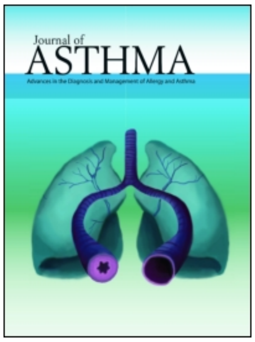

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Association of outdoor air pollution with the prevalence of asthma in children of Latin America and the Caribbean: A systematic review and meta-analysis

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ABSTRACT

Objective: This study aimed to evaluate the association between asthma prevalence and outdoor air pollution in children in Latin America and the Caribbean.
Data Sources: We searched studies in global and regional databases: PubMed, Scopus, LILACS and SciELO.
Study Selection: Articles following a cross-sectional design, studying children from 0 to 18 years old, and comparing the prevalence of asthma in two or more areas of LAC countries with different air pollution levels were included. The exclusion criteria comprised air pollution not related to human activities.
Results: Database searches retrieved 384 records, while 20 studies were retained for qualitative and 16 for quantitative analysis, representing 48 442 children. We found a positive association, i.e. a higher prevalence of asthma in children living in a polluted environment, with pooled odds ratio (OR) of 1.34 (95% CI: 1.17–1.54). Heterogeneity between studies was moderate (I^2: 68.39%), while the risk of bias was intermediate or high in 14 studies. In all the subgroup and sensitivity analyses, the pooled ORs were significant and higher than those found in the general analysis
Conclusions: Our results showed that living in a polluted environment is significantly associated with children having asthma in LAC. Limitations of this study include the low number of studies performed in LAC countries, differences in methodologies and the risk of bias in individual studies.

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Air pollution; asthma; child health; latin america; meta-analysis

Introduction

Nearly 623 million people are currently living with some level of asthma-related symptoms (1), while 250 000 deaths can be attributed to this disease each year (2). In Latin America, the prevalence of asthma has a wide variation between countries, from 9.3% in Argentina to 30.9% in Cuba, with a pooled estimate of 18% and a mortality rate of 26.3 per 100 000 deaths (3). However, data for asthma morbidity and mortality in Latin America is insufficient and limited to isolated population groups (4). Children under 20 years of age who live in Latin America and the Caribbean (LAC) are exposed to the effect of environmental threats such as urban air pollution and global climate change, among others (5). The urbanization process is rising in LAC, with increased motorization of the urban population, and increased household combustion of solid fuels (6). Specifically for asthma, air pollution can have deleterious effects on lung development and function in children (7). The short-term effects of air pollutants on asthma exacerbations and hospitalizations in children and adults have been studied in several meta-analyses (8–11), while a smaller number of meta-studies assessed the association between air pollution and the prevalence or incidence of asthma (12–14). However, all these global meta-analyses included almost exclusively studies from USA, Canada, Europe, Asia and Oceania, and were conducted mostly in high-income countries. At present, there is only one published meta-analysis that assessed the effect of particulate matter (PM) on human health specifically in LAC, although not particularly aimed at asthma (15). Nevertheless, regional factors as socio-economic and climatic or meteorological conditions are likely to modify the effect of air pollution on asthma, and this fact justifies the regional analysis. On the other hand, several observational studies in LAC are being conducted, often with diverse methodologies and heterogeneous geographical representation. Thus, this meta-analysis has the triple goal of obtaining pooled estimates of the association between asthma prevalence and outdoor air pollution in children in LAC, revealing the gaps of information, and finally describing the heterogeneities in methodologies between the studies conducted in this region.

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Methods

Overview

We prepared this article according to the PRISMA guidelines for systematic reviews and meta-analysis (16). The protocol for this study was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under registration number CRD42016047054 before the formal screening of search results. The present study comprises a systematic review of published articles and a meta-analysis of summary estimates for the main effect sizes.

Search strategy and selection criteria

We searched studies published in English, Spanish, Portuguese or French between Jan 1, 2000 and Aug 26, 2016. The retrieved studies should explore the relationship between outdoor air pollution due to particulate matter or gases and the prevalence of asthma in children from 0 to 18 years old. Asthma ascertainment was assessed through medical diagnostic, medical records, observed symptoms, self-reported asthma, or measured by specific questionnaires. The study populations were the general community, students attending schools or patients from hospitals and other health centers. The inclusion criteria for the retrieved articles were:

- Studies following a cross-sectional observational design, also known as prevalence or transversal studies, which allowed for the estimation of asthma prevalence in two or more defined areas with different levels of outdoor air pollution.
- Assessment of air pollution represented by NO_2, SO_2, PM_{10}, $PM_{2.5}$, carbon monoxide (CO), O_3 or other known pollutants; otherwise, exposure to air pollution represented by the distance to different sources of industrial- or traffic-related pollution, e.g. distance to highways, industries, or other sources. If this was not possible, a subjective classification of areas was also accepted.
- Studies carried out in LAC countries.
- For being included in quantitative meta-analysis, studies should also report the odds ratios (ORs) and 95% confidence intervals (95% CIs), or the absolute number of cases in each area.

The articles were excluded if the source of air pollution was not related to traffic, industries or other sources not directly related to human activities. The studies assessing natural exposures, e.g. sandstorms or volcanic ash, were also excluded. Other reasons for exclusion were the study of occupational or intentional exposures.

We searched articles in global and regional databases: Medical Literature Analysis and Retrieval System Online (MEDLINE) via PubMed, Scopus, Literatura Latino-Americana e do Caribe em Ciencias da Saude (LILACS) and Scientific Electronic Library Online (SciELO). The latter two databases contain articles from some LAC journals unavailable in global databases, including thesis, conference proceedings and other grey literature. The search terms were organized in four major groups: the disease and symptoms, the exposure, the study design and the location (countries) where the studies were carried out. The detailed search strategy with terms and combinations can be seen in Table A1 of the Appendix. In addition, a manual search in reference lists from other systematic reviews was performed to find additional relevant studies. In case an article did not provide the exact data needed for the quantitative analysis, the corresponding author was contacted by e-mail to ask for additional information, within an acceptable time frame. Two reviewers (PO and JR) independently screened all records retrieved from database searches and performed the assessment of titles, abstracts, and finally the full-text articles. Any disagreement was resolved by consensus with the help of a third reviewer (BB).

