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Short-term exposure to ozone, nitrogen dioxide, and sulphur dioxide and emergency department visits and hospital admissions due to asthma: A systematic review and meta-analysis

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ABSTRACT

Background: Air pollution is a major environmental hazard to human health and a leading cause of morbidity for asthma worldwide.

Objectives: To assess the current evidence on short-term effects (from several hours to 7 days) of exposure to ozone (O_3), nitrogen dioxide (NO_2), and sulphur dioxide (SO_2) on asthma exacerbations, defined as emergency room visits (ERVs) and hospital admissions (HAs).

Methods: We searched PubMed/MEDLINE, EMBASE and other electronic databases to retrieve studies that investigated the risk of asthma-related ERVs and HAs associated with short-term exposure to O_3, NO_2, or SO_2. We evaluated the risks of bias (RoB) for individual studies and the certainty of evidence for each pollutant in the overall analysis. A subgroup analysis was performed, stratified by sex, age, and type of asthma exacerbation. We conducted sensitivity analysis by excluding the studies with high RoB and based on the E-value. Publication bias was examined with the Egger's test and with funnel plots.

Results: Our literature search retrieved 9,059 articles, and finally 67 studies were included, from which 48 studies included the data on children, 21 on adults, 14 on the elderly, and 31 on the general population. Forty-three studies included data on asthma ERVs, and 25 on asthma HAs. The pooled relative risk (RR) per 10 $\mu g/m^3$ increase of ambient concentrations was 1.008 (95%CI: 1.005, 1.011) for maximum 8-hour daily or average 24-hour O_3, 1.014 (95%CI: 1.008, 1.020) for average 24-hour NO_2, 1.010 (95%CI: 1.001, 1.020) for 24-hour SO_2, 1.017 (95%CI: 0.973, 1.063) for maximum 1-hour daily O_3, 0.999 (95%CI: 0.966, 1.033) for 1-hour NO_2, and 1.003 (95%CI: 0.992, 1.014) for 1-hour SO_2. Heterogeneity was observed in all pollutants except for 8-hour or 24-hour O_3 and 24-hour NO_2. In general, we found no significant differences between subgroups that can explain this heterogeneity. Sensitivity analysis based on the RoB showed certain differences in NO_2 and SO_2 when considering the outcome or confounding domains, but the analysis using the E-value showed that no unmeasured confounders were expected. There was no major evidence of publication bias. Based on the adaptation of the *Grading of Recommendations Assessment, Development and Evaluation*, the certainty of evidence was high for 8-hour or 24-hour O_3 and 24-hour NO_2, moderate for 24-hour SO_2, 1-hour O_3, and 1-hour SO_2, and low for 1-hour NO_2.

Abbreviations: NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulphur dioxide; WHO, World Health Organization; AQGs, air quality guidelines; ERVs, emergency room visits; HAs, hospital admissions; RoB, risk of bias; ICD, International Classification of Diseases; ETS, ecological time-series; CCO, case-crossover; SD, standard deviation; RRs, relative risks; ORs, odds ratios; Perc-Incr, percentage change; PIs, prediction intervals; RR_U, RRs of the unmeasured confounder; $RR_{observed}$, RRs calculated by means of meta-analysis; CRFs, concentration-response functions; CoE, The certainty of evidence; GRADE, the Grading of Recommendations Assessment, Development and Evaluation.

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Conclusion: Short-term exposure to daily O_3, NO_2, and SO_2 was associated with an increased risk of asthma exacerbation in terms of asthma-associated ERVs and HAs.

1. Introduction

Air pollution is a major environmental hazard and the leading cause of morbidity and mortality globally (Cohen et al., 2017). Air pollution has been associated with the development of asthma (Guan et al., 2016), a chronic airway inflammatory disease punctuated by episodes of attacks which are frequently linked to an increased symptom burden and significantly impaired quality of life (Castillo et al., 2017). Accumulating evidence points to the association between short-term exposure to air pollution and asthma exacerbations (Orellano et al., 2017; Zheng et al., 2015). Nonetheless, the magnitude to which short-term exposure to air pollutants correlate with asthma exacerbations remains not entirely clear.

Systematic reviews and *meta*-analyses have been conducted to determine the pooled effect estimates of the adverse health effects of air pollutants (Orellano et al., 2017; Zheng et al., 2015), because individual studies have been conducted across various contexts and using different study methodologies. By pooling case-crossover studies published between 2000 and 2016, short-term exposure to nitrogen dioxide (NO_2), ozone (O_3) but not sulphur dioxide (SO_2) conferred significantly increased risks of asthma exacerbations (Orellano et al., 2017). Our study group previously documented a significant positive association between asthma exacerbations and short-term exposure to common air pollutants including particulate matter (Zheng et al., 2015). However, the two studies yielded some different findings (including the inconsistent effect of short-term exposure to SO_2 on asthma exacerbation), probably because of the different study design (inclusion and exclusion criteria, time frame) and analytical schemes (subgroup analyses). Furthermore, no recommendations regarding the association between air pollutants and asthma exacerbations were given because of the lack of assessment of the body of evidence for the existing literature.

Hitherto, the World Health Organization (WHO) has published several volumes of air quality guidelines (AQGs) to provide guidance to the public and decision makers on the health risks of air pollution. The AQGs need to be periodically revised and, where necessary, updated as new scientific evidence is generated. The present study might further shed light on the exposure–response relationship, including the subgroup analyses stratified by various confounding factors, the sensitivity analyses that were based on the risk of bias of the included studies, and the effect estimates based on the two- or three-pollutant exposure models. These will provide further scientific evidence which will allow future development of recommendations for ambient air quality.

We aimed to assess the current evidence on the short-term effects of exposure to O_3, NO_2 and SO_2 on asthma exacerbations defined as emergency room visits (ERVs) and hospital admissions (HAs).

2. Methods

2.1. Protocol and registration

A protocol, based on a WHO draft document, was developed. Protocol development was largely based on the standards set by Cochrane and adapted for application to observational studies and the *Preferred Reporting Items for Systematic Review and Meta-analysis Protocols* standards (Moher et al., 2015). Compared with our previous study (Zheng et al., 2015), the current updates included an extended literature search time frame, the focus on three gaseous air pollutants, a new risk of bias (RoB) framework, the addition of sensitivity analyses, the assessment of the certainty of evidence, and provision of recommendations. The protocol for this study was registered in PROSPERO (CRD42019134144).

2.2. Research question

A summary of the Population, Exposure, Comparator, Outcomes, and Studies (PECOS) question (Morgan et al., 2018) is presented below:

P: Among human population, what is the effect of

E: Short-term exposure to ambient air pollutants (O_3, NO_2, SO_2) versus

C: Exposure to lower (lowest) levels of air pollution (difference of 10 $\mu g/m^3$) on

O: ERVs or HAs due to asthma.

S: Ecological time-series (ETS) or case-crossover (CCO) studies.

