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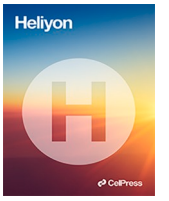

Research article

Exploring the association between ambient air pollution and COVID-19 risk: A comprehensive meta-analysis with meta-regression modelling

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ABSTRACT

Introduction: Air pollution is speculated to increase the risk of Coronavirus disease-2019 (COVID-19). Nevertheless, the results remain inconsistent and inconclusive. This study aimed to explore the association between ambient air pollution (AAP) and COVID-19 risks using a meta-analysis with meta-regression modelling.

Methods: The inclusion criteria were: original studies quantifying the association using effect sizes and 95 % confidence intervals (CIs); time-series, cohort, ecological or case-crossover peer-reviewed studies in English. Exclusion criteria encompassed non-original studies, animal studies, and data with common errors. PubMed, Web of Science, Embase and Google Scholar electronic databases were systemically searched for eligible literature, up to 31, March 2023. The risk of bias (ROB) was assessed following the Agency for Healthcare Research and Quality parameters. A random-effects model was used to calculate pooled risk ratios (RRs) and their 95 % CIs.

Results: A total of 58 studies, between 2020 and 2023, met the inclusion criteria. The global representation was skewed, with major contributions from the USA (24.1 %) and China (22.4 %). The distribution included studies on short-term (43.1 %) and long-term (56.9 %) air pollution exposure. Ecological studies constituted 51.7 %, time-series-27.6 %, cohorts-17.2 %, and case crossover-3.4 %. ROB assessment showed low (86.2 %) and moderate (13.8 %) risk. The COVID-19 incidences increased with a 10 $\mu g/m^3$ increase in $PM_{2.5}$ [RR = 4.9045; 95 % CI (4.1548–5.7895)], PM_{10} [RR = 2.9427: (2.2290–3.8850)], NO_2 [RR = 3.2750: (3.1420–3.4136)], SO_2 [RR = 3.3400: (2.7931–3.9940)], CO [RR = 2.6244: (2.5208–2.7322)] and O_3 [RR = 2.4008:

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(2.1859–2.6368)] concentrations. A 10 μg/m^3 increase in concentrations of $PM_{2.5}$ [RR = 3.0418: (2.7344–3.3838)], PM_{10} [RR = 2.6202: (2.1602–3.1781)], NO_2 [RR = 3.2226: (2.1411–4.8504)], CO [RR = 1.8021 (0.8045–4.0370)] and O_3 [RR = 2.3270 (1.5906–3.4045)] was significantly associated with COVID-19 mortality. Stratified analysis showed that study design, exposure period, and country influenced exposure-response associations. Meta-regression model indicated significant predictors for air pollution-COVID-19 incidence associations.

Conclusion: The study, while robust, lacks causality demonstration and focuses only on the USA and China, limiting its generalizability. Regardless, the study provides a strong evidence base for air pollution-COVID-19-risks associations, offering valuable insights for intervention measures for COVID-19.

1. Introduction

The Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 12, 2020. The disease manifests with a variety of clinical presentations, ranging from asymptomatic infection to fatal respiratory failure [1,2]. Significant progress has been made in controlling the pandemic with the development of efficacious vaccines and the implementation of vaccination campaigns [3]. Alongside vaccination, COVID-19 control has involved various intervention measures, including diagnostic, pharmacologic treatments, isolation, lockdowns, mask-wearing, social distancing, contact tracing, frequent hand washing, and public health messaging [4]. Despite these efforts, the disease continues to have a negative impact on global healthcare systems. For example, as of May 8, 2023 a total of 13,350, 487,934 vaccine doses had been administered worldwide. By 3:49 p.m. CEST, May 11, 2023, approximately 765,903,278 confirmed cases and 6, 927,378 deaths had been reported worldwide [WHO Coronavirus (COVID-19) Dashboard; https://covid19.who.int]. To date, the pandemic and its implications have had a massive negative impact on the socio-economic status, cultural practices, and livelihood of people globally [5–9]. Therefore, there is a need to urgently identify modifiable risk aspects to reduce COVID-19 disease burden.

The common risk factors for adverse COVID-19 outcomes include chronic airway diseases (i.e., asthma and lung cancer), diabetes and heart diseases [10]. The hypothesis that air pollution is a potential risk factor for the disease outcome of COVID-19 has been proposed recently [11]. This hypothesis is anchored on previous literature that link air pollution exposures to harmful health effects [12–20]. Briefly explained, exposure to long-and-short term air pollution may trigger production of free radical in the organism. This can exert pressure on the respiratory system, decrease resistance to infections and worsen disease prognosis [21–23]. For instance, PM (particulate matter) obstructs the airway [24]. After passing through the lungs' alveolar sacs and deeper into the blood, PM may induce pro-inflammatory and thrombogenic effects by generating chemical compounds and metal-induced-oxidative stress [18,25–27] that can trigger and exacerbate COVID-19 [28]. Other air pollution elements, such as sulfur dioxide (SO_2), ozone (O_3) carbon monoxide (CO), and nitrogen dioxide (NO_2) may damage lungs, create oxidative stress and endothelial dysfunction [28–32]. Additionally, some scholars have hypothesized that air pollution might worsen COVID-19 outcome by causing surfaces of the respiratory tract to over-express the coronavirus receptor ACE-2 (angiotensin converting enzyme 2) [33].

Although epidemiological studies [23,34–43] have reported on the association between AAP exposure and COVID-19 outcomes, most of these are individual studies with confounding variables and yield inconsistent conclusions. Such contradictory results reflect studies with many biases, which warrant cautiousness in inferring their results. For instance, whereas some scholars have independently reported a positive correlation between long-term exposure to $PM_{2.5}$ and COVID-19 incidences [37,38], others have reported contrary results [39]. Elsewhere, a statistically important correlation between $PM_{2.5}$, NO_2, O_3, PM_{10}, and COVID-19 cases was documented [30], whereas a non-statistically significant correlation between CO, PM_{10}, and COVID-19 cases was reported [44]. Contrary to many studies, it was autonomously reported that NO_2 was either negatively or not correlated with COVID-19 deaths [45,46]. The potential reasons behind inconsistencies in these epidemiological studies are multifaceted and may arise from various factors. First, variations in study design can lead to variations in results. Additionally, differences in data collection methods, including the measurement of air pollution levels and COVID-19 cases can impact the findings of these studies [47]. Second, failure to adequately account for confounding factors such as population density, socio-economic status, access to healthcare, age distribution, and comorbidities can lead to biased estimates of the association between air pollution and COVID-19 [48]. Third, variations in air pollution levels, climate, healthcare infrastructure, and public health policies across different regions can lead to differences in the observed exposure-response association [49]. Fourth, variability in the assessment of air pollution exposure, including the choice of air pollution metrics, and the use of satellite-based vs. ground-based monitoring data, can all lead to inconsistencies in study results [50]. Finally, methodological flaws that include using inappropriate statistics and emphasizing on statistical significance while ignoring the magnitude of the effect have been pointed out in air pollution-COVID-19 association studies [48,51,52].

Notably, studies reviewing air pollution-COVID-19 association base their arguments on the pandemic's very early stages and feature geographically scattered evidence [53–55]. While earlier data was crucial and provided significant epidemiological insights during the initial days of the pandemic, it would be interesting to understand whether the stage of the pandemic influences the effect estimates. Elsewhere, it has been recognized that existing meta-analyses, such as those conducted by Refs. [34,47] did not cover the complete body of research on the subject. Given all these, understanding the role of environmental factors, such as air pollution, in influencing COVID-19 risk remains crucial. Herein, we aimed to explore the association between ambient air pollution and COVID-19 incidences and mortality, using a meta-analysis with meta-regression modelling. Results of this study offer insights into the concept of

air pollution–COVID-19 association, which forms a basis upon which novel intervention measures for COVID-19, plus future pandemics of similar nature, may be formulated.

2. Methods

2.1. Research question

The eligibility criterion for this study was in conformity with the PECO [Population, Exposure, Comparator, and Outcome)] framework, which was used to frame the research question for the meta-analysis and establish inclusion criteria during the screening process [56]. A summary of the PECO question is presented below.

P: Among the human population, what is the effect of
E: Ambient air pollutants (PM2.5, PM10, SO2, CO, NO2, O3) per
C: Increase in concentration of the pollutants (i.e., 10 μg/m^3 increase) on
O: COVID-19 risk (e.g., incidence and/or mortality)

2.2. Search strategy

Electronic databases namely PubMed, Web of Science, Embase and Google Scholar were systemically searched for eligible literature up to 31, March 2023. The following search queries were used: ("air pollution" OR "air pollutants" OR "particulate matter" OR "PM_{10}" OR "$PM_{2.5}$" OR "SO_2 (sulfur dioxide)" OR "NO_2 (nitrogen dioxide)" OR "CO (carbon monoxide)" OR "O_3 (ozone)") and ("COVID-19" OR "SARS-CoV-2" OR "Coronavirus") (Table S1). Eligible articles published in English were included after full texts, titles, and abstracts were carefully screened. Further search for eligible studies was conducted manually in the reference list of the retrieved articles. HAM developed the search strategy, which YSH reviewed. Two authors (HAM and YSH) independently selected the literature by screening the title and abstract of possibly suitable studies and evaluating the full-article. Any differences between the two authors about inclusion were resolved by consulting with a third reviewer (H-FP).