Risk of bias

The risk of bias in individual studies was evaluated by means of a modified version of the Newcastle-Ottawa scale (NOS) for case-control and cohort studies (17). We developed this modification maintaining the original three dimensions: selection of the study group, exposure ascertainment, and comparability, using the same system of a minimum of zero and a maximum of nine stars. Individual study risk of bias was then graded as high (1–3 stars), intermediate (4–6 stars), or low (7–9 stars), as in the original scale. Maintaining the original dimensions and scores was appropriate for comparability purposes. An explanation of each question adapted for this study is presented in Table A2 of the Appendix.

The potential risk of publication bias was evaluated by different methods (18). First, the visual examination of funnel plots asymmetry. Second, we numerically assessed the potential for publication bias by means of the Egger's regression test. Third, the trim and fill method by Duval and Tweedie was used to estimate the likely number of studies that could have been missed due to publication bias. The OR estimated by this method was not used as a valid summary effect size, but as an approximation of the sensitivity of the results related to unpublished articles. The missing individual ORs estimated by this method were then incorporated in the funnel plot in order to visualize the potential influence of unpublished studies.

Data analysis

Data from studies was extracted by means of a data extraction form. This data included the first author and year of publication, year and country where the survey was carried out, number of participants, participants' age and gender, exposure assessment, pollutants and levels, type of survey, adjustment for other covariables, and the number of participants in each group or the ORs with their 95% CI. If the ORs and 95% CI were not mentioned in the study but the number of participants in each group (exposed, non-exposed, with or without asthma symptoms) was available, crude ORs and 95% CIs were calculated. Table A3 of the Appendix describes the rules for effect sizes selection in those studies where two or more effect sizes were reported.

For the summary measure we employed a random-effect model, assuming that the included studies are a random selection of all possible results. This allowed us to infer that the summary effect size that we estimated is representative of the real situation in LAC. We used the DerSimonian-Laird estimator with the Knapp and Hartung adjustment for standard errors. The Hartung and Knapp method is a modification of the DerSimonian-Laird procedure to handle small number of studies (19). The heterogeneity between studies was analyzed with the statistic I-squared considering low, moderate, and high to I-squared values of 25%, 50%, and 75% (20). A subgroup analysis was carried out according to the source of pollution and the children's age.

A series of sensitivity analyses were performed to evaluate the validity and robustness of the summary measures. First, the random-effect model was performed excluding articles on the basis of the NOS value, removing studies with high and intermediate risk of bias. Second, an outlier analysis was carried out to detect articles with extreme effect sizes that may distort the conclusions (21). Outliers were characterized by a studentized deleted residual larger than 1.96. Third, a leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that the findings were not driven by any single study.

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/).

Results

Literature search

The study selection process can be seen in Figure 1. Database searches retrieved 384 records that were managed to remove duplicates. After removing 102 duplicates,

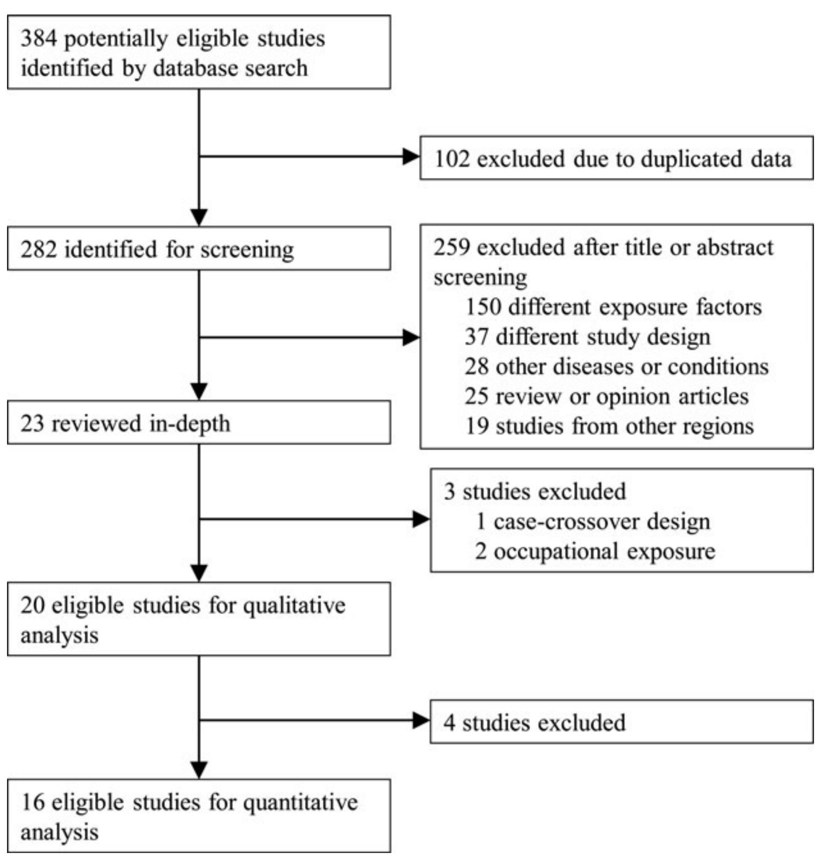

Figure 1. Study identification and selection process.

title and abstract screen on 282 records were completed by reviewers, and 23 articles were selected for full-text eligibility assessment. Three full-text articles were excluded, one article was excluded for being a case-crossover design, and two studies because the exposure was occupational. Finally, 20 studies published between 2004 and 2015 were selected for qualitative analysis, and 16 for quantitative analysis, representing 48 442 children. Four studies could not be included in the quantitative analysis. One study only used continuous measures of lung function, i.e. the peak expiratory flow, without reporting the number of asthma cases or ORs. In the other three studies the number of participants, the group of exposure or the ORs were not reported and corresponding authors could not be reached.

Characteristics and risk of bias of included studies

The selected studies were from Brazil (seven), Colombia (six), Peru (two), Bolivia (one), Chile (one), Argentina (one), French West Indies (one), and Honduras and El Salvador (one). Regarding the World Bank classification, these countries are in the group of high-income countries (one), upper-middle-income countries (five) and lower-middle-income countries (three). The majority of studies were structured around school-based surveys (12), while five studies used home-based surveys and three studies used hospital-based surveys. The general description of studies can be seen in Table 1.

