

Review

Does Polluted Air Increase COVID-19 Severity? A Critical Review of the Evidence and Proposals to Clarify a Potentially Dramatic Interaction

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Abstract

Several broad ecological analyses have been conducted, mostly in urban settings in Europe and North America, suggesting that air pollution may be associated with greater severity of SARS-CoV-2 infection. Following the identification of possible measurement and confounding biases, we review published studies using alternative study designs, whose main finding was a crude association between COVID-19 severity and PM_{2.5} long-term exposure. These preliminary studies are lacking adequate control for confounders and data for other major pollutants. Their results are inconsistent regarding short-term exposures, and virtually all were from high-income countries, limiting their generalizability. We consider the role of alternative study designs in elucidating further such a potential association, by using individual baseline and health outcome data and epidemiological methods to control for potential confounders. To further investigate the role of air pollution in COVID-19 severity between early 2020 and late 2021, we propose to design retrospectively case-control and case-crossover studies using data from public health and air pollution registries, as these may represent the best compromise between validity, reproducibility, and cost. Public health and air pollution registries may provide adequate data sources in industrialized countries and some middle-income countries, facilitating the study of air pollution and COVID-19.

Keywords: COVID-19; air pollution; epidemiology and environment; review literature

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1. Introduction

Air pollution, both indoor and outdoor, is considered by the World Health Organization as one of the major environmental threats to human health resulting in up to 7 million premature deaths each year [1–3]. Its multisystem injury results in considerable disease burden and increased mortality (Table 1). Some of the most relevant pollutants include particulate matter smaller than 2.5 µm or 10 µm (PM_{2.5} and PM₁₀), nitrogen dioxide (NO₂), nitrogen oxides (NO_x), sulfur dioxide (SO₂), and O₃. Finer particulate matter such as PM_{2.5} is of noteworthy concern as it is known to penetrate deep into the lungs and enter the bloodstream [1]. The Air Quality Index (AQI) has been used as an indicator comprising

several of the aforementioned air pollutant concentrations and forecasts [4]. The exposures considered in health impact research have encompassed the long-term (a year or longer) and the short-term (shorter, usually days or weeks).

Table 1. Main air pollutants, sources, and health effects.

Air Pollutant	Anthropogenic Sources	Health Effects ^a
Particulate matter (PM)	Motor vehicles Engines Industrial processes Construction sites Unpaved roads Cigarette smoke Biomass burning Agriculture	Cardiovascular disease Cerebrovascular disease Dementia Chronic obstructive lung disease Eye irritation and eye disease Cancer Adverse birth outcomes
Nitrogen oxides (NO _x)	Fuel-burning motor vehicles Power plants Residential fuel-burning	Reduced lung function Asthma Exacerbation of chronic respiratory and cardiovascular disease Cancer
Ozone (O ₃)	Nitrogen oxides Volatile organic compounds	Lung irritation and damage Aggravated chronic respiratory disease Immune system impairment
Sulfur dioxide (SO ₂)	Petroleum derivatives and coal burning Motor vehicles Refineries Power plants Paper mills	Headaches and anxiety Cardiovascular disease

^a All pollutants are related to increased all-cause mortality [1,5].

An association between higher air pollutant levels, especially PM_{2.5}, and higher aggregated COVID-19 concomitant mortality has been reported, suggesting a higher case-fatality ratio [6–8]. The published reports on such an association have so far been based mostly on so-called ecological studies conducted during the first year of the pandemic [9]. Ecological studies estimate the health effects of air pollution exposure at a population level (entire cities, regions, or countries) rather than at an individual level. Overall pollution levels are compared with group-level severe morbidity and mortality outcome data, such as hospitalization and death rates, usually from administrative sources.

If adequately analyzed, ecological studies allow the identification of a possible overall negative association between human health and air pollution, but their design does not allow any adjustment for confounding variables, nor accounting for heterogeneity in exposure and disease occurrence within the geographical areas used as the unit of analysis [10]. Illustrating these shortcomings, Villeneuve and Goldberg performed an analysis of county-level PM_{2.5} exposure and COVID-19 cumulative mortality in the USA, grossly adjusted for various county-level confounders (demographic and socio-economic data), over three time periods during the pandemic. Their study yielded an exposure–response curve whose shape changed substantially between time periods, in some instances being sinusoidal, in others linear. This finding suggests that associations identified with the ecological studies method may be spurious [11].

While acknowledging the relative ease and speed of ecological studies to detect a potential association between air pollution and severe morbidity or mortality, this method offers limited insight on potential mechanisms at work. Therefore, it is necessary to use other designs that offer systematic pathways to indicate that an association may be causal.

In addition, it is worthwhile to acquire a better understanding of the possible effects of different types of pollution, whether indoor or outdoor.