2.3. Inclusion and exclusion criteria

After duplicates were eliminated, the title, abstract, and full text of the retrieved items were examined separately. If they conformed to the standards, then they were considered for inclusion in the study. The following criteria were considered to include the articles: (1) quantitatively measures the association between air pollution exposures and COVID-19 incidence and mortality, their effect sizes [RR (relative risk/risk ratio), HR (hazard ratio) or OR (odds ratio)] and corresponding 95 % CIs (confidence intervals); (2) time series, cohort, case-crossover, and ecological; (3) studies that focused on ambient air pollution; (4) original and peer-reviewed studies on human subject; (5) published in English. The exclusion criteria included: (1) reviews, toxicology studies, letters, opinions, commentary, or summaries, and (2) articles lacking effect size estimates and (or) 95 % CIs on authors' follow-up. (3) Studies conducted on animals and those in which therapeutic gases like O_3 were provided in a clinical setting. (4) Data having common errors. A framework as suggested by Ref. [57] was adapted, where manifold lag-estimates were described in the papers. Where reported, a single lag-estimate for an exposure-response association pair was directly included in the study. Whereas, where manifold lag-estimates were described, the commonly used lag in the included studies and (or) single lags, but not distributed lags were considered. The reporting conformed to the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)" (Table S.3) guidelines [58].

2.4. Data extraction and quality (risk of bias) assessment

Two authors (HAM and YSH) independently retrieved data from all the eligible studies, which comprised: (1) the study features [the author(s), year of publication, country, exposure window (long-term or short-term) and study period]; (2) COVID-19 incidence and mortality; (4) air pollutants concentration and increment of air pollution (10 μg/m^3; 1 μg/m^3; 1 ppm/m^3;1 ppb/m^3 increase) used in effect estimates; (5) effect size estimates (ORs, RRs, HRs, IRR) and their 95 % CIs of air pollution-COVID-19 risk relationship. Notably, all of the included studies contributed at least one effect size to each exposure-outcome association and where a study presented independent data from multiple cities, multiple numbers of effect sizes were used.

A study with a high conformity to methodological set standards may still have a high risk of bias (ROB) that can influence the direction or magnitude of the exposure-response association. The included studies were subjected to the "nine parameters" provided by the Agency for Healthcare Research and Quality (AHRQ) to assess the ROB/quality [47,59]. The parameters are: sample acquisition, inclusion criteria, study duration, missing data handling, outcome evaluation, uninformed evaluators, exclusion criteria, covariate control and information integrity. Every parameter was assessed and scored based on the characteristics of a specific article. The "YES" and "NO" scores were awarded one and zero points, respectively. Scores were grouped as high, moderate and low ROB [60] if they ranged between 1 and 3, 4–6, and 7–9, correspondingly (Table S. 2). The findings for each parameter were examined separately, without taking into consideration a single outcome for the entirety of the article. A dialogue with a third party (H-FP) helped to clarify differences and inconsistencies in the quality assessment process.

2.5. Statistical analyses

A meta-analysis was performed on the relationship between air pollution exposures (O_3, NO_2, $PM_{2.5}$, SO_2, PM_{10}, CO) and COVID-19 incidence and mortality. Following that the units of measurement for the effect estimates (95 % CIs) in the individual studies were different; we transformed them into a standardised format per 10 μg/m^3 increases in air pollution [60]. The following conversion formulas were used: 1) O_3:1 ppb = 48/22.4 mg/m^3 2) CO: 1 ppb = 28/22.4 mg/m^3 3) NO_2: 1 ppb = 46/22.4 mg/m^3 4) SO_2: 1 ppb = 64/22.4 mg/m^3. When case incidence is low IRR OR and HR is fair approximation of RR [61,62]. Thus, in pooled analyses, we used RRs as the common relationship metric with small intervals and conditional probabilities in mind [63]. Since most studies employed linear models, we determined the standardized relative risk (RR) for each study, assuming a linear exposure-outcome association, using the formula below [62,64].

$$RR_{(standardised)} = RR_{(original)}^{\text{increment }(standardised)/\text{increment }(original)}$$

Where, 10 μg/m^3 represents the increment (*standardised*) for the air pollutants. The $RR_{original}$ represents the effect size of the association between air pollutants and COVID-19 risk. The increment (*original*) represents the increase in air pollutant concentration for the individual study. A random-effects model was employed to calculate the pooled RRs estimates (95 % CIs) per 10 μg/m^3 increase in air pollutants concentrations. Following the diverse study designs, analytical techniques, topographies, lag exposures and populations; we anticipated a significant heterogeneity between individual studies. Thus, we employed a random-effects model to accommodate the variability exhibited by the effect sizes. Heterogeneity among studies was evaluated using I^2 statistics. Heterogeneity was considered low, moderate and high at the value of I^2 ≥25 %, ≥50 % and ≥75 % respectively or the value of Q statistic at $P \leq 0.05$ [65]. The significance ($p \leq 0.05$) of the pooled effect estimates (RR) was determined using the Z test [66].

Funnel plots and Egger's test were employed to determine potential publication bias [67]. Sensitivity analysis for the COVID-19 outcomes was performed, where the number of studies was ≥5, to test whether the pooled results were affected by a single study. The impact of specific publications on the combined effect estimates was assessed by eliminating every study from the analysis one at a time. If the effect size obtained after eliminating a study did not differ significantly from the pooled effect sizes, then the influence of a specific study on the pooled effect sizes was not statistically significant, therefore the overall finding was robust. We further performed a sub-group analysis by exposure period (long term and short term), country of study, and the study design, to evaluate if these aspects would influence the significance of the pooled effect estimates. Short-term exposure refers to exposure to air pollution during the pandemic whereas long-term exposure refers to exposure that occurs years before the onset of the disease. We further performed a meta-regression, with a mixed-effects-model, to evaluate the influence of multiple moderators (year of publication, ROB, and exposure

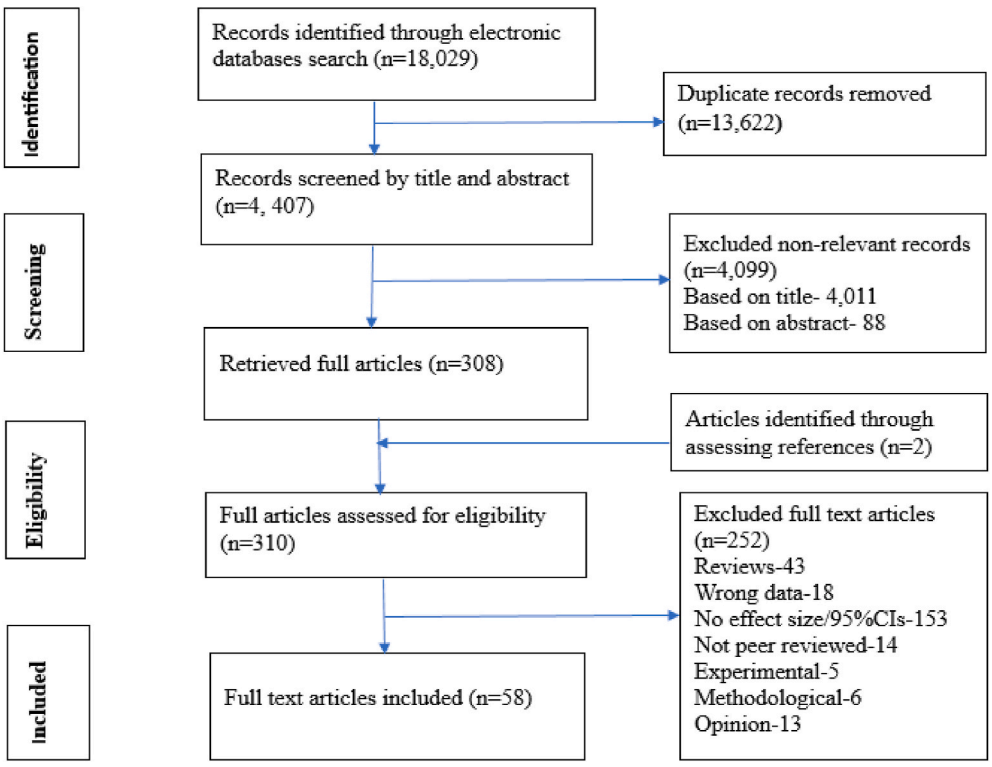

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of identification, screening, eligibility and inclusion of studies.

Table 1
The study characteristics.

