Health effects of exposure to sulfur dioxide, nitrogen dioxide, ozone, and carbon monoxide between 1980 and 2019: A systematic review and meta-analysis

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Abstract
The burden of disease attributed to the indoor exposure to sulfur dioxide (SO₂), nitrogen dioxide (NO₂), ozone (O₃), and carbon monoxide (CO) is not clear, and the quantitative concentration–response relationship is a prerequisite. This is a systematic review to summarize the quantitative concentration–response relationships by screening and analyzing the pooled effects of population-based epidemiological studies. After collecting literature published between 1980 and 2019, a total of 19 health outcomes in 101 studies with 182 health risk estimates were recruited. By meta-analysis, the leave-one-out sensitivity analysis and Egger's test for publication bias, the robust and reliable effects were found for SO₂ (per 10 μg/m³) with chronic obstructive pulmonary diseases (COPD) (pooled relative risks [RRs] 1.016, 95% CI: 1.012–1.021) and cardiovascular diseases (CVD) (RR 1.012, 95%CI: 0.97–1.018), respectively. NO₂ (per 10 μg/m³) had the pooled RRs for childhood asthma, preterm birth, lung cancer, diabetes, and COPD by 1.134 (1.084–1.186), 1.079 (1.007–1.157),
1 | INTRODUCTION

Air pollution is one of the leading risk factors for global burden of disease (GBD) and has long been a public health concern.\(^1\) Sulfur dioxide (SO\(_2\)), nitrogen dioxide (NO\(_2\)), ozone (O\(_3\)), and carbon monoxide (CO) are four criteria gaseous pollutants included in the WHO air quality guidelines, the Chinese ambient air quality standard, and indoor air quality standard.\(^2\)\(^-\)\(^5\) Higher proportions of exposure to them occur in indoor environment since people spend at least 80% of their time indoors, and the existence of indoor sources can accumulate to extremely high levels. On the contrary, studies linking these four pollutants and diseases have been more reported on outdoor levels due to much wider accessibility of large-scale ambient pollution data. Therefore, the summary on the concentration–response (C–R) relationship of SO\(_2\), NO\(_2\), O\(_3\), and CO is needed to recruit all studies at either indoor or outdoor levels.

Up till now, a broader spectrum of diseases has been linked to these 4 gaseous air pollutants. Recently, a national study carried out in 272 Chinese cities has shown that a 10 \(\mu g/m^3\) increase in 2-day average ambient concentration of SO\(_2\) leads to 0.59% increment in mortality of total nonaccidental causes, 0.70% of total cardiovascular diseases (CVD), and 0.55% of total respiratory diseases in China, while that of NO\(_2\) is 0.9%, 0.9%, and 1.2%.\(^6\)\(^,\)\(^7\) It also showed that a 10 \(\mu g/m^3\) increase in 8-h maximum concentration of ambient O\(_3\) would lead to 0.24% increase in mortality of total nonaccidental causes.\(^5\) Besides, as a strong oxidative gas, O\(_3\) has been associated with increased circulatory and respiratory mortality, and morbidities of central nervous system diseases (e.g., Alzheimer’s disease and Parkinson’s disease).\(^8\)\(^-\)\(^11\)

Exposure to CO is associated with multiple health outcomes as well. It is reported that about 50000 Americans are affected by CO poisoning each year, with adverse health effects varying from headache and dizziness to coma and death.\(^12\) In addition, chronic CO exposure influences cardiovascular health, which leads to a significant increase of 1.12% in CVD mortality per 1 \(mg/m^3\) increase of CO.\(^13\)\(^,\)\(^14\)

However, the health effects of gaseous air pollutants are still inconsistent. Lack of standard selection criteria and data analysis method as well as insufficient number of studies might bring inconsistent results. To form a consistent C–R relationship with robust reliability, this systematic review aimed to summarize the health effects of SO\(_2\), NO\(_2\), O\(_3\), and CO with strict meta-analysis method and obtain the quantitative C–R relationships. By searching studies globally in the last 2 decades, this study will provide essential data and evidence for estimation of the burden of disease attributable to indoor SO\(_2\), NO\(_2\), O\(_3\), and CO.