In seeking to identify current knowledge gaps and explore ways to address them, we formulate two critical research questions regarding the association between air pollution and COVID-19 severity. We discuss the importance of minimizing measurement biases and assessing the magnitude of confounding biases when conducting and analyzing individual-based epidemiological studies. We then review the latest large datasets provided by routine observational studies using individual-level data, which were established for other purposes than studying the association between air pollution and COVID-19 severity.

Finally, we propose two complementary study design options to attempt to clarify such a potentially devastating causal association.

2. Research Questions

- Among individuals infected with SARS-CoV-2, does exposure to higher levels of long-term outdoor air pollution worsen the course of infection and disease?
- Among individuals infected with SARS-CoV-2, does exposure to higher levels of short-term outdoor air pollution worsen the course of infection and disease?

2.1. Measurement Issues: Diagnostic Tests, Infection Severity, Air Pollution Levels

Failure to accurately determine SARS-CoV-2 infection severity or air pollution levels is likely to reduce the power of epidemiological studies to detect an association between the two, especially if the magnitude of the effect is small [12]. In well-enough resourced settings, the widespread availability of microbiological diagnostic means (PCR and, later, antigen testing), with both high sensitivity and specificity for SARS-CoV-2 in particular, provided the opportunities for discriminating between different pathogenic etiologies of clinical respiratory infections [13]. Infection severity can be assessed by outcomes such as respiratory failure, e.g., $\text{PaO}_2/\text{FiO}_2$ ratios or death. In less well-endowed settings, severity can be assessed by proxies such as hospital and ICU admission, which may be prone to various biases, depending on local admission policies and clinical judgment [14].

The measurement of air pollution data may be affected by the monitoring instruments' precision, calibration, and location, as well as weather conditions [15]. Integrating several data sources such as monitoring stations, land-use maps (e.g., depicting which areas are assigned to road traffic, residential, industrial, or agricultural use), and satellite measurements, when possible, will allow a more comprehensive assessment of the local factors governing air quality. The higher the spatial resolution used (i.e., the smaller the areas studied), the better individual exposures can be estimated [16].

2.2. Confounding Effects and Possible Strategies to Untangle Them

A confounder is a risk factor for the disease, i.e., COVID-19, that is also associated with the risk factor of interest, e.g., $\text{PM}_{2.5}$ pollution, but is not a consequence of it [17]. If not controlled for, confounders such as socio-economic status (SES) may be responsible for spurious associations and therefore require careful control for during data analyses.

The utilization of SES data is frequently contingent upon its availability, and the interpretation of related findings has shown to be quite variable across studies and health outcomes. One approach is to use individual markers, including employment status, occupational group, years of education completed, highest educational level attained, or individual or household income. Another approach is to use aggregated area markers, including average house value, percentage of single-parent families, or per capita income. [18]. Lower SES has been well described as a risk factor for severe COVID-19 outcomes [19]. It is also associated with geographical areas' living standards and pollution

levels and is one of the first confounding factors to control for in stratified or more complex analyses. Moreover, in interpreting results from imperfect primary data, one should bear in mind potential non-differential misclassification when assigning an average aggregated SES to an individual based on their area of residence as considerable heterogeneity may exist within the same area (neighborhood, community) [20]. Low-income people may reside in an affluent area and vice versa. Such non-differential misclassification will always tend to decrease the real magnitude of any association between air pollution and COVID-19 severity [21].

Exposure to air pollution stemming from indoor sources such as cooking fuel combustion, fireplaces, or tobacco smoke is known to increase the possible impact of outdoor sources [22]. If such data are available, indoor air pollution should be controlled for as a potential confounder in relation to outdoor pollution during data analysis. This allows the potential impacts of air quality to be specifically ascribed to outdoor pollution with a higher degree of accuracy.

Finally, age, smoking, and comorbidities such as hypertension, chronic lung and heart disease, or immune deficiency have been reported as risk factors for disease severity, including COVID-19 [23]. Hence, these variables, as well as SES, none of which are a priori consequence of air pollution, should also be considered as potential confounders in epidemiological analyses designed to study the association between air pollution and COVID-19 severity.

2.3. What Have We Learnt from Studies Other than Ecological Studies?

To assess and summarize the existing evidence on the potential association between air pollution and COVID-19 severity, which is not based on ecological studies, we conducted a scoping review, in compliance with the PRISMA guidelines, the protocol of which is presented in the Supplementary Materials. The objective of this scoping review was to screen, summarize, and identify knowledge gaps based on studies using individual-level outcome data. As the research questions are of a broad and exploratory nature, a scoping review was deemed to best accommodate the diverse array of pollutant exposures and severity outcomes, as well as study designs and methodologies. No quality appraisal was undertaken, as the aim was to garner research which could, as a first step, inform future research designs, not to include or exclude studies based on quality.

