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REVIEW

# Short-term effects of fine particulate matter pollution on daily health events in Latin America: a systematic review and meta-analysis

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**Abstract**
*Objectives* Ambient air pollution is among the leading risks for health worldwide and by 2050 will largely overcome deaths due to unsafe sanitation and malaria, but local evidence from Latin America (LA) is scarce. We aimed to summarize the effect of short-term exposure to fine particulate air pollution ($PM_{2.5}$) on morbidity and mortality in Latin America and evaluate evidence coverage and quality, using systematic review and meta-analysis.
*Methods* The comprehensive search (six online databases and hand-searching) identified studies investigating the short-term associations between $PM_{2.5}$ and daily health events in LA. Two reviewers independently accessed the internal validity of the studies and used random-effect models in the meta-analysis.
*Results* We retrieved 1628 studies. Nine were elected for the qualitative analysis and seven for the quantitative analyses. Each 10 μg/m$^3$ increments in daily $PM_{2.5}$ concentrations was significantly associated with increased risk for respiratory and cardiovascular mortality in all-ages (polled RR = 1.02, 95% CI, 1.02–1.02 and RR = 1.01, 95% CI , 1.01–1.02, respectively).
*Conclusions* Short-term exposure to $PM_{2.5}$ in LA is significantly associated with increased risk for respiratory and cardiovascular mortality. Evidence is concentrated in few cities and some presented high risk of bias.

**Keywords** Air pollution · Particulate matter · Fine particulate matter · PM2.5 · Mortality · Latin America · Systematic review and meta-analysis

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## Introduction

Ambient air pollution is among the leading risks for health worldwide (GBD 2015 Risk Factors Collaborators 2016), and by 2050 will largely overcome deaths due to unsafe sanitation and malaria (Organisation for Economic Co-operation and Development 2012).

Particulate matter (PM) is a complex mixture of solid and liquid compounds widely used as an indicator for air pollution. Its composition and size vary substantially according to emission sources and prevailing weather conditions. The smaller its size the greater its potential to impact health, given the increased chance of penetration in the respiratory tract (Health Effects Institute 2002). Epidemiological evidence of the effects of fine particulate matter [PM with aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$)] on morbidity and mortality is consistent, particularly on cardiovascular and respiratory systems (Anderson et al. 2004;

Pope et al. 2006). Biological evidence supporting plausible mechanisms is clear and includes pulmonary oxidative stress, inflammation and altered cardiac autonomic function (Pope et al. 2006). However, evidence in Latin America (LA) is scarce and systematic reviews and meta-analysis (SRMA) on the effects of $PM_{2.5}$ on daily health events rarely pool evidence from LA (Adar et al. 2014; Shah et al. 2015). The World Health Organization (WHO) is updating current ambient Air Quality Guidelines, which establishes standards for pollutants at concentrations considered sufficiently safe for human health (World Health Organization 2015). Transferability of existing concentration response functions (CRF) developed for European and North American cities to other countries with significant differences in air pollution levels are being questioned. According to the experts consulted by WHO, re-evaluation of the existing CRFs for $PM_{2.5}$ is necessary, given the observed changes in the risk at extreme concentrations. Experts also underscored that current evidence shows association of short-term $PM_{2.5}$ exposure with mortality at levels below the current guideline, among other new evidences that need to be evaluated (World Health Organization 2015).

When the WHO air quality guidelines were last updated in 2005 (World Health Organization 2006), monitoring systems were scarce in cities from developing nations, including LA's cities. Most of the data available in developing regions were exclusively for total suspended particles concentrations, an overcome measure of particulate air pollution that includes particulates of bigger size. After a decade, evidence in LA remains delayed compared to North America and Europe. While developed countries are concerned with the health effects of fine ($PM_{2.5}$), ultrafine (PM with aerodynamic less than 100 nm) and coarse [PM with aerodynamic diameter 10–2.5 ($PM_{10-2.5}$)] particles, few cities in LA depict evidence for these pollutants. Only eight Latin American countries have set National Air Quality Standards for $PM_{2.5}$ (Green and Sanchéz 2012), all above the final target of 25 $\mu g/m^3$ for 24-hour average, current suggested by WHO (World Health Organization 2006). In 2012, the ESCALA multi-city study has established methodological foundation for future research in LA and provided high-quality evidence from nine cities to support air pollution control policies in the region (Romieu et al. 2012). However, the evidence was limited to the effects of $PM_{10}$ on mortality.