2 | METHODS

2.1 | Literature screening and selection

Focusing on the health effects of SO\(_2\), NO\(_2\), O\(_3\), and CO, we systematically searched literatures published between January 1980 and January 2019 mainly in four databases, Web of Science, PubMed, WANGFANG (a scientific literature database in Chinese language), and CNKI (China National Knowledge Infrastructure, a database in Chinese). The health outcomes were selected referring to International Program for Chemical Safety (IPCS), reviews on Web of Science and PubMed, and advice from experts in the Chinese Burden of Disease Attributable to Indoor Air Pollutants (CBD-IAP).

The specific search strings were listed in Appendix S1: Table S1.

Any population-based original or review articles on epidemiological studies on the health effects were considered with no restrictions on age, gender, locations (countries), ethnics, and pollutants of indoor or outdoor origin. At least three rounds of literature screening were performed for each selected article. In the first round, duplicates, patents, and books were removed. The remained articles were further screened by their titles and abstracts with the following studies excluded: (1) not written in English or Chinese; (2) not population-based epidemiological studies (either cross-sectional, case–control or cohort studies); (3) not reporting the quantitative exposure–response relationships such as
odds ratio (OR), relative risk (RR), hazard ratio (HR), or excess risk (ER) between SO\textsubscript{2}, NO\textsubscript{2}, O\textsubscript{3}, or CO and health outcomes; (4) only based on social medication burden, such as hospital admissions and hospitalization rate. In the third round, articles were selected in detail based on their full texts. The following criteria were applied to further exclude (1) the same exclusion criteria as mentioned above; (2) studies based on occupational exposure; (3) health outcomes which had less than 3 independent effect sizes (OR, OR, HR, or ER) corresponding to different exposure levels. Finally, in the recruited studies, key information and C-R relationship data were extracted and put to meta-analysis. The key information consists of study period, study location, study design, sample size, mean concentration, and the quantitative effect size. Besides, whether the study used one-pollutant model or multiple-pollutant model in the statistical analysis was also recorded.

### 2.2 Quality assessment

Quality assessment was performed for all the included studies obtained above. The Newcastle-Ottawa scale was used to evaluate the quality of cohort and case-control studies, while the critical tools of the Joanna Briggs Institute were used for cross-sectional and time-series studies.\textsuperscript{15,16} Studies with ≥7 scores, 4–6 scores, and ≤3 scores are classified as high-quality, moderate-quality, and low-quality studies, respectively. Low-quality studies will be excluded in the further meta-analysis.

### 2.3 Statistical analysis

Before meta-analysis, all ORs were transformed into RR, as described by Equation (1).

\[
RR = \frac{OR}{1 - p_0 + p_0 \cdot OR}
\]

where \(p_0\) is the prevalence of diseases in the unexposed group (if no data reported, the prevalence in the total population in the same time period and country reported in the GBD database was used as a replacement).\textsuperscript{17} The reported HRs were assumed to be equal to the RRs. The ERs can be converted into RRs by Equation (2):

\[
RR = 1 + ER
\]

All RRs obtained from the literature were transformed to an increment of 10 \(\mu g/m^3\) for SO\textsubscript{2}, NO\textsubscript{2}, and O\textsubscript{3}, and 1 mg/m\textsuperscript{3} for CO. The meta-analysis provided the relative risks per unit increment of SO\textsubscript{2}, NO\textsubscript{2}, O\textsubscript{3}, and CO concentration, denoted as \(RR_0\), and then, the final C-R relationships were calculated by Equation (3):

\[
RR_C = \begin{cases} 
RR_0^{C/C_0}, & C \leq C_{\text{max}} \\
RR_0^{C_{\text{max}}/C_0}, & C > C_{\text{max}} 
\end{cases}
\]