The review encompassed all publications between 2019 and 2023 that provided data on individual outcomes of COVID-19 in various populations. This referred to data obtained directly from individual study participants, including aspects such as disease presentation, hospitalization and death, and their estimated exposure to air pollution. We included all cohort, case-crossover, and case-control studies published in peer-reviewed journals, “gray” works, or presented in conference papers. Studies not designed to cover air pollution as an exposure, COVID-19 severity as an outcome, and/or using aggregated outcome data such as mortality or hospitalization rates were excluded. Papers not reporting original research were also excluded.

Following an initial identification of 160 reports, 102 were screened for eligibility, and a total of 22 reports were finally included in this review (Figure 1). Table 2 presents a summary of the included studies according to their main features. Data included setting, sample size, methodology, source population, measured exposures and outcomes, adjustment for age, sex, and other confounders, and lastly, a summary statement of their main findings. A total of 19 reports out of the 22 were registry-based cohort studies, 2 were case-crossover studies [24,25], and 1 was a case-control study [26]. A majority of $n = 16$ were considered high-quality as per the Newcastle-Ottawa Scale (Supplementary Table S1). A relevant proportion of cohort studies ($n = 8$ among a total of $n = 19$) ranked poorly on the

representativeness of their samples, while all except for one were favorably scored for their ascertainment of exposure and outcomes.

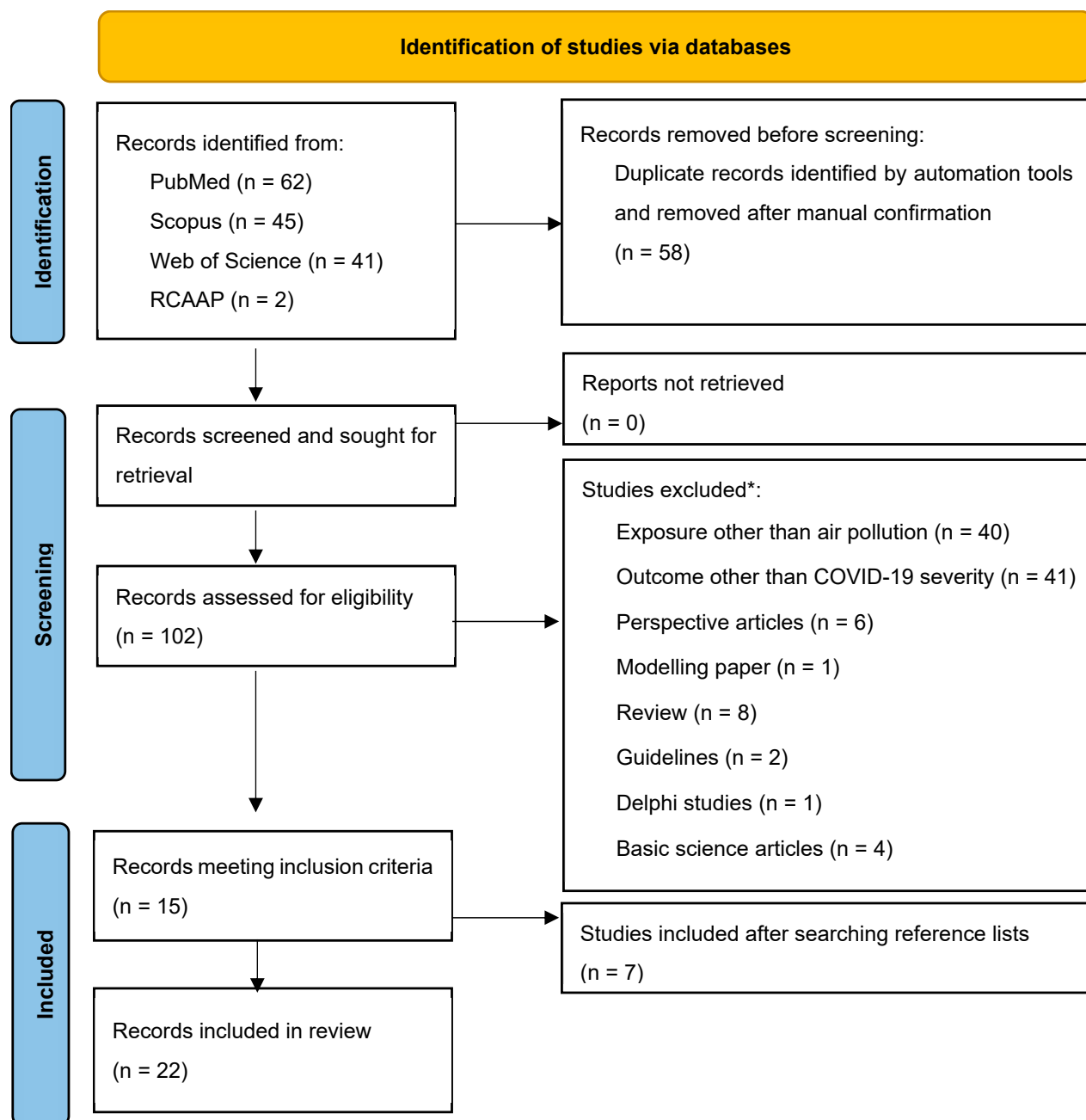


Figure 1. PRISMA flowchart of included studies included in the literature review. * Some studies were excluded for more than a single reason.

