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## Ambient air pollution and COVID-19 risk: Evidence from 35 observational studies

Si-Tian Zang<sup>a,b</sup>, Jie Luan<sup>a,b</sup>, Ling Li<sup>c</sup>, Hui-Xin Yu<sup>a,b</sup>, Qi-Jun Wu<sup>a,b</sup>, Qing Chang<sup>a,b</sup>, Yu-Hong Zhao<sup>a,\*</sup>

<sup>a</sup> Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Heping District, Shenyang, Liaoning, 110004, China

<sup>b</sup> Clinical Research Center, Shengjing Hospital of China Medical University, No. 39 Huaxiang Road, Tiexi District, Shenyang, Liaoning, 110022, China

<sup>c</sup> Center for Precision Medicine Research and Training, University of Macau, Avenida da Universidade Taipa, Macau, 999078, China

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### ABSTRACT

**Background and aims:** The coronavirus disease 2019 (COVID-19) pandemic is severely threatening and challenging public health worldwide. Epidemiological studies focused on the influence of outdoor air pollution (AP) on COVID-19 risk have produced inconsistent conclusions. We aimed to quantitatively explore this association using a meta-analysis.

**Methods:** We searched for studies related to outdoor AP and COVID-19 risk in the Embase, PubMed, and Web of Science databases. No language restriction was utilized. The search date entries were up to August 13, 2021. Pooled estimates and 95% confidence intervals (CIs) were obtained with random-/fixed-effects models. PROSPERO registration number: CRD42021244656.

**Results:** A total of 35 articles were eligible for the meta-analysis. For long-term exposure to AP, COVID-19 incidence was positively associated with 1  $\mu\text{g}/\text{m}^3$  increase in nitrogen dioxide ( $\text{NO}_2$ ; effect size = 1.042, 95% CI 1.017–1.068), particulate matter with diameter  $<2.5 \mu\text{m}$  ( $\text{PM}_{2.5}$ ; effect size = 1.056, 95% CI 1.039–1.072), and sulfur dioxide ( $\text{SO}_2$ ; effect size = 1.071, 95% CI 1.002–1.145). The COVID-19 mortality was positively associated with 1  $\mu\text{g}/\text{m}^3$  increase in nitrogen dioxide ( $\text{NO}_2$ ; effect size = 1.034, 95% CI 1.006–1.063),  $\text{PM}_{2.5}$  (effect size = 1.047, 95% CI 1.025–1.1071). For short-term exposure to air pollutants, COVID-19 incidence was positively associated with 1 unit increase in air quality index (effect size = 1.001, 95% CI 1.001–1.002), 1  $\mu\text{g}/\text{m}^3$  increase  $\text{NO}_2$  (effect size = 1.014, 95% CI 1.011–1.016), particulate matter with diameter  $<10 \mu\text{m}$  ( $\text{PM}_{10}$ ; effect size = 1.005, 95% CI 1.003–1.008),  $\text{PM}_{2.5}$  (effect size = 1.003, 95% CI 1.002–1.004), and  $\text{SO}_2$  (effect size = 1.015, 95% CI 1.007–1.023).

**Conclusions:** Outdoor air pollutants are detrimental factors to COVID-19 outcomes. Measurements beneficial to reducing pollutant levels might also reduce the burden of the pandemic.

### 1. Introduction

Coronavirus disease 2019 (COVID-19) is induced by a previously undiscovered coronavirus, designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Lu et al., 2020). Since SARS-CoV-2 was first discovered in December 2019, as of April 25, 2021, more than four million fatalities have been attributed to COVID-19, accounting for approximately 2% of the infected cases ( $>214$  million) (Guan et al., 2020; World Health Organization, 2021). Although the pandemic has

now lasted for more than 1.5 years, there are thousands of new cases and deaths daily worldwide with few regions spared (World Health Organization, 2021). The pathogenicity, lethality, rapid propagation, unexpected sequelae (such as decreased olfactory function and neuronal damage) of COVID-19, as well as the continuous emergence of more lethal and highly infectious variant clusters, are seriously threatening and challenging public health (Barrantes, 2020; Brann et al., 2020; China Daily, 2021). Notably, vaccines cannot 100% protect people from SARS-CoV-2 infection (Lopez Bernal et al., 2020). Therefore, exploring

\* Corresponding author. Department of Clinical Epidemiology, Shengjing Hospital of China Medical University, No. 36 Sanhao Street, Shenyang, Liaoning, 110004, China.

E-mail addresses: [stzang@cmu.edu.cn](mailto:stzang@cmu.edu.cn) (S.-T. Zang), [jluan@cmu.edu.cn](mailto:jluan@cmu.edu.cn) (J. Luan), [yc07610@connect.um.edu.mo](mailto:yc07610@connect.um.edu.mo) (L. Li), [hxyu@cmu.edu.cn](mailto:hxyu@cmu.edu.cn) (H.-X. Yu), [wuqj@sj-hospital.org](mailto:wuqj@sj-hospital.org) (Q.-J. Wu), [changq@sj-hospital.org](mailto:changq@sj-hospital.org) (Q. Chang), [zhaoyuhong@sj-hospital.org](mailto:zhaoyuhong@sj-hospital.org) (Y.-H. Zhao).

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the factors influencing COVID-19 transmission and mortality have significant implications for the prevention and intervention strategies concerning this pandemic.

Generally, both individual susceptibility and ambient conditions contribute to COVID-19 transmission and mortality (De Angelis et al., 2021; Pranata et al., 2021). The ambient air quality index (AQI) is determined by airborne carbon monoxide (CO), nitrogen dioxide (NO<sub>2</sub>), ozone (O<sub>3</sub>), particulate matter with diameter <10 μm (PM<sub>10</sub>) and <2.5 μm (PM<sub>2.5</sub>), and sulfur dioxide (SO<sub>2</sub>) (Ministry of Ecology and Environment of the People's Republic of China, 2021). Globally, air pollution (AP) is the fourth greatest source of lethality (Health Effects Institute, 2020). Several epidemiological studies have linked AP to the COVID-19 pandemic (De Angelis et al., 2021; Stieb et al., 2020; Travaglio et al., 2021). However, the conclusions of individual studies are inconsistent. For example, positive associations between long-term exposure to PM<sub>2.5</sub> and COVID-19 incidence were identified (De Angelis et al., 2021; Travaglio et al., 2021) but another study found no such association (Stieb et al., 2020).

No meta-analysis has yet quantitatively focused on the influence of AP on COVID-19 risk and there are inconsistent conclusions of individual studies, while the pandemic is spreading vigorously. To explore the quantitative effect of outdoor AP on COVID-19 incidence and mortality, we conducted the first meta-analysis on the association of AP-COVID-19, to inspire relevant decision-makers to formulate more effective strategies for prevention and control of this unprecedented pandemic.