where \(C\) is concentrations of SO\textsubscript{2}, NO\textsubscript{2}, O\textsubscript{3}, or CO, \(C_{\text{max}}\) is the unit concentration mentioned above, \(C_{\text{max}}\) is the maximum concentration of each air pollutant reported in the included studies in the corresponding meta-analysis. Since the natural logarithm of RR is asymptotically subject to the normal distribution, when RR (or the transformed RR) and 95%CI in each recruited manuscript was transferred to \(RR_0\) to same unit concentration, the \(RR_0\) was calculated as RR to power of the ratio of \(C_{\text{max}}\). It should be noted that a conservative estimate was provided when the exposure level was higher than the maximum concentration reported in the literature, because the extrapolation of the exponential relationship might reach unrealistically high at levels higher than the reported maximum levels.

The meta-analysis in the polled studies was performed by R software (version 4.1.1, package “meta” [V5.1-1]). The weight of each included study and the 95% confidence interval of pooled relative risk were obtained by the inverse variance method in the package “meta.” \(I^2\) was used to assess heterogeneity. When \(I^2 < 50\%\), the fixed effect model was applied. Otherwise, the random effect model was applied. The meta-analysis was further performed in the subgroups stratified by study location (China), types of study design (cohort, case-control, case-crossover, time-series, and cross-sectional studies), and concentration measurement methods, to identify the possible source of heterogeneity. The exposure estimation based on residence or school address was considered as residential or school assessment while the others were ambient air pollutants.

The methods included field measurements and model prediction. The field measurements included fixed station monitoring and on-site measurements. Model prediction included dispersion modeling, Community Multiscale Air Quality Model System (CMAQ) modeling, chemistry-transport modeling, land use regression (LUR) modeling, and QBME modeling. In each subgroup, the requirement of at least 3 independent effect sizes (RR, OR, HR, or ER) corresponding to different exposure levels was applied.

The sensitivity analysis of meta-analysis was performed to evaluate the pooled effects of remaining literatures after excluding any individual study (the leave-one-out method), in order to identify whether there were influential studies on the pooled associations. Egger’s test was applied to test the publication bias. If the Egger’s test showed the existence of significant publication bias, the trim and fill method were applied to see whether the significance of the meta-analysis results changed. If not, publication bias was ruled out. A significance level of \(p < 0.05\) was applied in all analyses.

### 3 RESULTS

#### 3.1 Literature searching and screening

The flowchart of literature searching and screening is shown in Figure 1. Initially, a total of 12,686, 20,440, 12,888, and 19,499 articles were identified on the health effects of SO\textsubscript{2}, NO\textsubscript{2}, O\textsubscript{3}, and CO, respectively. After 3 rounds of literature screening and selection,
the final 44, 81, 31, and 16 articles were included containing 182 risk estimates (47, 86, 33, and 16 risk estimates for \( \text{SO}_2 \), \( \text{NO}_2 \), \( \text{O}_3 \), and \( \text{CO} \), respectively).\(^6\) The numbers of included risk estimates stratified by pollutants and types of study designs are shown in Appendix S1: Table S2. The detailed list of recruited studies on the study time, location, sample size, and risk estimates with 95% confidence interval (CI) is in Appendix S1: Table S3. The regional distribution of studies was unbalanced, and most epidemiological studies were performed in China, Europe, and North America. In addition, the quality assessment results for each recruited study are shown in Appendix S1: Table S3. Almost all studies had high quality, except one moderate-quality study conducted in the United States from 1990 to 2014.