ID	Author(s)/year	exposure	Period	country	design	COVID-19 outcome[ESE]	Air pollutants	Risk of bias
1	Adhikari and Yin, 2020	short-term	March 1 to April 20, 2020	USA	Time series	Incidence, Mortality [RR]	PM2.5, O3	Low
2	Azuma et al., 2020	short-term	March 13 to April 6, 2020	Japan	Cohort	Incidence [RR]	PM2.5, NO2	Low
3	Berg et al., 2021	long-term	March 1 to August 31, 2020	USA	Ecological	Incidence, Mortality [RR]	PM2.5	Low
4	Bonilla et al., 2023	long-term	during 2020	Latin America	Ecological	Mortality [RR]	PM2.5	Low
5	Bozack et al., 2022	long-term	March 8, 2020, to August 30, 2020	USA	Cohort	Mortality [RR]	PM2.5	Low
6	Cao et al., 2021	short-term	January 25 to February 29, 2020	China	Time series	Incidence [OR]	PM2.5, PM10, NO2, SO2,CO, O3	Low
7	Charlton et al., 2023	long-term	September 1, 2020 to18 January throughout 2022	UK	Cohort	Mortality [HR]	PM2.5, PM10, NO2,	Low
8	Chen et al., 2022	long-term	throughout 2020	Canada	Ecological	Mortality [OR]	PM2.5, NO2, O3	Low
9	Chen et al., 2022	short term	March 1 to October 31, 2020	USA	Cohort	Mortality [OR]	PM2.5, NO2	Low
10	Coker et al., 2020	long-term	January 1 to April 30, 2020	Italy	Ecological	Mortality [RR]	PM2.5, O3, PM10	Low
11	Dales et al., 2021	short-term	March 16 to August 31, 2020	Chile	Time series	Mortality [RR]	PM2.5, NO2,CO, O3	Low
12	De Angelis et al., 2021	long-term	Feb 20 to April 16, 2020	Italy	Ecological	Incidence [IRR]	PM10, NO2	Low
13	Dettori et al., 2021	long-term	Up to 4th -June-2020	Italy	Ecological	Mortality [RR]	PM2.5, PM10, NO2	Low
14	English et al., 2022	long-term	February 2020 to February 2021	USA	Ecological	Incidence, Mortality [OR]	PM2.5	Low
15	Fang et al., 2021	long-term	Up to September 12, 2020	USA	Ecological	Incidence [RR]	PM2.5	Low
16	Fernández et al., 2020	short-term	January 21st to May 18th, 2020	Spain	Time series	Incidence [RR]	PM10, O3	Low
17	Fiasca et al., 2020	short-term	March to October 2020	Italy	Ecological	Incidence [RR]	PM2.5, NO2	Low
18	Garcia et al., 2022	long-term	March 16, 2020 to March 7, 2021	USA	Ecological	Mortality [RR]	PM2.5, PM10, NO2, O3	Low
19	Hadei et al., 2021	short-term	Feb 20th, 2020 to Jan 4th, 2021	Iran	Ecological	Mortality [RR]	PM2.5, PM10, NO2, O4	Low
20	Hassan et al., 2021	long-term	up to 2020	Bangladesh	Ecological	Incidence [RR]	PM2.5, NO2, CO	moderate
21	Hoang et al., 2020	short-term	Feb 24 to Sept 12, 2020	South Korea	Time series	Incidence [RR]	PM2.5, PM10, NO2, SO2,CO, O3	Low
22	Hoang et al., 2020b	short-term	Feb 24 to May 5, 2020	South Korea	Time series	Incidence [RR]	SO2, CO, NO2	Low
23	Huang and Brown, 2021	long-term	Up to September 13, 202	German	Ecological	Incidence [RR]	PM10, NO2, PM2.5, SO2	Low
24	Hutter et al., 2020	long-term	until April 21, 2020	Austria	Ecological	Incidence, Mortality [HR]	PM10, NO2	Low
25	Jerrett et al., 2023	long-term	06-01-2020 and 01-31-2022	USA	Cohort	Mortality [HR]	PM2.5, NO2, O3	Low
26	Jiang and Xiu 2020	short-term	Jan 25 and April 7, 2020	China	Time series	Mortality [RR]	PM2.5	Low
27	Jiang et al., 2020	long-term	January 25 to February 29, 2020	China-Wuhan China-XiaoGan China-Huanggang	Cohort	Incidence [RR]	PM2.5, PM10, NO2, SO2,CO, O3	Low
28	Kim et al., 2022	short-term	up to 28 February 2021	USA	case-crossover	Mortality [RR]	PM2.5, O3	Low
29	Koch et al., 2022	long-term	April 16 until May 16, 2020	German	Ecological	Incidence, Mortality [RR]	PM2.5, NO2, O4	Low
30	Konstantinoudis et al., 2021	long-term	March 2 to June 30, 2020	UK	Ecological	Mortality [RR]	PM2.5, NO2	Low

(*continued on next page*)

Table 1 (*continued*)

ID	Author(s)/year	exposure	Period	country	design	COVID-19 outcome[ESE]	Air pollutants	Risk of bias
31	Liu et al., 2023	Short-term	Sep-2020	China	Cohort	Incidence [OR]	PM2.5, PM10, NO2, SO2,CO, O3	Low
32	Lorenzo et al., 2021	short-term	January 23 to April 6, 2020	Singapore	Time series	Incidence [RR]	PM10, SO2, PM2.5	Low
33	Lu et al., 2021	short-term	January 20 to Feb 29, 2020	China	Time series	Incidence [RR]	NO2, SO2, O3, PM2.5	Moderate
34	Ma et al., 2021	short-term	January 21 to Feb 29, 2020	China	Time series	Incidence [RR]	NO2, SO2, PM10, PM2.5	Moderate
35	Ma et al., 2023	short-term	March 2022, June 2022	China	Time series	Incidence [RR]	PM2.5, PM10, NO2, SO2,CO, O3	Low
36	Norouzi and Asadi, 2022	long-term	Mar 1, 2019 to Aug 31, 2019	Iran	Ecological	Mortality [RR]	PM2.5, NO2,	Low
37	Perone, 2022	long-term	2019 up to 2021	Italy	Ecological	Incidence [RR]	PM2.5, PM10, NO2,	moderate
38	Petroni et al., 2020	long-term	Up to July 11, 2020	USA	Ecological	Mortality [RR]	PM2.5, O3	Low
39	Qeadan et al., 2021	long-term	Up to June 2, 2020	USA	Ecological	Mortality [RR]	PM2.5	Moderate
40	Sahoo, 2021	short-term	January 30 to April 23, 2020	India	Time series	Incidence [RR]	NO2, SO2, PM10, PM2.6	Moderate
41	Sanchez-Piedra et al., 2021	long-term	February 3 to July 14, 2020	Spain	Ecological	Mortality [IRR]	PM2.5, NO2	Moderate
42	Setti et al., 2020	short-term	Feb 24th to March 13th, 2020	Italy	Time series	Incidence [OR]	PM10	Moderate
43	Sheridan et al., 2022	long-term	March–December 2020	UK	Cohort	Incidence, Mortality [OR]	PM2.5, PM10, NO2,	Low
44	Shim et al., 2022	long-term	January 2020 and April 2020.	South Korea	Ecological	Incidence [OR]	PM2.5, PM10, NO2, SO2,CO	Low
45	Sidell et al., 2022	long term	03/1/2020 to 02/28/2021.	USA	Cohort	Incidence [RR]	PM2.5, NO2, O3	Low
46	Stieb et al., 2020	long-term	Up to May 13, 2020	Canada	Ecological	Incidence [RR]	PM2.5	Low
47	Travaglio et al., 2021	long-term	Up to Apil 31, 2020	UK	Ecological	Incidence, Mortality [OR]	NO2, O3,	Low
48	Yu et al., 2022	short-term	May 5, 2020, to March 31, 2021	Sweden	case-crossover	Incidence [RR]	PM2.5, PM10	Low
49	Valdés Salgado et al., 2021	long-term	throughout 2020	Chile	Ecological	Incidence, Mortality [IRR]	PM2.5, PM10,	Low
50	Veronesi et al., 2022	long-term	up to March 2021	Italy	Cohort	Incidence [RR]	PM2.5, PM10, NO2, O3	Low
51	Wang et al., 2020	short-term	January 1 to March 2, 2020	China	Time series	Incidence [RR]	PM2.5, PM10,	Low
52	Wu et al., 2020a	long-term	To June 18, 2020	USA	Ecological	Mortality [RR]	PM2.5	Low
53	Wu et al., 2020b	long-term	Up to April 21, 2020	China	Ecological	Incidence [RR]	PM2.5, PM10, NO2,O3	Low
54	Xu et al., 2022	short-term	March 1st and June 30th, 2020.	USA	Ecological	Incidence [RR]	PM2.5, O3	Low
55	Zhang et al., 2021	short-term	January 1 to April 6, 2020	China	Time series	Incidence [RR]	PM2.5, PM10, NO2, SO2,CO, O3,	Low
56	Zheng et al., 2021	long-term	December 31, 2019 to 3/6/2020	China	Ecological	Incidence [RR]	PM2.5, PM10, NO2	Low
57	Zhou et al., 2021	short-term	15 Jan. to 18 Mar. 2020	China	Ecological	Incidence [RR]	PM2.5, NO2, SO2,CO,O3,	Low
58	Zhu et al., 2020	short-term	January 23 to Feb 29, 2020	China	Time series	Incidence [RR]	PM2.5, PM10, NO2, SO2,CO, O3,	Low

Abbreviation: PM_{10}, particulate matter with diameter <10 μm; $PM_{2.5}$, particulate matter with diameter <2.5 μm; CO, carbon monoxide; NO_2, nitrogen dioxide; O_3, ozone; SO_2, sulfur dioxide; ESE, Effect size estimate; RR, Risk ratio/relative risk; OR, odd ratio; IRR, incidence rate ratio/rate ratio; HR, hazard ratio.

period) on the effect sizes of the exposure-response association. To have sufficient power, meta-regression was only carried out for covariates where more than 10 studies were reported [68]. The findings were presented in the form of tables and figures. The analyses were performed using R (4.3.1) software and Review Manager (RevMan) Version 5.4.1, 2020 [http://www.cc-ims.net/revman] (The Cochrane Collaboration, Copenhagen, Denmark). In all the analyses, statistical significance was determined at $p \leq 0.05$.

