COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Statement on the state of the science linking long-term air pollution exposure with SARS-CoV-2 infection and adverse COVID-19 outcomes

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Summary

Since the start of the pandemic in 2020, a large amount of research has been published linking air pollution and COVID-19 but these studies have varied in quality and content. Previous research has established that long-term exposure to air pollution contributes to the development and worsening of conditions such as cardiovascular and respiratory disease. These conditions have been shown to increase the risk of severe COVID-19 disease compared to healthy individuals. Previous research has also found that exposure to outdoor and indoor air pollutants can put people at risk of other respiratory infections and worsen outcomes. Hence, it has been proposed that air pollution may contribute to SARS-CoV-2 infection and COVID-19 severity.

This statement evaluates the current 'state of the science' on the association between air pollution and COVID-19. It focuses on individual-level studies linking long-term exposure to air pollution with SARS-CoV-2 infection and COVID-19 outcomes in human populations (epidemiological studies), and on studies of how air pollution might affect the body's response to the virus (mechanistic studies).

We conclude that, in the context of evidence for the effect of air pollution on lung infections more generally, long-term air pollution may be a contributory factor in worsening the symptoms of COVID-19. Currently, there are a limited number of good quality studies on COVID-19 and these studies are often inconsistent in their findings. Based on evidence reviewed, published up to the end August 2022, there is not enough epidemiological evidence to suggest that long-term exposure to air pollution increases the risk of infection with the SARS-CoV-2 virus that causes COVID-19 disease. There is more evidence that long-term exposure to $PM_{2.5}$ air pollution can increase the severity of COVID-19 disease once someone is infected with SARS-CoV-2, with an increased risk of hospitalisation following infection. The evidence for an increased risk of death from COVID-19 is less clear, with few studies available. A small number of studies are available relating to possible mechanisms and these suggest ways air pollution can alter the body's immune function and, consequently, increase risk of infection with the SARS-CoV-2 virus and disease severity. We did not find convincing evidence to support air pollution particles having an important role in transporting viable SARS-CoV-2 virus in the environment.

We acknowledge that studies linking air pollution and COVID-19 are difficult to conduct and hard to interpret. Studies need careful control for other factors that may influence exposure to the virus and severity of disease. Higher concentrations of air pollution are more likely to occur in more deprived areas containing individuals at higher risk of infection and severe disease. In addition, measures implemented to prevent the spread of the disease (for example 'lockdown', additional time working from home, wearing of facemasks) will affect both health outcomes and levels of air pollution.

We do not consider it appropriate to attempt to quantify the effects of air pollution on COVID-19 outcomes at present, but this may change as more evidence becomes available. More research

is required, particularly to help understand the influence that air pollution may have on susceptibility to, and recovery from COVID-19, immune function and the body's response to vaccination.

Introduction

Early in the pandemic, several studies suggested that short-term and long-term exposure to air pollution was a risk factor for both infection with the SARS-CoV-2 virus and severity of COVID-19. These early studies reported associations with larger effect estimates than established exposure-response coefficients typically seen for other health effects associated with air pollution. However, many of the early studies were either based on correlations or were ecological (group-level) studies, which did not fully account for other possible explanations for apparent associations between air pollution and COVID-19.

There are a number of methodological issues which make studies of associations between air pollution and COVID-19 outcomes difficult to conduct and interpret. Studies may be limited by biases relating to the ascertainment of health outcomes and different stages of the pandemic. Careful confounder control is important in these studies. Air pollution levels are likely to be higher in densely populated inner-city areas, which have higher levels of deprivation and may also have more individuals whose occupations put them at risk of SARS-CoV-2 virus exposure. These occupationally exposed populations can include higher proportions of minority groups, which may also be at risk for other reasons such as genetic factors (Downes et al. 2021), living in multi-generational households, or reduced vaccine uptake due to vaccine hesitancy. Some of the measures implemented to protect public health during the pandemic affected both health outcomes and levels of air pollution, introducing another possible source of confounding. Additional challenges are that not all exposures to SARS-CoV-2 lead to detectable infection using current antigen and antibody tests, and/or symptoms. These methodological challenges have been described in the literature, for example Villeneuve and Goldberg 2020 and Hansell 2021.