### 3.2 | Meta-analysis

Table 1 summarizes the pooled relative risks of the 19 pollutant-outcome pairs identified in this review (the forest plots are shown in Appendix S1: Figure S1-S4). Among them, 15 pollutant-outcome pairs had high heterogeneity \( (I^2 > 50\%) \) and the random effect models were applied in analysis while the other 4 pairs with low heterogeneity \( (I^2 < 50\%) \) by fixed effect models. In total, 13 out of 19 associations were significant in the meta-analyses \( (p < 0.05) \). Across all health outcomes, the CVD effects and preterm birth were the most widely studied in all 4 air pollutants, followed by respiratory diseases (COPD, lung cancer, childhood asthma), Parkinson's disease, metabolism disease, and others.

Specifically, 5 health outcomes were identified in association with \( \text{SO}_2 \) in the literature: childhood asthma, COPD, CVD, lung cancer, and preterm birth. By meta-analysis, the relationship remained significant for childhood asthma, COPD, and cardiovascular diseases. Each 10 \( \mu \text{g/m}^3 \) increase of \( \text{SO}_2 \) concentration resulted in 11.1% increase in the risk of childhood asthma (RR 1.111, 95% CI: 1.076-1.147), followed by COPD (RR 1.016, 95% CI: 1.012-1.021) and CVD (RR 1.012, 95% CI: 1.007-1.018).

For \( \text{NO}_2 \), the reported significant health effects included CVD, childhood asthma, COPD, diabetes mellitus, lung cancer, Parkinson’s disease, and preterm birth. The meta-analyses showed most associations still remained significant except for CVD. In detail, each 10 \( \mu \text{g/m}^3 \) increase of \( \text{NO}_2 \) was associated with the largest increase of risk for childhood asthma (RR 1.134, 95% CI: 1.084-1.186), followed by preterm birth (RR 1.079, 95% CI: 1.007-1.157), lung cancer (RR 1.055, 95% CI: 1.010-1.101), Parkinson’s disease (RR 1.030, 95% CI: 1.007-1.053), diabetes mellitus (RR 1.019, 95% CI: 1.009-1.029), and COPD (RR 1.016, 95% CI: 1.012-1.120).

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**FIGURE 1** Flow chart of literature searching and screening on population-based epidemiology studies of \( \text{SO}_2 \), \( \text{NO}_2 \), \( \text{O}_3 \), and \( \text{CO} \).
# TABLE 1  Pooled relative risks of the pollutant-outcome pairs for SO$_2$, NO$_2$, O$_3$, and CO, respectively