## 2. Methods

We conducted the meta-analysis according to the PRISMA and MOOSE guidelines (Supplementary Tables 1–2) (Moher et al., 2009; Stroup et al., 2000). Registered PROSPERO number: CRD42021244656.

### 2.1. Study search

We searched for studies related to AP and COVID-19 incidence or mortality in three databases: Embase, PubMed, and Web of Science. The search term was constructed on the basis of ('air quality' OR 'CO' OR 'NO<sub>2</sub>' OR 'nitrogen oxides' OR 'O<sub>3</sub>' OR 'PM<sub>10</sub>' OR 'PM<sub>2.5</sub>' OR 'SO<sub>2</sub>') AND ('COVID-19'), detailed in Supplementary Table 3. The search date entries were up to August 13, 2021, with no language restriction on the search. Additionally, we manually searched related references for enlargement of selection scope. The study search was done independently by two authors (S-TZ and JL), and any disagreement was resolved by a third author (Y-HZ).

### 2.2. Study selection

There was no language restriction on study selection. The research inclusion criteria follow: peer-reviewed; the study subjects were human; original research; observational study (cohort, ecological, time-series, cross-sectional, or case-control); the exposure was AQI, CO, NO<sub>2</sub>, nitrogen oxides (NO<sub>x</sub>), O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, or SO<sub>2</sub>; the outcome was COVID-19 incidence and/or mortality; COVID-19 with medical diagnostic criteria; with effect size and 95% confidence intervals (CIs) of the relationship between AP and COVID-19 risk; and effect size of the relationship between AP and COVID-19 incidence and/or mortality was expressed as dose-response.

The research exclusion criteria follow: not peer-reviewed; the study subjects were non-human; non-original research (review or meta-analysis); no effect size or 95% CI; no dose-response relationship; and data with obvious errors. After duplications were excluded, the title, abstract, and full text were evaluated separately, and finally included in the study if they met the criteria. The study selection was done independently by two authors (S-TZ and HX-Y), and any disagreement was resolved by a third author (Y-HZ).

### 2.3. Data extraction

The extracted terms including the first author, country, type of exposure window (long- or short-term), the number of lag days when the type of exposure window was short-term, exposure (AQI, CO, NO<sub>2</sub>, NO<sub>x</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, or SO<sub>2</sub>), outcome (COVID-19 incidence and/or mortality), pollutant dose, effect size, and 95% CI. In addition, publication year, exposure window duration, research type, number of cases and participants, adjusted covariates, pollutant concentration, and pollutant measurement method were extracted. The data were extracted independently by two authors (S-TZ and LL), and any disagreement was resolved by a third author (Y-HZ).

### 2.4. Risk of bias (quality) assessment

The quality of the included studies was evaluated based on nine parameters suggested by the Agency for Healthcare Research and Quality (Lam et al., 2017; Zeng et al., 2015). These included sample acquisition, inclusion criteria, research period, uninformed evaluators, outcome evaluation, exclusion criteria, covariate control, handling of missing information, and information integrity. Answer each question according to the characteristics of each article. Each parameter was addressed based on the responses from the articles. The "yes" response was equivalent to one point, while the "no" response corresponded to zero points. Scores of 1–3, 4–6, and 7–9 indicated high, moderate, and low risk of bias, respectively.

### 2.5. Statistical analysis

The following formula was used to standardize the effect sizes (Shah et al., 2013):

$$effect\ size_{(standardized)} = effect\ size_{(original)} \frac{Increment_{(standardized)}}{Increment_{(original)}}$$

where effect size<sub>(standardized)</sub> and effect size<sub>(original)</sub> represent the effect size of the association between air pollutants and COVID-19 risk with the Increment<sub>(standardized)</sub> and Increment<sub>(original)</sub> of pollutant concentration, respectively. The unit of concentration for air pollutants NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, or SO<sub>2</sub> used by the Ministry of Ecology and Environment of the People's Republic of China was μg/m<sup>3</sup> (Ministry of Ecology and Environment of the People's Republic of China, 2021). Thus, 1 μg/m<sup>3</sup> served as the Increment<sub>(standardized)</sub> for NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub>, as well as for CO and NO<sub>x</sub>. The random- and fixed-effects models were used to determine the effect size when heterogeneity was >50% and ≤50%, respectively (Ades et al., 2005; Fellmeth et al., 2018). An I-squared (I<sup>2</sup>) test was used to detect heterogeneity between studies, categorized into low-, medium-, and high-heterogeneity groups based on 50% and 75% boundaries (Higgins et al., 2003). The subgroup analysis was based on the following three aspects: whether the pollutant concentration prediction model was used, whether incidence and mortality have been normalized with respect to the population, and the national income level (high- or low-/middle level). Meta-regression was used to determine whether the three aforementioned factors were the source of heterogeneity. Publication bias of included articles was detected by Egger's test (Egger et al., 1997). Sensitivity analysis was performed for each meta-analysis when the included effect size was greater than that for the two items (Trikalinos et al., 2006). The number of studies was reduced by one at a time to see if the pooled results after the exclusion were significantly different from the overall pooled results, that is, whether the excluded studies made an impact on the overall results. If the effect size obtained after the exclusion was not statistically different from the overall pooled effect size, the effect of a given study on the overall effect size was not statistically significant and the overall result was robust. If the value obtained after a study was excluded was very different from the total pooled result, the study had an impact on the overall result, which was not robust. In addition, the evidence confidence was

evaluated by GRADE guidelines (Murad et al., 2017). We used Stata (version 15.0, StataCorp LLC, USA) for statistical analysis, with significance determined as  $P < 0.05$  (two-sided).

### 3. Results

#### 3.1. Study search and selection

There were 1128, 1790, and 2407 items retrieved from the Embase, PubMed, and Web of Science databases, respectively. Three items were also manually identified for the selection scope enlargement. First, 1995 duplicates were excluded and then 3131 and 70 records were excluded based on the title and abstract, respectively. Full texts of 132 records were evaluated and in the end 35 articles that met the criteria were included in the study (Fig. 1) (Adhikari and Yin, 2020; Azuma et al., 2020; Berg et al., 2021; Cabrera-Cano et al., 2021; Coker et al., 2020; Dales et al., 2021; De Angelis et al., 2021; Elliott et al., 2021; Fang et al., 2021; Hoang and Tran, 2020; Hoang et al., 2020; Huang and Brown, 2021; Jiang et al., 2020; Konstantinou et al., 2021; Linares et al., 2021; Lorenzo et al., 2021; Lu et al., 2021; Ma et al., 2021; Qeadan et al., 2021; Petroni et al., 2020; Rodriguez-Villamizar et al., 2020; Sahoo, 2021; Sanchez-Piedra et al., 2021; Setti et al., 2020; Stieb et al., 2020; Travaglio et al., 2021; Valdés Salgado et al., 2021; Wang et al., 2020; Wu et al., 2020a, 2020b; Xu et al., 2020; Zhang et al., 2021; Zheng et al., 2021; Zhou et al., 2021; Zhu et al., 2020).