Possible causal pathways

Several potential causal pathways by which air pollution concentrations may affect both infection with the SARS-CoV-2 virus and COVID-19 disease severity have been suggested (Walton et al. 2021; Isaac et al. 2022). These relate to:

Virus exposure

Air pollution could increase exposure to SARS-CoV-2 if airborne particles act as a carrier for the virus. This would be most likely to lead to increased risk of infection but could also result in more severe disease (due to a higher viral load).

Increased risk of infection, following exposure

Both short- and long-term exposure to air pollutants can impair innate host defences against respiratory infections (EPA, 2016). Mechanisms include reduced effectiveness of the barrier function of the nasal and respiratory tract epithelium, impaired clearance of organisms by the mucociliary escalator, and alterations in the function of alveolar macrophages. Changes in innate immune cell function, such as those of macrophages and dendritic cells, may affect the ability of the immune system to initiate an effective response, causing a delayed response, and enabling viral load to increase, worsening severity. Alternatively, the kinetics of the response may be normal but its magnitude may be ineffective in limiting viral spread. A third possibility is that innate cells are programmed to drive inflammatory responses resulting in excessive cytokine production (a cytokine storm) and tissue damage. Factors such as age and comorbidities will further influence this.

Exposure to air pollution can upregulate expression of the cell-surface receptors (ACE2 and TMPRSS2) known to allow SARS-CoV-2 to enter cells, thus potentially facilitating enhanced viral entry and driving a higher viral load.

If air pollution affects the adaptive immune system (impacting lymphocytes and immune memory responses), it might make re-infection more likely.

Increased risk of severe symptoms, once infected

A hyper-inflammatory response has been implicated in the severe consequences of COVID-19 disease. Long-term exposure to air pollution induces a sustained inflammatory response within the lungs and elsewhere in the body, which might worsen impacts of COVID-19 disease following infection. Short-term exposure to air pollution can also cause a heightened inflammatory response, and so may also increase the likelihood of severe consequences of COVID-19 disease.

Long-term exposure to air pollution increases the likelihood of an individual having chronic respiratory or cardiovascular disease or can make these diseases more severe. Individuals with these conditions are at higher risk of more severe COVID-19 disease.

Disease states in the lung caused by air pollution exposure may induce greater stress or activation of the innate immune system making it less able to cope with subsequent exposures, for example SARS-CoV-2 virus, when compared to a non-diseased lung. Confounding variables, such as age, gender and lifestyle (for example physical activity status) might also influence immune response.

If air pollution affects the innate and adaptive immune system, it might alter the body’s ability to fight infection, shifting the kinetics of immune responses, enabling excessive cytokine production resulting in more severe or prolonged disease.

Exposure to air pollution may accelerate age-related decline in lung-associated immune function, increasing susceptibility to more severe or prolonged disease.

Effects on recovery from infection

It is plausible that the air pollution exposure affects recovery from respiratory infections including COVID-19 and development of post-infection sequelae and long COVID.

Vaccine effectiveness

If air pollution affects the innate response needed to programme adaptive immunity and directly impacts the adaptive immune system, with consequences for immune memory, it might affect vaccine effectiveness.

Previous COMEAP discussions

Early in the COVID-19 pandemic, COMEAP established a small working group of members to provide ad-hoc advice to government departments and agencies on issues such as the quality of the available studies, and the appropriateness of methods, used to investigate potential interactions between air quality and COVID-19.

COMEAP was also asked by the Air Quality Expert Group (AQEG) to consider the question ‘Based on what is already known about air pollutants as respiratory irritants or inflammatory agents, can any insights be gained into the impact of air quality on viral infection?’ COMEAP’s response to this question is included in AQEG’s report on the effects, on air quality, of interventions implemented to reduce the spread of COVID-19, published in July 2020 (Defra, 2020).

COMEAP held a workshop on 15 November 2021 on research on COVID-19 and air pollution. This provided an opportunity to discuss on-going research in which Members were involved at that time. This included reviews of the available literature as well as primary research.

Since then, more studies on this topic have been published, along with a number of literature reviews. This statement is intended to provide an overview of the evidence up to the end of August 2022 and a view on the ‘state of the science’ on this topic.