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Health outcomes</th>
<th>Pollutant-health effect pairs</th>
<th>RR [95% CI] per unit increase</th>
<th>Unit</th>
<th>Maximum average concentration$^a$</th>
<th>$I^2$</th>
<th>p value for heterogeneity</th>
<th>Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO$_2$</td>
<td>Cardiovascular disease</td>
<td>20</td>
<td>1.012 (1.007, 1.018)</td>
<td>10 μg/m$^3$</td>
<td>112.4 μg/m$^3$</td>
<td>96%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Asthma (childhood)$^b$</td>
<td>5</td>
<td>1.111 (1.076, 1.147)</td>
<td>10 μg/m$^3$</td>
<td>82 μg/m$^3$</td>
<td>60%</td>
<td>0.04</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>3</td>
<td>1.016 (1.012, 1.021)</td>
<td>10 μg/m$^3$</td>
<td>40 μg/m$^3$</td>
<td>35%</td>
<td>0.22</td>
<td>Fixed</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>8</td>
<td>1.127 (0.978, 1.298)</td>
<td>10 μg/m$^3$</td>
<td>66.9 μg/m$^3$</td>
<td>82%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Preterm birth</td>
<td>11</td>
<td>1.200 (0.948, 1.520)</td>
<td>10 μg/m$^3$</td>
<td>51.67 μg/m$^3$</td>
<td>92%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>Cardiovascular disease</td>
<td>29</td>
<td>1.059 (0.991, 1.131)</td>
<td>10 μg/m$^3$</td>
<td>50.3 ppb</td>
<td>97%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Asthma (childhood)$^b$</td>
<td>11</td>
<td>1.134 (1.084, 1.186)</td>
<td>10 μg/m$^3$</td>
<td>54.8 μg/m$^3$</td>
<td>55%</td>
<td>0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
<td>6</td>
<td>1.016 (1.012, 1.120)</td>
<td>10 μg/m$^3$</td>
<td>60.7 μg/m$^3$</td>
<td>49%</td>
<td>0.08</td>
<td>Fixed</td>
</tr>
<tr>
<td></td>
<td>Diabetes Mellitus</td>
<td>10</td>
<td>1.019 (1.009, 1.029)</td>
<td>10 μg/m$^3$</td>
<td>44 μg/m$^3$</td>
<td>29%</td>
<td>0.18</td>
<td>Fixed</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>11</td>
<td>1.055 (1.010, 1.101)</td>
<td>10 μg/m$^3$</td>
<td>54 μg/m$^3$</td>
<td>98%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Parkinson's disease</td>
<td>6</td>
<td>1.030 (1.007, 1.053)</td>
<td>10 μg/m$^3$</td>
<td>13.71 μg/m$^3$</td>
<td>51%</td>
<td>0.07</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Preterm birth</td>
<td>13</td>
<td>1.079 (1.007, 1.157)</td>
<td>10 μg/m$^3$</td>
<td>68.44 μg/m$^3$</td>
<td>94%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td>O$_3$</td>
<td>Cardiovascular disease</td>
<td>18</td>
<td>1.002 (0.983, 1.022)</td>
<td>10 μg/m$^3$</td>
<td>94 μg/m$^3$</td>
<td>98%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Lung cancer</td>
<td>4</td>
<td>0.951 (0.791, 1.144)</td>
<td>10 μg/m$^3$</td>
<td>51.7 μg/m$^3$</td>
<td>85%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Parkinson's disease</td>
<td>4</td>
<td>1.067 (1.018, 1.118)</td>
<td>10 μg/m$^3$</td>
<td>40.6 ppb</td>
<td>0%</td>
<td>0.55</td>
<td>Fixed</td>
</tr>
<tr>
<td></td>
<td>Preterm birth</td>
<td>7</td>
<td>1.039 (1.004, 1.075)</td>
<td>10 μg/m$^3$</td>
<td>75 μg/m$^3$</td>
<td>93%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td>CO</td>
<td>Cardiovascular disease</td>
<td>6</td>
<td>1.024 (1.011, 1.038)</td>
<td>1 mg/m$^3$</td>
<td>1.54 mg/m$^3$</td>
<td>81%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Parkinson's disease</td>
<td>4</td>
<td>1.574 (1.069, 2.317)</td>
<td>1 mg/m$^3$</td>
<td>0.62 ppm</td>
<td>73%</td>
<td>0.01</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>Preterm birth</td>
<td>6</td>
<td>1.191 (0.996, 1.423)</td>
<td>1 mg/m$^3$</td>
<td>2.61 ppm</td>
<td>88%</td>
<td>&lt;0.01</td>
<td>Random</td>
</tr>
</tbody>
</table>

$^a$Since most recruited studies focused on childhood asthma and there was no sufficient data supporting the meta-analysis for adult asthma, the meta-analysis on asthma was actually on childhood asthma.

$^b$The maximum concentration for each pollutant-outcome pair in recruited studies.
O₃ and CO were significantly associated with Parkinson's disease by RR of 1.067 (95% CI: 1.018–1.118) and 1.574 (95% CI: 1.069–2.317), respectively. O₃ was further significantly associated with preterm birth by RR 1.039 (95% CI: 1.004–1.075) and CO additionally with CVD by RR of 1.024 (95% CI: 1.011–1.038).

### 3.3 | Subgroup analysis

The 13 significant associations identified in the meta-analysis mentioned above were further analyzed in subgroups, stratified by locations and study design types. The results were showed in Appendix S1: Table S4.