Given the very high levels of $PM_{2.5}$ pollution in Africa, Asia and Middle East (Brauer et al. 2012), air pollution in LA receives less attention in global analysis. However, between 1990 and 2013, $PM_{2.5}$ annual mean level trends increased in parts of South America and decreased in parts of Southeast Asia (Brauer et al. 2012).

In this systematic review, we aimed to summarize the evidence of the short-term effects of $PM_{2.5}$ on daily health events in Latin American populations. We also aimed to identify the Latin American cities covered with local evidence on short-term health effects of $PM_{2.5}$ and to evaluate the quality of the evidence identified.

## Methods

This study followed a protocol previously registered at PROSPERO (registration CRD42015029673) and is reported according to both: PRISMA Statement recommendations for transparent reporting of systematic reviews (Moher et al. 2009) and MOOSE Guidelines for meta-analyses and systematic reviews of observational studies (Stroup 2000).

### Search strategy and eligibility criteria

We searched six online databases (PubMed, Embase, Scopus, Web of Science, Cochrane and Lilacs) up to September 2015 to identify studies conducted in LA that analysed the associations of short-term exposure to $PM_{2.5}$ with daily health events (mortality, hospital admission and emergency room visits). Search combined terms for exposure (e.g. "air pollution", or "particulate matter"), outcome (e.g. "hospital admission") and population (e.g. "Latin America" or name of countries). Controlled vocabulary of databases was included in the search string. We did not impose language or date restrictions to the search. We searched the reference lists of relevant reviews and studies for additional manuscripts and used Mendeley software for uploading the references. For detailed search strategy, see the Supplemental Material, S1.

### Eligibility criteria included

(a) Original published time-series or case cross-over studies with a minimum period evaluated of one uninterrupted year, conducted in LA.
(b) Studies that reported quantitative measurements of daily short-term exposure (up to a lag of 7 days) to ambient $PM_{2.5}$.
(c) Studies that reported daily emergency room visits, hospital admissions, and/or mortality for all natural causes and/or all or selected respiratory causes and or all or cardiovascular causes. Related International Code of Disease (ICD 9th and 10th revision) for the causes included were ICD-9 001–799, ICD-10 A00-T98 and Z00-Z99 (all natural causes), ICD-9 460–519, ICD-10 J00-J99 (respiratory causes) and, ICD-9 390–459, ICD-10 I00-I99 (cardiovascular cases).
(d) Studies that calculated or provided enough information to estimate the relative risk of the daily health

event associated with an increment of 10 μg/m$^3$ in $PM_{2.5}$ levels.

(e) Studies that reported the risk exclusively by subgroups other than age, daily event or disease groups of interest for this review (e.g. by season or chemical composition of the particle) were excluded.

### Study selection

First, two independent reviewers screened all abstracts and titles for studies that potentially met the inclusion criteria. Then, reviewers evaluated full studies for final inclusion in the SR (Systematic Review) and recorded reasons for exclusion (see the Supplemental Material). Similar to reviews on global (Atkinson et al. 2014) and European evidence (Anderson et al. 2004), we selected only one study by setting to avoid overlapping of populations (see protocol at PROSPERO, registration CRD42015029673). We solved disagreements between reviewers by consensus along the stages.

### Data collection process and items

Data items included citation information (e.g. year of publication) and characteristics of the location (e.g. main air pollution sources), population (e.g. age), exposure (e.g. $PM_{2.5}$ levels) and outcomes (e.g. total number of events) (see Table 1). We also collected information necessary to conduct meta-analysis of the relative risks related with 10 μg/m$^3$ increments in $PM_{2.5}$ levels (e.g. association measurements and its 95% Confidence Interval (CI)) and methodological characteristics necessary to assess the quality of the included studies (see Table 2). One reviewer extracted the data into Microsoft Excel 2013 and a second reviewer confirmed the information. Disagreements were solved by discussion.

### Risk of bias in individual studies

Since there is no specific tool to evaluate methodological quality of time-series and case cross-over studies, two independent reviewers conducted a qualitative assessment, which classified studies as high or low risk of bias, according to criteria previously registered at the protocol of this study. We also verified funding sources and the conflicts of interest reported, which are recently being considered potential source of bias (Lam et al. 2014).