#### 3.2. Study characteristics

Characteristics of the included studies are detailed in Table 1 and Supplementary Tables 4–6. The 35 included articles were published in 2020–2021. Of these, 15 studies came from low-/middle-income countries (Chile [n = 2], China [n = 10], Colombia [n = 1], India [n = 1], and Mexico [n = 1]) and 20 from high-income countries (Canada [n = 1], Germany [n = 1], Italy [n = 3], Japan [n = 1], Korea [n = 2], Singapore [n = 1], Spain [n = 2], UK [n = 3], and USA [n = 6]). There were three (8.6%, 3/35) cohort studies, 17 (48.6%) ecological studies, and 15 (42.9%) time-series studies. All COVID-19 case information came from official reports from governments of countries or localities. All studies were adjusted for covariates such as humidity and temperature. Eight

studies (22.9%) used evaluation models to assess the concentration of air pollutants on the basis of data from monitoring stations. A total of 29 (82.9%) studies had a low risk of bias and six (17.1%) had a moderate risk of bias. Ten studies had a normalized incidence and mortality with respect to the population. The latest collection of COVID-19 case information occurred on December 31, 2020. A total of 10 and 15 studies reported the association between long- and short-term exposure to air pollutants and COVID-19 incidence, respectively. In addition, 12 and two studies reported the association between long- and short-term exposure to air pollutants and COVID-19 mortality, respectively.

#### 3.3. Long-term exposure to air pollutants and COVID-19

##### 3.3.1. Long-term exposure to air pollutants and COVID-19 incidence

The COVID-19 incidence was positively associated with a  $1 \mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$  (effect size = 1.042, 95% CI 1.017–1.068,  $I^2 = 98.3\%$ ),  $\text{PM}_{2.5}$  (effect size = 1.056, 95% CI 1.039–1.072,  $I^2 = 94.9\%$ ), and  $\text{SO}_2$  (effect size = 1.071, 95% CI 1.002–1.145,  $I^2 = 97.2\%$ ). No association was found between long-term exposure to  $\text{PM}_{10}$  and COVID-19 incidence (effect size = 0.994, 95% CI 0.975–1.015,  $I^2 = 98.9\%$ ). However, COVID-19 incidence was negatively associated with a  $1 \mu\text{g}/\text{m}^3$  increase in CO (effect size = 0.258, 95% CI 0.126–0.529,  $I^2 = 99.4\%$ ) and  $\text{O}_3$  (effect size = 0.983, 95% CI 0.972–0.994,  $I^2 = 98.4\%$ ; Fig. 2, Supplementary Tables 7–11, and Supplementary Figs. 1–6).

Subgroup analysis showed that the association between  $\text{PM}_{2.5}$  and COVID-19 incidence was still positive when subgroup analysis was performed by country income (high- or low-/middle-income). The association between  $\text{NO}_2$  and COVID-19 incidence was positive in studies from low-/middle-income countries (effect size = 1.052, 95% CI 1.030–1.075), but there was no association for high-income countries (effect size = 1.026, 95% CI 0.990–1.063). The association between  $\text{NO}_2$  and COVID-19 incidence was positive when subgroup analysis used normalized incidence with respect to the populations (“yes” or “no”). Subgroup analysis showed that the association between  $\text{PM}_{10}$  and COVID-19 incidence was significant in studies with normalized incidence with respect to the populations (effect size = 1.009, 95% CI 1.007–1.011).

##### 3.3.2. Long-term exposure to air pollutants and COVID-19 mortality

The COVID-19 mortality was positively associated with a  $1 \mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$  (effect size = 1.034, 95% CI 1.006–1.063,  $I^2 = 97.5\%$ ) and  $\text{PM}_{2.5}$  (effect size = 1.047, 95% CI 1.025–1.071,  $I^2 = 86.3\%$ ). No association was found between long-term exposure to  $\text{NO}_x$  (effect size = 1.074, 95% CI 0.951–1.214,  $I^2 = 90.9\%$ ),  $\text{O}_3$  (effect size = 0.918, 95% CI 0.759–1.110,  $I^2 = 99.0\%$ ), or  $\text{PM}_{10}$  (effect size = 1.059, 95% CI 0.936–1.199,  $I^2 = 85.3\%$ ; Fig. 2, Supplementary Tables 12–13, and Supplementary Figs. 7–11).

Subgroup analysis showed that the association between  $\text{NO}_2$  and COVID-19 mortality was positive in studies from low-/middle-income countries (effect size = 1.035, 95% CI 1.023–1.047), but there was no association for high-income countries (effect size = 1.034, 95% CI 0.997–1.071). The association between  $\text{PM}_{2.5}$  and COVID-19 mortality was still positive when subgroup analysis was performed using the assessment model for pollutants (“yes” or “no”).

#### 3.4. Short-term exposure to air pollutants and COVID-19

##### 3.4.1. Short-term exposure to air pollutants and COVID-19 incidence

The COVID-19 incidence was positively associated with a 1 unit increase in AQI (effect size = 1.001, 95% CI 1.001–1.002) and a  $1 \mu\text{g}/\text{m}^3$  increase in  $\text{NO}_2$  (effect size = 1.014, 95% CI 1.011–1.016),  $\text{O}_3$  (effect size = 1.001, 95% CI 1.000–1.002),  $\text{PM}_{10}$  (effect size = 1.005, 95% CI 1.003–1.008),  $\text{PM}_{2.5}$  (effect size = 1.003, 95% CI 1.002–1.004), and  $\text{SO}_2$  (effect size = 1.015, 95% CI 1.007–1.023). However, there was no association between COVID-19 incidence and short-term exposure to CO (effect size = 1.000, 95% CI 1.000–1.001; Fig. 3, Supplementary

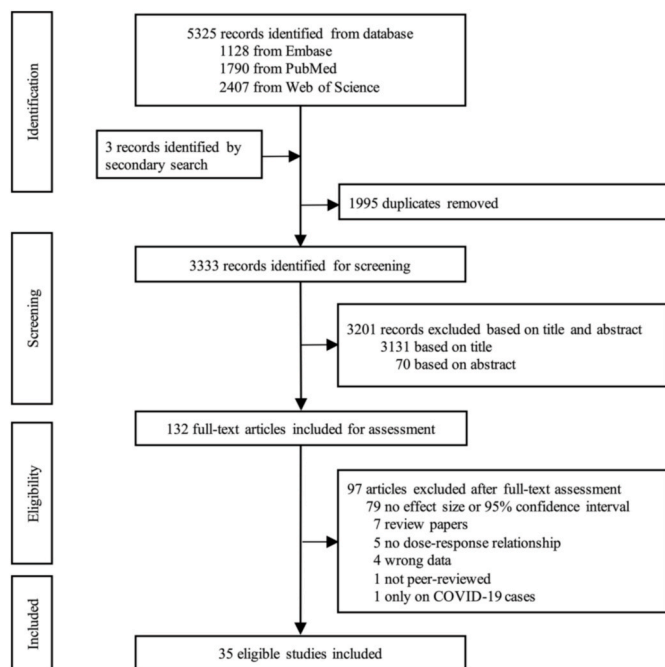


Fig. 1. Literature selection.