2.3. Eligibility criteria

Studies that fulfilled the following criteria were included: (1) Population: general human population (including subgroups at risk), of all ages, in developed and developing areas, both urban and rural; (2) Exposures: short-term exposure (from several hours to 7 days) to ambient O_3, NO_2 and SO_2 expressed in a concentration unit ($\mu g/m^3$, ppb); (3) Comparators: exposure to lower (lowest) levels of O_3, NO_2 and SO_2 in the same population; (4) Outcomes: ERVs or HAs due to asthma, defined according to International Classification of Diseases (ICD), Ninth Revision (ICD-9) code 493.xx and ICD, and Revision 10 (ICD 10, code J45); (5) Studies: human epidemiological studies, comprising ETS and CCO studies published in peer reviewed journals in any language (abstract in English).

The exclusion criteria were: animal studies, *ex vivo* and toxicological studies, summaries, commentaries and editorials, case reports and case series; duplicate publications; studies solely evaluating the effects of long-term exposure to air pollutants; non-peer reviewed articles; no original data reported; modelling studies. We also excluded qualitative studies and review articles.

2.4. Information sources

Studies matching the PECOS question were searched in PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, EBM Reviews-Cochrane Database of Systematic Reviews, Web of Science, Ovid, Highwire, and *Western Pacific Region Index Medicus*. References of the identified relevant articles (and reviews/guidelines) were scanned. Data search included studies up to *January 2018*. We performed an update of the data search in *August 2018*. A literature search strategy using free text and MeSH terms was developed for each database, considering all eligibility criteria. Terms and keywords included asthma, wheeze, air pollution, nitrogen dioxide, nitrogen oxide, and sulphur dioxide. No age restriction was imposed. We also included the systematic reviews that have addressed a potentially relevant question for further scanning of the eligible studies. See details in Table A.1.

2.5. Study selection

Three reviewers (X.Y.Z., P.O. and W.J.G.) independently screened the titles and abstracts and identified the articles that could be excluded. The remaining articles were further assessed independently (X.Y.Z., P.O. and W.J.G.) based on the full-text. Any disagreement on inclusion was resolved by discussion and, if no consensus could be reached, a third reviewer was consulted (H.L.L.). If possible, additional consultation with the same third reviewer was sought to resolve questions about eligibility. Reasons for excluding articles were also recorded.

2.6. Data collection process

Data extraction was conducted by three independent authors (X.Y.Z., P.O. and W.J.G.). In case of any major disagreement, this was resolved by a further discussion (H.L.L. and M.J.). We extracted the data which were entered into Supplementary File S.1. Data extraction followed these principles: 1) In case any publication reported multiple health outcomes, each record would be documented in the Excel form separately; 2) In case two or more effect estimates (raw or adjusted) were reported for health outcomes, the estimates (unadjusted, adjusted, the ones mostly reported by the authors) were reported for each pollutant; 3) When adjusted and unadjusted (crude) estimates were reported, we prioritized the inclusion of the adjusted estimates (e.g. effect sizes adjusted by ambient temperature). If multiple lag estimates were reported, the selection algorithms were: 1) the most frequently used lag in all selected studies; 2) single lags, but not cumulative/distributed lags, were selected as a priority.

2.7. Data items

The following characteristics were extracted (see Supplementary File S.1): (1) Citation details: study and title of the article; 2) Study characteristics: period, study design, location (continent/country/city); (3) Study population: age group and sex; (4) Exposure: unit of measurement, the 5th-95th percentile, the 10th-90th percentile, median concentration, standard deviation (SD), interquartile range, maximal and minimal concentration, and metric description, e.g. annual mean. Due to the relevance of the 5th percentile as a proxy of the lowest level of exposure in a study, these values were registered, when available. If a study did not report the 5th percentile, but the SD or the 10th percentile were available, we would estimate the 5th percentile using a normal approximation. If only the range was available, we estimated the SD as the range divided by four (Hozo et al., 2005); (5) Outcome assessment: the number of asthma-related ERVs (including general practitioner's house calls, primary care visits) and HAs; (6) Data to calculate the effect estimates and their confidence intervals, including lag-times and pollutant's level increase. Association measures were relative risks (RRs), odds ratios (ORs), and percentage excess (increment) or change (PercIncr) ; (7) Other information: deviation from linearity, declared conflicts of interest, citation data.

2.8. Risk of bias assessment

A new domain-based RoB evaluation tool, developed by experts convened by the WHO, was applied for assessment. The RoB assessment tool was revised and adapted to the short-term exposure. We evaluated the RoB for individual studies based on confounding, selection bias, exposure assessment, outcome measurement, missing data and selective reporting domains. Furthermore, each domain included one or more subdomains. A detailed description of this tool can be seen in the WHO website (World Health Organization, 2020). Each subdomain could be judged as having low, moderate, or high RoB. If only one subdomain of the same domain was judged as having high RoB, the entire domain was classified as having high RoB. The same principle was applied to the subdomains with moderate vs. low RoB. Specific criteria applied to this systematic review can be seen in Table A.2. The results for each domain were analyzed separately, without considering a single result for the whole article/dataset. The assessment of RoB across studies was performed as one of the sensitivity analyses (elaborated later).

2.9. Statistical analysis

The RRs were the effect measures incorporated into the *meta*-analysis. Our *meta*-analysis compared the RRs corresponding to the standardized increment in pollutant concentration (e.g. 10 μg/m^3, assuming a linear exposure-outcome association). All effect estimates originally expressed as the interquartile (or percentile) increases were converted into those as per 10 μg/m^3 increase in the pollutant concentration. When ORs were reported in a study, they were assumed to approach the RRs, under the "rare-disease assumption" (Pace and Multani, 2018), given the fact that a cumulative incidence of the outcome being lower than 10% was demonstrated or assumed in all articles. Effects expressed as PercIncr were also recalculated to reflect an RR for a concentration unit increase in the pollutant, assuming a linear relationship.

For the summary measure (pooled RRs), a random-effects model was employed, assuming that the included studies were a random selection of all possible results. The DerSimonian-Laird estimator was used for the pooled RRs (DerSimonian and Laird, 1986), a straightforward method that allows the incorporation of heterogeneity in the analysis. When the pooled effect size was calculated from 20 or fewer effect sizes, the Hartung and Knapp adjustment was employed (Hartung and Knapp, 2001). When the same study population was used in several publications, only the largest and the most complete study (i.e. multicity studies, or studies with wider temporal or geographical coverage) was included. In all cases, multicity studies were preferred over single-city studies. We pooled all effect estimates associated with general populations in the overall and sensitivity analyses, and analyzed the data regarding specific population (i.e. the elderly, children) separately in subgroup analyses. One estimate was reported for any specific health outcome within an individual study. For the single publication that reported both ERVs and HAs, each record was documented in the Excel form separately. The ERVs and HAs were initially pooled and subsequently separated for subgroup analysis.