In all studies except for one [24], individual demographics were considered for Relative Risk or Odds Ratio adjustment. In the majority (n = 14), comorbidity data were also considered. SES data were mostly available as aggregated data in just over 50% of the studies (n = 13), either depicting community, county, or area-level income averages, education attainment levels, or unemployment rates. In three studies [27–29], individual-level SES data or proxies thereof were considered. Among these, one conducted in the USA portrays medical insurance as a proxy of SES [28], one in Britain relies on data from a biobank [29], and finally one in Denmark sourced income data from a national patient registry [27]. No control for SES was performed in 6 of the included studies [24–26,30–32].

Table 2. Summary of included studies.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Beloconi et al. [33]	2023 Cohort	Switzerland	n = 28,540	Hospitalized patients	PM _{2.5} and NO ₂ 1 sq km 5-year averages	ICU admission Death	Individual comorbidities, Aggregated socio-economics	PM _{2.5} associated with higher mortality (OR 1.16 [95% CI 1.04–1.28] but not with ICU admission NO ₂ associated with both (OR 1.17 [95% CI 1.05, 1.30] and 1.15 [1.03, 1.27] Results held only for the first pandemic wave	8 *
Bowe et al. [34]	2021 Cohort	USA	n = 169,102	US Armed Forces Veterans COVID-19 cases	PM _{2.5} 1 sq km 2018 averages	Hospitalizations	Individual demographics, race, Aggregated socio-economics	PM _{2.5} associated with a 10% (95% CI: 8–12%) higher risk of hospitalization	8 *
Bozack et al. [28]	2022 Cohort	New York City	n = 6542	Hospitalized patients	PM _{2.5} , black carbon and NO ₂ 1 km radius 2019 averages	Death ICU Intubation	Individual demographics, race, individual insurance	PM _{2.5} associated with death and ICU admission (RR 1.11 [95% CI 1.02–1.21] and 1.13 [95% CI 1.00–1.28] Black carbon and NO ₂ were not	8 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Chen C et al. [35]	2022 Cohort	Ontario	n = 151,105	Ontario’s Case and Contact Management System COVID-19 cases	PM _{2.5} , NO ₂ , and O ₃ average postal code-specific annual concentrations 5-year averages	Death ICU admission Hospitalizations	Individual demographics (age, sex, and race), healthcare access, Aggregated socio-economics	PM _{2.5} associated with hospital and ICU admission (OR 1.06 [95% CI 1.01–1.12] and death (1.09 [95% CI 0.98–1.21]) O ₃ associated with all three outcomes (1.15 [95% CI 1.06–1.23], 1.30 [95% CI 1.12–1.50] and 1.18 [95% CI 1.02–1.36] NO ₂ associated with hospital admission (OR 1.09 [95% CI 0.97–1.21])	8 *
Elliott J et al. [29]	2021 Cohort	UK	n = 473,550 (459 COVID deaths)	UK Biobank COVID-19 cases	PM _{2.5} , PM ₁₀ , and NOx Unspecified spatial resolution 2010 averages	COVID-19 mortality	Individual demographics (age, sex, and ethnicity), comorbidities, and socio-economics	No associations found between pollutants and mortality	6 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Chen Z et al. [36]	2022 Cohort	California, USA	n = 75,010	Kaiser Permanente (insurance company) COVID-19 cases	NOx Residential address 1-month and 1-year (previous to COVID diagnosis) averages	ICU admissions Intensive respiratory support (IRS) Death	Individual demographics (Age, sex, ethnicity), comorbidities, insurance type, Aggregated socio-economics	Exposure to non-freeway near roadway NOx associated with increased risk of IRS and ICU admission [OR (95% CI): 1.07 (1.01, 1.13) and 1.11 (1.04, 1.19), respectively]; increased risk of mortality (HR = 1.10, 95% CI = 1.03, 1.18)	6 *
Hoskovec L et al. [37]	2022 Cohort	Denver, USA	n= 55,273	Denver Public Health COVID-19 cases	PM _{2.5} Address-based inverse distance weighing 2019 averages	ICU admission Death	Individual demographics (age, sex, pregnancy, and ethnicity) Aggregated socio-economic data	Exposure to PM _{2.5} was associated with an increased risk of being hospitalized (OR 1.24 [95% CI 1.08–1.43]) and admitted to the ICU when combined with high levels of ozone (1.83 [95% CI 1.01–3.33]) and temperature (1.48 [95% CI 1.12–2.00])	6 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Hyman S et al. [38]	2023 Cohort	Manchester, UK	n = 313,657	Greater Manchester COVID-19 cases	PM _{2.5} , PM ₁₀ , O ₃ , NO ₂ , SO ₂ , and benzene 1 sq km grid 2019 averages	Hospitalization Death	Individual age, sex, ethnicity, BMI, smoking status, history of comorbidities Area-level socio-economic status	Significant associations with hospital admissions and PM _{2.5} , PM ₁₀ , NO ₂ (OR 1.27 [95% CI 1.25–1.30], 1.15 [95% CI 1.13–1.17], and 1.12 [95% CI 1.10–1.14]; death and PM _{2.5} and PM ₁₀ (OR 1.39 [95% CI 1.31–1.48] and 1.23 [95% CI 1.17–1.30])	8 *
Jerrett M et al. [39]	2023 Cohort	Southern California, USA	n = 21,415	Insurance network hospitalized patients	PM _{2.5} , O ₃ , NO ₂ , ultra-fine particulate matter (PM _{0.1}), PM chemical species, and PM sources 1 sq km 5-year averages	Death	Individual age, sex, ethnicity, comorbidities, insurance (Medicaid) Community-level socio-economics	PM _{2.5} associated with death among hospitalized patients HR = 1.12 [95% CI 1.06, 1.17]	6 *