**Table 1**  
Characteristics of the studies included in the meta-analysis.

Study	Country	Design	Period	Outcome	Outcome normalized respect to the population	Pollutant	Risk of bias
<b>Long-term exposure</b>							
Berg et al. (2021)	USA	Ecological	March 1 to August 31, 2020	COVID-19 incidence, COVID-19 mortality	NA	PM <sub>2.5</sub>	Low
Cabrera-Cano et al. (2021)	Mexico	Ecological	February to June 2020	COVID-19 mortality	1.09/100,000–76.97/100,000	NO <sub>2</sub> , PM <sub>2.5</sub>	Low
Coker et al. (2020)	Italy	Ecological	January 1 to April 30, 2020	COVID-19 mortality	NR	PM <sub>2.5</sub> , O <sub>3</sub> , PM <sub>10</sub>	Low
De Angelis et al. (2021)	Italy	Ecological	February 20 to April 16, 2020	COVID-19 incidence	NR	NO <sub>2</sub> , PM <sub>10</sub> , PM <sub>2.5</sub>	Low
Elliott et al. (2021)	UK	Cohort	January 31 to September 21, 2020	COVID-19 mortality	NR	NO <sub>x</sub> , PM <sub>10</sub> , PM <sub>2.5</sub>	Low
Fang et al. (2021)	USA	Ecological	Up to September 12, 2020	COVID-19 incidence	NR	PM <sub>2.5</sub>	Low
Huang and Brown (2021)	Germany	Ecological	Up to September 13, 2020	COVID-19 incidence	NA	NO <sub>2</sub> , PM <sub>10</sub> , PM <sub>2.5</sub> , SO <sub>2</sub>	Low
Jiang et al. (2020)	China	Cohort	January 25 to February 29, 2020	COVID-19 incidence	NR	PM <sub>2.5</sub>	Low
Konstantinoudis et al. (2021)	UK	Ecological	March 2 to June 30, 2020	COVID-19 mortality	NR	NO <sub>2</sub> , PM <sub>2.5</sub>	Low
Qeadan et al. (2021)	USA	Ecological	Up to June 2, 2020	COVID-19 mortality	NR	PM <sub>2.5</sub>	Moderate
Petroni et al. (2020)	USA	Ecological	Up to July 11, 2020	COVID-19 mortality	NR	O <sub>3</sub> , PM <sub>2.5</sub>	Low
Rodriguez-Villamizar et al. (2020)	Colombia	Ecological	Up to July 17, 2020	COVID-19 mortality	Mean 0.75/1,000,000	PM <sub>2.5</sub>	Low
Sanchez-Piedra et al. (2021)	Spain	Ecological	February 3 to July 14, 2020	COVID-19 mortality	NR	NO <sub>2</sub> , PM <sub>2.5</sub>	Moderate
Stieb et al. (2020)	Canada	Ecological	Up to May 13, 2020	COVID-19 incidence	Mean 114.0/100,000	PM <sub>2.5</sub>	Low
Travaglio et al. (2021)	UK	Ecological	Cases: up to April 26, 2020; deaths: up to April 31, 2020	COVID-19 incidence, COVID-19 mortality	NR	NO <sub>2</sub> , NO <sub>x</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , PM <sub>10</sub>	Low
Valdés Salgado et al. (2021)	Chile	Ecological	2020	COVID-19 incidence, COVID-19 mortality	Mean: incidence 4501/100,000, mortality 71/100,000.	PM <sub>10</sub> , PM <sub>2.5</sub>	Low
Wu et al. (2020a)	USA	Ecological	Up to June 18, 2020	COVID-19 mortality	Mean 15.5/100,000	PM <sub>2.5</sub>	Low
Wu et al. (2020b)	China	Ecological	Up to April 21, 2020	COVID-19 incidence	NR	NO <sub>2</sub> , O <sub>3</sub> , PM <sub>10</sub> , PM <sub>2.5</sub>	Low
Zheng et al. (2021)	China	Ecological	December 31, 2019 to March 6, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>10</sub> , PM <sub>2.5</sub> , SO <sub>2</sub>	Low
<b>Short-term exposure</b>							
Adhikari and Yin (2020)	USA	Time-series	March 1 to April 20, 2020	COVID-19 incidence, COVID-19 mortality	NR	PM <sub>2.5</sub> , O <sub>3</sub>	Low
Azuma et al. (2020)	Japan	Cohort	March 13 to April 6, 2020	COVID-19 incidence	Median: 132.5/1,000,000	NO <sub>2</sub> , PM <sub>2.5</sub>	Low
Dales et al. (2021)	Chile	Time-series	March 16 to August 31, 2020	COVID-19 mortality	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub>	Low
Hoang and Tran (2020)	Korea	Time-series	February 24 to September 12, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub>	Low
Hoang et al. (2020)	Korea	Time-series	February 24 to May 5, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , SO <sub>2</sub>	Low
Linares et al. (2021)	Spain	Time-series	February 1 to December 31, 2020	COVID-19 incidence	NA	NO <sub>2</sub> , O <sub>3</sub> , PM <sub>10</sub>	Low
Lorenzo et al. (2021)	Singapore	Time-series	January 23 to April 6, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub>	Low
Lu et al. (2021)	China	Time-series	January 20 to February 29, 2020	COVID-19 incidence	NR	NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , SO <sub>2</sub>	Moderate
Ma et al. (2021)	China	Time-series	January 21 to February 29, 2020	COVID-19 incidence	NR	NO <sub>2</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub>	Moderate
Sahoo (2021)	India	Time-series	January 30 to April 23, 2020	COVID-19 incidence	NR	NO <sub>2</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub>	Moderate
Setti et al. (2020)	Italy	Time-series	February 24th to March 13th, 2020	COVID-19 incidence	Less and most polluted provinces: median 3 and 26 cases over 100,000 inhabitants, respectively.	PM <sub>10</sub>	Moderate
Wang et al. (2020)	China	Time-series	January 1 to March 2, 2020	COVID-19 incidence	NR	PM <sub>10</sub> , PM <sub>2.5</sub>	Low
Xu et al. (2020)	China				NR	AQI	Low

(continued on next page)

Table 1 (continued)