The heterogeneity between studies was assessed using the 80% prediction intervals (PIs), which was adopted to estimate the 80% interval in which the true RR in a new air pollution study will lie (Chiolero et al., 2012). We have chosen not to measure heterogeneity using the I^2 parameter, because this statistic is a relative measure, and it is difficult to judge the absolute heterogeneity. The use of PIs has been strongly advocated in the literature (Borenstein et al., 2009), as it provides an estimate of the distribution of the true effect sizes. This parameter shows whether the effect is consistent, or if it varies substantially; it also shows if the effect is harmful in all populations, or if there is no effect in some populations. The rule was that when the PI included the null effect (IntHout et al., 2016), some degree of heterogeneity was suspected. In this case the source of heterogeneity would be explored by performing subgroup analysis.

We performed subgroup analyses as follows: sex (male/female); age (children/adults/the elderly), different types of asthma exacerbations (ERVs/HAs); and study design (CCO/ETS). Sensitivity analysis was performed by excluding the following studies: studies with high RoB in one or more domains; and studies with conflicts of interest (i.e. commercial interests). In addition, we carried out independent analyses pertaining to the effect estimates from 24-hour concentrations (NO_2, SO_2), from 8-hour and 24-hour concentrations (O_3), and from 1-hour concentrations (O_3, NO_2, SO_2).

We also evaluated the potential unmeasured confounders through the calculation of the E-value (VanderWeele and Ding, 2017). This type of sensitivity analysis considers a potential unmeasured confounder (U), which is associated with the exposure and with the disease. A comparison would be made between the RRs of the unmeasured confounder (RR_U) and the RRs calculated by means of *meta*-analysis ($RR_{observed}$), but considering a wider range of pollutants increase (50 μg/m^3). The E-value, a representation of the minimum strength of association that an unmeasured confounder would need to explain away the association between the pollutant and the outcome, was then calculated by using the following equation:

$$E-value = RR_{observed} + \sqrt{RR_{observed} \times (RR_{observed} - 1)}$$

This E-value calculated for each pollutant was compared with the ambient temperature, a well-known confounder. We selected RR_U values

from a systematic review on temperature and asthma as reported in the review by Cong and colleagues (Cong et al., 2017). The rule was that when the RR_U was higher than the lower confidence limit of the E-value, comparatively weaker confounder associations could explain away the observed association, i.e. the presence of unmeasured confounders is plausible.

The potential publication bias was assessed by means of the visual exploration of funnel plots to check for asymmetry, and by the use of the Egger's test. All analyses and graphics were performed using the "meta" package (version 4.9–2) (Schwarzer et al., 2015) in the statistical software R, version 4.0.0 (https://www.r-project.org/) (Albert and Rizzo, 2012).

2.10. Concentration-response functions

The shape of the concentration–response functions (CRFs) was analyzed for each pollutant, to assess the suitability of linear assumptions regarding the RRs calculations, and the possibility of the threshold's occurrence. The CRF can be displayed as a graph that shows the relationship between the levels of adverse health responses in exposed populations (vertical axis) and the levels of ambient concentrations of a pollutant (horizontal axis), and is widely used to predict the public health impacts of proposed reductions in air pollutants (Cox, 2017).

2.11. Co-pollutant models

In order to control for the confounding effect of more than one pollutant, we have further performed an analysis of the co-pollutant models, i.e. the inclusion of articles that have incorporated more than one pollutant in the regression models. Results from the two- or three-pollutant models were incorporated in the pooled estimates, when available.

2.12. Certainty of evidence across studies

The certainty of evidence (CoE) for each pollutant was judged using an adaptation of the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach (Morgan et al., 2016), developed by a group of experts convened by the WHO (Supplementary File S.2). The CoE was assessed across five domains: limitations in studies, indirectness, inconsistency, imprecision, and publication bias. In short, the procedure was as follows: an evidence based on a number of articles was initially judged as being of moderate CoE, and was then potentially downgrading according to these five domains. The approach implies that there is always a risk of unmeasured confounding in observational studies. Therefore, it started at moderate CoE. After this first analysis, three other domains were evaluated, allowing for the upgrading of the CoE if indicated. These additional domains were the large magnitude of the effect, the occurrence of all possible confounding factors shifting towards the null effect, and the evidence of a concentration–response gradient (equivalent to CRFs). After applying this tool, the overall CoE was rated as: high, meaning that further research is very unlikely to change the confidence in the estimate of the effect; moderate, meaning that further research is likely to have an important impact on the confidence in the estimate of the effect; low, meaning that further research is very likely to have an important impact on the confidence in the estimate of the effect; or very low, meaning that the estimate of the effect is very uncertain. Some domains of this tool were evaluated using results of the RoB, heterogeneity, sensitivity, and publication bias analyses, which were previously described in the methodology. Below we describe the domains that were considered.

Domains used to downgrade the level of evidence

Limitations in studies: the evidence was downgraded if there were statistical differences between studies showing high versus moderate or low RoB in the sensitivity analysis. If the sensitivity analysis for RoB showed a considerable influence on the pooled effect-size, the conclusions were based on the high-quality studies only, and the evidence was not downgraded. This was a judgement and there were no clear *a priori* cut-off points.

Indirectness: the evidence was not downgraded based on this domain, as the research question in the included studies always reflected the original question.

Inconsistency: the evidence was downgraded if severe heterogeneity was detected, i.e. the PI included unity and was more than twice the random effects *meta*-analysis confidence interval.

Imprecision: the evidence was downgraded if the number of asthma exacerbations used when calculating the pooled effect size was below 150,000. This number was lower than the value proposed in the adapted GRADE approach (Supplementary File S.2), because that value was computed for the rate ratios in long-term studies. We have adopted our own cut-off value for short-term studies, using data from a selected multi-city study (Zu et al., 2017), in which a significant positive effect size was found considering approximately 150,000 events. The rationale was that if the number of events was sufficient for a given study to derive significant effect sizes, the same number would be adequate for performing *meta*-analysis.

Publication bias: the evidence was downgraded if publication bias was detected by visual inspection of the funnel plots or through the Egger's test.

Domains used to upgrade the level of evidence

Large effect size: unmeasured confounders and the results of the E-value were used, i.e. when the RR_U was higher than the lower confidence limit of the E-value (the presence of unmeasured confounders is plausible), the evidence was not upgraded. Otherwise, the evidence was upgraded.

Confounding domain: the evidence was not upgraded using this domain, as several potential confounders could shift the RR in both directions.

Concentration- response gradient domain: the evidence was upgraded when a positive linear or non-linear association was detected between the exposure and the outcome, i.e. the increase in the exposure to higher levels of air pollutants leads to an increase in the risk of exacerbations.