In the subgroup analysis stratified by locations, we focused on the subgroup performed in China since around half of risk estimates were carried out in China. The results showed that 5 out of 13 significant associations were no longer significant in the Chinese population: NO₂-lung cancer, NO₂-Parkinson's disease, NO₂-preterm birth, O₃-preterm birth, and CO-CVD.

In the subgroup analyses stratified by study designs, those with at least 3 independent health effect sizes in one subgroup were tested again. Those effects with all recruited studies applying the same type of study design (SO₂-childhood asthma and CO-Parkinson's disease) were not re-analyzed and kept the same meta-analysis results. Among all types of study designs, more studies were cohort and time-series studies. A total of 6 pairs of pollutant-health outcomes remained consistently robust either in the total meta-analysis, in the subgroup analysis in China or in subgroups of study design types: SO₂-cardiovascular disease, SO₂-childhood asthma, SO₂-COPD, NO₂-childhood asthma, NO₂-COPD, and NO₂-diabetes mellitus.

In the subgroup analysis stratified by concentration measurements, we found out 10 associations (including 13 pairs), 3 pairs were based on residence (field measurement), 9 were based on ambient (field measurement) and 1 was based on ambient (model prediction). Due to lack of enough studies based on residences or school concentration assessment, the subgroup meta-analysis results were available more in those with ambient concentration assessment (Table S4).

### 3.4 | Sensitivity analysis and publication bias

In the sensitivity analysis, the leave-one-out method was applied in which one study was excluded once a time and repeated in turn to assess the pooled effects of the remaining studies. The results showed the pooled significant health effects of the remaining studies were not substantially changed, except for the relationship between Parkinson's disease and NO₂ and Parkinson's disease and O₃ (Appendix S1: Figure S5-S8).
The Egger’s test was used to check the potential publication bias. Among the 13 significant health effects in the polled meta-analysis, associations between SO\textsubscript{2}-childhood asthma (p = 0.012), NO\textsubscript{2}-childhood asthma (p < 0.001), NO\textsubscript{2}-COPD (p = 0.012), and O\textsubscript{3}-preterm birth (p = 0.012) did not pass the Egger’s test preliminarily. After applying the trim and fill method, the significance of the effects of NO\textsubscript{2}-childhood asthma, NO\textsubscript{2}-COPD was altered and passed the tests but not for SO\textsubscript{2}-childhood asthma or O\textsubscript{3}-preterm birth.

In summary, a total of 9 robust and reliable significant health effects were identified with 4 air pollutants. They were 2 for SO\textsubscript{2} (SO\textsubscript{2}-CVD and SO\textsubscript{2}-COPD), 5 for NO\textsubscript{2} (NO\textsubscript{2}-childhood asthma, NO\textsubscript{2}-COPD, NO\textsubscript{2}-diabetes mellitus, NO\textsubscript{2}-lung cancer, NO\textsubscript{2}-preterm birth) and 2 for CO (CO-Parkinson’s disease and CO-preterm birth). All these pollutant-health outcome pairs passed both sensitivity analyses and Egger’s tests (including the trim and fill method), and they were illustrated in the forest plots (Figure 2-4). For O\textsubscript{3}, the current review could not observe a reliable and consistent C-R relationship.

4 | DISCUSSION

This systematic review and meta-analysis comprehensively and quantitatively evaluated the health effects of four criteria gaseous air pollutants: SO\textsubscript{2}, NO\textsubscript{2}, O\textsubscript{3}, and CO. More studies (over 50%) were performed in China and on the health effects of NO\textsubscript{2} followed by SO\textsubscript{2}, CO, and O\textsubscript{3}. Nine out of 19 pollutant-outcome pairs were found to be robust and reliable with no publication bias. They consisted of 2 for SO\textsubscript{2} (SO\textsubscript{2}-CVD and SO\textsubscript{2}-COPD), 5 for NO\textsubscript{2} (NO\textsubscript{2}-childhood asthma, NO\textsubscript{2}-COPD, NO\textsubscript{2}-diabetes mellitus, NO\textsubscript{2}-lung cancer, NO\textsubscript{2}-preterm birth), and 2 for CO (CO-Parkinson’s disease and CO-preterm birth). The adverse health effects were mainly on cardiovascular, respiratory, nervous system, and metabolism diseases. No robust health effects were identified for O\textsubscript{3}. This study provided evidence and basis for further estimation of the health burden attributable to these four gaseous pollutants.