In Table 2, the assessment of exposures, asthma ascertainment and associations can be observed. Almost half of the studies (nine) performed some kind of estimation of pollutant concentrations, mainly PM_{10} but including in some cases NO_2, SO_2 and O_3. In the other studies, the assessment of exposure to air pollutants was estimated through means of some measure of proximity to air pollution sources as highways, roads, or industries. In only one study the exposure to air pollution was evaluated through a questionnaire administered to parents; in all the others, the exposures were observed or measured. The outcome of interest, i.e. the asthma prevalence, was evaluated through questionnaires in all studies, complemented with medical records, spirometry, or peak expiratory flow measures in four studies. In all studies but two, the association between asthma prevalence and air pollution was controlled for potential effect modifiers or confounders by means of regression models. These covariates included individual variables as age, gender, body mass index, habits; and socio-economic variables as income, housing characteristics and others. In thirteen studies the indoor air pollution was also taken into account as a possible confounder. Only one study considered the effect of weather in the associations. The majority of studies (14) found a significant positive association between asthma prevalence and at least one air pollutant or between asthma and proximity to a known source of air pollution, while one study found a significant negative association. The risk of bias was low in six studies, intermediate in twelve studies, and high in two studies. The main problems with the risk of bias were the absence of an adequate description of non-respondents (19 studies), the lack of justification of the sample size (eight studies), and the selection of study groups (seven studies).

Quantitative analysis

Quantitative analysis was performed in 16 studies. However, three studies had more than one independent analysis group; hence the pooled estimate was a composition of 21 independent ORs. We found a positive association between asthma and outdoor air pollution, i.e. a higher prevalence of asthma in children living in a polluted environment, with pooled OR of 1.34 (95% CI: 1.17–1.54). The forest plot associated with this analysis can be seen in Figure 2. The heterogeneity between studies was moderate (I^2: 68.39%), i.e. more than 68% of the variance in heterogeneity was due to the variation between studies. In the subgroup analysis, the ORs for children under two years of age and children under seven, and for studies analyzing only traffic-related or only industrial-related air pollution, were in all cases higher than that of the general analysis. All these results can be seen in Table 3. In the sensitivity analysis considering studies with only low, or low and intermediate risk of bias, and in the sensitivity analysis that excluded outliers, the pooled ORs were significant and higher than those found in the general analysis (Table 4). The exclusion of one study at a time produced ORs ranging from 1.31 to 1.37, and always significant (Table 4).

Figure 3 shows the funnel plot produced in the general analysis. There was a small degree of asymmetry, i.e. publication bias. However, the Egger's regression test did not indicate significant publication bias ($p = 0.107$). The Trim and Fill method showed that possibly 7 studies would be missing on the left side (Figure 3) and that the true effect size could be lower than that of the original analysis, but also significant (OR: 1.21; 95% CI: 1.09–1.35).

Discussion

Our study found few studies carried out in LAC countries analyzing the association between outdoor air pollution and asthma prevalence in children. However, the results showed that living in a polluted environment is significantly associated with having asthma in children in LAC. Moreover, this association still proved to be significant for

Table 1. Characteristics of the included studies.

Reference	Country	Country income	Dates	Survey	Participants	Age	Male
Alvarez Miño et al, 2013 (28)	Colombia	Upper-middle	2009	School-based	305	6–14 ;years	41%
Amadeo et al., 2015 (29)	French West Indies	Upper-middle	2008–2009	School-based	1 436	8–12 ;years	46%
Azalim et al., 2014 (30)	Brazil	Upper-middle	N/A	School-based	1 302	6–7 and 13–14 ;years	52%
Baumann et al., 2011 (31)	Peru	Upper-middle	2009–2010	Home-based	725	13–15 ;years	50%
Bueso et al., 2010 (32)	Honduras and El Salvador	Lower-middle	2008	Hospital-based	1 827	1 ;year	52%
Carbajal-Arroyo et al., 2007 (33)	Peru	Upper-middle	2003	School-based	6 287	6–7 and 13–14 ;years	49%
Herrera et al., 2011 (34)	Colombia	Upper-middle	2009–2010	Home-based	678	0–7 ;years	54%
Herrera et al., 2016 (35)	Chile	High	2009	School-based	275	6–15 ;years	54%
Magalhaes-Rios et al., 2004 (36)	Brazil	Upper-middle	2000	School-based	5 148	13–14 ;years	48%
Lopes de Moraes et al., 2010 (37)	Brazil	Upper-middle	2006	Home-based	209	0–14 ;years	56%
Moraes et al., 2013 (38)	Brazil	Upper-middle	2009–2010	Hospital-based	1 060	1 ;year	35%
Quiroz-Arcentales et al., 2013 (39)	Colombia	Upper-middle	N/A	Home-based	1 627	0–10 ;years	49%
Rodriguez et al., 2010 (40)	Colombia	Upper-middle	2007	Home-based	768	0–7 ;years	56%
Rodriguez-Moreno et al., 2013 (41)	Colombia	Upper-middle	2012–2013	School-based	553	5–14 ;years	49.5%
Sarmiento-Suarez et al., 2013 (42)	Colombia	Upper-middle	2012	School-based	5 407	0–5 ;years	52%
Sole et al., 2007 (43)	Brazil	Upper-middle	N/A	School-based	16 209	13–14 ;years	N/A
Solis-Soto et al., 2013 (44)	Bolivia	Lower-middle	2011	School-based	2 340	9–15 ;years	48%
Toledo et al., 2016 (45)	Brazil	Upper-middle	2012	School-based	1 039	13–14 ;years	52%
Vieira et al., 2012 (46)	Brazil	Upper-middle	2009	Hospital-based	64	6–10 ;years	42%
Whichmann et al., 2009 (47)	Argentina	Upper-middle	2005–2006	School-based	1 183	6–12 ;years	54%

Note: N/A, no data available

Table 2. Exposures, asthma ascertainment, and associations in selected studies.