3. Results

3.1. Study selection

Our search initially identified 9,059 articles pertaining to the association between asthma exacerbations and the three outdoor air pollutants as of Aug 26th, 2018. Of the studies that were retrieved, 1,532 duplicate studies were excluded after the initial review. 7,527 studies were subject to title/abstract screening, and 251 articles were selected for full-text eligibility assessment. Next, we performed an independent assessment which led to the exclusion of 184 studies. Citation details for the excluded articles, with reasons for exclusions, are displayed in Table A.3. Fig. 1 shows the flowchart of assessment of the eligible studies.

3.2. Description of included studies

Supplementary File S.1 shows the 67 studies that were finally included. Most studies belonged to ETS designs (n = 47), whereas the remaining were CCO studies. Most studies were conducted in developed countries (e.g. European countries, United States), whereas some were performed in developing countries (e.g. China, Latin American countries). However, no study was originated from Africa. The date of publication mainly focused on the period between the 1990 s and the 2010 s. Forty-eight studies included the data on children, 21 on adults, 14 on the elderly, and 31 on the whole general population. We used these 31 articles for the estimation of pooled effect sizes in the overall analysis. Forty-three studies analyzed asthma ERVs, and 25 analyzed HAs for asthma. Pollutants were measured as the average 24-hour (24-h) concentrations (O_3, NO_2, and SO_2), maximum 8-hour (8-h) daily

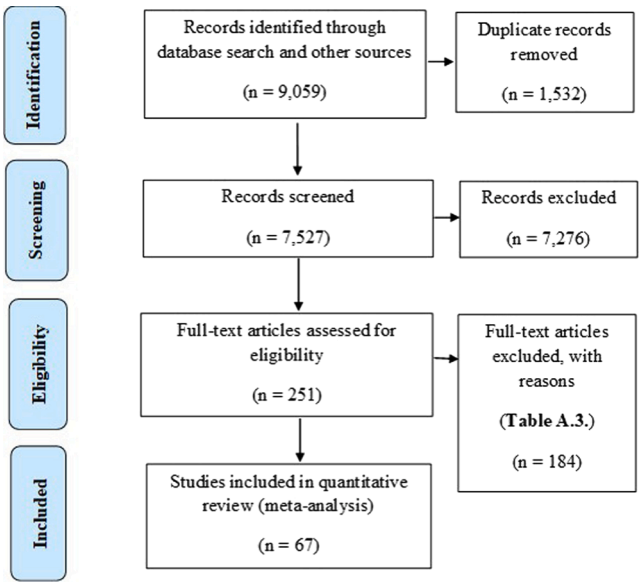

Fig. 1. Flowchart of assessment of eligible studies.

concentrations (O_3), or maximum 1-hour (1-h) daily concentrations (O_3, NO_2, and SO_2). We carried out independent analyses for the results from 24-h concentrations (NO_2, SO_2), from 8-h and 24-h concentrations (O_3), and from 1-h concentrations (O_3, NO_2, SO_2).

3.3. RoB assessments

Most, but not all, studies have adjusted for the temperature, humidity, seasonality, and day-of-week. Public holidays and influenza epidemics were not frequently considered (38.7% of articles). Poisson regression or conditional logistic regression were adopted for the adjustment of confounders, depending on the study design, with almost all studies using GLMs with auto-correlated errors, GAMs with splines, or CCO designs with bidirectional and/or time-stratified control sampling. The methods for exposure measurement were in general homogeneous (by using one or more monitoring stations in the city). Hospital registry systems were mostly used for collection of the health outcomes (by adopting the ICD codes), but in five studies self-reported event was the main outcome. Although data were imputed by using statistical models in some studies, in the majority of articles (22 studies) the imputation methods or the number of missing data were not reported. Only three studies had some evidence of selective reporting. The description of the RoB analysis per domain and subdomain in individual studies, together with the rationale to justify each judgment, are presented in Supplementary File S.3. A summary of the results of the RoB analysis per domain is shown in Figure A.1.

3.4. Overall analysis

Most studies reported a positive significant association between the pollutant concentrations and asthma-related ERVs and HAs. As per 10 $\mu g/m^3$ increase in the concentration, the pooled RRs were 1.008 (95%CI: 1.005, 1.011), 1.014 (95%CI: 1.008, 1.020) and 1.010 (95%CI: 1.001, 1.020) for O_3, NO_2, and SO_2, when the maximal 8-hour daily or average 24-hour concentrations were considered. For the maximal 1-hour daily concentration of O_3, NO_2, and SO_2, the associations were non-significant, with the pooled RRs of 1.017 (95%CI: 0.973, 1.063), 0.999 (95%CI: 0.966, 1.033) and 1.003 (95%CI: 0.992, 1.014) as per 10 $\mu g/m^3$ increase in the concentration. We noted a substantial heterogeneity for all exposures, with the exception of O_3 (8-h or 24-h) and NO_2 (24-h). The magnitude of the association with 95% confidence intervals, PIs, and relevant metrics are presented in Table 1. The forest plots for these analyses are shown in Figs. 2 to 7.

3.5. Subgroup analyses

Subgroup analyses are shown in Table A.4. for age, sex, and type of exacerbation (outcome). The strength of association did not differ significantly when stratified by the age, sex, or the type of exacerbations (HAs or ERVs). We have also compared the association between the age strata from the same study, in order to control for the variation arising from the heterogeneity among different studies (Table A.5). The only difference between subgroups was seen in NO_2 (24-hour), although the associations in each stratum were all non-significant. Despite the lack of statistical differences, the strength of association was consistently greater in children and, to a lesser extent, the elderly, as compared with adults. The subgroup analysis based on different study designs is shown in Table A.6. We found no overall significant difference between these subgroups, and some associations were non-significant in ETS or CCO study designs, possibly due to the small numbers. The analysis stratified by sex could only be performed for O_3, due to the limited number of studies of other pollutants.

3.6. Sensitivity analysis

We have further analyzed the studies with low/moderate versus high RoB (Table A.7). For those exposures with sufficient studies to perform *meta*-analysis, no overall differences were observed between the studies showing low/moderate RoB as compared with studies showing high RoB. The exceptions were NO_2 (24-h) and SO_2 (24-h), which showed differences related to the outcome domain, and O_3 (8-h or 24-h) in which differences were observed for the confounding domain.

The analysis by the declared CoI was not performed, because only one of the included papers declared the potential conflicts.

The E-values with 95% CIs and RR_Us are displayed in Table A.8. For the three pollutants the RR_Us were below the lower limit of the E-value, suggesting that unmeasured confounders might not have a major influence on the association. The E-values for O_3, NO_2, and SO_2 measured as the maximal 1-hour daily concentrations were not analyzed because these associations were non-significant.

Table 1
Exposures, outcomes and pooled effect sizes.