### Summary measures

We calculated summary effects associated with $PM_{2.5}$ levels in the statistical software RevMan 5.1 by daily event type (emergency room visits, hospital admissions and mortality), cause (total non-external causes, respiratory and cardiovascular causes) and age group (all-ages, elderly and children), if at least two association measurements were available from two different studies. Given that we calculated a polled effect for an entire continent, variations regarding population, outcomes and exposure characteristics among the cities included in the quantitative analysis were expected. For this reason, we used random effects model to estimate the summary measures and present them as Relative Risk (RR) with a 95% Confidence Interval (95% CI) for each increment of 10 μg/m$^3$ in $PM_{2.5}$ 24-hour average levels.

The lag (number of days between the exposure and the health event) reported by studies varied greatly and it was not possible to group the studies by lag structure. The lag used to calculate the summary measure was the lag reported. We chose the lag with the highest effect, if more than one lag was reported.

We used Cochrane Q test (significance level: 0.1) and $I^2$ statistic to test statistical heterogeneity. $I^2$ statistic quantifies heterogeneity by calculating the proportion of variation occurred by heterogeneity rather than by chance (Higgins et al. 2003). For $I^2$, we considered that values ranging from 0 to 30, 30 to 50 and >50 indicated low, moderate and high heterogeneity, respectively. We also reduced potential heterogeneity due to populations and outcome cause differences by polling evidence grouped by cause/age pairs. We planned to perform subgroup analysis by pollutant model (single vs. multi-pollutant), pollution source (rural vs. urban) and risk of bias between studies (combining low risk of bias studies only), if heterogeneity was statistically significant. Non-quantitative data were presented descriptively.

### Publication bias assessment

If 10 or more studies are included in the review, we accessed publication bias through funnel plot and Egger test (Egger et al. 1997).

## Results

### Study selection

Search retrieved 1628 studies, nine were elected for the qualitative analysis and seven for the quantitative analyses (Fig. 1). Elected studies were conducted in three countries (Chile, Brazil and Mexico), distributed in six cities, mostly with less than a million inhabitants. None of the studies investigated the effects of $PM_{2.5}$ on emergency room visits.

Automotive was the main source of air pollution reported, followed by biomass burning and industrial

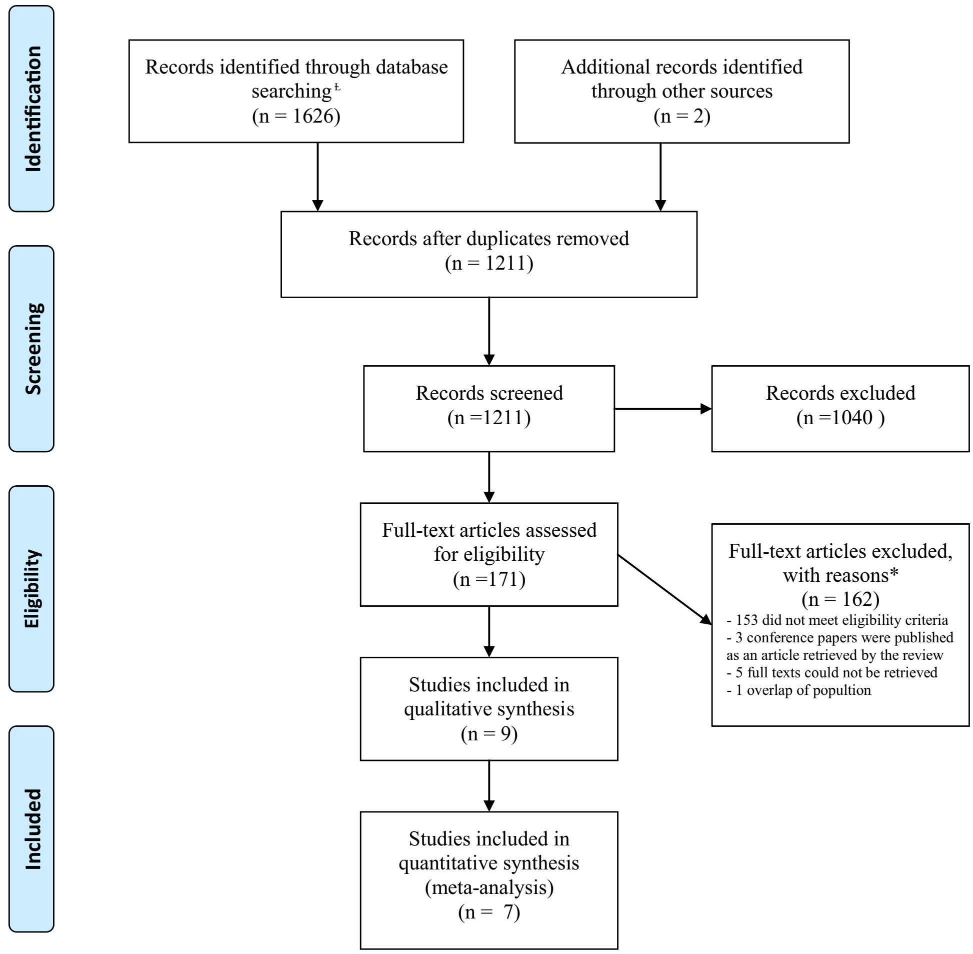
**Table 1** Characteristics of the studies included in the systematic review of the effects of fine particulate matter on daily health events in Latin America