Our pooled RRs of SO\textsubscript{2} and NO\textsubscript{2} were consistent with literatures. As a well-known inorganic chemical irritant, SO\textsubscript{2} was found to have the potential to promote airway inflammation and eosinophilia, and then induced bronchospasm and airway fibrosis,\textsuperscript{113} and NO\textsubscript{2}, as a precursor of O\textsubscript{3} and typical pollutant of traffic tale gas, triggered bronchial inflammation, elicited lipid peroxidation and induced the generation of various free radicals.\textsuperscript{114,115} In the review of Lai et al., SO\textsubscript{2} and NO\textsubscript{2} were positively and significantly associated with the mortality of COPD, which was consistent with the results in our study.\textsuperscript{116} Gao et al. found that the lung function of COPD participants was adversely associated with ambient SO\textsubscript{2} and NO\textsubscript{2} concentrations, while the systemic inflammation was positively

![Forest plot of meta-analysis between NO\textsubscript{2} and (A) asthma, (B) COPD, (C) diabetes mellitus, (D) lung cancer, and (E) preterm birth.](https://example.com/forest_plot.png)

**FIGURE 3** Forest plot of meta-analysis between NO\textsubscript{2} and (A) asthma, (B) COPD, (C) diabetes mellitus, (D) lung cancer, and (E) preterm birth.
associated with them, which was probably attributed to decreased Th2 cytokines and increased Th1 and Th17 cytokines.\textsuperscript{117} Besides, the association between NO\(_2\) and diabetes was significant in our study. In the meta-analysis of Eze et al., this association was significant (pooled RR = 1.08, 95% CI: 1.00–1.17 per 10 \(\mu g/m^3\) increase of NO\(_2\)) too.\textsuperscript{118} This association might be explained by the increased inflammation. NO\(_2\) was considered as a proinflammatory air pollutant, and current studies suggested that the inflammatory and metabolic processes might be linked by shared signal molecules and cascades.\textsuperscript{119,120}

CO was positively and significantly associated with cardiovascular diseases and Parkinson’s disease. As a consensus, the affinity of hemoglobin for CO is much higher than oxygen, which can bring adverse health effects by reducing delivery of oxygen.\textsuperscript{121} Besides, CO could engender a prooxidant milieu in aerobic mammalian cells and influence signaling related to reactive oxygen species (ROS).\textsuperscript{122} Studies have shown that air pollution involves neuroinflammatory processes and triggers oxidative stress, which may affect the risk of nervous system diseases.\textsuperscript{119,120}

O\(_3\) was positively and significantly associated with preterm birth, though the Egger’s test showed the presence of publication bias. Similarly, in a review published by Hak-Kan Lai et al., increased O\(_3\) was associated with a higher risk of preterm birth.\textsuperscript{116} Animal studies have shown that air pollution could cause decreased fertility, which was due to oxidative stress and inducing DNA adducts.\textsuperscript{123–125} and O\(_3\) is a superoxide air pollutant which could produce a high oxidative stress in pregnant animals. In addition, the inflammatory response to ozone exposure was enhanced in pregnant rats which played a role in preterm birth.\textsuperscript{126} In this review, the number of health studies on O\(_3\) was relatively small and did not observe a robust significant C-R relationship. The inconsistent measurement of O\(_3\) as 8-hour maximum level or as a daily level could make the high heterogeneity which we observed in this review. With increasing exposure to O\(_3\) both indoor and outdoor, further research is urgently needed to set up a reliable C-R relationship for O\(_3\).