Study	Country	Design	Period	Outcome	Outcome normalized respect to the population	Pollutant	Risk of bias
Zhang et al. (2021)	China	Time-series Time-series	January 29 to February 15, 2020 January 1 to April 6, 2020	COVID-19 incidence COVID-19 incidence	NR	AQI, CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , PM <sub>10</sub> , SO <sub>2</sub>	Low
Zhou et al. (2021)	China	Time-series	January 15 to March 18, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>2.5</sub> , SO <sub>2</sub>	Low
Zhu et al. (2020)	China	Time-series	January 23 to February 29, 2020	COVID-19 incidence	NR	CO, NO <sub>2</sub> , O <sub>3</sub> , PM <sub>10</sub> , PM <sub>2.5</sub> , SO <sub>2</sub>	Low

Abbreviations: AQI, ambient air quality index; CO, carbon monoxide; NA, not available; NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; NR, not reported. O<sub>3</sub>, ozone; PM<sub>10</sub>, particulate matter with diameter <10 µm; PM<sub>2.5</sub>, particulate matter with diameter <2.5 µm; SO<sub>2</sub>, sulfur dioxide.

Tables 14–19, and Supplementary Figs. 12–18).

The association between NO<sub>2</sub> and COVID-19 incidence was positive when subgroup analysis was performed considering country incomes (high-income: effect size = 1.026, 95% CI 1.021–1.031 and low-/middle-income: effect size = 1.002, 95% CI 1.001–1.003). The positive association persisted when subgroup analysis used normalized incidence with respect to the populations (“yes” or “no”). Subgroup analysis also showed a positive association between CO and COVID-19 incidence in studies from low-/middle-income countries (effect size = 1.000, 95% CI 1.000–1.001,  $P < 0.05$ ). The association was also present with exposure to O<sub>3</sub> (effect size = 1.001, 95% CI 1.001–1.001), PM<sub>10</sub> (effect size = 1.005, 95% CI 1.003–1.008), and PM<sub>2.5</sub> (effect size = 1.001, 95% CI 1.001–1.002). Subgroup analysis revealed a positive association between O<sub>3</sub> and COVID-19 incidence in studies utilizing normalized incidence with respect to the populations (effect size = 1.009, 95% CI 1.005–1.013). The association between PM<sub>10</sub> and COVID-19 incidence remained positive with subgroup analysis employing normalized incidence with respect to the populations (“yes” or “no”). This association persisted with exposure to PM<sub>2.5</sub>.

#### 3.4.2. Short-term exposure to air pollutants and COVID-19 mortality

The COVID-19 mortality was not associated with 1 µg/m<sup>3</sup> increase in O<sub>3</sub> (effect size = 0.978, 95% CI 0.929–1.029) and PM<sub>2.5</sub> (effect size = 0.959, 95% CI 0.857–1.073; Fig. 3, Supplementary Tables 20; Supplementary Figs. 19–20).

#### 3.5. Publication bias, and robustness

Publication bias detection was performed for 15 associations identified in the present study. A total of 12 (80%) associations were without publication bias (Supplementary Table 21). Studies involving the association between COVID-19 incidence and long-term exposure to the air pollutants including CO, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub>, did not have a publication bias. There was also no publication bias in studies involving the association between COVID-19 incidence and short-term exposure to the following air pollutants: CO, O<sub>3</sub>, PM<sub>10</sub>, and SO<sub>2</sub>. Publication bias was found in studies involving the association between COVID-19 incidence and short-term exposure to PM<sub>2.5</sub> or NO<sub>2</sub>, as well as between COVID-19 mortality and long-term exposure to PM<sub>2.5</sub>. It is likely that the bias was present because the meta-analysis did not include an exhaustive list of research studies on the topic. Researchers tend to report positive instead of negative results, while small-sample and low-quality studies are not easy to publish.

Studies involving the association between COVID-19 incidence and long-term exposure to NO<sub>2</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub> were robust. This means that a single study did not have a significant impact on the overall pooled results. The same was true for studies on association between COVID-19 mortality and long-term exposure to NO<sub>2</sub> and PM<sub>2.5</sub> and between COVID-19 incidence and short-term exposure to NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub> (Supplementary Figs. 21–35).

#### 3.6. Evidence confidence

The evidence confidence for the association between COVID-19 incidence and long-term exposure to CO, NO<sub>2</sub>, O<sub>3</sub>, PM<sub>10</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub> was low. The results were similar for the association between COVID-19 mortality and long-term exposure to NO<sub>2</sub> and PM<sub>2.5</sub>, between COVID-19 incidence and short-term exposure to CO, O<sub>3</sub>, PM<sub>10</sub>, and SO<sub>2</sub>, as well as between COVID-19 mortality and short-term exposure to O<sub>3</sub> (Supplementary Table 22).

#### 4. Discussion

The present study included 35 studies on the impact of air pollutants on COVID-19 incidence or mortality. It was determined that both long- and short-term exposure to NO<sub>2</sub>, PM<sub>2.5</sub>, and SO<sub>2</sub> was associated with higher COVID-19 incidence. Long-term exposure to PM<sub>2.5</sub> increased COVID-19 mortality. The COVID-19 incidence was positively associated with an increase in AQI. Short-term exposure to O<sub>3</sub> and PM<sub>10</sub> was associated with higher COVID-19 incidence. The burden of the pandemic in most regions worldwide is increasing, underscoring the importance and urgency of attenuating AP in order to address the situation.

A general warning concerning the Need for a Medical Reading of Environmental Data should be taken seriously (Iriti et al., 2020). Approximately 80% of European urban populations are exposed to air pollutant levels that are higher than those set by the World Health Organization (European Environment Agency, 2019). Significantly, air pollution increases all-cause mortality (Chen and Hoek, 2020). Epidemiology studies have confirmed that air pollution does not only increase the risk of respiratory diseases, such as lung cancer and influenza, but also increases the risk of breast cancer, cognitive diseases such as Alzheimer's disease, cerebrovascular diseases like stroke, and metabolic diseases like diabetes (Chen and Hoek, 2020; Chen et al., 2017; Guo et al., 2021; Liu et al., 2019; Tsai et al., 2019; Yang et al., 2019; Yu et al., 2020). Therefore, Iriti et al. (2020) have pointed out that the hygiene departments should study the environmental data and strengthen the cooperation with environmental agencies to jointly contribute to reducing the adverse impact of air pollution on human health.