3. Results

3.1. Literature search and characteristics of included studies

A total of 18,029 items were retrieved from PubMed, Web of Science, Embase and Google Scholar electronic databases. Primarily, 13, 622 duplicates were removed, followed by 4099 non-relevant items, such as books, based on the title and the abstract. The total number of full articles assessed for legibility were 310 (308 retrieved full articles plus 2 identified through reference access), and finally, 58 articles (Table S4) that met the inclusion criteria were selected. Fig. 1 illustrates the search strategy employed.

Table 1 is an illustration of the descriptive statistics for the included studies. The articles were published between 2020 and 2023. The geographical representation of the studies was as follows: USA (14; 24.1 %), China (13; 22.4 %), Italy (7; 12.1 %), UK (4; 6.9 %), and South Korea (3; 5.2 %). Germany, Canada, Chile, Iran and Spain each had two studies (3.4 %). Austria, India, Japan, Singapore, Sweden, Bangladesh, and Latin America each contributed one study (1.7 %). Studies reporting on short-term and long-term exposure to air pollutants accounted for 25 (43.1 %) and 33 (56.9 %) of the total, in that order. The study design distribution was as follows: ecological; 51.7 % (30), time-series; 27.6 % (16), cohorts; 17.2 % (10) and case-crossover 3.4 % (2). Based on the COVID-19 outcome, incidence and mortality were reported 36 (55.4 %) and 29 (44.6 %) times in the studies, respectively. The ROB evaluation, as guided by the "Agency for Healthcare Research and Quality", revealed low and moderate ROB at 86.2 % (50) and 13.8 % (8), respectively (Table S. 2).

3.2. Air pollution and COVID-19 incidence

The number of COVID-19 incidences increased significantly with a 10 μg/m^3 increase in the concentrations of $PM_{2.5}$ [RR = 4.9045, 95 % CI; 4.1548–5.7895, I^2 = 100 %; N = 38], PM_{10}, [RR = 2.9427, 95 % CI; 2.2290–3.8850, I^2 = 100 %; N = 28], NO_2 [RR = 3.2750, 95 % CI; 3.1420–3.4136, I^2 = 100 %; N = 29], SO_2 [RR = 3.3400, 95 % CI; 2.7931–3.9940, I^2 = 99 %; N = 15], CO [RR = 2.6244, 95 % CI; 2.5208–2.7322, I^2 = 100 %; N = 14] and O_3 [RR = 2.4008, 95 % CI; 2.1859–2.6368, I^2 = 100 %; N = 20], at p = 0.00001. The results of the sub-group analysis revealed variation in effect sizes subject to the exposure period. With a 10 μg/m^3 increment in pollutant concentration, the effect sizes for air pollution and COVID-19 incidence association were higher for long-term than short-term exposures (Table 2). There was a statistical significance in the subgroup difference between short term and long term exposure for $PM_{2.5}$ (I^2 = 90.3 %, P = 0.0001: Fig. S.2), NO_2 (I^2 = 76.6 %, P = 0.01: Fig. S. 10) and SO_2 (I^2 = 97.9 % P = 0.00001: Fig. S. 14). On the other hand, the subgroup difference between short term and long term exposure for PM_{10} (P = 0.65: Fig. S. 6), CO (P = 0.13: Fig. S. 18) and O_3 (P = 0.34 Fig. S. 22) per 10 μg/m^3 increase in concentration was not statistically significant.

Since study methodology may potentially modify the exposure-response relationship, we performed a stratified analysis by study design (Table 3). The results show that the highest exposure-response per 10 μg/m^3 increment for $PM_{2.5}$, NO_2, SO_2, and O_3 concentrations was revealed in cohort studies, whereas the highest exposure-response per 10 μg/m^3 increment for PM_{10} and CO was revealed in ecological studies. There was no evidence for heterogeneity of the associations for SO_2 under ecological studies (p = 0.65). The results of the subgroup difference revealed that the effect sizes differed significantly between study designs for $PM_{2.5}$ (Fig. S. 4), PM_{10} (Fig. S. 8), NO_2 (Fig. S. 11), SO_2 (Fig. S. 16), CO (Fig. S. 20) and O_3 (Fig. S. 23), at p = 0.00001.

Since the region of study may be a potential effect modifier on the exposure-response combination, we performed stratified analysis by country. There was variation in air pollution-COVID-19 incidence association across countries. The highest effect sizes per 10 μg/m^3 increment for $PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, and O_3 was revealed in USA [RR = 4.2506; 95 % (1.7505–10.321) I^2 = 100], South Korea [RR = 2.7183; 95 % (2.7156–2.721), I^2 = 0], Germany [RR = 4.1460 [2.4258–7.0861) I^2 = 85], China [RR = 10.1528 (5.9921–17.2026) I^2 = 100], RR = 2.8658 (2.6188–3.1361) I^2 = 100] and RR = 6.8696 (1.6254–29.04343) I^2 = 93], respectively. Interestingly, a 10 μg/m^3 increment for $PM_{2.5}$ [RR = 1.0125 [0.8225–1.2465] did not influence COVID-19 incidence in Bangladesh. A 10 μg/m^3 increment for PM_{10} did not influence in Singapore [RR = 1.0005 (1.0002–1.0008] and Spain [RR = 1.0111

Table 2
Pooled effect size for short-and-long term exposure to air pollution and their association with COVID-19 incidence.

Air pollutant	Incidence					
	Exposure period	No of effect sizes	RR (95%CI)	Heterogeneity test		Overall effect Z
				I^2 (%)	p-value	p-value
$PM_{2.5}$	Short-term	16	3.0312 [2.3304–3.9428]	100	0.00001	0.00001
	Long-term	22	6.5580 [5.3430–8.0493]	99	0.00001	0.00001
PM_{10}	Short-term	13	2.4701 [1.6531–3.6910]	100	0.00001	0.00001
	Long-term	15	2.7202 [2.3882–3.0984]	100	0.00001	0.00001
NO_2	Short-term	13	3.0422 [2.8668–3.2282]	100	0.00001	0.00001
	Long-term	15	4.6373 [3.5120–6.1231]	100	0.00001	0.00001
SO_2	Short-term	8	2.6551 [2.4604–2.8652]	95	0.00001	0.00001
	Long-term	7	50.982 [22.059–117.829]	100	0.00001	0.00001
CO	Short-term	7	2.6338 [2.6013–2.6667]	100	0.00001	0.00001
	Long-term	7	2.8431 [2.5791–3.1340]	99	0.00001	0.00001
O_3	Short-term	11	2.2957 [1.9870–2.6524]	100	0.00001	0.00001
	Long-term	9	2.5509 [2.1766–2.9896]	100	0.00001	0.00001

Table 3
Pooled effect size of air pollutant and their association with COVID-19 incidence by study design.

Air pollutant	Incidence					
	Study design	No of effect sizes	RR (95%CI)	Heterogeneity test		Overall effect Z
				I^2 (%)	p-value	p-value
$PM_{2.5}$	Ecological	19	3.0718 [2.8074–3.3611]	97	0.00001	0.00001
	Time series	12	2.8414 [1.9932–4.0504]	100	0.00001	0.00001
	Cohort	8	6.2232 [4.3281–8.9481]	87	0.00001	0.00001
PM_{10}	Ecological	11	2.9313 [2.7861–3.0842]	96	0.00001	0.00001
	Time series	11	2.3717 [1.5773–3.5662]	100	0.00001	0.00001
	Cohort	7	1.9054 [1.6145–2.2488]	92	0.00001	0.00001
NO_2	Ecological	13	3.0127 [2.8823–3.1489]	91	0.00001	0.00001
	Time series	9	3.1232 [2.9808–3.2724]	90	0.00001	0.00001
	Cohort	8	4.6501 [3.1699–6.8215]	98	0.00001	0.00001
SO_2	Ecological	4	2.7164 [2.7145–2.7183]	0	0.65	0.00001
	Time series	7	2.7123 [2.4255–3.0331]	96	0.00001	0.00001
	Cohort	4	9.4144 [2.7822–31.856]	92	0.00001	0.0003
CO	Ecological	4	2.7241 [2.7031–2.7452]	83	0.003	0.00001
	Time series	7	2.7056 [2.6965–2.7146]	89	0.00001	0.00001
	Cohort	4	2.6895 [2.6194–2.7614]	99	0.00001	0.00001
O_3	Ecological	5	2.4619 [1.4745–4.1104]	100	0.00001	0.0006
	Time series	10	2.4196 [1.8898–3.0980]	100	0.00001	0.00001
	Cohort	4	2.5232 [2.3139–2.7514]	98	0.00001	0.00001

[0.9905–1.0320]. Also no effect was recorded in the UK: RR = 1.0803 [1.0460–1.1156], Spain: RR = 1.0450 [1.0197–1.0709] and Singapore: RR = 1.0275 (1.0159–1.0392) for every 10 μg/m^3 increment in O_3. The results of the subgroup difference revealed that the effect sizes between countries was statistically significant for $PM_{2.5}$ (Fig. S. 3), PM_{10} (Fig. S. 7), NO_2 (Fig. S. 12), SO_2 (Fig. S. 15) and O_3 (Fig. S. 24), all at p = 0.00001. The subgroup difference was not statistically significant between countries for CO at P = 0.35 (Fig. S. 19).