| References | Study period | City (Country) | Air pollution sources[†] | Inhabitants reported[•] | $PM_{2.5}$ mean (SD) in μg/m$^3$ | Population in years | Outcome (cause) | Number of events | Pollutant model | Risk of bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Dales et al. (2010)[ŧ] | 1998–2005 | Santiago metropolitan region (Chile) | NI | 5.370.000 | 32.9 (20.2) | All-ages | HA(CV° :I00-I99) | 282.645 | Both | Low |
| Cesar et al. (2013) | 2011–2012 | Piracicaba (Brazil) | Biomass, automotive | 350.000 | 26.8 (16.7) | <10 | HA(R:J00-J98) | 437 | Single | High |
| Ignotti et al. (2010) | 2000–2004 | Alta Floresta (Brazil) | Biomass | 101.278 | 20.4 (32.6) | <5 | HA(R:J00-J98) | 481 | Single | High |
| Silva et al. (2013) | 2005 | Cuiabá (Brazil) | Biomass | 550.562 | 7.5 (10.4) | <5 | HA(R:J00-J98) | 1.152 | Single | Low |
| Loomis et al. (1999)[ŧ] | 1993–1995 | Ciudad de México (Mexico) | Automotive, industrial | 2.500.000 | 27.4(10.5) | <1 | M(A:A00-T98, Z00-Z99) | 2.798 | Both | Low |
| Borja-Aburto et al. (1998) | 1993–1995 | Ciudad de México (Mexico) | Automotive, industrial | 2.500.000 | 27.0 (11.0) | All-ages, >65 | M(A,R:J00-J98),CV:I00-I99) | 1.152 | Both | Low |
| Sanhueza et al. (1998) | 1988–1993 | Santiago (Chile) | NI | NI | 81.0 (NI) | All-ages, >65 | M(A:A00-T98, Z00-Z99) | 76.442 (A,>65) | Both | Low |
| Valdes et al. (2012) | 1998–2007 | Santiago (Chile) | NI | NI | 34.0 (NI) | All-ages | M(R:J00-J98),CV:I00-I99) | 92.891 | Single | High |
| Reyna et al. (2012) | 2003–2007 | Mexicali (Mexico) | Automotive, unpaved roads | 856.000 | 60.6 (32.3) | All-ages | M(A*:A00-T98, Z00-Z99) | 872.350 | Single | Low |

*SD* standard deviation, *ICD* international code of disease 10th revision, *NI* not informed, *PM* particulate matter, *M* mortality, *HA* hospital admissions, *E* emergency room visits, *A* all non-external causes, *CV* cardiovascular disease, *R* respiratory disease, *Single* single-pollutant model, *Multi* multi-pollutant model, *Both* single and multi-pollutant model. Not all studies evaluated the whole population of the city investigated, therefore some inhabitants reported reflect the population of the area covered by the hospitals included in the analysis, not all the city

*Reyna et al. (2012) also evaluated respiratory mortality, but did not present the associations with short-term exposure to $PM_{2.5}$ for this outcome. °Study evaluated specific cardiovascular disease I26 an I80 according to the International Classification of Disease, 10th Revision (ICD-10). ŧNot included in the quantitative analysis. Dales et al. (2010) was the only study that evaluated cardiovascular hospitalizations and Loomis et al. (1999) the only study that evaluated mortality in children

Fig. 1 Flow diagram describing search, screening and eligibility of the studies on short-term effects of fine particulate matter on daily events in Latin America




* see the Supplemental Material for the complete list of studies excluded by reason. Databases searched: PubMed, Embase, Scopus, Web of Science, Cochrane and Lilacs up to September 2015

sources. $PM_{2.5}$ daily mean varied from 7.5 to 81.0 μg/m$^3$ among the included studies (Table 1).