Study	Exposure assessment	Asthma ascertainment	Adjustment for other variables	Association between exposure and asthma
Alvarez Miño et al, 2013 (28)	Concentration of PM_{10}	Questionnaire and spirometry	Indoor air pollution, individual and socio-economic variables	Positive association
Amadeo et al., 2015 (29)	Concentration of O_3, NO_2, SO_2 and PM_{10}	Peak expiratory flow	Individual and weather variables	Positive association with O_3
Azalim et al., 2014 (30)	Concentration of PM_{10}	Questionnaire	Indoor air pollution and individual variables	Negative association
Baumann et al., 2011 (31)	Proximity to traffic-related sources of air pollution	Questionnaire and spirometry	Indoor air pollution, individual and socio-economic variables	Positive association
Bueso et al., 2010 (32)	Air pollution reported by parents	Questionnaire	Individual variables	Positive association
Carbajal-Arroyo et al., 2007 (33)	Proximity to traffic-related sources of air pollution	Questionnaire	Individual variables	Positive association in children 6–7 ;years
Herrera et al., 2011 (34)	Concentration of PM_{10}	Questionnaire	Indoor air pollution and individual variables	No significant association
Herrera et al., 2016 (35)	Proximity to open-pit mines	Questionnaire and medical records	Indoor air pollution	No significant association
Magalhaes-Rios et al., 2004 (36)	Concentration of PM_{10}	Questionnaire	Indoor air pollution, individual and socio-economic variables	Positive association
Lopes de Moraes et al., 2010 (37)	Proximity to a petrochemical industry	Questionnaire	Indoor air pollution and socio-economic variables	Positive association
Moraes et al., 2013 (38)	Air pollution reported by parents	Questionnaire	N/A	Positive association
Quiroz-Arcentales et al., 2013 (39)	Concentration of PM_{10}	Questionnaire	Indoor air pollution	Positive association
Rodriguez et al., 2010 (40)	Concentration of PM_{10}	Questionnaire	Indoor air pollution and socio-economic variables	No significant association
Rodriguez-Moreno et al., 2013 (41)	Proximity to traffic-related or industrial sources of air pollution	Questionnaire	Indoor air pollution, individual and socio-economic variables	No significant association
Sarmiento-Suarez et al., 2013 (42)	Proximity to traffic-related sources of air pollution	Questionnaire	Individual and socio-economic variables	Positive association
Sole et al., 2007 (43)	Concentration of O_3, NO_2, and SO_2	Questionnaire	Socio-economic variables	Positive association
Solis-Soto et al., 2013 (44)	Proximity to traffic-related sources of air pollution	Questionnaire	Indoor air pollution	No significant association
Toledo et al., 2016 (45)	Proximity to traffic-related sources of air pollution	Questionnaire	N/A	Positive association
Vieira et al., 2012 (46)	Concentration of O_3 and NO_2	Questionnaire	Indoor air pollution, individual and socio-economic variables	Positive association
Whichmann et al., 2009 (47)	Proximity to a petrochemical industry	Questionnaire	Indoor air pollution, individual and socio-economic variables	Positive association

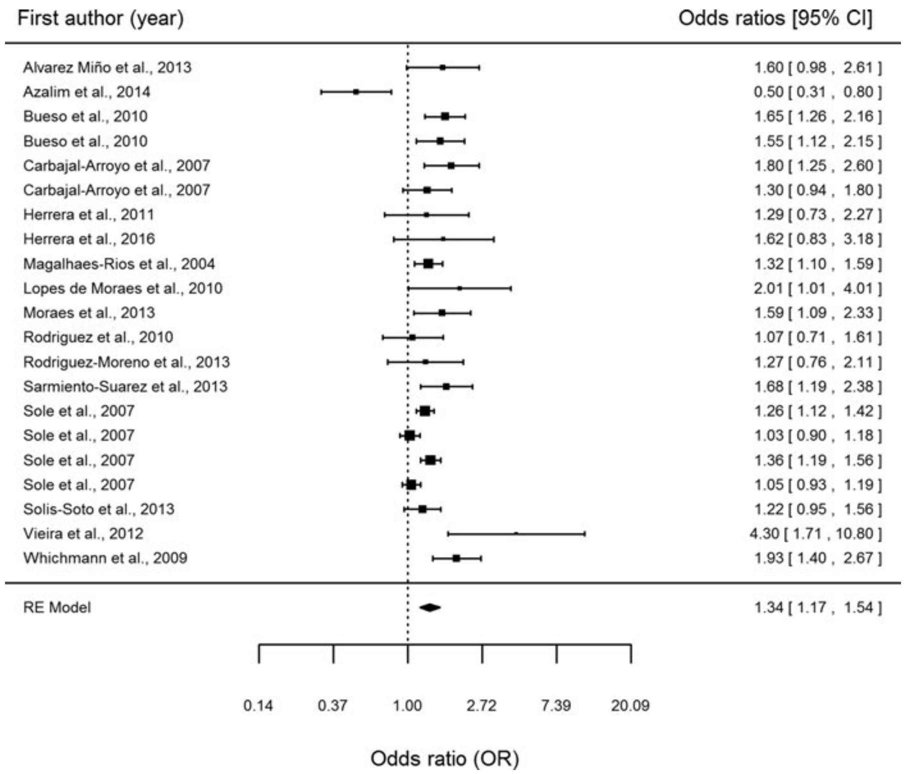

Figure 2. Forest plot of 16 studies (21 effect sizes) examining the association between outdoor air pollution and asthma prevalence in Latin America and the Caribbean.

a diversity of subgroup analyses, i.e. for younger children, and for different pollution sources. A series of sensitivity analyses confirmed these results. To the best of our knowledge, this is the first meta-analysis that evaluates the association between air pollution and asthma in LAC. Our results seem to confirm the hypothesis that the estimates from other regions can be generalized to LAC countries, and alerts regional decision-makers about the harms of air pollution in these settings.

There exist different possible mechanisms through which the common atmospheric pollutants can cause asthma or trigger asthma exacerbations. Exposure to PM might induce airway inflammation and oxidative stress (a feature of severe asthma), leading to exacerbations and possibly the onset of asthma (22). With respect to gases, the major gaseous pollutants are SO_2, CO, and NO_2 as well as O_3 (23). O_3 exposure results in airway inflammation, airway hyper-responsiveness, and decrements in lung function in healthy and asthmatic adults, whereas SO_2 causes more prominent bronchoconstriction, especially in asthmatic individuals, and NO_2 induces little lung inflammation at common ambient concentrations (22). Beside these direct effects, pulmonary inflammation can indirectly influence the worsening of asthma symptoms by affecting host defenses and enhancing infections with rhinovirus (RV), influenza, and respiratory syncytial virus (RSV), which in turn are considered the main causes of asthma exacerbations (24).