Lavigne E et al. [24]	2023 Case-crossover	Alberta and Ontario, Canada	n = 78,255	Emergency Department visits of COVID-19 cases	PM _{2.5} , O ₃ , NO ₂ 10 sq km Daily averages over a 3-day period	Emergency Department visits	Aggregated sex and age No socio-economic data	Exposure to PM _{2.5} and NO ₂ were associated with ED visits for COVID-19 (OR 1.010; 95% CI 1.004 to 1.015 and OR 1.021; 95% CI 1.015 to 1.028)	4 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Lopez-Feldman et al. [40]	2021 Cohort	Mexico	No info on sample size	Mexico City confirmed COVID-19 cases	PM _{2.5} Mexico City municipalities short- (daily) and long-term (2000–2018)	Death	Individual age and sex Aggregated socio-economics	Long-term PM _{2.5} exposure related to death ($p = 0.048$)	7 *
Mendy et al. [41]	2021 Cohort	Ohio	n = 14,783	COVID-19 cases diagnosed at the University of Cincinnati healthcare system	PM _{2.5} $0.01^\circ \times 0.01^\circ$ grid 2009–2018 averages	COVID-19 hospitalization	Individual sex, age, and comorbidities Aggregated socio-economics	Long-term PM _{2.5} exposure is associated with increased hospitalization in COVID-19 OR: 1.18, 95% CI: 1.11–1.26	7 *
Pegoraro et al. [30]	2021 Cohort	Italy	n = 6483	COVID-19 cases diagnosed at GP's in Italy IQVIA Database	PM ₁₀ Italian regions 30-day period preceding the Index Date	Pneumonia cases	Individual age, sex, and comorbidities No socio-economic data	PM ₁₀ exposure associated with higher likelihood of pneumonia (OR 1.93 [95% CI 1.55–2.39])	6 *
Ponzano et al. [26]	2022 Case-control	Italy	n = 49	Multiple sclerosis patients diagnosed with COVID-19	PM _{2.5} , PM ₁₀ , and NO ₂ resolution not specified 2018–2020	Pneumonia cases	Individual age, sex, comorbidities, disease type, and treatment No socio-economic data	Higher long-term exposure to PM _{2.5} , PM ₁₀ , and NO ₂ increased the odds of COVID-19 pneumonia (OR 2.26 [95% CI 1.29;3.96], 2.12 [95% CI 1.22;3.68], and 2.12 [95% CI 1.22;3.69])	8 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Rigolon et al. [42]	2023 Cohort	Denver, USA	n = 18,042	COVID-19 cases diagnosed at Uni Colorado health system	PM _{2.5} Census block groups 2016	Hospitalization	Individual demographics, race, comorbidities; Aggregated socio-economics	Incidence Rate Ratio for hospitalization 1.19 [95% CI 1.151–1.230]	7 *
Di Ciaula et al. [32]	2022 Cohort	Apulia, Italy	n = 147	Hospitalized patients	NO ₂ and PM _{2.5} Unspecified spatial resolution 2 weeks before admission	Mortality	Individual demographics, comorbidities No socio- economic data	NO ₂ OR for mortality 1.045 [95% CI 1.003–1.088]; PM _{2.5} not significant	7 *
Kogevinas et al. [43]	2021 Cohort	Catalonia	n = 481	COVID-19 and non-COVID-19 individuals recruited from previous healthy cohorts	PM _{2.5} 100 sq m grids based on hybrid models 2018–2019 averages	Hospitalization	Individual demographics, BMI, comorbidities Aggregated socio-economics	Relative Risk Ratio for hospitalization 1.83 (1.01, 3.31) for NO ₂ ; 2.12 (1.13, 3.96)	7 *
English et al. [44]	2022 Cohort	California, USA	n = 3.1 million (n = 49,691 deaths)	COVID-19 cases obtained from the California Department of Public Health	PM _{2.5} 1 sq km 2000–2018 averages	Death	Individual demographics Aggregated race/ethnicity and socio-economics	Individuals living in the highest quintile of exposure had mortality risks 51% higher than those in the lowest quintile	7 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Bronte et al. [45]	2023 Cohort	Spain	n = 1548	Hospitalized patients	PM ₁₀ , PM _{2.5} , O ₃ , NO ₂ , NO, and NO _x Spatial resolution not specified 2019 averages	Death C Reactive Protein levels PaO ₂ /FiO ₂	Individual demographics and comorbidities Aggregated socio-economics	PM ₁₀ , NO ₂ , NO, and NO _x increased risk of death (5.33%, 3.59%, 10.79%, and 2.24% <i>p</i> < 0.05)	7 *
Zhang et al. [27]	2023 Cohort	Danmark	n = 3.7 million (n = 138,742 infections)	Nationwide cohort	NO ₂ , PM _{2.5} , PM ₁₀ , black carbon, and O ₃ 1 sq km complex land model 1979–2019 averages	Hospitalization Death	Individual age and sex, individual and aggregated socio-economics No comorbidities	PM _{2.5} and NO ₂ associated with hospitalizations (HR 1.09 (95% CI 1.01–1.17) and HR 1.19 (95% CI 1.12–1.27) and death (HR 1.23 (95% CI 1.04–1.44) and HR 1.18 (95% CI 1.03–1.34)	9 *
Kim H et al. [25]	2022 Case-crossover	Cook County, USA	n = 7462	COVID-19 death reports	PM _{2.5} and O ₃ Inverse-distance weighing interpolation 21 days before death	Death	Individual age, sex, race, and comorbidities No socio-economic data	Short-term increases in PM _{2.5} and O ₃ associated with increased risk of death (69.3% [95% confidence interval (CI): 34.6, 113.8] and 29.0% (95% CI: 9.9, 51.5), respectively)	7 *