Pollutant	Outcome	Number of effect sizes	RR (95% CI)	p-value	PI	Egger's test (p-value)
O_3 (8-h or 24-h)	ERV or HA	27	1.008 (1.005 – 1.011)	less than 0.001	1.001 – 1.015	0.062
O_3 (1-h)	ERV or HA	3	1.017 (0.973 – 1.063)	0.235	0.962 – 1.076	N/A
NO_2 (24-h)	ERV or HA	22	1.014 (1.008 – 1.012)	less than 0.001	1.000 – 1.028	0.120
NO_2 (1-h)	ERV or HA	5	0.999 (0.966 – 1.033)	0.939	0.961 – 1.038	N/A
SO_2 (24-h)	ERV or HA	23	1.010 (1.001 – 1.020)	0.035	0.987 – 1.033	0.358
SO_2 (1-h)	ERV or HA	4	1.003 (0.992 – 1.014)	0.446	0.993 – 1.013	N/A

RR, pooled relative risks per 10 $\mu g/m^3$ increase in the pollutant concentration; 95% CI, 95% confidence interval; p-value, significance of the association; PI, 80% prediction interval; ERV, emergency room visits; HA, hospital admissions; N/A, not applicable (less than 10 studies).

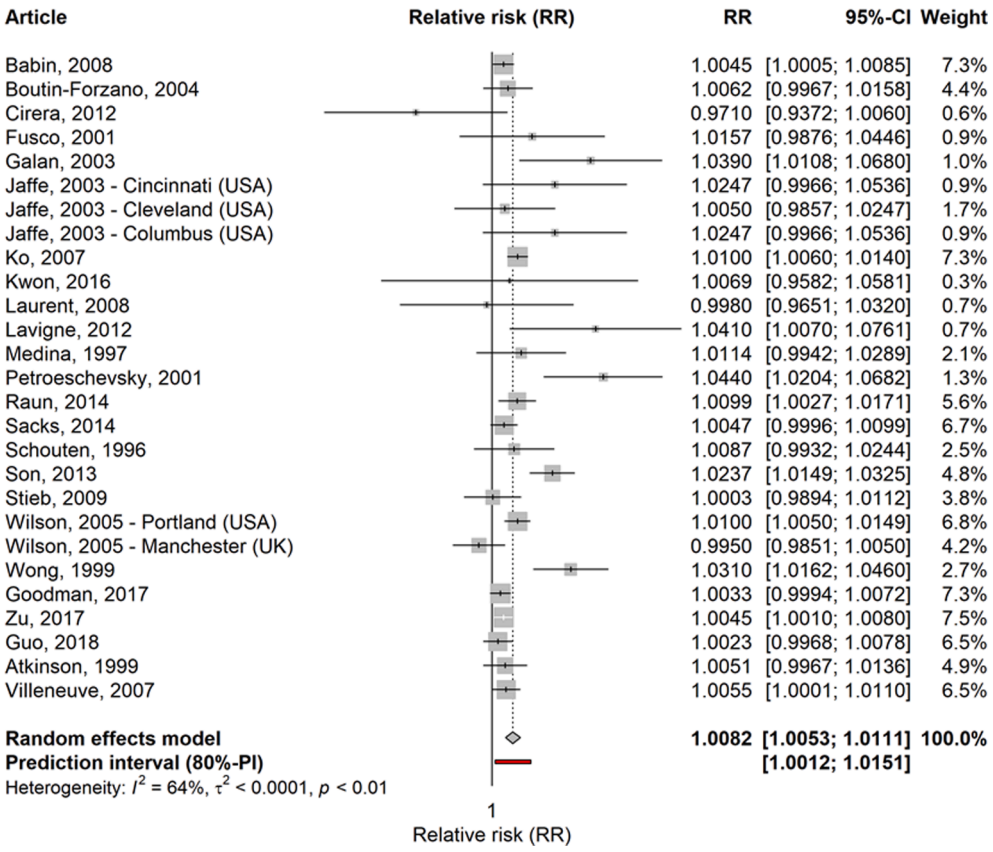

Fig. 2. Forest plot of 24 articles (27 effect sizes) examining the association between O_3 (8-h or 24-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

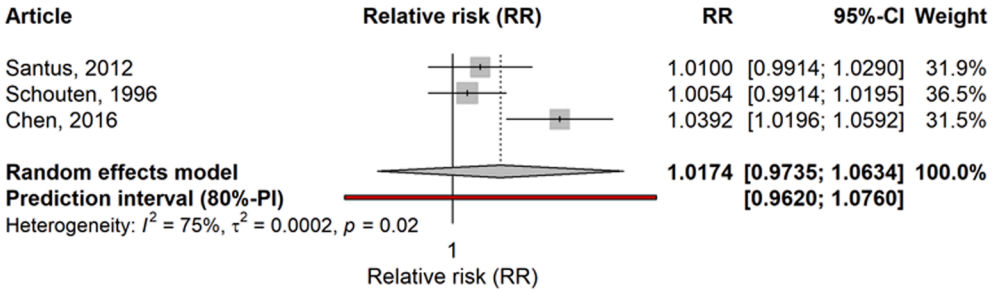

Fig. 3. Forest plot of 3 articles examining the association between O_3 (1-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

3.7. Publication bias assessment

Publication bias was assessed in O_3, NO_2 and SO_2 when measured as the 8-hour or 24-hour concentrations, as the concentrations calculated for 1-hour concentrations comprised less than 10 studies (Table 1). There was no clear evidence of asymmetry in the funnel plots. All these results were confirmed by the Egger's test. The funnel plots for all pollutants with 10 or more effect sizes are shown in Figure A.2.

3.8. Concentration-response functions

In all studies, the description regarding the concentrations only included the full-period averages, ranges and dispersion of the pollutants, but not daily values. Accordingly, only a description regarding the shape of the CRFs and potential thresholds was carried out, as reported in those papers in which this analysis was performed. The linearity assumptions were investigated in 10 studies, by means of semi-parametric regressions (GAMs). The existence of non-linear behavior and potential thresholds were mainly analyzed through visual inspection of the graphics produced by the GAMs.

The papers analyzing the CRFs are mentioned in Supplementary File S.1, where a specific column is added to show in which studies the evidence of deviation from linearity is found. Six articles (Cai et al., 2014; Erbas et al., 2005; Guo and Chen, 2018; Jaffe et al., 2003; Li et al., 2011; Zu et al., 2017) reported the evidence of non-linear behavior for O_3 (8-h or 24-h), NO_2 (24-h and 1-h), and SO_2 (24-h and 1-h). Regarding the limits, one article (Li et al., 2011) documented a threshold for NO_2 (24-h) at 41.36 μg/m^3, and other article (Erbas et al., 2005) focusing on NO_2 (1-hour) documented the thresholds at 84.6, 75.2, 37.6 and 28.2 μg/m^3. As for O_3 (8-h or 24-h), only one article (Zu et al., 2017) estimated a threshold at 80 μg/m^3. Similar thresholds were not found or reported for SO_2. The number of articles analyzing the non-linear behavior for each