The most studied decade was the 2000s (44%), followed by the 1990s (35%), 2010s (23%) and 1980s (5%). All elected studies were time-series studies published as articles. Only one was a multi-city study (evaluated the metropolitan area). Elected studies were mostly published in English (89%), and 56% of the included studies used single-pollutant models exclusively (see Supplemental Material, TableS1).

The quality assessment revealed that 33% of the included studies presented high risk of bias, 43% if we consider only studies elected for the quantitative analysis. Frailties in statistical adjustments (e.g. not using the Akaike criteria), in exposure characterization (not using monitoring networks) and controlling for confounders (not controlling for short trends such as for day of the week) were the main reasons why studies were classified as high risk of bias. When reported, conflict of interest was absent and financial sources were related to governmental agencies and University-related grants (Table 2).

Measurements combined for meta-analysis were derived from single-pollutant models, except for total mortality in elderly, where evidence was available for single- and multi-pollutant models. All meta-analysis combined evidence from two different studies, except from hospital admissions where evidence from three were combined. Given the low number of studies combined and their characteristics, we did not perform subgroup analysis by pollution source (rural vs. urban) and risk of bias (low vs. high risk of bias).

## Mortality

Meta-analysis of the risks for respiratory mortality in all-ages associated with $PM_{2.5}$ levels showed a significant 2% increased risk (RR per 10 μg/m$^3$ = 1.02, 95% CI, 1.02–1.02; $I^2$ = 0%) (Fig. 2). Meta-analysis of the risk for cardiovascular mortality associated with $PM_{2.5}$ levels showed a significant 1% increased risk (RR *per* 10 μg/m$^3$ = 1.01, 95% CI,

**Table 2** Quality assessment of the included studies in the systematic review of the effects of fine particulate matter on daily health events in Latin America

| | Selection | | Exposure | | | Confounders | | | | Statistical adjustments of the model | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | ICD | Source◊ | Source◊◊ | Network | Daily | Long trends | Short trends | Temp | Hum | Auto-correlation | Akaike | Risk of bias** | Founding source | Conflict of interest |
| Dales et al. (2010)[ł] | Y | Y | N | Y | Y | N | N | Y | Y | Y | Y | Low | NI | No conflict |
| Cesar et al. (2013) | Y | Y | Y | N* | Y | N | N | Y | N | N | N | High | Governmental research agency | No conflict |
| Ignotti et al. (2010) | Y | Y | Y | N* | Y | N | N | Y | Y | N | N | High | Governmental research agencies | NI |
| Silva et al. (2013) | Y | Y | Y | N* | Y | Y | Y | Y | Y | N | N | Low | NI | No conflict |
| Loomis et al. (1999)[ł] | Y | Y | Y | N | Y | Y | N | Y | N | Y | Y | Low | NI | No conflict |
| Borja-Aburto et al. (1998) | Y | Y | Y | N | Y | Y | N | Y | Y | Y | Y | Low | NI | NI |
| Sanhueza et al. (1998) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Low | Governmental research agency and University-related grants | NI |
| Valdes et al. (2012) | Y | Y | Y | N | N | Y | Y | Y | Y | N | N | High | NI | No conflict |
| Reyna et al. (2012) | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | N | Low | University-related grants | NI |

*ICD* International code of disease informed, *Y* yes, *N* no, *U* unclear, *NI* not informed, *Network* monitoring network, *Daily* daily measurements, *Akaike* Akaike criteria, *Temp* temperature, *Hum* humidity

[†]Studies included in the quantitative analysis, N* satellite, ◊Source of the outcome data, ◊◊Source of the exposure data, [ł]not included in the quantitative analysis. Dales et al. (2010) was the only study that evaluated cardiovascular hospitalizations and Loomis et al. (1999). **Studies > 3 N were classified as high risk of bias.

