD) and asthma [60]. Air pollution may be related to asthma exacerbations through oxidative stress, airway remodeling and inflammation, and sensitization to aeroallergens [61,62]. Further, pulmonary inflammation can indirectly influence the worsening of asthma symptoms by affecting host defenses [63] and enhancing infections with rhinovirus (RV), influenza, and respiratory syncytial virus (RSV), which in turn are considered the main cause of asthma exacerbations [64]. Specifically, O_3 exposure causes airway inflammation, airway hyper-responsiveness, and decrements in lung function, while SO_2 mainly leads to bronchoconstriction [64] and NO_2 probably triggers bronchial inflammation as a precursor of O_3 [64]. On the other hand, exposure to PM might cause oxidative stress, airway hyper-responsiveness, and airway remodeling, either alone or in combination with allergic sensitization [65]. In the atmosphere, different PM sizes can be found. The coarse fraction ($\text{PM}_{10-2.5}$) can penetrate into the upper airways, but the fine fraction ($\text{PM}_{2.5-1}$) can be deposited in the lung, especially in the alveoli, although it could pass to the systemic circulation [63]. It should be noted that besides the size of PM, the chemical composition is very important to understand the health effects of particulate matter. There are also differences in the individual susceptibility to air pollutants. Children are more affected than adults and boys more affected than girls, while a diet high in fruits and vegetables and of antioxidant vitamin supplements could be a protective factor, and obesity might increase susceptibility to the adverse effects of air pollution [62].

In this article, the heterogeneity of the included studies was significant for SO_2 , PM_{10} , $\text{PM}_{2.5}$ and O_3 , and could not be completely controlled by the modifying effect of the moderators that were considered here, including the lag, the elevation and the latitude of the cities that were under analysis. It is possible that other effect modifiers, which were not available in the included articles, could have influenced these results. However, the heterogeneity was resolved for all pollutants in the sensitivity analysis.

The funnel plots showed a degree of asymmetry for the NO_2 , the PM_{10} and the CO. This asymmetry may suggest that small studies showing no statistically significant effects remain unpublished, and then the true effect could be overestimated [66]. Another possible explanation could be that small studies may have weaker methodological quality than larger studies, leading to an overestimation of the true effects [67]. Regarding the first possibility, our complementary search of grey literature allowed us to identify seven additional studies with the same design and objectives. However, in these studies the association between air pollutants and asthma exacerbations was positive and significant, meaning that the reason to be unpublished

in journals was not related to null results. As to the second possible explanation, for NO₂ and CO all the effect sizes that presented the highest standard errors came from a single study [39] that showed a low value (5 stars) of the NOS scale. Nonetheless, for PM₁₀ the effect sizes that showed the maximum values of standard errors came from one study that was classified as high-quality [27] according to the NOS scale. It is worth noting that this study was the one that included only adults. Taking these results into consideration, it is possible that the asymmetry of funnel plots showed by the NO₂ and the CO can be due to a weak methodological quality of one study which contributes with 5 observations, and not to publication bias. On the other hand, for PM₁₀ the funnel plot asymmetry does not seem to be related to methodological quality, and thus publication bias cannot be ruled out.

In general, the relatively small risks and ORs detected through this meta-analysis may lead one to assume that the potential effect of outdoor air pollutants at a population level is negligible, and thus the impact of public health measures could be dismissed. However, nearly 300 million people suffer from asthma globally [4]. A large amount of people are susceptible to moderate and severe exacerbations related to outdoor air pollution, and a very large number of people are exposed to outdoor pollutants, for example by living near polluted roads. Considering these two facts, a combination of small relative risks and high prevalence of exposure can contribute to a moderate population attributable fraction. Thus, a public health intervention aimed at mitigating the effects of air pollutants and targeted to the entire population might have significant benefits for the society.