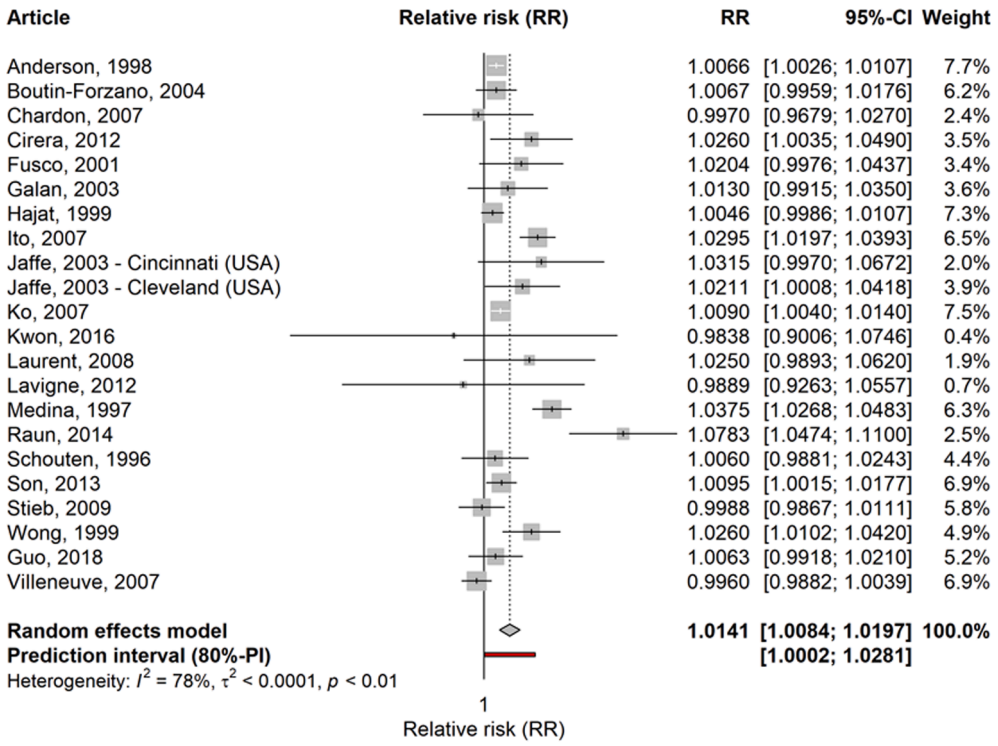

Fig. 4. Forest plot of 21 articles (22 effect sizes) examining the association between NO_2 (24-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

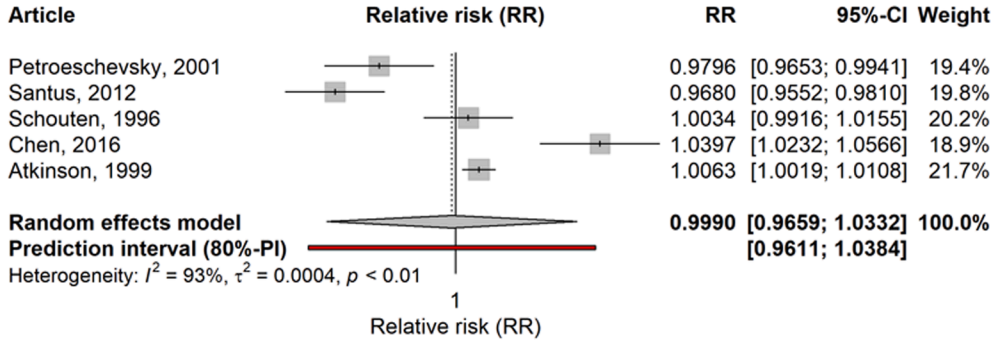

Fig. 5. Forest plot of 5 articles examining the association between NO_2 (1-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

combination is shown in Table A.9.

3.9. Co-pollutant models

Although a few articles reported the three-pollutant models, we were unable to find three or more articles assessing the same co-pollutants, and thus a pooled association value was not calculated. For the two-pollutant models, at least three articles were found that could be pooled together for O_3 (8-h or 24-h) and SO_2 (24-h). In all cases, the associations became non-significant (Table A.10). As can be seen in File S.1, a majority of articles analyzing the co-pollutant models showed high Pearson's correlation coefficients between the pollutants included in the models (8 out of 9 studies).

3.10. Certainty of evidence

According to the GRADE approach, the CoE for the associations between O_3 (8-h or 24-h) and NO_2 (24-h) and HAs or ERVs for asthma was high. The level of evidence was not downgraded in any of the domains that were considered. On the contrary, the evidence was upgraded due to the "large effect size" domain, given the results of the E-value analysis (i.e. the low probability for the presence of an unmeasured confounder). Another domain that contributed to the elevation of the level of evidence was the "concentration–response gradient", as these associations were statistically significant. Similarly, the level of evidence for SO_2 (24-h) was moderate, due to the downgrade in two domains. For this association, the differences between high and low/moderate RoB studies were observed in light of the heterogeneity between the studies, while the level of evidence was upgraded due to large effect size and concentration–response gradient. As for 1-hour exposures, the evidence was moderate for O_3 and SO_2, and low for NO_2, although these associations were non-significant. All these results are shown in Table 2.

4. Discussion

Our study has extended the previous findings (Orellano et al., 2017; Zheng et al., 2015) by confirming that higher levels of average 24-hour concentrations of NO_2, and SO_2, and higher levels of maximal 8-hour or