Several systematic reviews and meta-analyses have evaluated the association between asthma and outdoor air pollution, mainly the short-term effects of air pollutants measured as asthma exacerbations or hospitalizations in panel or time series studies (8–11). Despite the effects in aggravating asthma symptoms, air pollution has been linked to the development of childhood asthma (25). Gasana and colleagues (12) have found in a

Table 3. Subgroup analysis.

Subgroup analysis	Coefficient	Standard Error	OR (95%CI)[a]	p-value	N[b]
Children < 2 years	0.4728	0.0194	1.60 (1.54–1.57)	< 0.01	3
Children < 7 years	0.4385	0.0606	1.55 (1.38–1.75)	< 0.01	7
Traffic-related pollution	0.3394	0.0828	1.40 (1.19–1.65)	< 0.01	9
Industrial-related pollution	0.3883	0.0717	1.47 (1.28–1.70)	< 0.01	8

Note:
[a]Odds ratios with 95% confidence intervals.
[b]Number of studies considered.

Table 4. Sensitivity analysis

Sensitivity analysis	Coefficient	Standard Error	OR (95%CI)[a]	p-value	N[b]
Excluding studies with high risk of bias	0.2735	0.0705	1.31 (1.14–1.51)	< 0.01	19
Excluding studies with high and intermediate risk of bias	0.3026	0.1281	1.35 (1.05 – 1.74)	0.04	11
Excluding outliers[c]	0.3003	0.0449	1.35 (1.24 – 1.47)	< 0.01	19
Excluding one effect size at a time					
Alvarez Miño et al., 2013 (28)	0.2896	0.0673	1.34 (1.17–1.52)	< 0.01	21
Azalim et al., 2014 (30)	0.3177	0.0511	1.37 (1.24–1.52)	< 0.01	21
Bueso et al., 2010 (32)	0.2818	0.0673	1.33 (1.16–1.51)	< 0.01	21
Bueso et al., 2010 (32)	0.2879	0.0679	1.33 (1.17–1.52)	< 0.01	21
Carbajal-Arroyo et al., 2007 (33)	0.2808	0.0661	1.32 (1.16–1.51)	< 0.01	21
Carbajal-Arroyo et al., 2007 (33)	0.2978	0.0686	1.35 (1.18–1.54)	< 0.01	21
Herrera et al., 2011 (34)	0.2968	0.0677	1.35 (1.18–1.54)	< 0.01	21
Herrera et al., 2016 (35)	0.2916	0.0671	1.34 (1.17–1.53)	< 0.01	21
Magalhaes-Rios et al., 2004 (36)	0.2987	0.0698	1.35 (1.18–1.55)	< 0.01	21
Lopes de Moraes et al., 2010 (37)	0.2869	0.0658	1.33 (1.18–1.52)	< 0.01	21
Moraes et al., 2013 (38)	0.2878	0.0676	1.33 (1.17–1.52)	< 0.01	21
Rodriguez et al., 2010 (40)	0.305	0.0673	1.36 (1.19–1.55)	< 0.01	21
Rodriguez-Moreno et al., 2013 (41)	0.2975	0.0678	1.35 (1.18–1.54)	< 0.01	21
Sarmiento-Suarez et al., 2013 (42)	0.2839	0.067	1.33 (1.16–1.51)	< 0.01	21
Sole et al., 2007 (43)	0.3053	0.0708	1.36 (1.18–1.56)	< 0.01	21
Sole et al., 2007 (43)	0.317	0.0665	1.37 (1.21–1.56)	< 0.01	21
Sole et al., 2007 (43)	0.2973	0.0703	1.35 (1.17 – 1.55)	< 0.01	21
Sole et al., 2007 (43)	0.3163	0.0671	1.37 (1.20 – 1.56)	< 0.01	21
Solis-Soto et al., 2013 (44)	0.3029	0.069	1.35 (1.18 – 1.55)	< 0.01	21
Vieira et al., 2012 (46)	0.2791	0.0594	1.32 (1.18 – 1.49)	< 0.01	21
Whichmann et al., 2009 (47)	0.2738	0.0645	1.31 (1.16 – 1.49)	< 0.01	21

Note:
[a]Odds ratios with 95% confidence intervals.
[b]Number of effect sizes considered.
[c]Two studies excluded: Azalim et al., 2014 and Vieira et al., 2012.

systematic review and meta-analysis of cohort and cross-sectional studies that a higher prevalence of asthma or wheeze in children was associated with higher levels of exposure to NO_2, NO_x, CO and SO_2, while higher exposure to NO_2 and PM was associated with a higher incidence of asthma. Coincidently, a systematic review and meta-analysis of birth cohort studies showed that a higher exposure to traffic-related air pollution, black carbon and

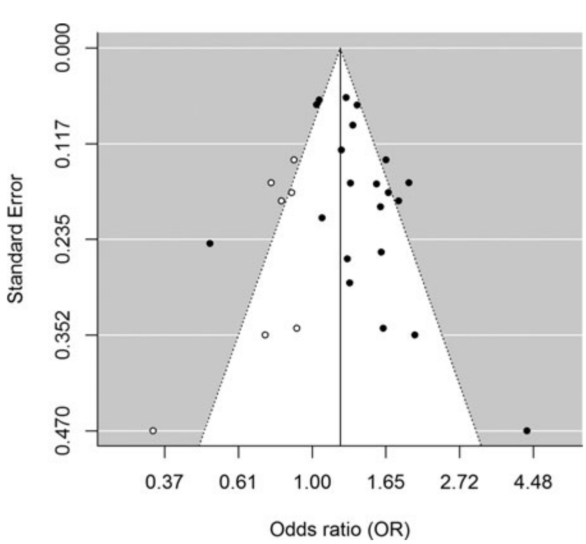

Figure 3. Funnel plot showing the relationship between standard errors and effect sizes in included studies (black dots) and potentially unpublished studies (white dots) estimated by the Trim and Fill method.