3.3. Air pollution and COVID-19 mortality

Increased risk of COVID-19 mortality was significantly associated with a 10 μg/m^3 increase in concentration of $PM_{2.5}$, PM_{10}, NO_2 and O_3 corresponding to RR = 3.0418 [95 % CI; 2.7344–3.3838, I^2 = 99 %; N = 25], RR = 2.6202 [95 % CI; 2.1602–3.1781, I^2 = 98 %; N = 8], RR = 3.2226 [95 % CI; 2.1411–4.8504, I^2 = 100 %; N = 12], and RR = 2.3270 [95 % CI; 1.5906–3.4045, I^2 = 100 %; N = 11], respectively (p = 0.00001). The association between CO and COVID-19 mortality was not statistically significant [RR = 1.8021 [95 % CI; 0.8045–4.0370, I^2 = 100 %; N = 2] at p = 0.15. Studies focusing on SO_2 pollutant were limited thus the variable was not evaluated.

The results of the combined mortality effects sizes based on the exposure time were evaluated (Table 4). There was a higher association between air pollution and COVID-19 mortality with a 10 μg/m^3 increment in concentrations for long term exposure than short term exposure. While PM_{10} revealed a higher effect size for short-term than long-term exposure, the heterogeneity level was significantly low for short-term (p = 0.18). The results of the subgroup difference revealed that the effect sizes between short term and long term exposure was statistically significant for $PM_{2.5}$ (p = 0.00008: Fig. S. 26). The subgroup difference was not statistically significant between short-term and long-term exposure for PM_{10} (P = 0.80: Fig. S. 30) and NO_2 (p = 0.30: Fig. S. 34) and O_3 (p = 0.68: Fig. S. 39) per 10 μg/m^3 increase in concentration.

Risk ratios (RRs) and the 95 % CIs of air pollutants for COVID-19 mortality by different study designs are presented in Table 5. There was variability in the effect sizes with a 10 μg/m^3 increase in the concentration of the tested air pollutants. No heterogeneity was revealed for COVID-19 mortality in cohort studies with a 10 μg/m^3 increase in O_3 concentration. Additionally, there was no significant

Table 4
Pooled effect size of short-term and long-term exposure to air pollutant and their association with COVID-19 mortality.

Air pollutant	Mortality					
	Exposure period	No of effect sizes	RR (95%CI)	Heterogeneity test		overall effect Z
				I^2 (%)	*p-value*	p-value
$PM_{2.5}$	Short-term	5	2.8534 [2.7279–2.9848]	92	0.00001	0.00001
	Long-term	19	3.3592 [3.1039–3.6354]	85	0.00001	0.00001
PM_{10}	Short-term	3	2.6832 [2.4446–2.9427]	42	0.18	0.00001
	Long-term	5	2.5406 [1.6678–3.8701]	99	0.00001	0.00001
NO_2	Short-term	3	2.7240 [2.7090–2.7390]	0	0.044	0.00001
	Long-term	9	3.1577 [1.8653–5.3456]	100	0.00001	0.00001
O3	Short-term	5	2.1707 [1.2294–3.8328]	100	0.00001	0.008
	Long-term	6	2.4628 [1.9904–3.0473]	98	0.00001	0.00001

impact on COVID-19 mortality in time series studies with a 10 μg/m^3 increase in O_3 concentration (p = 0.07). The results of the subgroup difference revealed that the effect sizes between study designs was statistically significant for PM_{10} (p = 0.001: Fig. S. 32) and O_3 (p = 0.00001: Fig. S. 41). The subgroup difference was not statistically significant between study designs $PM_{2.5}$ (P = 0.92: Fig. S. 28) and NO2 (P = 0.80: Fig. S. 36).

The largest effect size for $PM_{2.5}$ [RR = 3.9411 95 % CI; 2.8993–5.3574, I^2 = 89 %], PM_{10} [RR = 4.4371 95 % CI; 1.3703–14.3676]; I^2]N/A], NO_2 [RR = 6.6512 95 % CI; 5.7142–7.7419, I^2]N/A] and O_3 [RR = 3.24, 95 % CI; 2.75–3.82, I^2]N/A] were revealed in the USA, Austria, Spain and Canada, respectively. There was no strong effect of air pollution on COVID-19 mortality recorded in Germany for $PM_{2.5}$ [RR = 1.6755 (0.8751–3.2078)], Chile for O_3 [RR = 1.11 (1.10–1.11)], Italy for PM_{10}, [RR = 1.1584 (1.0613–1.2643)] and NO_2 [RR = 1.0030 (1.0005–1.0055)]. Results for the subgroup difference showed statistical significance between countries for $PM_{2.5}$ (Fig. S. 27), PM_{10} (Fig. S. 31), NO_2 (Fig. S. 35) and O_3 (Fig. S. 40) per 10 μg/m^3 increase in concentration.

3.4. Publication bias and sensitivity analysis

Studies reporting on the association between long term exposure to air pollution and COVID-19 incidences did not reveal publication bias, except for SO_2. Studies reporting on the association between short-term exposures to CO, O_3, PM_{10}, SO_2 and COVID-19 did not show publication bias (Fig. S42-Fig. S. 45; Table S5). Noteworthy, publication bias was detected in studies that reported on $PM_{2.5}$ and COVID-19 incidences and mortality (due to short-term exposure) and on NO_2 and COVID-19 mortality (based on study design, country and exposure window) (Fig S46). Sensitivity analysis results showed that individual study influence on pooled effect size estimations was not statistically significant at $p \leq 0.05$. The effect sizes obtained after removing a study did not vary with the overall pooled effect size, thus the overall results were considered robust.

3.5. Meta-regression modelling

Meta-regression model for COVID-19 incidence revealed predictors of heterogeneity in varied rates among studies reporting on COVID-19 incidences (Fig. 2). The effect sizes significantly increased over years (YOP) for $PM_{2.5}$ (Coefficient: 0.4157; 95 % CI: 0.0275–0.8038; $p < 0.01$), PM_{10} (Coefficient: 0.7462; 95 % CI: 0.0851–1.5776; $p < 0.05$), NO_2 (Coefficient: 0.4756; 95 % CI: 0.0064–0.9576; $p < 0.05$), CO (Coefficient: 0.0373; 95 % CI: 0.0063–0.0810; $p < 0.05$) and SO_2 (Coefficient: 0.6083; 95 % CI: 0.0765–1.2932; $p < 0.05$). The YOP was not able to significantly predict the effect of O_3 on COVID-19 incidence (Coefficient: 0.0075; 95 % CI: 0.5216-0.5367; $p < 1.0$). Risk of bias (ROB) was significantly associated with COVID-19 incidence for CO (Coefficient: 0.2958; 95 % CI: 0.2358–0.3559; $p < 0.0001$). Contrarily, the ROB was not able to significantly predict the effects of $PM_{2.5}$, NO_2, SO_2 and O_3 on COVID-19 incidences ($p < 1.0$). Variability in incidence was further explained by exposure window for PM_{10} (Coefficient: 1.5473; 95 % CI: 2.9652, −0.1294; $p < 0.01$), NO_2 (Coefficient: 2.6097; 95 % CI: 4.0379, −1.1815; p = 0.0003) and SO_2 (Coefficient: 3.6213; 95 % CI: 6.3892, −0.8534; $p < 0.0103$), O_3 (Coefficient −0.3149; 95 % CI: 0.6060, −0.0237; p = 0.0340). The exposure window did not significantly predict the effects of $PM_{2.5}$ (p = 0.2201) and CO (p = 0.0825) on COVID-19 incidences. With reference to the meta-regression model, the ability of the tested covariates to predict the effect of $PM_{2.5}$, NO_2 and O_3 on COVID-19 mortality was not statistically significant [YOP ($PM_{2.5}$ p = 0.6260; NO_2 p = 0.6941; O_3 p = 0.3913), exposure window ($PM_{2.5}$ p = 0.8988; NO_2 p = 0.2889; O_3 p = 0.2063) and ROB ($PM_{2.5}$ p = 0.8327; NO_2 p = 0.6266)] (Fig. 3). Meta-regression for mortality (PM_{10}, SO_2 and CO) was not performed because less than 10 studies were reported.