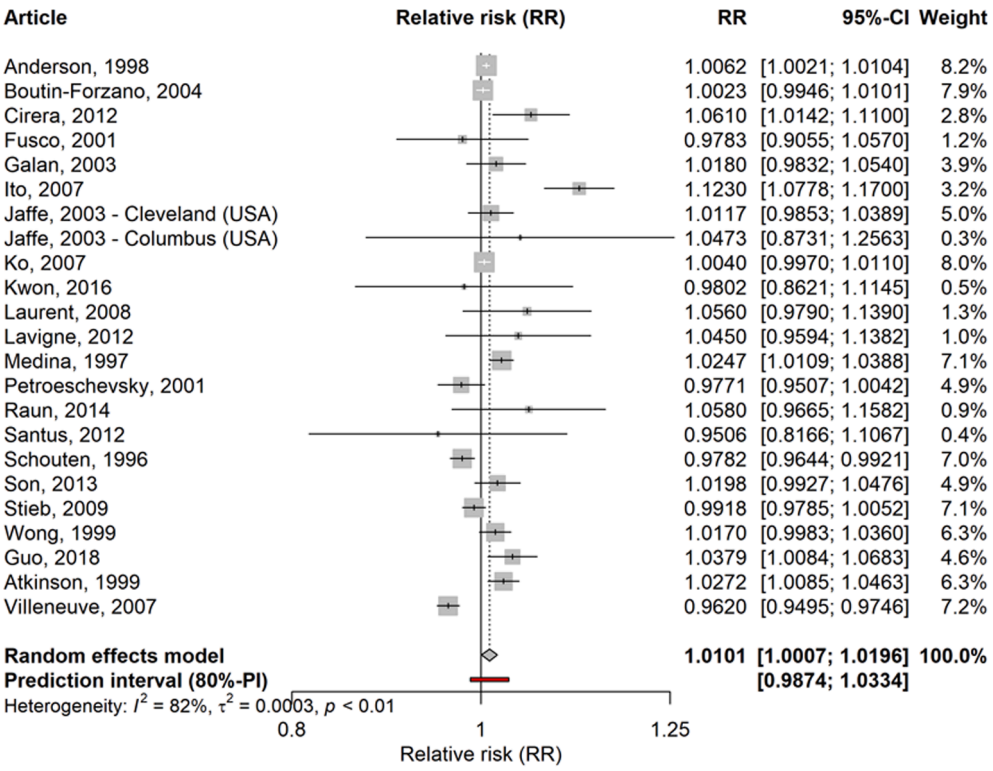

Fig. 6. Forest plot of 22 articles (23 effect sizes) examining the association between SO_2 (24-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

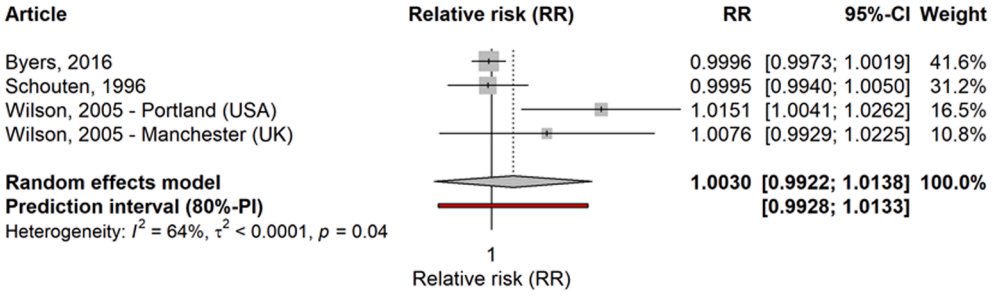

Fig. 7. Forest plot of 3 articles (4 effect sizes) examining the association between SO_2 (1-h) and asthma exacerbations. Relative risks per 10 μg/m^3 increase in the pollutant concentration.

average 24-hour concentrations of O_3 were associated with significantly increased risks of asthma-related exacerbations, defined as the ERVs and HAs. Although the measured concentration ranges varied considerably, most studies documented a positive correlation between air pollution and asthma exacerbations in the overall and subgroup analyses. On the contrary, the results of maximal 1-hour daily concentrations for the three pollutants did not demonstrate significant associations with asthma exacerbations, possibly due to the small number of articles that have taken into account these measures.

Few *meta*-analyses have been conducted to examine how short-term exposure to air pollutants correlated with asthma exacerbations (Atkinson et al., 2014; Lai et al., 2013; Li et al., 2019; Orellano et al., 2017; Zhang et al., 2016; Zheng et al., 2015). However, direct comparisons with some articles cannot be made due to different reasons, i.e. the results of the other papers focused on specific regions (Zhang et al., 2016), pollutants (Li et al., 2019), or age groups (Atkinson et al., 2014). In our study, the effect sizes for 24-h NO_2 and SO_2, and for 8-h or 24-h O_3, were mostly consistent with our previous publication (Zheng et al., 2015) but smaller than those reported in a *meta*-analysis that primarily included CCO studies (Orellano et al., 2017). This could be explained by differences in study design (ETS or CCO vs. CCO studies alone), the time frame (up to year 2018 vs. year 2000–2016) and the number of eligible studies (67 vs. 22).

The RoB was high in a considerable proportion of studies in the missing data domain only, because these studies did not report the imputation methods or the number or proportion of the missing data, which might have led to bias in the analysis. Another domain that was less representative than the previous one was the outcome. In these studies, the classification of asthma exacerbations was based on self-reporting (via emergency phone calls), instead of medically-diagnosed asthma exacerbations. Additional reasons for the bias in this domain were the lack of ICD instruments to classify asthma conditions. Issues in the confounding domain were also detected, but only in a few articles. Other domains were not relevant in the analysis, nor have further been considered in the subgroup or GRADE analyses.

Taking into account our criteria for definition, the heterogeneity among the studies was not substantial for two of the three pollutants, i.e. O_3 and NO_2, when considering 24-hour or 8-hour concentrations. This

Table 2
Certainty of evidence profile for each exposure-outcome combination.

Exposure - Outcome	Limitations in studies	Indirectness	Inconsistency	Imprecision	Publication bias	Large effect size	Confounding	Concentration-response gradient	Certainty of evidence
	Downgrade					Upgrade			
O_3 (8-h or 24-h) – ERV or HA	(0) Statistical differences between studies with low/moderate versus high RoB, but the pooled effect in low/moderate RoB articles is significant	(0) The research question in the studies reflects the original question	(0) 80% prediction interval did not include unity	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	High ⊗⊗⊗⊗
NO_2 (24-h) – ERV or HA	(0) Statistical differences between studies with low/moderate versus high RoB, but the pooled effect in low/moderate RoB articles is significant	(0) The research question in the studies reflects the original question	(0) 80% prediction interval did not include unity	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis.	High ⊗⊗⊗⊗
SO_2 (24-h) – ERV or HA	(-1) Statistical differences between studies with low/moderate versus high RoB	(0) The research question in the studies reflects the original question	(-1) 80% prediction interval included unity, and was twice the width of the 95%CI	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not detected	(+1) Unmeasured confounding would not suffice to explain away the effect estimate	(0) Several potential confounders that would shift the RR in both directions.	(+1) Significant positive association detected in the main analysis	Moderate ⊗⊗⊗○
O_3 (1-h) – ERV or HA	(0) Differences between studies with low/moderate versus high RoB were not evaluated.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(0) Number of asthma exacerbations higher than 150,000.	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions	(0) No significant association detected in the main analysis	Moderate ⊗⊗⊗○
NO_2 (1-h) – ERV or HA	(0) No differences between studies with low/moderate versus high RoB.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(-1) Number of asthma exacerbations lower than 150,000	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions.	(0) No significant association detected in the main analysis	Low ⊗○○○
SO_2 (1-h) – ERV or HA	(0) Differences between studies with low/moderate versus high RoB were not evaluated.	(0) The research question in the studies reflects the original question	(0) 80% prediction interval included unity, but is not twice the 95%CI	(0) Number of asthma exacerbations higher than 150,000	(0) Publication bias was not evaluated	(0) E-value was not calculated, because the pooled RR is not significant.	(0) Several potential confounders that would shift the RR in both directions	(0) No significant association detected in the main analysis	Moderate ⊗⊗⊗○