Our approach

We have based this evaluation of the 'state of the science' on literature reviews from authoritative sources and have also undertaken a narrative review of published studies of long-term exposure that use individual level data. We have commented on key quality issues such as study design (prospective cohort being the highest quality), study size, air pollution exposure assessment method and confounder control, but did not conduct a formal quality scoring. The statement focuses on studies of the effects of long-term exposure which used individual-level data. These are less prone to the limitation of short-term, time-series studies (discussed below) given a large enough cohort, proper follow-up and control for key confounders.

We have not evaluated studies of effects of short-term exposure. These types of studies generally employ a time-series analysis approach, and there was considerable heterogeneity in study design and findings reported in the literature. Early studies, necessarily, cover a short time-period and lack statistical power. They are also liable to confounding by interventions to reduce transmission of the virus. In addition, these studies may be limited by biases relating to the ascertainment of health outcome at different stages of the pandemic. It is likely that more recent short-term studies, with improved study design will become available and we will keep the evidence from short-term exposure studies under review.

We identified papers and reviews from a search of EMBASE, Ovid MEDLINE, Scopus and Web of Science, initially conducted for a systematic review MSc dissertation (Schneider, 2022) on air pollution and COVID-19 (see further details in Annex A), and a PubMed search by a Member using terms 'air pollution, COVID-19' and from Members' and Secretariat's own files up to the end August 2022. Although we identified most studies during this time period, we did not undertake a formal systematic review. We reviewed 17 studies of long-term air pollution exposure (using exposure metrics such as annual averages), which used individual-level data (the highest quality epidemiological study design). We examined literature reviews that have covered many of the other available ecological studies and the statement also includes a description of 4 key ecological studies relating to long-term exposure (2 early studies from the United States and 2 using UK data).

Consideration is also made of studies investigating mechanisms by which air pollution could influence SARS-CoV-2 infection and COVID-19 outcomes. Although the focus is on the epidemiological evidence for the effects of long-term exposure, much of the mechanistic evidence deals with short-term exposure. This is inevitable as these types of studies are easier to undertake experimentally. Nevertheless, effects seen in these studies can provide useful information on the underlying mechanism linking air pollution and COVID-19 disease.

Summary of evidence considered and members' views

Effects of lock-down (and re-opening) on air quality: implications for studies

Studies investigating the effects, on air quality, of restrictions to reduce the spread of SARS-CoV-2 have confirmed a reduction in NO_2 concentrations resulting from restrictions on travel. However, use of de-weathering techniques to remove the influence of meteorology suggest that NO_2 reductions in the UK during the first, and most restrictive, lockdown (mid-March to April 2020) were less than expected, that is that would typically arise in an average year given the estimated reduction in emissions (Defra, 2020) (Shi et al. 2021). There were also some suggestions that UK $PM_{2.5}$ concentrations during this first lockdown period were lower than they would have been in the absence of restrictions, although the effect had been somewhat masked by the influence of polluted air imported from Europe. The interpretation of the available data from different countries, and the role of secondary PM arising from NO_x emissions, is complicated by the fact that restrictions had been implemented at different times in different countries. A small increase in ozone concentrations, likely linked to the reduced NO_x emissions, was also reported.

We compared measured ambient concentrations of NO_2 and $PM_{2.5}$ for 2020 and 2021 with pre-pandemic values for 2019 in order to provide an overall indication of the possible impact of SARS-CoV-2 related lockdowns on the concentrations of these pollutants in the UK on an annual mean basis. Network mean concentrations have been compared for non-roadside sites in the UK Automatic Urban and Rural Network. The 2020/2019 ratio for NO_2 was 0.75 (71 sites) and the 2021/2019 ratio for NO_2 was 0.81 (65 sites). The 2020/2019 ratio for $PM_{2.5}$ was 0.80 (54 sites) and the 2021/2019 ratio for $PM_{2.5}$ was 0.79 (51 sites). These ratios are broadly consistent with estimates of changes in quarterly GB road traffic activity published by DfT, which suggest that overall traffic activity in 2020 was 76% of the 2019 value and 84% of the 2019 value in 2021. Emissions from most non-road transport activities in 2020 were also impacted having been reduced to roughly 90% of those in 2019, returning to close to normal in 2021. Aviation emissions were much reduced to about 40% of 2019 values in both 2020 and 2021 but these do not impact ground-level NO_2, $PM_{2.5}$ and ozone appreciably away from the airport perimeter.