Table 2. Cont.

Authors	Publication Year Study Design	Setting	Sample Size	Population	Environmental Exposure (Pollutants, Geographical Resolution and Periods)	Measured Outcome	Adjustment	Findings	Newcastle-Ottawa Scale
Izadi et al. [31]	2022 Cohort	23 countries	n = 14,044	Global Rheumatic Alliance Registry	Average monthly PM _{2.5} Country and US state	COVID-19 mortality	Individual demographics, comorbidities; characteristics of rheumatic disease; No socio-enconomic adjustment	PM _{2.5} increased odds of death (OR 1·10 per 10 µg/m ³ [95% CI 1·01–1·17])	7 *

ICU—Intensive Care Unit; OR—Odds Ratio; HR—Hazard Ratio. * refer to a rating on a scoring scale.

Considerable differences in spatial resolution should also warrant caution when estimating the effects of air quality exposures, as 1 square km was the most commonly used ($n = 7$), while 5 articles used much larger units [24,30,31,36,40], and others ($n = 4$) did not specify the resolution used [26,29,32,45].

The time span for long-term exposures varied widely between a single year (the most commonly used time span, $n = 9$) and 40 years [27]. Longer time spans cover longer periods of exposures, which might be of added value since the hazards of pollution are deemed to be cumulative but harbor a greater risk for information bias, as the chances that individuals may have moved residence are greater, rendering them liable to be assigned inaccurate exposures [42].

Measures of severity included the development of clinically diagnosed pneumonia, hospitalization, Intensive Care Unit (ICU) admission, and death. A total of 5 studies, based on community-dwelling COVID-19 patients, i.e., not hospitalized at baseline, studied hospitalization as an endpoint [27,33,34,36,37]. All these studies showed a crude, i.e., not controlled for socio-economic status, but only for individual demographics, positive association between increased severity and $PM_{2.5}$ exposure; three studies (out of a total of 3 studies in which such an association was analyzed) showed a crude positive association with NO_2 [27,33,35], and one study (out of 3) showed a crude positive association with O_3 [35]. In 2 out of 3 studies where ICU admission was an endpoint, $PM_{2.5}$ was found to be significantly predictive in a crude analysis [28,37], an association which held in only one of these studies after adjustment for demographics and health insurance [28].