Certainty of evidence, starting from moderate certainty (⊗⊗⊗○); CRFs, concentration–response functions; (), between brackets is the downgrading of levels in that domain; RoB, risk of bias in individual studies; RR, relative risk.

was confirmed in the subgroup analyses stratified by age, sex, type of exacerbation, and study design, which showed that the differences between subgroups were statistically non-significant, indicating that the effect of air pollution was similar in any sub-population. The only exception was the association between NO_2 (24-h) when the age subgroups were analyzed in the same papers, in which a notable difference between subgroups was detected, but with non-significant associations in each stratum. This relative homogeneity among the included studies has strengthened the precision of our estimates and the level of the evidence. Despite the lack of statistical differences between subgroups, these analyses demonstrated that children and, to a lesser extent, the elderly were more susceptible to the adverse effects of air pollution (i.e. the magnitude of association was greater in these subgroups than in adults), which was consistent across the three pollutants. Moreover, the greater susceptibility among children and the elderly was consistent with the previous studies (Orellano et al., 2017; Zheng et al., 2015; Zu et al., 2017). The immature growth of airways and the defective host-defense in children, and ageing of the respiratory system in the elderly population, might have underlay their greater susceptibility to asthma exacerbation following short-term exposure to air pollution.

Because asthma exacerbation *per se* was highly heterogeneous, we have stratified asthma exacerbations into asthma ERVs and HAs. Our pooled analysis indicated an overall comparable risk of asthma exacerbations associated with the exposure to air pollutants. Hence, our findings remained valid regardless of the type (and probably, the severity) of asthma exacerbations. For SO_2 (24-h), the heterogeneity was substantial, and not explained by means of the subgroup analyses. Nevertheless, the magnitude of association was greater in children, as was in the other pollutants. The heterogeneity was substantial when considering O_3, NO_2, and SO_2 (1-hour), but subgroup analyses for these measures were not performed because of the limited number of articles.

We have further performed a sensitivity analysis by excluding the studies with high RoB. When considering the 8-h or 24-h concentrations, we found differences in RoB subgroups for the exposure to O_3, NO_2, and SO_2. These differences were related to the methods used for confounding control, the use of self-reporting for asthma exacerbations (e.g. phone calls), and the lack of a validated instrument for asthma classification (e.g. the ICD instrument). It is expected that the misclassification in the outcome variable can have important effects in the presence of bias in one or another direction. This was the case of SO_2, where the analysis that solely analyzed the studies showing low/moderate RoB became non-significant. On the contrary, for both NO_2 and O_3 the analysis still demonstrated statistical significance in the articles showing low/moderate RoB (confounding and outcome domains), indicating that its effect in asthma was unaffected by the quality of the included studies. There were no differences for 1-hour concentrations (NO_2), possibly due to the limited number of studies available.

The E-values were only evaluated in 8-hour or 24-hour O_3, NO_2 and SO_2. In all three cases, the entire 95% confidence interval of the E-values were higher than the RR_U, specifically the association between temperature and asthma exacerbations. Therefore, the presence of unmeasured confounders would be unlikely.

Asymmetry in the funnel plots was neither identified by visual inspection nor estimated by the Eggeŕs test. In this sense, publication bias would not have substantially affected the general conclusions of this study, or the size or precision of the true effect.

As for CRFs, non-linear behaviors with the possible thresholds for NO_2 and O_3 have been reported in some articles, although the proportion of articles analyzing CRFs was low. These thresholds were consistent with the previous limits considered in the AQGs for 24-hour NO_2 (40 $\mu g/m^3$ annual mean), but considerably lower for 1-hour NO_2 (200 $\mu g/m^3$). The threshold reported for O_3 was also lower than the limits reported in the AQGs (100 $\mu g/m^3$ for 8-hour or 24-hour mean). However, these results would still be insufficient to justify the need for a revision of the thresholds of the air pollutants.

The analysis of co-pollutant models showed that the pooled associations observed in single-pollutant models were no longer significant after the inclusion of a second pollutant. These results brought concerns about the validity of the reported associations and the causal relationship between the three air pollutants and asthma exacerbations. However, two factors might have influenced these results. First, the study of co-pollutant models was implemented in a small proportion of articles (10 out of 31 studies included in the main analysis). In these studies, the different combinations of exposures and adjusted pollutants led to a small number of effect sizes in each pooled association, with no more than four articles per combination, which might have been responsible for the loss of the statistical power. Second, almost all studies showed high correlation coefficients between the pollutants included in the regression models, with values being greater than 0.4 (Dai and Zhou, 2017). These high correlations represent a potential problem related to multicollinearity of predictor variables, which in turns affects the validity of the associations. In many cases, the multicollinearity between predictor variables can have the effect of inflating the standard errors, leading to type II errors (Mason and Perreault, 1991), and to the aforementioned issue of the lack of statistical power. By any means, the analysis of co-pollutant models is insufficient to fully elucidate the causal relationship between the air pollutants and asthma exacerbations, and warrants further discussions.

Strengths of our study comprised the inclusion of an extensive array of literature reports, and the panel of subgroup and sensitivity analyses. We have also applied a rigorous RoB assessment and the GRADE scale to evaluate the level of scientific evidence. It is worth noting the high certainty of evidence for 24-hour exposures as judged for O_3 and NO_2, even though the level of evidence related to SO_2 was moderate, and needs further analysis. Additionally, publication bias was not substantial for this review, as demonstrated by the funnel plots, which means that our results were not affected by the presence of unpublished studies.

Nonetheless, there were some limitations that should be taken into account. First, despite our efforts, the potential sources of the substantial heterogeneity among the included studies was not fully elucidated. Second, asthma-related ERVs and HAs comprise severe forms of asthma exacerbations. In real-world practice, the documentation of milder forms of asthma exacerbations can be technically challenging because underreporting has been common. Third, differences in the representation between continents were observed, e.g. the number of studies from North America, Europe and Asia was much higher than the number of studies from Latin America, while Africa was not represented in the included studies. Several moderators can have a substantial influence on the associations, and the global estimates can be difficult to be extrapolated to all regions. In this sense, there is a clear need for strengthening epidemiological research in developing countries. Fourth, the approach we used in the modified GRADE tool involved an arbitrary judgement in some domains. For instance, in the imprecision domain, the tool gives as an example a value of 940,000 person-years after an estimation that involves a formula for sample size calculation in long-term exposure studies, while the tool does not assign a value for short-term studies, and there was no indication for which method this calculation should be performed. Therefore, in our study an arbitrary value of 150,000 events was selected, using the results of a representative multi-city study (Zu et al., 2017). This study evaluated the association between asthma-related hospital admissions and ozone concentration, but these results might not be directly transferable to infer the association with the concentration of NO_2 or the risk of ERVs.

In conclusion, short-term 8-hour or 24-hour exposure to O_3, NO_2, and SO_2 correlates with increased risks of asthma-associated ERVs and HAs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or the stated policy of the World Health Organization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106435.

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