Other systemic effects of COVID-19 such as neurological symptoms should not be underestimated (Bellocchio et al., 2020). The damage to the central nervous system is manifested as cephalodynia, cerebrovascular disorders like brain hemorrhage, encephalopathy, light-headedness, Rasmussen's syndrome with convulsions, and spinal cord inflammation. The symptoms of damage to the peripheral nervous system are manifested as acute inflammatory polyradiculoneuropathy, ataxy, hyposmia, hypogeusia, decreased chemosensory function, and skeletal muscle injury. In addition, Patel et al. (2020) have demonstrated that COVID-19 causes abnormality in gastrointestinal function, such as vomiting and diarrhea. COVID-19 complications also include cardiovascular injury, hepatitis, and myocardial damage (Zhang et al.,

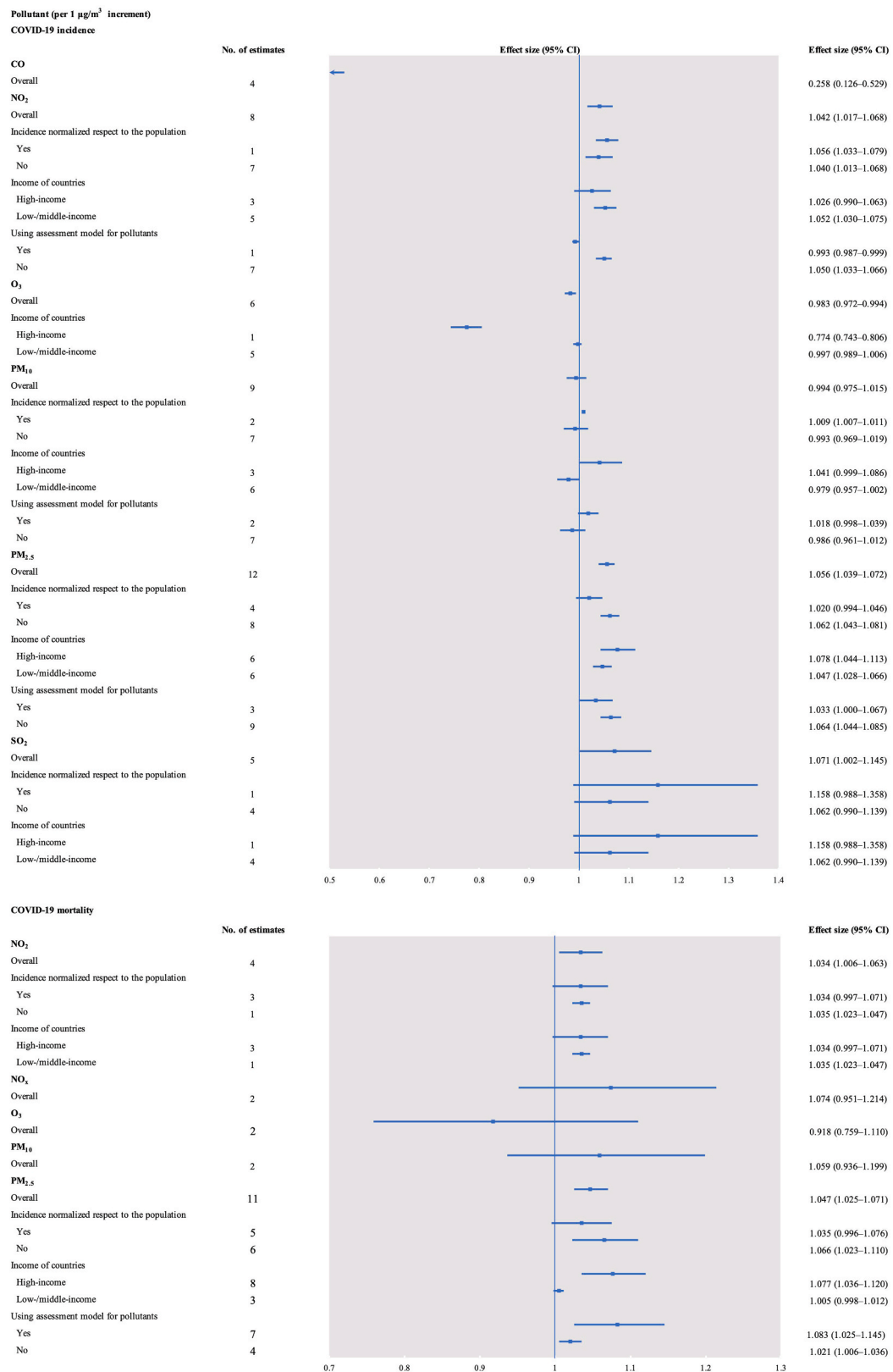


Fig. 2. Forest plots of the association between long-term exposure to air pollutants and COVID-19 risk. CO, carbon monoxide; NO<sub>2</sub>, nitrogen dioxide; NO<sub>x</sub>, nitrogen oxides; O<sub>3</sub>, ozone; PM<sub>10</sub>, particulate matter with diameter <10 µm; PM<sub>2.5</sub>, particulate matter with diameter <2.5 µm; SO<sub>2</sub>, sulfur dioxide.