Epidemiological studies investigating air pollution and COVID-19 outcomes can be broadly divided into studies of long-term air pollution exposure (using exposure metrics such as annual averages) and effects of short-term exposure (for example, daily averages). Studies of long-term exposure to air pollution consider exposures in years prior to the pandemic and do not take account of changes in exposure during the pandemic years. Studies of effects of short-term exposure examine associations with temporal (day-to-day) variations in concentrations that

occurred during the period of the pandemic. Measures taken to control the spread of the virus during the pandemic ('lock-downs' or travel restrictions) led to reduced concentrations of some pollutants. Hence, when considering short-term exposure, daily average concentrations of some air pollutants during periods of high infection rates may be lower than equivalent daily averages pre-pandemic. This statement focuses on studies of effects of long-term exposure.

All of the studies considered in this statement investigated outdoor pollutant concentrations. There is much less information available on concentrations of indoor air pollutants generally, including during the pandemic. For some pollutants, the main sources are from outdoors and therefore will increase or decrease in line with outdoor concentrations, although perhaps with a time lag. The decrease in ambient NO_x concentrations and increase in ozone concentrations in urban areas during the periods of travel restrictions has implications for indoor air quality. Indoor ozone drives numerous chemical reactions and the main source of indoor ozone is from outdoors (in the absence of ozone-emitting electrical equipment indoors, such as photocopiers and laser printers). Results from an indoor air quality model showed that a 30% increase in ambient ozone concentrations coupled to a 35% decrease in ambient NO_x concentrations (from measurements during the spring 2020 lockdown), led to a predicted 50% increase in indoor ozone concentrations for a typical UK residence (Defra, 2020) Furthermore, this increase in indoor ozone led to an increase in formaldehyde concentrations by about 30% and enhanced PM concentrations during indoor cleaning activities. In both cases, these enhancements were caused by an increase in chemical processing indoors. This is because ozone reacts with fragrance chemicals such as limonene in cleaning products, and the resultant chemistry produces formaldehyde and PM as reaction products (amongst others).

People's activities and time spent at home changed during and after pandemic restrictions, in response to guidance issued and restrictions imposed. To fully understand impacts of air pollution on COVID-19, it will be important to consider the extent to which exposure in various micro-environments (such as the home, office, street, and green spaces) might have changed. Exposure will depend on time spent in different microenvironments and changes in the pollution within these microenvironments. However, such detailed information is not currently available.

Studies reviewed have also not taken into consideration the impact of face masks in reducing personal exposure to air pollutants and SARS-CoV-2 virus. Many types of masks used during the pandemic did not provide a close facial fit and were ineffective at filtering PM and other air pollutants. However, some masks, which were widely used in some areas (notably in Asia) during the pandemic, can provide substantial particle filtration if fitted correctly, and will have reduced exposure both to $PM_{2.5}$ and the virus.

We also note that some attempts have been made to estimate health benefits arising from reductions in air pollutant emissions related to COVID-19 lock-down measures. We regard such estimates as likely to be very uncertain. Firstly, the relationship between outdoor pollutant concentrations and personal exposure is likely to have been very different from those in the

epidemiological studies from which the coefficients used in quantification were drawn. Secondly, baseline mortality and morbidity rates would also be different.

Epidemiological evidence

Systematic reviews

A literature review by Walton et al. 2021, which several COMEAP and Quantification of Air Pollution Risks in the UK (QUARK) members were involved in drafting, used a review for the European Parliament of air pollution and COVID-19 by Brunekreef et al. 2021 as its starting point and extended the review to include more recent literature up to May 2021.

The epidemiological (time-series) evidence investigating associations of COVID-19 cases, hospital admissions or deaths with short-term elevations in air pollutants up to May 2021 considered in the review was found to be mixed and generally considered of poor quality.