4. Discussion

The COVID-19 pandemic has resulted in a range of consequences affecting health [69–71], socioeconomic factors [72,73], and culture [74]. The trajectory of the pandemic remains uncertain, and there is a possibility of it persisting and transforming into a future outbreak with epidemic or pandemic potential [75]. Consequently, there is a crucial need for epidemiological insights to comprehend the environmental risk factors associated with adverse COVID-19 outcomes and facilitate targeted responses [76]. In this study, we

Table 5
Pooled effect size of air pollutant and their association with COVID-19 mortality analyzed based on different study designs.

Air pollutant	Mortality					
	Study design	No of effect sizes	RR (95%CI)	Heterogeneity test		overall effect Z
				I^2 (%)	p-value	p-value
$PM_{2.5}$	Ecological	16	3.4131 [2.4961–4.6670]	100	0.00001	0.00001
	Cohort	5	3.5493 [2.6050–4.8359]	77	0.005	0.00001
	Time series	3	2.7094 [1.5608–4.7033]	88	0.0002	0.0004
PM_{10}	Ecological	5	2.5060 [1.6469–3.8134]	99	0.00001	0.00001
	Cohort	3	2.5909 [2.5728–2.6091]	74	0.001	0.00001
NO_2	Ecological	8	3.4667 [1.8365–6.5442]	100	0.00001	0.0001
	Cohort	4	2.8249 [2.6111–3.0563]	90	0.001	0.00001
O3	Ecological	6	2.4780 [1.8563–3.3081]	98	0.00001	0.00001
	Cohort	2	2.7211 [2.7143–2.7279]	0	0.54	0.00001
	Time series	3	1.1288 [0.9904–1.2866]	18	0.27	0.07

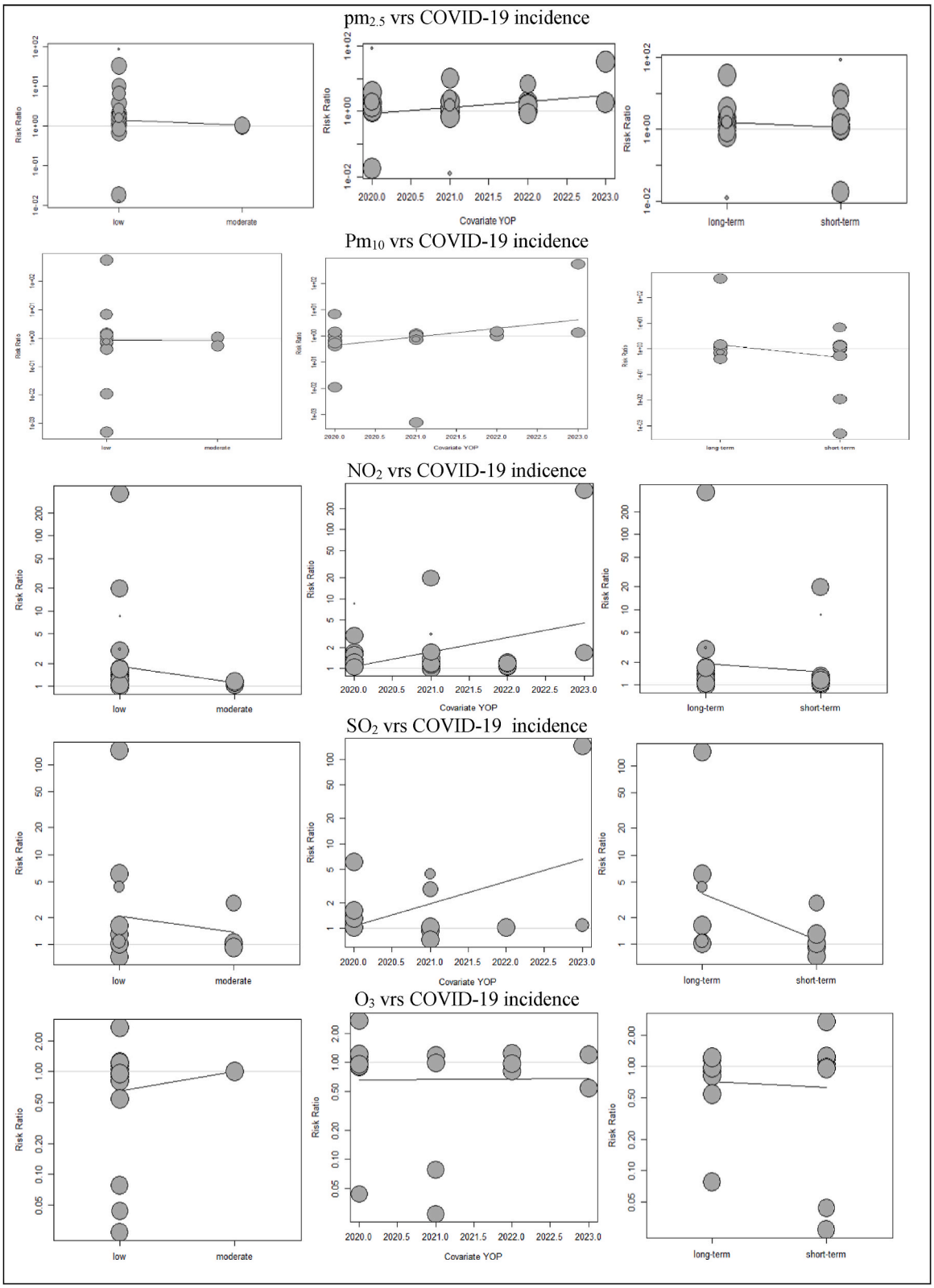

Fig. 2. Bubble plots showing results of the meta-regression model for air pollution COVID-19 incidences. From left to right: Risk of bias (low or moderate), YOP (year of publication) and exposure window (long or short term).

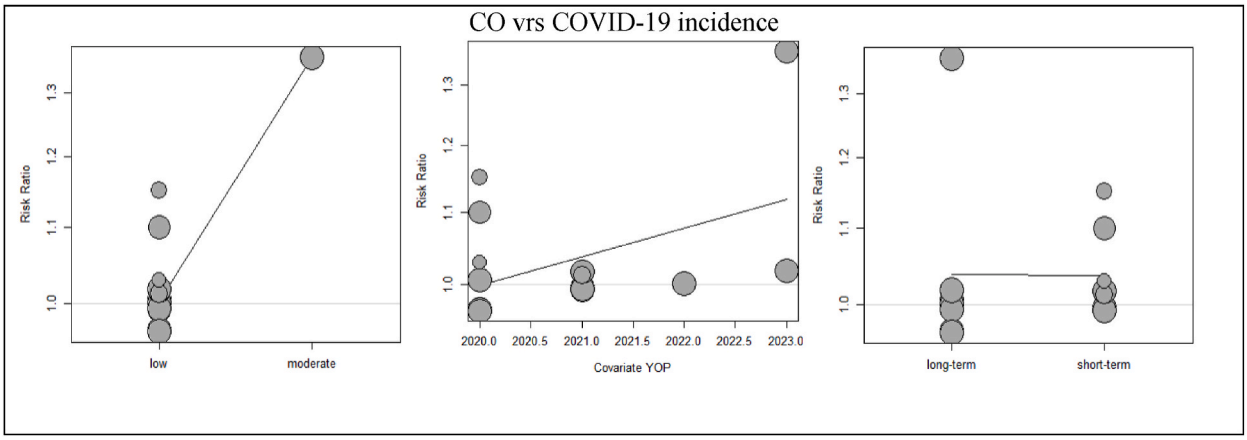

Fig. 2. (*continued*).

systematically synthesized findings from 58 individual studies investigating the association between air pollution exposure and COVID-19 risks. Similar to our findings, previous studies have also reported an uneven distribution of individual studies concerning geography, exposure window, and study design [47,55,77]. This suggests variation in the methodologies used across studies, which could potentially impact the consistency and reliability of the results. In the context of our meta-analysis, this uneven distribution highlights the need for standardized approaches to study design and methodology. Consistent methods in future research may improve evidence on the link between air pollution and COVID-19 risk, enabling more accurate risk assessment and informing public health interventions.

In line with the previous studies [34,47,55,78], we report a significant association between air pollution and COVID-19 incidence and mortality. Comparatively, $PM_{2.5}$ emerged as the primary contributor to the increase in COVID-19 incidences, followed by SO_2, NO_2, PM_{10}, CO, and O_3 Consistent with our meta-analysis, previous research [77], identified PM_{10}, O_3, $PM_{2.5}$, NO_2 and CO as the top five pollutants most frequently associated with COVID-19 cases. These findings highlight the diverse range of air pollutants that may contribute to the severity of COVID-19, emphasizing the need for comprehensive strategies to mitigate air pollution and reduce COVID-19 risk. Furthermore, studies [41,42,79,80] have reported a significant link between $PM_{2.5}$ concentrations and COVID-19 occurrences corroborating our findings. This reinforces the importance of $PM_{2.5}$ as a key environmental risk factor for COVID-19 severity and underscores the need for targeted interventions to reduce $PM_{2.5}$ exposure and mitigate COVID-19 risk. Previously, a study [30] observed that increased NO_2 concentration was significantly correlated with increased daily COVID-19 incidences in 120 cities in China [30]. Similarly, other studies [42,44] documented a positive correlation between NO_2 concentration COVID-19 incidence in XiaoGan and Wuhan. These findings suggest that NO_2 may also play a significant role in COVID-19 risk and highlight the importance of addressing NO_2 pollution to reduce the risk.