This study had several limitations. The first was the use of non-randomized observational studies that failed to control bias due to the confounding effects of several factors. The second limitation was that the majority of studies which were included used secondary data sources for the asthma hospitalizations and emergency visits. These two points do not allow the control of confounding factors, for example by controlling the change in medications or the exposure to secondhand smoke in the evaluated cases. A third limitation was that air pollutant concentrations were estimated in a different way in different studies, such as using alternative models or an unequal number of monitoring sites. Besides, the lags considered were often different, and these points would have caused the high heterogeneity between studies. The limited number of moderators could be considered the fourth limitation, as there are probably several other factors that modify the association between air pollutants and asthma exacerbations. One of these factors is the country income: almost all studies were conducted in high-income countries, and accordingly the effect of these pollutants in the asthma exacerbations could not be extrapolated to developing countries. Finally, this article only considered studies following a case-crossover design. This might be seen as a limitation in the sense that a number of studies have likely been excluded from the analysis, particularly time-series studies. The equivalence of results obtained from time-series Poisson regression and from case-crossover studies using conditional logistic regression has been proposed by Lu et al. [68]. However, there exist at least three differences between these methods. First, case-crossover designs appear to be less efficient than Poisson time-series designs, i.e. showing lower statistical power [69–71]. Second, case-crossover designs are less vulnerable to bias [69–71] and, unlike time-series analyses, individual data can be included to estimate effect modifications and to control for confounders by design [72]. Third, time-series regression based on generalized additive models involves several arbitrary decisions, e.g. the type of smoother or the number of degrees of freedom [69]. Carracedo-Martínez et al. [72] performed a thorough review of the literature comparing these methodologies. Taking these points into consideration, both study designs are potentially exposed to different biases, are subject to other assumptions, and display a dissimilar efficiency. Accordingly, we consider that our choice of a unique study design could be considered as a major strength, because it enables the obtention of more compatible and

precise association values. However, our results should be interpreted as complementary and not antagonistic to other broader studies that included both case-crossover and time-series designs.

Conclusions

In conclusion, this meta-analysis provides evidence of the association between major air pollutants and moderate or severe asthma exacerbations. Moreover, this study proposes a methodological approach to obtain a single association value pooling different lags and studies, through the use of a multilevel meta-analytic model. Other similar studies should be carried out to confirm or discard the present findings, to update these results, and to achieve more accurate association values. This article also highlights the importance of confounders in the association of air pollutants and asthma exacerbations. The implications of these results for public health interventions and individual prevention are also suggested. Finally, it was pointed out that almost all observational studies included in this meta-analysis come from developed countries, and therefore extrapolating these results to developing countries requires caution. In this sense, the development of similar studies should be promoted to evaluate the associations between air pollutants and asthma under different income scenarios.

Supporting information

S1 File. PROSPERO protocol.

(PDF)

S2 File. Forest plots of selected pollutants.

(PDF)

S1 Table. PRISMA Checklist.

(PDF)

S2 Table. Detailed literature search.

(PDF)

S3 Table. Newcastle-Ottawa criteria.

(PDF)

S4 Table. Heterogeneity test for moderators (lags, latitude, elevation) according to the multilevel meta-regression model in the sensitivity analysis.

(PDF)

Acknowledgments

The authors would like to thank the anonymous reviewers and the academic editor for their insightful suggestions and support provided during the editorial process.

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Conceptualization: PO NQ.

Formal analysis: PO NQ.

Funding acquisition: PO NQ.

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Methodology: PO NQ.

Project administration: PO NQ.

Software: PO.

Supervision: PO.

Visualization: PO.

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Writing – review & editing: PO NQ JR BB JV.

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PROSPERO International prospective register of systematic reviews

Effect of outdoor air pollution on severe asthma exacerbations: systematic review and meta-analysis of case-crossover studies

Pablo Orellano, Julieta Reynoso, Brenda Balbi, Julia Vasquez, Nancy Quaranta

Citation

Pablo Orellano, Julieta Reynoso, Brenda Balbi, Julia Vasquez, Nancy Quaranta. Effect of outdoor air pollution on severe asthma exacerbations: systematic review and meta-analysis of case-crossover studies. PROSPERO 2015:CRD42015032323 Available from http://www.crd.york.ac.uk/PROSPERO_REBRANDING/display_record.asp?ID=CRD42015032323

Review question(s)

What is the magnitude of the short-term effects of outdoor air pollutants (NO₂, SO₂, CO, O₃, PM₁₀ and PM_{2.5}) on severe asthma exacerbations?

Searches

A search for published research articles will be conducted in the following bibliographic databases: MEDLINE via PubMed, Scopus, and Google Scholar. The search strategy will include terms related to the disease, the exposure factors, and the design of the studies.

Studies published between January 2000 and the date of the search will be retrieved and independently assessed for eligibility by two reviewers. Only articles published in English will be considered.

An example of the search strategy is presented below.

Pubmed: asthma[All Fields] AND "case crossover"[All Fields] AND (pollut*[All Fields] OR contam*[All Fields]) AND (hospitali*[All Fields] OR admissio*[All Fields] OR emergency[All Fields] OR attac*[All Fields]).

Google Scholar: "case crossover" AND intitle:asthma AND intitle:pollution AND (intitle:hospital OR intitle:hospitalizations OR intitle:admissions OR intitle:emergency OR intitle:attack).