$PM_{2.5}$ increased the risk of subsequent asthma (13). However, contrary to our results, in that analysis proximity to a major road did not show a strong association with asthma. Another systematic review and meta-analysis focusing on children and evaluating cohort, birth cohort, and cross-sectional studies found positive associations with black carbon, NO_2, NO_x, $PM_{2.5}$ and PM_{10} (14). Importantly, all these meta-studies found problems regarding the heterogeneity between individual studies, the approach to confounding control, the standardization of study methods to measure air pollution, the consideration of individual susceptibilities, and outcome definitions. Moreover, several other environmental and socio-economic factors acting as covariates may influence the effect of air pollutants on asthma (13). It is worth mentioning that two of these systematic reviews and meta-analyses only considered studies published in English, in international databases, and considered mostly studies carried out in developed countries. Thus, information that accounts for the effect of air pollution on asthma prevalence adapted to this region is needed, especially one that considers the socio-economic and cultural characteristics of these populations, biological, and meteorological factors. In our meta-analysis, the search was not restricted to articles published in English, to global databases or to widespread journals. It will be necessary, in the future, to carry out other systematic reviews and meta-analysis evaluating not only the prevalence of asthma associated with air pollution but the risk of developing asthma, and the influence of air pollutants on exacerbations of asthma analyzed through time series designs in LAC countries.

This study was subject to a number of limitations. First, few studies that evaluate the association of pollution and health outcomes in general are published in LAC, and this necessary influences the power of pooled estimates from meta-analyses. In addition, these few studies usually have different methodologies regarding survey procedures, outcome definitions and exposure assessments. Second, in a high proportion of studies the exposure was assessed via proximity to a previously defined source of air pollution. This kind of exposure assessment can lead to bias, because of the influence of winds and other environmental factors that may affect the dispersion of air pollutants in the atmosphere (26). Furthermore, the concentration of pollutants was measured in less than half of the studies. This fact was probably related to the high costs associated with validated equipment required for analyzing outdoor air quality. For example, Riojas-Rodríguez and colleagues have found that only 17 of the 33 LAC countries have any information on ground level air quality (6). Third, the risk of bias in individual studies was generally high or intermediate, which may impact the validity of our results. The greatest weakness was in general in the selection procedure, i.e. the representativeness of the sample, the justification of the sample size and the percentage of non-respondents. However, some studies also had problems with the ascertainment of the exposure or the outcome, or with the control for confounding factors. Beyond these limitations, two strengths of this meta-analysis are worth being mentioned. First, the Egger's test did not show evidence of publication bias, while the funnel plot showed only a small degree of asymmetry. This fact is probably related to the inclusion of regional databases that consider journals publishing papers based on regional and local studies. In addition, the Trim and Fill method estimated a small number of potential missing studies that should not modify the significance of the pooled effects. Second, the subgroup analyses showed that the estimates remained unchanged or slightly modified in a wide range of scenarios, i.e. for different age groups, and for different sources of air pollution. The sensitivity analyses also failed to modify the pooled estimates. On the other hand, our results are in consonance with previous meta-analyses carried out in other regions, although the shape of the dose-response relationship is likely to be different in different regions (27).

Conclusions

In summary, our meta-analysis contributes to an increasing body of knowledge indicating a significant association between outdoor air pollution and asthma in children in LAC, as other meta-analyses previously brought evidence of the same relationship in other regions. At the same time, our study warns us about the need for increasing the number of researches and equipment for the measure of outdoor air pollution and its effects on human health in LAC, while it suggests the use of standardized methodologies in order to facilitate obtaining regional estimates.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Acknowledgement