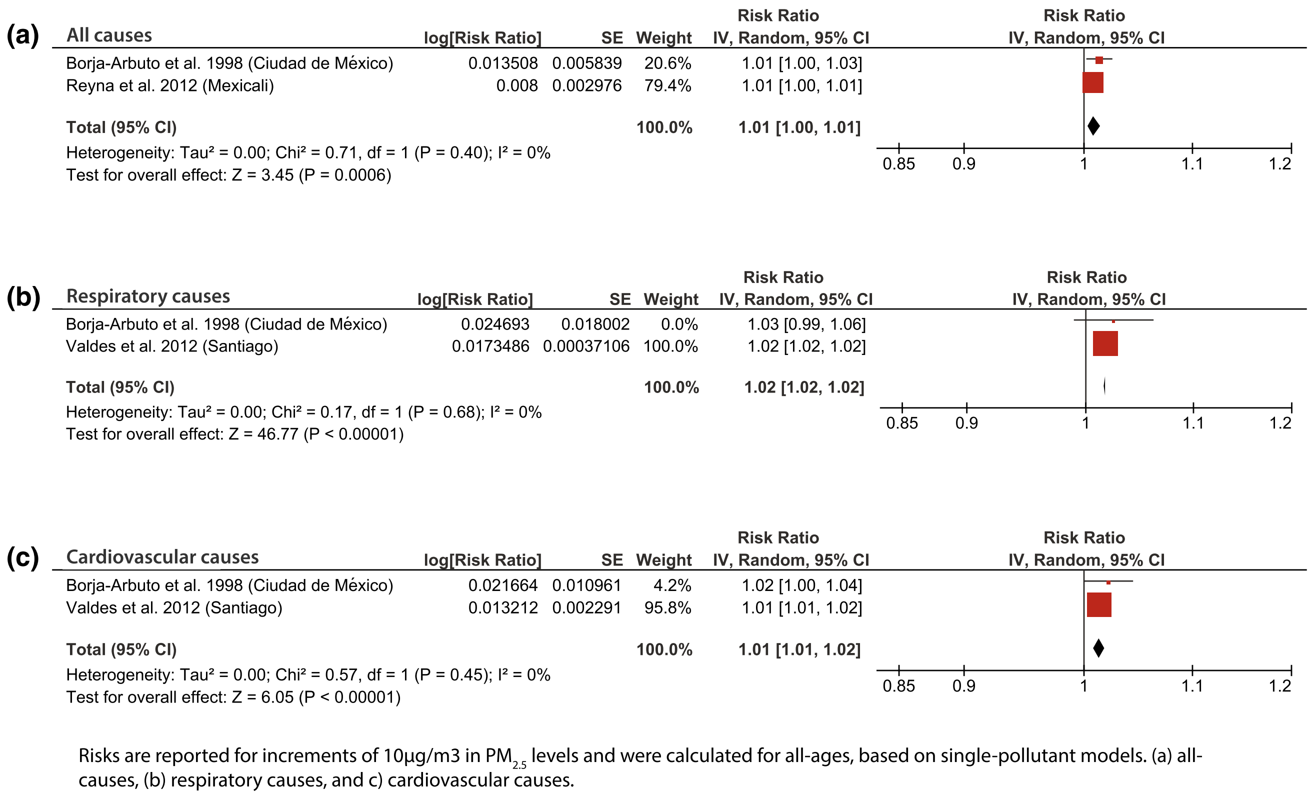



**Fig. 2** Forest plots for the risks for daily mortality by cause associated with short-term exposure to PM2.5 levels in Latin America

1.01–1.02; $I^2=0\%$) (Fig. 2). One of the studies combined presented high risk of bias.

Risk for total mortality was not significant neither for all-ages (RR per 10 µg/m$^3$ = 1.01, 95% CI, 1.00–1.01; $I^2=0\%$) (Fig. 2), nor for elderly (RR per 10 µg/m$^3$ = 1.01, 95% CI, 1.00–1.02; $I^2=55\%$) The risk for total mortality in elderly remained not significant when we combined measures based on multi-pollutant models, all adjusted for $O_3$: RR per 10 µg/m$^3$ = 1.01, 95% CI, 0.99–1.03; $I^2=73\%$ (see Supplemental Material, Figure S1). All studies combined presented low risk of bias.