Types of study to be included

In order to increase the precision of the effect sizes, only studies of the same design will be included. Therefore, exclusively case-crossover studies reporting odds ratio (OR) as the measure of association will be considered, preferably with bi-directional selection of control periods.

Condition or domain being studied

Severe asthma exacerbations. An asthma exacerbation is defined as an episode of wheezing or shortness of breath in a person with asthma, and may include the need for oral or systemic corticosteroids. A severe asthma exacerbation also requires hospitalization of the patient or at least an emergency room visit.

Participants/ population

Participants will include individuals of both sexes and all ages exposed to different pollution levels. Persons with known concomitant conditions that may interfere in the association between asthma and air pollution will be excluded.

Intervention(s), exposure(s)

The exposure will be traffic-related or industrial air pollution, measured as an increase in the air concentration of the most frequently monitored air pollutants: nitrogen dioxide (NO₂), sulfur dioxide (SO₂), carbon monoxide (CO), ozone (O₃) and suspended particulate matter (PM₁₀ and PM_{2.5}).

Comparator(s)/ control

Not applicable.

Context

Giving the high risk of bias potentially associated with observational study designs, only the articles published in indexed peer-reviewed journals will be included. Additionally, a careful assessment of the study quality will be performed, in order to ensure the validity of the results.

Outcome(s)

Primary outcomes

Severe asthma exacerbations are defined as an episode of wheezing or shortness of breath that include the need for oral or systemic corticosteroids, and require hospitalization or an emergency room visit.

Secondary outcomes

None.

Data extraction, (selection and coding)

Two independent reviewers (PO and JR) will screen the retrieved articles by title and abstract to complete the first stage, and select those articles that potentially meet the inclusion criteria. In a second stage the same reviewers will read the full text of the primary selected articles to evaluate the inclusion of data for meta-analysis. Any disagreement will be discussed and resolved by consensus or arbitration by a third investigator (BB). Reasons for exclusion will be recorded for each article. In case of missing data, the corresponding author of the study will be contacted.

A data extraction form will be developed in Excel, and filled in with information of each study. This information will include: first author, year of publication, country, participant characteristics, outcome measures and exposure. Other variables that will be included are the lag time between the exposure and the outcome, latitude, elevation, annual concentration of main pollutants and other variables that might be acting as moderators.

Risk of bias (quality) assessment

The quality of included studies will be assessed by two independent reviewers (PO and JR) using a modified Newcastle-Ottawa Scale for case-control studies in meta-analysis, with a scale ranging from 1 to 9 stars (1–3 stars for poor quality, 4–6 for intermediate and 7–9 for high quality). Any disagreement will be discussed and resolved by consensus or arbitration by a third investigator (BB).

The risk of publication bias and other biases will be assessed checking the symmetry of funnel plots for each pollutant, and through regression methods like the Egger's test and the Rank correlation test. The impact of missing studies in the association measure will be assessed and corrected using the trim and fill method.

Methods for removing outlier studies based on regression diagnostic techniques adapted for meta-analysis will be followed. These will include the Cook's distance and the analysis of regression residuals. Outlying studies will be excluded from the meta-analysis.

Strategy for data synthesis

The retrieved odds ratio for each study will be normalized to represent the difference in each pollutant's concentration at a same scale between case and control periods. The natural logarithm and standard errors of the odds ratios will be calculated based on the 95% confidence intervals mentioned in each article. A summary measure of association will be estimated considering three models: a random effect model, a mixed model using co-variables as moderators (meta-regression analysis), and a multilevel mixed model that will also take into account the inclusion of odds ratios from different subgroups within a same study. The mixed model and the multilevel mixed model will include the time lag between the exposure and the outcome, the latitude and elevation of the city where the study was performed, the annual outdoor concentration of each selected pollutant, and the year of publication as potential moderators that could explain the heterogeneity between the studies. The best nested model will be selected using the likelihood ratio test. The heterogeneity between the studies will be analyzed with the statistic I-squared, considering moderate heterogeneity with values > 30% and severe heterogeneity with values > 50%.

A sensitivity analysis will be carried out by means of repeatedly fit of the random effect model, leaving out one study at a time and assessing the impact of this procedure on the summary measure. If possible, a sensitivity analysis based on the quality of included studies will also be performed.

Analysis of subgroups or subsets

None planned.

Dissemination plans

A manuscript with the study results will be submitted to a specialized peer-reviewed journal in this field.

Contact details for further information

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Anticipated or actual start date

02 November 2015

Anticipated completion date

30 June 2016

Funding sources/sponsors

Consejo Nacional de Investigaciones Cientificas y Tecnicas (CONICET), Argentina.