The effect sizes for COVID-19 mortalities were greater for NO_2 followed by $PM_{2.5}$, PM_{10}, O_3 and CO. These findings from our meta-analysis emphasize the significant impact of air pollutants, particularly NO_2 and $PM_{2.5}$, on COVID-19 mortality. This highlights the urgent need for targeted interventions to reduce exposure to these pollutants. Furthermore, the consistent associations between PM_{10}, O_3, $PM_{2.5}$, and CO concentrations and increased COVID-19 mortality emphasize the importance of comprehensive air quality management strategies. Implementing measures to improve air quality could potentially reduce the risk of COVID-19 mortality, thereby protecting vulnerable populations and reducing the burden on healthcare systems [81]. Similar to our findings, previous studies have also reported a significant association between ambient air pollution and COVID-19 mortality. For instance, a study evaluating the connection between NO_2 exposure and new coronavirus fatality in European countries [82], linked COVID-19-related mortalities to long-term NO_2 exposures. Similarly, an empirical study carried out [83] in three major French cities correlated NO_2 concentration with COVID-19-related mortalities. Furthermore, it was [77] documented that $PM_{2.5}$ and NO_2 were most frequently correlated with increased deaths. Elsewhere [43], it was discovered that $PM_{2.5}$ was consistently related to increased death rates across multiple models, regardless of model adjustment for NO_2 or year. Several other studies have equally linked increased COVID-19 mortalities to PM_{10}, O_3, $PM_{2.5}$ and CO concentrations [23,40,47,78,84–86]. Regarding COVID-19 mortality, we could not make clear conclusions about SO_2 because of the small number of articles reported.

The association between ambient air pollution and COVID-19 incidence and mortality can be explained through various mechanisms. Particulate matter ($PM_{2.5}$ and PM_{10}) can enter the lungs through the nose and throat [87]. Thus, persons who are constantly exposed to PM are at risk of having increased chronic airway inflammation [88]. This type of inflammation may result in augmented production of mucus and lessened cilia activity, increasing the risk of developing respiratory diseases following SARS-CoV-2 infections [26,87]. Carbon monoxide (CO) is toxic and can cause lung damage [79] by binding more strongly to hemoglobin than oxygen [89], leading to hypoxic tissue injury or possibly death from asphyxia [89]. Exposures to SO_2 make patients more vulnerable to viral respiratory infections [90] due to prolonged immune-induced (via tumor necrosis factor, interleukin-8, and interleukin-17) inflammatory activities in the respiratory system [91]. Prolonged exposure to O_3 may lead to oxidative stress-induced free radical production. This may alter immune and cardio-respiratory systems, exposing individuals to adverse effects of SARS-CoV-2 infections [92]. Generally,

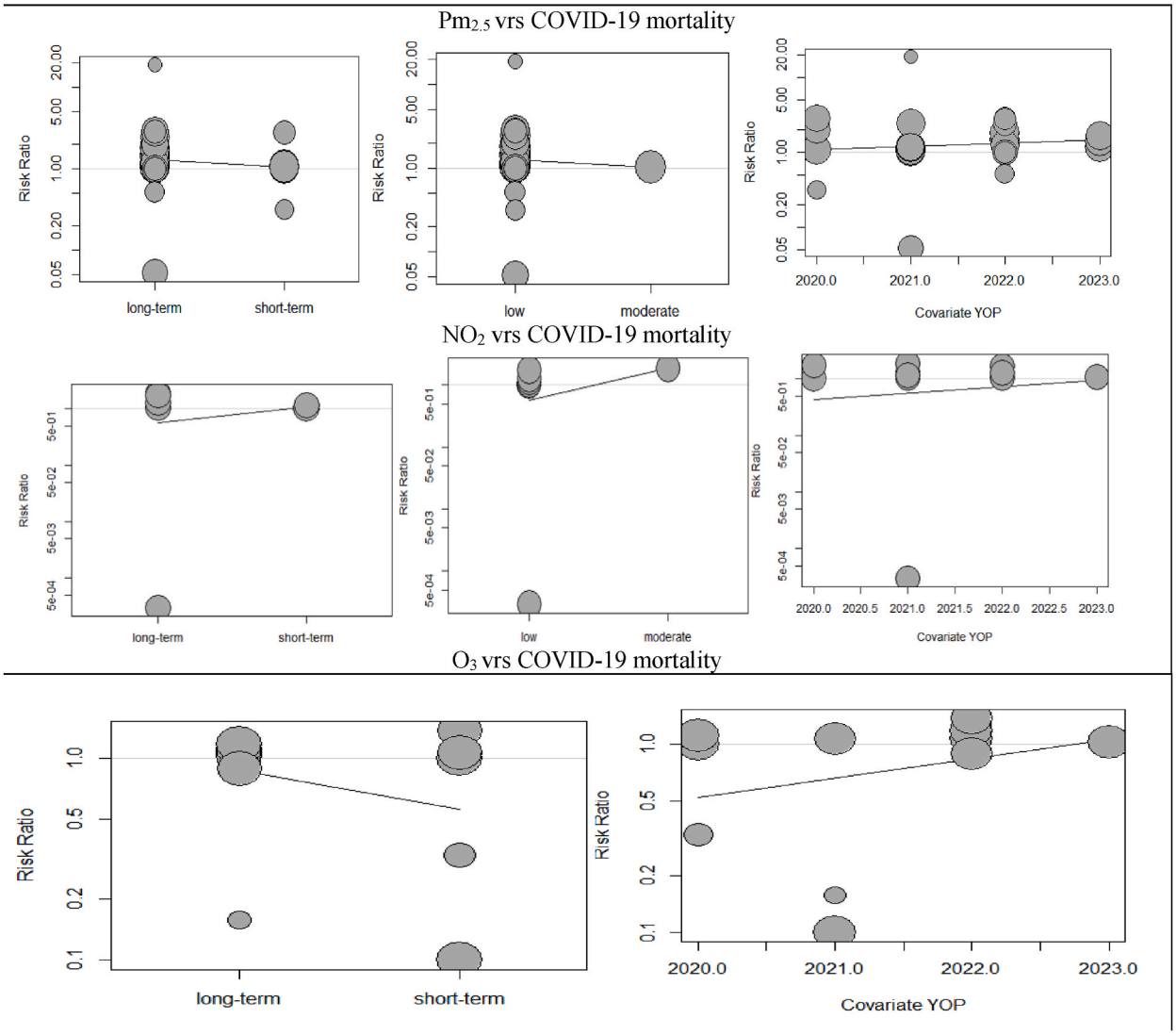

Fig. 3. Bubble plots showing results of the meta-regression model for air pollution COVID-19 mortality. From left to right: exposure window (long or short term), Risk of bias (low or moderate) and YOP (year of publication).

inflammatory response and oxidative stress are plausible biological mechanisms for the effect of air pollution on COVID-19. Pollutants may directly damage lung function via inflammation, immune response dysregulation, or oxidative stress, rendering patients more susceptible to SARS-CoV-2 infection [21,88,93,94]. Indirectly, air pollution can induce respiratory, cardiovascular, and metabolic diseases, which increase an individual's vulnerability to COVID-19 risks [44,88]. Furthermore, air pollution can elevate the ACE-2 on the surfaces of the respiratory tract, raising the potential to develop severe COVID-19 [33,94].

The current meta-analysis, by assessing the overall effect sizes for COVID-19 incidence and mortality, highlighted the importance of comparing these effects based on study design, exposure interval, and study region. Notably, the pooled effect sizes varied across these variables, suggesting that diverse populations may experience different benefits from specific COVID-19 control strategies. Our analysis found that the effect sizes for COVID-19 mortality were greater for long-term exposure compared to short-term exposure for all the pollutants, except for PM_{10}, (mortality). This suggests that chronic air pollution, prior to SARS-CoV-2 infection, may have contributed to the adverse effects of the disease [21,53,88,93]. This hypothesis is supported by previous studies [95], demonstrating a significant association between chronic PM exposure and COVID-19-related mortality. Furthermore, long-term exposure to NO2, PM10, and PM2.5 was found to significantly increase both COVID-19 incidence and COVID-19-related deaths [38,78,96]. These findings highlight the critical role of chronic air pollution in exacerbating COVID-19 outcomes. Research has shown that chronic respiratory illnesses, such as emphysema and bronchial obstruction, resulting from long-term air pollution exposure may increase individuals' vulnerability to SARS-CoV-2 infection and severity [97]. Studies further support the concept that long-term exposure to air pollution causes overexpression of ACE-2 (the receptor for SARS-CoV-2), leading to increased susceptibility to infection [33,87].