For hospital admissions, meta-analysis showed no statistical association between $PM_{2.5}$ levels and daily hospital admissions and presented significant high heterogeneity: RR per 10 µg/m$^3$ = 1.03, 95% CI 0.99–1.08; $I^2=68\%$) (Fig. 3). The studies combined used satellite-derived measurements and two depicted high risk of bias.

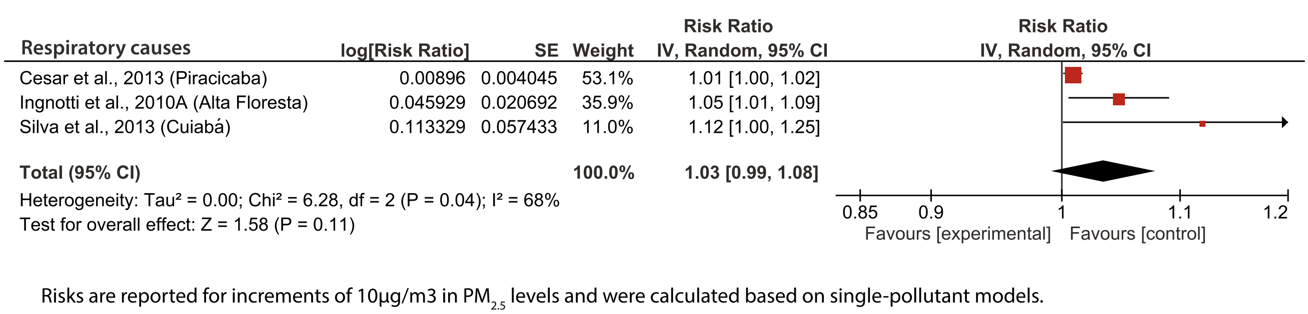



**Fig. 3** Forest plots for the risks for daily respiratory hospitalization in children associated with short-term exposure to PM2.5 levels by pollutant model in Latin America

## Discussion

Our results showed significant associations between short-term exposure to $PM_{2.5}$ in LA and increased risk for respiratory and cardiovascular mortality in all-ages. The risks for each 10 µg/$m^3$ increment in $PM_{2.5}$ levels ranged between 1 and 2% and heterogeneity between studies was low. On the other hand, risks associated with short-term exposure to $PM_{2.5}$ for total mortality in all-ages and in elderly and respiratory hospitalization in children were not significant. Imprecision might explain why some meta-analysis were not statistically significant in our review, since CIs of the combined studies tended to be larger in the non-significant meta-analysis (particularly for hospitalizations meta-analysis), compared to significant meta-analysis (respiratory and cardiovascular mortality). Frequently, multi-city studies find larger effects when the analysis is restricted to elderly populations (Romieu et al. 2012), because elderly are more vulnerable to air pollution adverse health effects. However, our meta-analysis for total mortality in elderly was not significant. Because populations are exposed to a complex mixture of air pollutants, not single pollutants, researchers (and policy makers) have been encouraged to move towards a multi-pollutant approach to air quality, rather than single-pollutant models (Dominici et al. 2012). In our review, most of the risks reported were based on single-pollutant models. Meta-analysis for multi-pollutant models (adjusted for $O_3$) was just feasible for total mortality in elderly, but the related risks were not significant in both pollutant models.

Our results are partially in accordance with other meta-analysis on the short-term association of $PM_{2.5}$ and daily health events in the world (Adar et al. 2014; Atinkson et al. 2014), pointing out that, while local evidence is scarce, extrapolating evidence from other regions to control particulate pollution in LA might be reasonable.

Compared to the present review, Atkinson and colleagues study (2014) identified fewer Latin American studies and did not evaluate all the outcomes considered in this review for Latin American region, possible due to differences in the search strategy adopted. We searched Lilacs, a specific database for scientific literature of Latin American, and other databases up to September 2015, while Atkinson's and colleagues review (2014) searched global databases exclusively up to May 2011. While our results are mostly in accordance with Atkinson's global findings, our results contrast with Atkinson's findings for LA for total, respiratory and cardiovascular mortality in all-ages. Both reviews combined evidence from two studies to perform meta-analysis, but in our review, CIs of the included studies were more precise.