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Appendix

Table A1. Detailed literature search

PubMed
("asthma"[Title/Abstract] OR "respiratory tract allergy"[Title/Abstract] OR "respiratory allergy"[Title/Abstract] OR "wheeze"[Title/Abstract] OR "wheezing"[Title/Abstract]) AND (traffic[Title/Abstract] OR road[Title/Abstract] OR roads[Title/Abstract] OR roadway[Title/Abstract] OR roadways[Title/Abstract] OR motorway[Title/Abstract] OR motorways[Title/Abstract] OR freeway[Title/Abstract] OR freeways[Title/Abstract] OR highway[Title/Abstract] OR highways[Title/Abstract] OR exhaust[Title/Abstract] OR emissions[Title/Abstract] OR pollution[Title/Abstract] OR pollutants[Title/Abstract] OR polluted[Title/Abstract] OR contamination[Title/Abstract] OR "particulate matter"[Title/Abstract] OR "suspended particles"[Title/Abstract] OR "coarse particles"[Title/Abstract] OR "respirable particles"[Title/Abstract] OR "fine particles"[Title/Abstract] OR "ultrafine particles"[Title/Abstract] OR "inhalable particles"[Title/Abstract] OR SPM[Title/Abstract] OR TSP[Title/Abstract] OR PM10[Title/Abstract] OR PM2.5[Title/Abstract] OR PM1[Title/Abstract] OR "black carbon"[Title/Abstract] OR "carbon monoxide"[Title/Abstract] OR nitrogen[Title/Abstract] OR "NO2"[Title/Abstract] OR NOx[Title/Abstract] OR hydrocarbon[Title/Abstract] OR ozone[Title/Abstract] OR O3[Title/Abstract] OR sulfur[Title/Abstract] OR SO2[Title/Abstract] OR SOx[Title/Abstract] OR hydrocarbons[Title/Abstract] OR "volatile organic"[Title/Abstract]) AND (children[Title/Abstract] OR adolescents[Title/Abstract] OR young[Title/Abstract] OR toddlers[Title/Abstract] OR infants[Title/Abstract] OR school[Title/Abstract] OR preschool[Title/Abstract] OR students[Title/Abstract] OR newborns[Title/Abstract] OR paediatric[Title/Abstract] OR pediatric[Title/Abstract] OR teens[Title/Abstract] OR teenagers[Title/Abstract] OR babies[Title/Abstract] OR juveniles[Title/Abstract] OR kids[Title/Abstract] OR kindergarten[Title/Abstract] OR minors[Title/Abstract] OR neonates[Title/Abstract]) AND ("cross sectional"[Title/Abstract] OR transversal[Title/Abstract] OR prevalence[Title/Abstract] OR survey[Title/Abstract] OR sampling[Title/Abstract] OR sample[Title/Abstract] OR questionnaire[Title/Abstract]) AND ("Antigua and Barbuda"[Title/Abstract] OR "Antigua and Barbuda"[Affiliation] OR "argentina"[Title/Abstract] OR "argentina"[Affiliation] OR "bahamas"[Title/Abstract] OR "bahamas"[Affiliation] OR "barbados"[Title/Abstract] OR "barbados"[Affiliation] OR "belize"[Title/Abstract] OR "belize"[Affiliation] OR "bolivia"[Title/Abstract] OR "bolivia"[Affiliation] OR "brazil"[Title/Abstract] OR "brazil"[Affiliation] OR "chile"[Title/Abstract] OR "chile"[Affiliation] OR "colombia"[Title/Abstract] OR "colombia"[Affiliation] OR "Costa Rica"[All Fields] OR "Costa Rica"[Affiliation] OR "cuba"[Title/Abstract] OR "cuba"[Affiliation] OR "dominica"[Title/Abstract] OR "dominica"[Affiliation] OR "Dominican Republic"[Title/Abstract] OR "Dominican Republic"[Affiliation] OR "ecuador"[Title/Abstract] OR "ecuador"[Affiliation] OR "El Salvador"[Title/Abstract] OR "El Salvador"[Affiliation] OR "grenada"[Title/Abstract] OR "grenada"[Affiliation] OR "guatemala"[Title/Abstract] OR "guatemala"[Affiliation] OR "guyana"[Title/Abstract] OR "guyana"[Affiliation] OR "haiti"[Title/Abstract] OR "haiti"[Affiliation] OR "honduras"[Title/Abstract] OR "honduras"[Affiliation] OR "jamaica"[Title/Abstract] OR "jamaica"[Affiliation] OR "mexico"[Title/Abstract] OR "mexico"[Affiliation] OR "nicaragua"[Title/Abstract] OR "nicaragua"[Affiliation] OR "panama"[Title/Abstract] OR "panama"[Affiliation] OR "paraguay"[Title/Abstract] OR "paraguay"[Affiliation] OR "peru"[Title/Abstract] OR "peru"[Affiliation] OR "Saint Kitts and Nevis"[Title/Abstract] OR "Saint Kitts and Nevis"[Affiliation] OR "Saint Lucia"[Title/Abstract] OR "Saint Lucia"[Affiliation] OR "Saint Vincent and the Grenadines"[Title/Abstract] OR "Saint Vincent and the Grenadines"[Affiliation] OR "suriname"[Title/Abstract] OR "suriname"[Affiliation] OR "Trinidad and Tobago"[Title/Abstract] OR "Trinidad and Tobago"[Affiliation] OR "uruguay"[Title/Abstract] OR "uruguay"[Affiliation] OR "venezuela"[Title/Abstract] OR "venezuela"[Affiliation] OR "anguilla"[Title/Abstract] OR "anguilla"[Affiliation] OR "aruba"[Title/Abstract] OR "aruba"[Affiliation] OR "British Virgin Islands"[Title/Abstract] OR "British Virgin Islands"[Affiliation] OR "Cayman Islands"[Title/Abstract] OR "Cayman Islands"[Affiliation] OR "Curacao"[Title/Abstract] OR "Curacao"[Affiliation] OR "Sint Maarten"[Title/Abstract] OR "Sint Maarten"[Affiliation] OR "Saint Martin"[Title/Abstract] OR "Saint Martin"[Affiliation] OR "Latin America"[Title/Abstract] OR "Latin"[Title/Abstract] OR "caribbean"[Title/Abstract])

Table A1. Detailed literature search

Scopus

TITLE-ABS-KEY ((asthma OR wheeze OR wheezing OR "respiratory tract allergy" OR "respiratory allergy") AND (traffic OR road OR roads OR roadway OR roadways OR motorway OR motorways OR freeway OR freeways OR highway OR highways OR exhaust OR emissions OR pollution OR pollutants OR polluted OR contamination OR "particulate matter" OR "suspended particles" OR "coarse particles" OR "respirable particles" OR "fine particles" OR "ultrafine particles" OR "inhalable particles" OR spm OR tsp OR pm10 OR pm2.5 OR pm1 OR "black carbon" OR "carbon monoxide" OR nitrogen OR "NO2" OR nox OR hydrocarbon OR ozone OR o3 OR sulfur OR so2 OR sox OR hydrocarbons OR "volatile organic") AND (children OR adolescents OR young OR toddlers OR infants OR school OR preschool OR students OR newborns OR paediatric OR pediatric OR teens OR teenagers OR babies OR juveniles OR kids OR kindergarten OR minors OR neonates) AND ("cross sectional" OR transversal OR prevalence OR survey OR sampling OR sample OR questionnaire)) AND (TITLE-ABS-KEY (("Antigua and Barbuda" OR argentina OR bahamas OR barbados OR belize OR bolivia OR brazil OR chile OR colombia OR "Costa Rica" OR cuba OR dominica OR "Dominican Republic" OR ecuador OR "El Salvador" OR grenada OR guatemala OR guyana OR haiti OR honduras OR jamaica OR mexico OR nicaragua OR panama OR paraguay OR peru OR "Saint Kitts and Nevis" OR "Saint Lucia" OR "Saint Vincent and the Grenadines" OR suriname OR "Trinidad and Tobago" OR uruguay OR venezuela OR anguilla OR aruba OR "British Virgin Islands" OR "Cayman Islands" OR curaçao OR "Sint Maarten" OR "Saint Martin" OR "Latin America" OR latin OR caribbean)) OR (AFFILCOUNTRY (("Antigua and Barbuda" OR argentina OR bahamas OR barbados OR belize OR bolivia OR brazil OR chile OR colombia OR "Costa Rica" OR cuba OR dominica OR "Dominican Republic" OR ecuador OR "El Salvador" OR grenada OR guatemala OR guyana OR haiti OR honduras OR jamaica OR mexico OR nicaragua OR panama OR paraguay OR peru OR "Saint Kitts and Nevis" OR "Saint Lucia" OR "Saint Vincent and the Grenadines" OR suriname OR "Trinidad and Tobago" OR uruguay OR venezuela OR anguilla OR aruba OR "British Virgin Islands" OR "Cayman Islands" OR curaçao OR "Sint Maarten" OR "Saint Martin" OR "Latin America" OR latin OR caribbean))))