Conflicts of interest

None known

Other registration details

This study will be registered in the Argentina's national registry for health research (Registro Nacional de Investigaciones en Salud).

Language

English

Country

Argentina

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Air Pollutants; Air Pollution; Asthma; Cross-Over Studies; Humans

Stage of review

Ongoing

Date of registration in PROSPERO

16 December 2015

Date of publication of this revision

16 December 2015

Stage of review at time of this submission

Preliminary searches

Started

Yes

Completed

Yes

Piloting of the study selection process

Yes

Yes

Formal screening of search results against eligibility criteria

No

No

Data extraction

No

No

Risk of bias (quality) assessment

No

No

Data analysis

No

No

PROSPERO

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6, S2 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

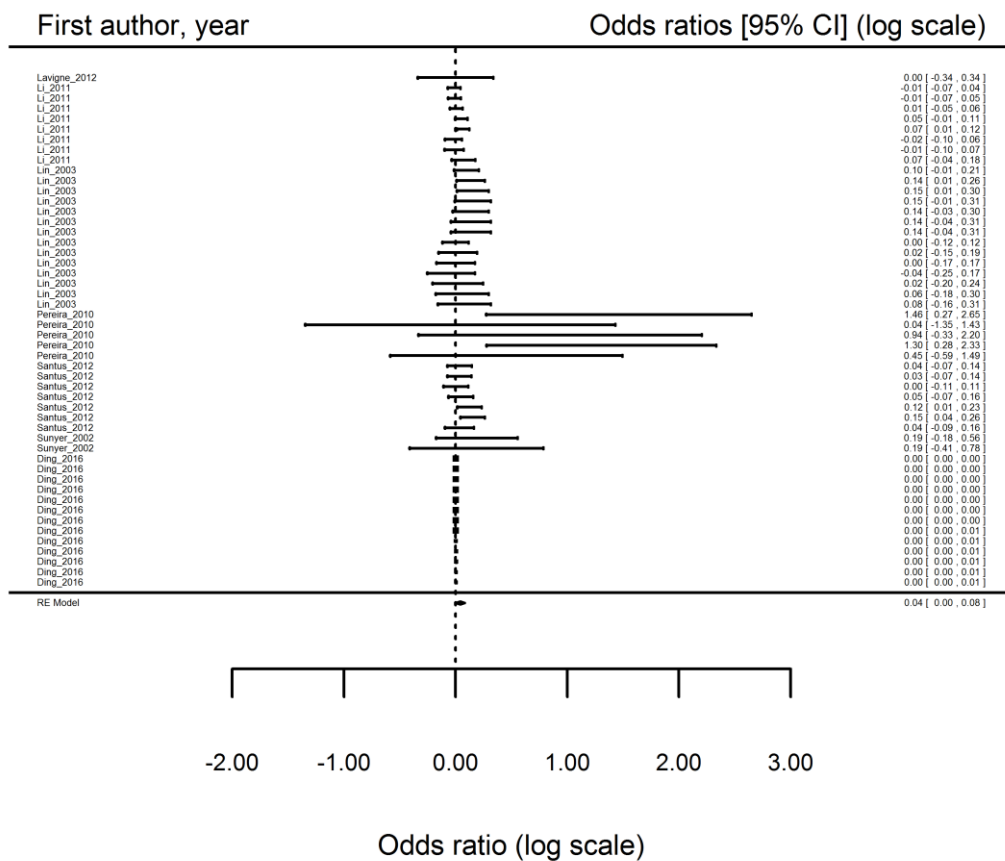


PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9-10, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	S2 File
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11-13, Fig 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Provided through submission system