Chronic air pollution combined with SARS-CoV-2 exposure creates a "double-hit" to the lungs. This weakens tissue remodeling and activates a local inflammatory response, resulting in acute lung damage [87].

Although the effect of PM_{10} was higher with short-term exposure, the association was not significant, and there was low heterogeneity in the pooled estimates. Previously [40], attributed the large effect exhibited by O_3 to a chance association resulting from the lack of a significant positive association of the exposure-response combination following subgroup analysis. Several potential mechanisms for a short-term association have been postulated. Air pollution can cause changes in the mucosal membranes of the respiratory system, making the cells more vulnerable to infection. While these systems would mostly function during infection, incubation, and the initial stages of the disease, damage to the mucous membranes could result in adverse disease consequences. Simultaneously, there may be an elevated rate of complication of clinical problems in individuals who already have concomitant disorders when shortly exposed to pollutants [98].

The effect of air pollutants on COVID-19 incidence and mortality varied across countries, with some revealing high disease risks while others showing null association. The variation in effect sizes observed in our study across countries may be attributed to country-specific intervention measures for COVID-19. Moreover, non-COVID-related factors such as pollution levels, socio-economic status, demographics and national income may have influenced exposure-response association. These suggestions are supported by previous studies that proposed variations in the spatial correlation between air pollutants and COVD-19 risks in diverse regions [55]. Specifically [78], increased $PM_{2.5}$ correlated with an increase in COVID-19 case fatality rate in a study of 49 Chinese cities. The authors did, however, underline the likelihood of confounding factors due to city-specific differences in age, population prevalence of underlying comorbidities, and severity of public health infection control measures. Heterogeneity in effect sizes of exposure-response correlations was associated with differences in country climate and medical care service availability [55,99]. Elsewhere, increased hospital bed capacity correlated with lower COVID-19 mortality [84]. Nonetheless, some studies [23,86,95] have reported contrary findings.

These findings underscore the need for more region-specific epidemiological research relating air pollution to COVID-19 risks to elucidate the relevant factors and develop country-specific intervention policies and measures. The effect sizes for the association between air pollution and COVID-19 incidence and mortality were found to be higher in cohort and ecological studies compared to other study designs. Ecological studies comprise population or community as a unit of observation as opposed to an individual. These findings substantiate earlier studies that reported overestimation of accuracy in studies subjected to certain study designs. For instance, a relative risk of increased $PM_{2.5}$ concentration for hospital admission among American veterans with COVID-19 was discovered in cohort studies [100]. Similarly, cohort studies conducted in Spain [101] and Mexico City [85] documented a positive correlation between $PM_{2.5}$ and COVID-19 severity using slightly different methods. Therefore, including research with diverse designs in meta-analyses may have a significant impact on their conclusions. The results for subgroup differences revealed varied trends, indicating the effect sizes for the association between an air pollutant and COVID-19 risk may vary based on the exposure period, study design or region. These findings highlight the importance of specificity in interpretation of air pollution-COVID-19 study outcomes.

Heterogeneity was discovered in nearly all the exposure-outcome associations. This supports previous studies [102], which posit that heterogeneity is a commonly observed phenomenon of epidemiological studies on air pollution. The authors attribute this phenomenon to the difference in populations, exposures, and study conditions. The non-significant shift in heterogeneity observed following stratified analysis suggests that other unmeasured factors may be functioning as modifiers for the exposure-response correlations. Indeed, the meta-regression analysis revealed YOP, ROB and exposure window as some of the predictors of heterogeneity among studies reporting on COVID-19 incidences. The limited publication bias in the current study may be linked to an exhaustive list of individual research studies considered for this meta-analysis. A comparatively higher publication bias was observed in studies, which was associated with the failure to include a comprehensive scope of the research topic [34,47]. Publication bias revealed in some of the stratified analyses may be linked to the tendency of researchers to publish positive results ignoring the negative ones, potentially leading to an overestimation of the true exposure-response association. Other potential sources of biases in stratified analysis results include selection bias, study quality, confounding variables, and geographical bias [103]. Selection bias may arise from inclusion criteria, over-representing certain studies, like those from specific regions or with larger sample sizes. Variation in study quality, such as small sample sizes or non-randomized designs, could also bias results. Unaccounted confounding variables, like socioeconomic status or access to healthcare, may impact exposure-response association. Geographical bias may exist as most studies were from the USA and China. These biases highlight the need for cautious interpretation of results and further research to minimize potential distortions in findings [103]. Sensitivity analysis showed that the influence of single studies on the pooled effect size estimates was not statistically significant. This indicates that structural modeling assumptions did not influence the association measures.

The current study's strengths are: first, it allows us to delve into the relationship between air pollution and COVID-19 outcome by the pollutant, exposure period, study design and area of study. This is significant because the impacts of air pollution on COVID-19 results are expected to be moderated by diverse regional and contextual circumstances. Second, we present an initial meta-analysis with meta-regression about the association between air pollution and COVID-19 incidence and mortality, providing valuable insights for future research. Third, a subgroup analysis helped to assess the differential risk associated with exposure-response combinations in various aspects. Fourth, by investigating the link between AAP and COVID-19 risk, it enhances our understanding of how environmental factors affect public health. This knowledge aids policymakers in developing more effective strategies to mitigate air pollution's impact on COVID-19 outcomes, thereby improving public health. Finally, sensitivity analysis was performed to assess the impact of studies perceived to be of lower quality, and their inclusion was deemed appropriate for the transparency and robustness of our findings. Particularly, the inclusion of these studies in the meta-analysis provides a comprehensive assessment of available evidence and an enhanced understanding of the research landscape. Furthermore, the inclusion facilitates the exploration of publication bias and heterogeneity within the evidence body [67,104].

Despite the strengths, this study remains with some limitations. First, as an epidemiological observational investigation, it does not

demonstrate causality to support the formulated hypothesis. Therefore, while the meta-analysis may suggest a link between air pollution and COVID-19 risk, further research, including randomized controlled trials or longitudinal studies, is necessary to establish causality. Second, the majority of individual studies in the meta-analysis allocated similar levels of air pollution exposure to everyone residing in vast geographical areas. Thus, geographic disparities in exposure were not recorded. Without accounting for geographic disparities in exposure, the meta-analysis may have underestimated or overestimated the true association between ambient air pollution and COVID-19 risk, potentially leading to measurement errors. Third, long-term air pollution exposure research typically evaluates average exposure to air pollution over one or more years and links it to eventual health consequences. These studies presume that the population investigated stayed in the same geographical location to directly correlate the association between past exposure and later results. However, the assumption that individuals remain in the same location for extended periods may not hold, particularly during a pandemic. Population mobility could lead to misclassification of exposure, potentially biasing the results of the meta-analysis. Fourth, ecological studies are vulnerable to confounding variables. The inclusion of studies that lack control for individual-level confounders may have skewed the association between ambient air pollution and COVID-19 risk, potentially leading to overestimation or underestimation of the true relationship. Finally, the study lacks geographical diversity because the bulk of the included studies were published in the USA and China, which are not generalizable to other nations with diverse climates. Air pollution levels and COVID-19 prevalence may vary significantly between different regions and countries, making it difficult to extrapolate these results to a global population. It is worth noting that none of the 58 articles examined data from Africa.

5. Conclusion

In conclusion, there was a significant association between PM_{10}, SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO and O_3 concentrations and COVID-19 incidence and mortality. Subgroup analysis showed that the study design, exposure interval, and country influenced the magnitude and direction of the exposure-response associations. In the meta-regression model, YOP, ROB, and exposure period significantly predicted the association between air pollution and COVID-19 incidences. Thus, the effects of air pollution on COVID-19 risks are moderated by diverse regional and contextual factors. Notably, the presence of studies perceived to be of lower quality suggests that the current studies have significant limitations or that there is a lack of consistent and reliable findings. Nonetheless, this meta-analysis contributes a comprehensive understanding of air pollution-COVID-19 risks association, emphasizing the need for targeted intervention measures and policies informed by regional and contextual factors in management of the disease. More research is necessary to explore specific exposure-response relationships and investigate underlying mechanisms contributing to COVID-19 risks, predominantly multiple-pollutant exposures.

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Ethics declaration

Informed consent was not required for this study because it did not involve human participants or animals.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Harry Asena Musonye: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yi-Sheng He:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Merga Bayou Bekele:** Writing – review & editing, Investigation. **Ling-Qiong Jiang:** Writing – original draft, Investigation. **Fan Cao:** Writing – original draft, Investigation. **Yi-Qing Xu:** Writing – review & editing, Investigation. **Zhao-Xing Gao:** Writing – review & editing, Investigation. **Man Ge:** Writing – review & editing, Investigation. **Tian He:** Writing – review & editing, Investigation. **Peng Zhang:** Writing – review & editing, Investigation. **Chan-Na Zhao:** Writing – review & editing, Investigation. **Cong Chen:** Writing – review & editing, Investigation, Formal analysis. **Peng Wang:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Hai-Feng Pan:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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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