LILACS

(asthma OR wheeze OR wheezing OR "respiratory tract allergy" OR "respiratory allergy") AND (traffic OR road OR roads OR roadway OR roadways OR motorway OR motorways OR freeway OR freeways OR highway OR highways OR exhaust OR emissions OR pollution OR pollutants OR polluted OR contamination OR "particulate matter" OR "suspended particles" OR "coarse particles" OR "respirable particles" OR "fine particles" OR "ultrafine particles" OR "inhalable particles" OR spm OR tsp OR pm10 OR pm2.5 OR pm1 OR "black carbon" OR "carbon monoxide" OR nitrogen OR "NO2" OR nox OR hydrocarbon OR ozone OR o3 OR sulfur OR so2 OR sox OR hydrocarbons OR "volatile organic") AND (children OR adolescents OR young OR toddlers OR infants OR school OR preschool OR students OR newborns OR paediatric OR pediatric OR teens OR teenagers OR babies OR juveniles OR kids OR kindergarten OR minors OR neonates) AND ("cross sectional" OR transversal OR prevalence OR survey OR sampling OR sample OR questionnaire) AND ("Antigua and Barbuda" OR argentina OR bahamas OR barbados OR belize OR bolivia OR brazil OR chile OR colombia OR "Costa Rica" OR cuba OR dominica OR "Dominican Republic" OR ecuador OR "El Salvador" OR grenada OR guatemala OR guyana OR haiti OR honduras OR jamaica OR mexico OR nicaragua OR panama OR paraguay OR peru OR "Saint Kitts and Nevis" OR "Saint Lucia" OR "Saint Vincent and the Grenadines" OR suriname OR "Trinidad and Tobago" OR uruguay OR venezuela OR anguilla OR aruba OR "British Virgin Islands" OR "Cayman Islands" OR curaçao OR "Sint Maarten" OR "Saint Martin" OR "Latin America" OR latin OR caribbean) AND (instance:"regional") AND (db:("LILACS"))

SciELO

(asthma OR wheeze OR wheezing OR "respiratory tract allergy" OR "respiratory allergy") AND (traffic OR road OR roads OR roadway OR roadways OR motorway OR motorways OR freeway OR freeways OR highway OR highways OR exhaust OR emissions OR pollution OR pollutants OR polluted OR contamination OR "particulate matter" OR "suspended particles" OR "coarse particles" OR "respirable particles" OR "fine particles" OR "ultrafine particles" OR "inhalable particles" OR SPM OR TSP OR PM10 OR PM2.5 OR PM1 OR "black carbon" OR "carbon monoxide" OR nitrogen OR "NO2" OR NOx OR hydrocarbon OR ozone OR O3 OR sulfur OR SO2 OR SOx OR hydrocarbons OR "volatile organic") AND (children OR adolescents OR young OR toddlers OR infants OR school OR preschool OR students OR newborns OR paediatric OR pediatric OR teens OR teenagers OR babies OR juveniles OR kids OR kindergarten OR minors OR neonates) AND ("cross sectional" OR transversal OR prevalence OR survey OR sampling OR sample OR questionnaire) AND ("Antigua and Barbuda" OR Argentina OR Bahamas OR Barbados OR Belize OR Bolivia OR Brazil OR Chile OR Colombia OR "Costa Rica" OR Cuba OR Dominica OR "Dominican Republic" OR Ecuador OR "El Salvador" OR Grenada OR Guatemala OR Guyana OR Haiti OR Honduras OR Jamaica OR Mexico OR Nicaragua OR Panama OR Paraguay OR Peru OR "Saint Kitts and Nevis" OR "Saint Lucia" OR "Saint Vincent and the Grenadines" OR Suriname OR "Trinidad and Tobago" OR Uruguay OR Venezuela OR Anguilla OR Aruba OR "British Virgin Islands" OR "Cayman Islands" OR Curaçao OR "Sint Maarten" OR "Saint Martin" OR "Latin America" OR Latin OR Caribbean)

Table A2. Newcastle-Ottawa criteria modified for this study

Detailed criteria for assigning stars
Selection: (Maximum 3 stars)
1) Representativeness of the sample:
a) All subjects or random sampling in home-based surveys. *
b) All subjects or random sampling in hospital-based or school-based surveys. *
c) Selected group of users.
d) No description of the sampling strategy.
2) Sample size:
a) The simple size was calculated considering an appropriate outcome. *
b) Sample size not justified.
3) Non-respondents:
a) Satisfactory response rate ($>$ 75%), and non-respondents described. *
b) The response rate is unsatisfactory ($<$ 75%), or there is no description of non-respondents.
Exposure: (Maximum 2 stars)
1) Ascertainment of the exposure:
a) Pollution defined by daily or hourly concentrations of CO, NO_2, SO_2, O_3, PM_{10} or $PM_{2.5}$, as measured by air quality monitoring stations. **
b) Pollution defined by distance to a defined air pollution source or other quantitative procedures. *
c) Pollution defined by arbitrary or subjective criteria.
Outcome: (Maximum 2 stars)
1) Assessment of the outcome:
a) Medically diagnosed condition, or disease diagnostic documented in medical records. **
b) Disease-related symptoms reported by patients or parents, or defined by questionnaires. *
c) No description.
Comparability: (Maximum 2 stars)
1) Control for confounding factors in the study design and/or analysis.
a) The study controls for indoor air pollution (e.g. secondhand smoke, presence of pets, wood stove). *
b) Additionally, the study controls for individual or socioeconomic factors. *
c) No control for confounding factors.

Table A3. Rules for effect sizes selection in studies with two or more effect sizes reported

- The preferred outcome was wheeze in the last 12 months, otherwise asthma, wheeze ever or wheeze during exercise.
- One or more episodes of wheeze over recurrent wheezing.
- ORs adjusted by covariates were preferred over crude ORs.
- When the same article showed different ORs for different countries, cities, areas, or age groups, all the ORs were considered as independent from each other and were included as different effect sizes in the analysis.