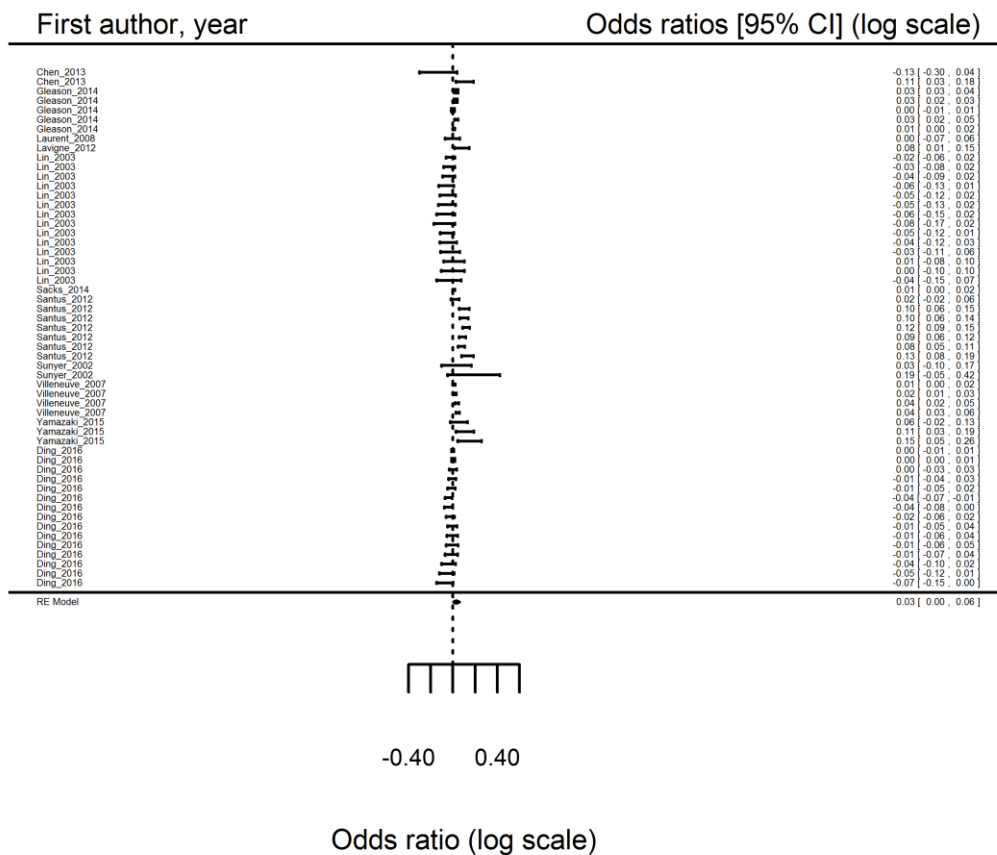
From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org. Page 2 of 2



Forest plot of 7 studies examining the association between CO and asthma exacerbations.

Each study reports one or more time-lags. The pooled odds ratio in logarithmic scale is indicated at the bottom of the figure.



Forest plot of 11 studies examining the association between O₃ and asthma exacerbations.

Each study reports one or more time-lags. The pooled odds ratio in logarithmic scale is indicated at the bottom of the figure.

S2 Table. Detailed literature search.

October 17, 2016

PubMed (asthma [Title/Abstract] OR wheeze[Title/Abstract]) AND (pollut*[Title/Abstract] OR contamin*[Title/Abstract]) AND (hospitaliz*[Title/Abstract] OR admission*[Title/Abstract] OR emergenc*[Title/Abstract] OR attack*[Title/Abstract]) AND "case crossover" [Title/Abstract]
Scopus TITLE-ABS-KEY ((asthma OR wheeze) AND (pollut* OR contamin*) AND (hospitaliz* OR admission* OR emergenc* OR attack*)) AND "case crossover")
Google Scholar (intitle:asthma OR intitle:wheeze) AND (intitle:pollutants OR intitle:pollution OR intitle:contaminants OR intitle:contamination) AND (intitle:hospitalizations OR intitle:admissions OR intitle:emergency OR intitle:attack) AND ("case crossover")

S3 Table. Newcastle-Ottawa criteria.

NOS question	NOS criteria applied to this study
Selection	
Is the case definition adequate?	Revision of clinical histories or primary record sources (1 star)
Representativeness of the Cases	Cases from all hospitals or clinics, or a representative sample of cases (1 star)
Selection of Controls	Always 1 star
Definition of Controls	Exclusion of patients with more than one exacerbation during a given period of time (1 star)
Comparability	
Comparability of cases and controls on the basis of the design or analysis	Always 1 star Control by the day of the week and temperature or humidity (1 additional star)
Exposure	
Ascertainment of exposure	Residential address of cases was verified (1 star)
Same method of ascertainment for cases and controls	Always 1 star
Non-response rate	Always 1 star

NOS: Newcastle-Ottawa scale.

S4 Table. Multilevel meta-regression for the sensitivity analysis.

Pollutant	Moderators	Q _E (P-value)
NO ₂	Lag + Latitude + Elevation	0.33
SO ₂	Lag + Latitude + Elevation	0.16
PM ₁₀	Lag + Latitude + Elevation	0.68
PM _{2.5}	Lag + Latitude + Elevation	0.06
CO	Lag + Latitude + Elevation	0.99
O ₃	Lag + Latitude + Elevation	0.12

NO₂: nitrogen dioxide; SO₂: sulfur dioxide; O₃: ozone; CO: carbon monoxide; PM₁₀: particulate matter < 10 µm; PM_{2.5}: particulate matter < 2.5 µm; Q_E: test for residual heterogeneity.