The high heterogeneity might mainly come from the various study designs and different study populations. For example, the associations, such as NO\(_2\)-CVD pair and O\(_3\)-preterm birth, had relatively high heterogeneity (I\(^2\) > 90%). In the subgroup analyses, these associations were significant in cohort study but not significant in time-series study. Considering the potential bias and the difficulty in explaining chronological order of exposure and health outcome, the field intervention experiment had the strongest strength of causality argument, followed by random controlled trial, cohort study.\textsuperscript{129} The time-series study, one of ecology studies, had the weakest strength of causality argument. Although cohort studies have a strong causal argument, they only accounted for less than 30% of all studies in this meta-analysis, which might be likely to cause confusion and the high heterogeneity. Around half of risk estimates included were performed in China in this meta-analysis. The Chinese were more likely to be exposed to a high level of SO\(_2\), NO\(_2\), O\(_3\), and CO, while population in Europe and North America is exposed to relatively low levels, and the exposure–response relationship was not the same at different concentrations.\textsuperscript{6,7,13} Also, the racial difference might contribute to the heterogeneity. In the last subgroup meta-analysis, significant results were mainly from those with ambient field measurement methods while much less studies were from purely indoor measurements or indoor prediction models. Since people spend a large part of time indoors, more studies especially in a large-scale are needed in the future based on indoor measurements.

There were still some limitations in our study. First, this systematic review and meta-analysis were based on non-randomized observational studies, which could not fully exclude bias due to the presence of confounding factors. Second, the numbers of risk estimates for exposure to SO\(_2\), NO\(_2\), O\(_3\), and CO in civil buildings were limited. As the C-R relationship is a function describing the association between
the risk of health outcomes and the concentration of pollutants, we included studies carried out both outdoors and indoors to evaluate the health impacts of these four gaseous pollutants. The recruited studies might not be a full collection of all related studies due to a continuous update of publications globally or certain limited database accessibility. In the future research, more database, including Embase and other expertise report, is expected to be included to enrich the research bank and for a more accurate estimation of the C-R relationships. Third, the maximum RR was constrained according to the maximum concentration listed in the study. Epidemiology studies involving RR estimations beyond the maximum concentration listed in the study. Data that support the findings of this study are available in the supplementary material of this article.

5 | CONCLUSIONS

To comprehensively evaluate the quantitative health impacts of SO_2, NO_2, O_3, and CO, this study conducted a systematic review and meta-analysis between various health outcomes and SO_2, NO_2, O_3, and CO concentration levels, based on articles published between 1980 and 2019. After the meta-analyses, sensitivity analyses, and publication bias tests, SO_2, NO_2, and CO exposure were found to have robust and significant associations with two outcomes (CVD and COPD), five outcomes (childhood asthma, COPD, diabetes mellitus, lung cancer, and preterm birth), and two outcomes (CVD and Parkinson’s disease), respectively. This study can help deepen our understanding of the health effects of SO_2, NO_2, O_3, and CO on human health, and provide data for the further research on their attributable burden of disease.

AUTHOR CONTRIBUTIONS

Zhuoru Chen, Hao Tang, and Xuehuan Gao extracted the data from included studies. Zhuoru Chen and Ningrui Liu conducted this systematic review, wrote the original draft, and processed the data including quality assessment, meta-analysis, sensitivity analysis, and publication bias test. This study is a part of Chinese Burden of Disease Attributable to Indoor Air Pollutants (CBD-IAP) project. Yinqing Zhang, Haidong Kan, Furong Deng, Bin Zhao, Xiangang Zeng, Yuxia Sun, Hua Qian, Wei Liu, Jinhan Mo, Xiaohong Zheng, Chen Huang, Chanjuan Sun, and Zhuohui Zhao designed the framework of the whole CBD-IAP project, including the estimation of C-R relationships. Zhuohui Zhao revised the manuscript and polished the language. All authors involved in writing-review and editing of the manuscript.

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CONFLICT OF INTEREST

The authors declared that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the supplementary material of this article.

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