Regarding mortality, a total of 14 studies used death as an endpoint. Community-dwelling individuals were recruited in 9 of these, while hospitalized patients were recruited in the remaining 5. Among these studies, a total of 10 reported a statistically significant crude association between $PM_{2.5}$ and mortality in analyses with varied adjustment methods for individual clinical characteristics and aggregated SES [25,27,28,31,33,35,36,39,40,44], whereas in 4 studies, no such significant association was found [29,32,37,45]. When reported ($n = 7$), statistical point estimates for the crude relative risk or odds ratio for mortality ranged from 1.10 to 1.39.

These analyses, characterized by very limited and heterogenous adjustments for confounders, if any, predominantly identified a statistically significant association with severity outcomes in instances where long-term $PM_{2.5}$ was the exposure concerned. This held for outcomes of death, hospitalization, and ICU admissions. The time span for long-term exposures varied widely between a single year (the most commonly used time span, $n = 9$) and 40 years [27]. There was no crude association for NO_2 , O_3 , and other pollutants, except for NO_2 and hospitalizations, where the small body of literature available was consistent in identifying a statistically significant association, albeit once more, with very limited and varied adjustment methods and virtually no control for SES. Evidence for an association between short-term exposures to any pollutants and SARS-CoV-2 infection severity was scarce and inconclusive as it was only analyzed in 6 of the 22 included studies, with conflicting results.

The general lack of individual SES data and the heterogeneity in spatial resolution pollution data present major limitations to the internal validity and consistency of overall results, respectively. Other major evidence gaps reside in few and inconsistent results regarding NO_2 and O_3 , the virtual absence of data from low- and middle-income countries (apart from Lopez-Feldman et al. who conducted a study in Mexico), possibly owing to resource constraints, global research inequalities, and/or competing health priorities. Lastly, there is a paucity of data on short-term exposures, which may be explained by the more cumbersome methodologies required in their study. These, however, may drive up

the risk of severe COVID-19 outcomes subsequently to peak emissions from sources such as traffic, wildfires, dust, and sandstorms, as suggested by an ecological study [46].

2.4. Beyond Ecological and Large Registry-Based Cohort Studies

Even though the mechanisms behind the putative association between air pollution and COVID-19 severity remain incompletely understood, several appear highly plausible. PM_{2.5} and NO₂ are known to induce airway inflammation and oxidative stress, processes that disrupt epithelial integrity and drive structural airway remodeling and hyperresponsiveness, thereby contributing to the pathogenesis of emphysema and the exacerbation of asthma [47–49]. Secondly, *in vivo* and *in vitro* evidence illustrate that alterations in airway microecology, macrophage function, and epithelium disruption following PM_{2.5} exposure impair microorganism clearance and facilitate cell infection [50]. Thirdly, diesel PM_{2.5}, one of the main components of aerial particulate material, highly upregulates the ACE2 receptor and the cofactor transmembrane protease serine 2 (TMPRSS2) in alveolar epithelial cells, thereby facilitating the entry of SARS-CoV-2 [51]. Lastly, a linear relation between serum levels of inflammatory markers such as IL-6, C reactive protein, fibrinogen, D-Dimer, and IL-1 [52,53] and exposure to air pollutants has been documented, both for long- [53] and short-term exposures [52]. The importance of inflammatory activation in clinically severe SARS-CoV-2 is widely documented [54], explaining the efficacy of immune modulators such as corticosteroids and tocilizumab (monoclonal anti-IL6 antibody) in reducing the mortality of COVID-19 respiratory failure. Such pathophysiological pathways underscore the need for robust epidemiological research that can establish the magnitude and relevance of these associations, namely those stemming from PM and NO₂.

Observational studies assessing the health effects of pollution encompass a number of different possible approaches.

Time series analyses on the one hand are useful in identifying and analyzing temporal trends and patterns relating exposures to outcomes [55]. However, such an approach typically relies on aggregated data (e.g., groups, population) analyzed at a certain temporal resolution (e.g., daily, monthly), preventing the analysis of individual-level associations.

Cross-sectional studies provide rapid, low-cost assessments of the prevalence of exposures and outcomes within a population at a given point in time and are, therefore, hardly appropriate in linking many variables of interest as the data used do not follow a temporal sequence.

Cohort studies present reliable and efficient designs when seeking to assess temporal relationships between environmental exposures and health outcomes, but they are resource-intensive and provide relevant data only after long time periods. Besides the ability to capture individual baseline variables, and by following individuals over time, such designs can capture their cumulative exposure to air pollution and subsequent clinical outcomes, such as a respiratory infection. They are, however, hardly suited to study SARS-CoV-2 infection if prospectively started at this point in time as SARS-CoV-2 infections and diseases have reduced dramatically compared to the pandemic levels. The same limitations apply to randomized controlled cluster trial studies using geographically separated distinct intervention, and comparison clusters present the most robust epidemiological evidence to ascertain a potential causal link between a given exposure/intervention and a given outcome. Unless the reduction in or protection from air pollution is planned in a stepwise manner over very large geographical distances between randomly selected regional clusters, their feasibility is currently precluded.