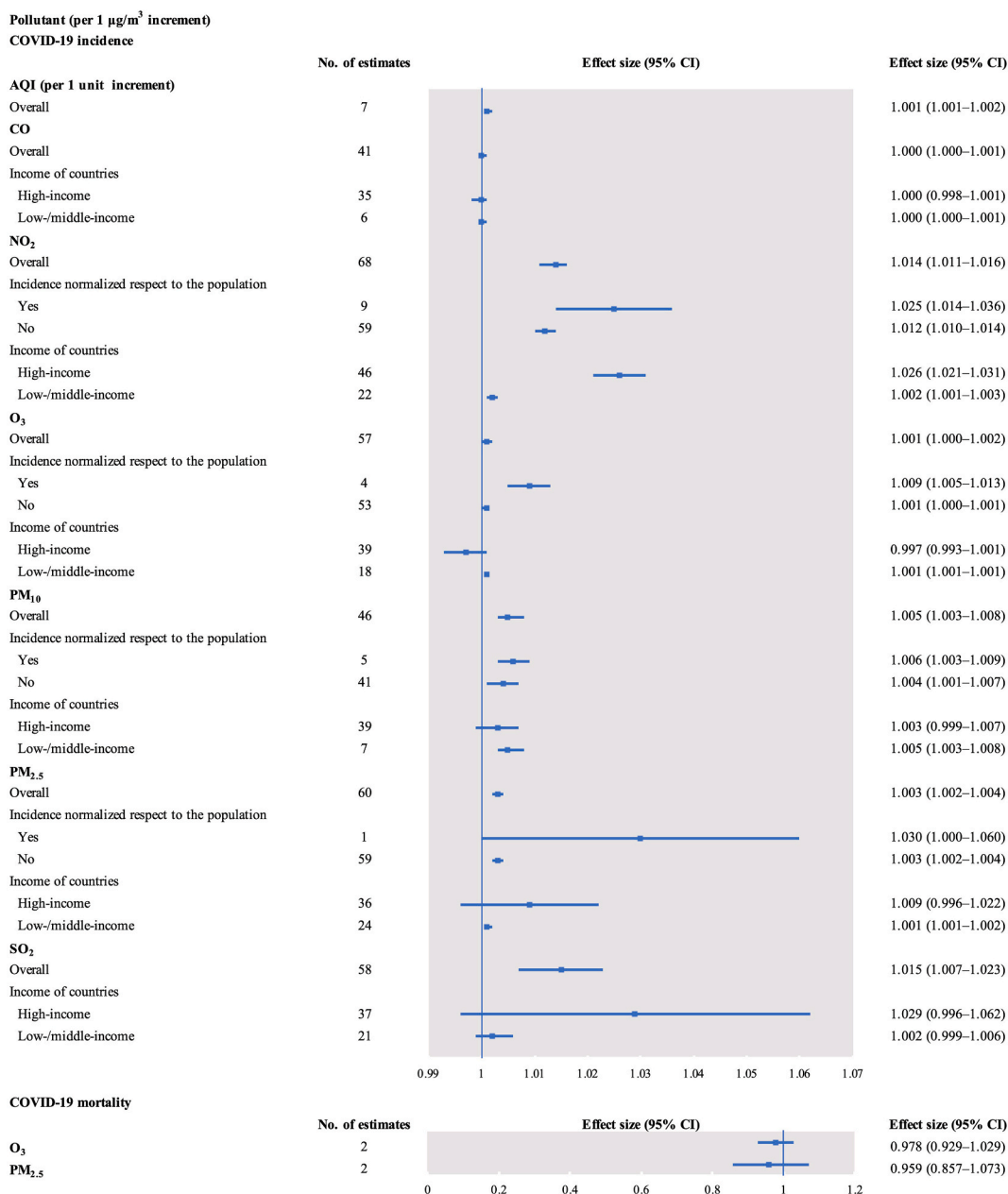


Fig. 3. Forest plots of the association between short-term exposure to air pollutants and COVID-19 risk. AQI, air quality index; CO, carbon monoxide; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; PM<sub>10</sub>, particulate matter with diameter <10  $\mu\text{m}$ ; PM<sub>2.5</sub>, particulate matter with diameter <2.5  $\mu\text{m}$ ; SO<sub>2</sub>, sulfur dioxide.

2020; Zheng et al., 2020).

In fact, the different restriction policies to contain the outbreak of COVID 19 for each country (for example lockdown period and entity), the population for each country, the healthcare capacity and access for each country, etc, could be confounder factors for the study. Moreover, non-COVID-related factors (e.g., meteorology and emissions from regional events) may play an important role in confounding short-term trends as well as the number of selected lag days, which were different among the considered studies.

Of the 35 included studies, ten had normalized incidence and mortality rates with respect to the population (Azuma et al., 2020; Berg et al., 2021; Cabrera-Cano et al., 2021; Huang and Brown, 2021; Linares et al., 2021; Rodríguez-Villamizar et al., 2020; Setti et al., 2020; Stieb et al., 2020; Valdés Salgado et al., 2021; Wu et al., 2020a). The heterogeneity among the studies when considering the association between long-term exposure to PM<sub>2.5</sub> was lower (8.8%) in the subgroup with incidence normalized with respect to the population than in the

subgroup without normalization (94.3%), indicating that normalized incidence with respect to the population decreases the heterogeneity among the studies. According to the subgroup analysis, long-/short-term exposure to NO<sub>2</sub> had a promotive effect on COVID-19 incidence regardless of incidence normalization, which was similar to the overall pooled effect. The association between short-term exposure to PM<sub>10</sub> or PM<sub>2.5</sub> and COVID-19 incidence remained positive when subgroup analysis utilized normalized incidence with respect to the populations (“yes” or “no”), which was similar to the overall pooled effect. The association between long-term exposure to PM<sub>10</sub> and COVID-19 incidence was significant in studies normalizing incidence with respect to the populations, which was different to the overall pooled effect. The association persisted with short-term exposure to O<sub>3</sub>. Normalizing incidence and mortality with respect to the population for pollutants that have not been demonstrated to promote the occurrence of COVID-19 can better reveal their adverse effects.

Healthcare capacity and access for each country, including number



of doctors and medical equipment, such as hospital beds, respirators, and personal protective equipment, per capita, can serve as confounding factors. Six of the 35 included articles have taken into account healthcare capacity of the different countries (Berg et al., 2021; Coker et al., 2020; Konstantinou et al., 2021; Petroni et al., 2020; Rodriguez-Villamizar et al., 2020; Wu et al., 2020a). They considered per-capita hospital beds as proxy for healthcare capacity. Specifically, Rodriguez-Villamizar et al. (2020) have shown that decreasing COVID-19 mortality is associated with increasing hospital bed capacity. Coker et al. (2020), Petroni et al. (2020), and Wu et al. (2020a) have identified a null association between hospital bed capacity and COVID-19 mortality. In addition, intensive care unit bed capacity not associated with COVID-19 mortality was demonstrated by Konstantinou et al. (2021). However, the above six studies were from high-income countries, and the included literature from low-/middle-income countries has not taken into account their healthcare capacity. In addition, disproportionate national income tends to lead to inconsistencies in healthcare capacity and national ability to handle and control public health incidents. Subgroup analysis indicated that long-term exposure to NO<sub>2</sub> was significantly associated with increased COVID-19 incidence or mortality in low-/middle-income countries. There was no such association in high-income countries. Similarly, a positive association between short-term exposure to CO and COVID-19 incidence has been demonstrated in studies from low-/middle-income countries, which persisted with exposure to O<sub>3</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub>. Null association was shown in high-income countries. This means that low-/middle-income countries may face more severe air pollution challenges when responding to this public health emergency. Therefore, low-/middle-income countries should take their healthcare capacity into account.

In addition, due to high levels of pollution and inadequate disease surveillance, low-/middle-income countries are experiencing a more severe COVID-19 burden than high-income countries. However, apart from those from China, there were few included studies from other low-/middle-income countries (28.6% from China, 5.7% from Chile, 2.6% from Colombia, 2.6% from India, and 2.6% from Mexico). Hence, more epidemiological research linking AP and COVID-19 risk from low-/middle-income countries is needed, such as from Africa and India, to adequately examine the detrimental effect of AP on COVID-19 risk.

Subgroup analysis showed that the association between long-term exposure to PM<sub>2.5</sub> and COVID-19 incidence remained positive when subgroup analysis evaluated countries' income (high- or low-/middle-income). The association between short-term exposure to NO<sub>2</sub> and COVID-19 incidence remained positive when subgroup analysis took country income into account. Although the air quality in high-income countries is relatively good, the impact of air pollution on COVID-19 risk cannot be ignored.