Evidence on the short-term effects of $PM_{2.5}$ in daily health events conducted in LA is scarce, concentrated in few locations and publication trend is not increasing. The scarcity of studies in the continent might be reflecting lack of exposure data, since only half of Latin American cities with monitoring stations for $PM_{10,}$ also monitors $PM_{2.5}$ (Green and Sanchéz 2012). Moreover, in some cities, $PM_{2.5}$ measurements started in recent years and occur in a few percentage of the existing monitoring stations (Ambiente 2014). In our review, all Brazilian studies included estimated population exposure through satellite estimations. Sophisticated satellite-based estimates are a promising tool to overcome the scarcity of exposure data, given that correlation with ground-level $PM_{2.5}$ mass might reach 81% (Van Donkelaar et al. 2016) and The Global Burden of Disease Study is already using satellite-based $PM_{2.5}$ estimates (Brauer et al. 2012).

One of the strengths of our review was to evaluate the internal validity of the included studies, which is not frequent in most SRMAs of epidemiological time-series studies, since, to our knowledge, no validated tool evaluates methodological quality of time-series. Despite advances in methodology of SRMAs involving epidemiological observational studies in general (Atkinson et al. 2014)[1] and of epidemiological studies of environmental health (EH) in particular (Sheehan and Lan 2015), it is still difficult to adapt the recommendations to assess the risk of bias in time-series studies. Cochrane Collaboration recommend tools for randomized controlled trials and non-randomized studies of intervention (Higgins and Green 2011), both not applicable to time-series design. Yet, time-series studies have been playing a relevant role in air pollution regulatory process, because they estimate the burden of disease attributable to air pollution exposure and the related CRF can be used in cost–benefit analysis (Bell et al. 2004). Time-series studies use regression models to assess the effects of short-term changes in $PM_{2.5}$ levels on acute health effects by estimating associations between day-to-day variations in both air pollution and in mortality and morbidity counts. The study design uses aggregated level data for exposure and outcome. Confounding bias arise from factors that vary in short time scales and may be associated with particulate and health (e.g. temperature). Statistical specificities (e.g. accounting for serial correlation in the residuals) also play a role (Bell et al. 2004).

Our quality assessment followed an *a priori* criteria and two reviewers independently assessed key methodologically potential sources of bias in human epidemiological observational studies in EH in general (e.g. exposure characterization and controlling for confounders) (Sheehan and Lan 2015) and of time-series design in particular (e.g. statistical adjustments) (Bell et al. 2004). Frailties in at least one of the potential source of bias domains were frequent; underlining that internal validity of time-series study design on EH SRMAs needs further investigations.

Since we retrieved less than 10 studies for each health endpoints (outcome/cause/age), we did not evaluate publication bias, a limitation of this review.

Multi-city studies standardize statistical approach, and therefore minimize potential risk of bias due to differences in statistical methodology of time-series studies (Bell et al. 2004). To the extent that time-series design usually uses secondary dada relatively accessible from public sources, efforts to conduct high-quality multi-city studies might be preferable than conducting meta-analysis based on individual studies data retrieved in a SR. However, $PM_{2.5}$ monitoring stations are scarce in LA (Green and Sánchez 2012) and the multi-city study for Latin American region[8] did not evaluate the effects of $PM_{2.5}$ on health, making this review relevant.

In summary, evidence in LA is scarce, concentrated and trend of publication is not increasing. Short-term exposure to $PM_{2.5}$ in the continent is significantly associated with increased risk for respiratory and cardiovascular mortality in all-ages in region. Our results are in accordance with evidence from other parts of the world, pointing out that, while local evidence is scarce, extrapolating evidence from other regions to control particulate pollution in LA might be reasonable. Quality assessment identified frailties in key methodological sources of bias in observational studies in EH in general (exposure characterization and controlling for confounders) and in time-series design in particular (statistical adjustments), thus assessing the internal validity of time-series study design in SRMA on EH needs further investigations.

**Compliance with ethical standards**

**Ethical statement** The present manuscript is an original work, has not been previously published whole or in part, and is not under consideration for publication elsewhere. We did not fabricate data. We did not present data, text or theories from other authors as if they are ours (no "plagiarism"). All authors contributed sufficiently to the scientific work, read the manuscript, agreed the work is ready for submission to a journal and accepted responsibility for the manuscript's content. All authors do not present actual or potential conflicts of interest regarding the submitted.

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