In case-control studies, individuals with a given health outcome, e.g., severe COVID-19 (cases) can retrospectively be included and anonymized from existing data collected during the pandemic and compared to anonymized individuals lacking the outcome

(controls) regarding their past environmental exposures. This is convenient when studying long latency periods between exposure and a given health impact. Compared to cohort studies, such studies are less costly and resource-intensive. Similarly, case-crossover approaches are one type of case-control studies where the exposure of cases during a period immediately preceding the outcome, the so-called hazard period, is compared with exposure during other periods, the so-called control periods. These approaches are particularly helpful in assessing short-term contributing factors. As cases act as their own controls, selected potential confounding variables are minimized by stable individual characteristics, but cumulative effects or complex exposure patterns cannot be captured.

To our knowledge, only a few case-control and case-crossover studies were actually conducted during the pandemic between early 2020 and mid-2022. The only case-control study identified during our research review addressed COVID-19 associated pneumonia as an outcome and was restricted to a group of patients suffering from chronic disease [26]. However, data for such designs can be assembled post hoc from hospital records and may offer a good compromise between internal validity, reasonable cost, adequately powered samples of cases and controls, and some degree of reproducibility in several geographic contexts. The major challenge will be to assemble series of cases and controls for which data on SES are available, i.e., available individually or based on individuals' area of residence. We propose that the case definition should include hard outcomes such as death or hospital admission from COVID-19 (often recorded as such) in order to avoid diagnostic bias. Time spans for historical exposures may encompass several years, bearing in mind that the longer these spans are, the longer the periods of exposures covered. This may bring a subsequent added value in capturing cumulative hazards of air pollution [56], but a greater risk for information bias as the likelihood that individuals may have moved residence is greater, leading to potential misclassification biases regarding air pollution exposures.

Case-crossover design in air pollution epidemiology is adequate to study the effects of varying short-term air pollution exposure on health outcomes with an abrupt onset, such as COVID-19 [42]. Case-crossover studies included in this review [24,25] both found crude associations between air pollution and COVID-19 disease severity for hazard periods ending on the outcome day and starting 3 days before, while several studies using aggregated clinical data found evidence suggesting an association using longer hazard periods [57,58]. A time-stratified case-crossover design, using conditional logistic regression analyses, could be an effective analysis strategy to assess the adequacy of different lag periods between exposure and severe disease while looking at exposure-response relationships to identify possible temporal patterns [59].

Last but not least, a possible significant hurdle to assemble cases and controls that are comparable, except for their disease status, is to gain access to available data. Many countries across the world monitored infection numbers, hospitalizations, and deaths in some regions along the pandemic (2020–2021). Data informing these reports are typically managed and stored by public health bodies or ministries of health departments. Even though these could theoretically present a source of valuable data for research purposes, many hindrances may be faced. In some countries, data may not be disaggregated at an individual level, which impairs the retrieval of pollution exposures and baseline demographics, SES data, and comorbidities. Furthermore, data protection and/or institutional policies can present additional hurdles for data acquisition.

3. Conclusions

Studying the impact of air pollution on COVID-19 severity is fraught with epidemiological and logistical challenges. Studies not based on ecological data have mostly used pre-established cohort samples, some tempting retrospectively to apply some adjustment

for selected potential confounding variables. Their findings suggest that exposure to long-term PM_{2.5} may be associated with increased COVID-19 severity but none in any conclusive way. Robust data on that possible association and on other pollutants and short-term exposure are completely lacking, as is data based on low- and middle-income countries. As a large amount of diagnostic and outcome data was collected and stored during the COVID-19 pandemic, there may be a window of opportunity to improve our knowledge on the role of air pollution in COVID-19 severity, a role which may possibly also be investigated for other lower respiratory tract infections when data are accessible. We propose that the current limited body of evidence can be improved by conducting case–control and case-crossover studies based on public health registry data, as these may constitute a medium to low-cost method based on data sources that, if accessible, are usually reliable.

Informative evidence should rely on measurements of both short- and long-term high-resolution exposures, across intersectional population samples, employing individual data to allow for confounder adjustment whenever feasible, and finally, using readily measured hard outcomes such as hospitalization, ICU admission, and death. This evidence could be very valuable in making a compelling case for increasing efforts to reduce air pollution exposures, a critical public health objective for mitigating avoidable morbidity and mortality.

Supplementary Materials: The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/world6040133/s1>, Scoping Review Protocol; Table S1: Newcastle-Ottawa Scale for included studies; Table S2: PRISMA Checklist.

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