The association between long-term exposure to PM<sub>2.5</sub> and COVID-19 mortality was positive when subgroup analysis used the assessment model for pollutants ("yes" or "no"). Adjusting for the confounding parameters that affect COVID-19 risk, such as population density and temperature, increased the accuracy of the relationship between AP and COVID-19 risk. In addition, the AP concentration assessed using a model that incorporated multiple parameters was closer to the true exposure level than the AP concentration released by the air monitoring station alone. The evidence presented here suggests that a less reliable exposure measurement method contributed to underestimation of the association between pollutants and COVID-19 risk.

In addition to the aforementioned factors, the heterogeneity among studies originated from the following aspects. First, with the development of the pandemic and the introduction of policies to lockdown and reduce social interactions in various countries, air quality has risen, resulting in large fluctuations in the concentration of air pollutants in distinct periods (Venter et al., 2020). Secondly, the scope of research objects covered by each study is diverse, including sample size and regions. Third, the incidence rates of the same ethnic group in different

regions of the same country also differ as identified by Rodriguez-Diaz et al. (2020). Fourth, some studies originating in China excluded Wuhan (the epicenter) (Zheng et al., 2021; Zhou et al., 2021), while others did not. Fifth, when studying the impact of short-term exposure to air pollutants on the COVID-19 risk, the difference in the number of selected lag days is also a source of heterogeneity. Jiang et al. (2020) linked a 4-day lag of air pollutants with COVID-19 incidence, since the reference incubation period was 4 days. In contrast, Lorenzo et al. (2020) linked 8- and 15-day lags of air pollutants with COVID-19 incidence.

Zheng et al. (2021) confirmed that long-term exposure to NO<sub>2</sub>, PM<sub>10</sub>, and PM<sub>2.5</sub> also facilitated severe COVID-19 incidence. Long-term NO<sub>x</sub> exposure increased both COVID-19 incidence and mortality according to Travaglio et al. (2021). Petroni et al. (2020) demonstrated that diesel PM was a malignant factor related to COVID-19 mortality (effect size = 2.82). Jiang and Xu (2020) identified AP as a detrimental factor for COVID-19 mortality. Smoking was significantly correlated with COVID-19 risk (Reddy et al., 2021). Long-/short-term PM<sub>10</sub> and PM<sub>2.5</sub> were positively correlated with case fatality rate (Yao et al., 2020a, 2020b, 2020b). Dating back to 2003, during the SARS epidemic period, Cui et al. (2003) that high AP was significantly correlated with case fatality rate risk of SARS (effect size = 2.18, 95% CI 1.31–3.65).

Setti et al. (2020) have proposed that PM is a potential SARS-CoV-2 vector and a promoting factor in SARS-CoV-2 transmission. Frontera et al. (2020) suggested that long-term exposure to air pollutants will cause overexpression of angiotensin-converting enzyme 2 (SARS-CoV-2's target), thereby leading to SARS-CoV-2 overloading. The other potential biological mechanism of the impact of AP on COVID-19 is inflammatory response and oxidative stress (Fiorito et al., 2017; Ogen, 2020; Olvera Alvarez et al., 2018; Wolf et al., 2016). On the one hand, air pollutants directly impair lung function through inflammation and oxidative stress, including decreased pulmonary defense function and phagocytic function of macrophages (Becker et al., 2003; Guarnieri and Sinha, 2014; Selley et al., 2020). On the other hand, air pollutants indirectly affect the occurrence and development of COVID-19 through a series of predisposing factors for COVID-19, such as diabetes and high blood pressure (Mantovani et al., 2020; Taylor et al., 2020). Air pollutants directly damage the vascular system, or indirectly damage it by stimulating inflammatory factors produced by the body, and affect the autonomic nervous system that regulates vascular functions, causing vascular endothelial dysfunction (Fiorito et al., 2018; Miller, 2014; Shanley et al., 2016). Air pollutants affect the insulin signaling pathway related to the onset of diabetes (Alderete et al., 2018; Lucht et al., 2019). Air pollutants also affect the methylation of genes related to the above mechanisms (Li et al., 2018).

Several advantages of these research results cannot be ignored. First, we conducted the first meta-analysis on the association between AP and COVID-19 incidence and mortality. Second, the effects of two types of AP exposure (long- and short-term) on the two outcomes of COVID-19 (incidence and mortality) were included, to comprehensively explore the relationship between AP and COVID-19 risk. Third, no language restriction was applied in the search and selection of items. Fourth, the included effects of AP on COVID-19 were all dose-response, which provides more accuracy than higher vs. lower comparisons. Fifth, all included studies had a low or moderate risk of bias. Finally, 89.5% of the studies of association between long-term AP exposure and COVID-19 risk were ecological, providing less variability in exposure of a population.

There were several disadvantages of this research. First, underestimation of COVID-19 cases might exist in some regions from where the included studies originated, due to inadequate disease surveillance. Second, although some studies controlled for confounders that might have affected outcomes, residual confounding caused by unknown, overlooked, and unmeasured confounders could not be eliminated. Third, diverse healthcare resources accessible to individuals, and authoritative intervention policies in various regions, biased the result validity to different degrees. Fourth, underestimation of the association

between pollutants and COVID-19 risk was partly attributed to less-controlled confounders, less-reliable exposure measurement method, and underestimation of COVID-19 cases. Fifth, few studies were eligible for the pooled estimates for the association between pollutants and COVID-19 mortality. Finally, ecological fallacies are often unavoidable and individual-level associations cannot be estimated using ecological research.

## 5. Conclusions

Due to lethality and high infectiousness, COVID-19 remains a significant threat to public health worldwide. With the continuous spread of COVID-19, AP has been linked to the pandemic in several epidemiological studies, with inconsistent conclusions. Our results demonstrated that air pollutants are detrimental factors to COVID-19 outcomes. Highly polluted and severely COVID-19 burdened, low-/middle-income regions should perform epidemiological research to accurately estimate the detrimental effect of AP on the pandemic risk. The evidence presented here suggests that measurements beneficial to reducing pollutant levels might also reduce the burden of the pandemic.

## Author contributions

Zhao Yu-Hong: Conceptualization, Methodology, Resources, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. Chang Qing: Software, Formal analysis, Validation, Writing - Review & Editing, Supervision. Wu Qi-Jun: Conceptualization, Methodology, Writing - Review & Editing, Supervision. Zang Si-Tian: Software, Validation, Formal analysis, Investigation, Data curation, Writing - Original draft preparation, Writing - Review & Editing, Visualization. Luan Jie: Software, Validation, Formal analysis, Investigation, Data curation, Writing - Original draft preparation, Writing - Review & Editing, Visualization. Li Ling: Software, Validation, Formal analysis, Investigation, Data curation, Writing - Original draft preparation, Writing - Review & Editing. Yu Hui-Xin: Software, Validation, Formal analysis, Investigation, Data curation, Writing - Original draft preparation, Writing - Review & Editing.

## 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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## Appendix A. Supplementary data

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