The review found that there were fewer epidemiological studies of associations with long-term air pollution exposure and most of these used an ecological design. However, the few studies with individual-level data had generally found statistically significant[1] associations for $PM_{2.5}$ with hospital admissions for COVID-19 (these individual-level studies are included in this statement and discussed further below). The review also argued that established links between air pollution and both heart and lung disease suggested that long-term exposure would make individuals more susceptible to severe COVID-19 symptoms.

In contrast to an early study suggesting that ambient particulate air pollution might increase transmission by acting as a carrier of the SARS-CoV-2 virus, subsequent studies suggested that particulate pollution was unlikely to be an important influence on this.

A more recent review and meta-analyses by Zang et al. 2021 of available studies published up to August 2021, most of which were of ecological design, reported associations between long-term average pollutant (NO_2 and $PM_{2.5}$) concentrations and COVID-19 incidence and mortality.

A subsequent systematic review and meta-analyses by Pickford et al. 2021 of mainly ecological studies included publications up to October 2020. It reported small but statistically significant associations between 10 $\mu g/m^3$ increases in long-term average $PM_{2.5}$ and NO_2 concentrations and increased mortality from COVID-19. Similarly, positive (adverse) associations were seen with COVID-19 incidence in studies of long-term exposure, however, the results were only statistically significant for NO_2.

Another review by Bourdrel et al. 2021 of evidence from in vitro, animal and human studies (including one study with individual-level data) published up to January 2021 reported similar

[1] 'Statistical significance' is at the 5% level whenever it is referred to throughout this document

conclusions to the ERG report. Although, noting that more evidence is required, it recognised that both short-term and long-term exposure may be important for increasing SARS-CoV-2 infection and COVID-19 severity and mortality through multiple mechanisms, including exacerbating chronic co-morbidities known to be risk factors for severe disease.

A systematic review (Hernandez Carballo et al. 2022) investigated the effects of air pollution on COVID-19 cases, severity and deaths in Europe and North America up to June 2021 and included 116 long and short-term exposure studies (including 8 with individual-level data included in this review and discussed below). The review concluded that long-term exposure to air pollution is most frequently positively associated with COVID-19 incidence, but for mortality the evidence is less consistent, with $PM_{2.5}$ and NO_2 most frequently associated with increased mortality. However, similar to Walton et al. 2021, the impact of short-term exposure to air pollution on COVID-19 was considered the most inconclusive due to the lower quality of the studies reviewed.

Ecological studies

Most of the early studies investigating exposure to air pollution and COVID-19 used an ecological design which relies on aggregate (group-level) rather than individual data for health outcomes, air pollution exposure and confounding factors. Such studies are generally faster to conduct than individual-level studies and are of public health relevance as they provide information about populations. However, the design has inherent biases when determining associations between exposure and health effects. Their use in determining causal inferences between ambient air pollution and COVID-19 outcomes has been questioned, for example, by Villeneuve and Goldberg, 2020. Studies using individual-level data are better able to adjust for confounding factors and, therefore, produce results at lower risk of confounding bias. We have, therefore, concentrated on evidence from individual-level studies in this statement.

We do consider ecological studies in this statement (i) in general terms, as they have contributed to systematic reviews of air pollution and COVID-19 outcomes and (ii) specific studies to inform COMEAP's view in this statement. These comprise 2 of the first high profile and well-conducted ecological studies from the United States, which were highly influential for future research, and 2 national-level ecological studies using UK data.

One of the earliest available and high quality ecological studies (Wu et al. 2020) investigated the effect of modelled $PM_{2.5}$ concentrations (from 2000 to 2016) on county-level COVID-19 mortality in early 2020 in the United States. The study reported a 11% increased risk of mortality for an increase in 1 $\mu g/m^3$ of $PM_{2.5}$. A second US study (Liang et al. 2020) covering a similar time period, but with better control for confounders, investigated both $PM_{2.5}$ and NO_2 concentrations. The study found a statistically significant increased risk of mortality with $PM_{2.5}$ of 19% (per 1 $\mu g/m^3$ of $PM_{2.5}$) from a single pollutant model, while the estimated risk reduced to 15% in a tri-pollutant model with NO_2 and O_3 and this result had borderline statistical

significance. It also found a significant increased risk of mortality with an increase in NO_2 concentration (16 to 17% per 2.6 µg/m^3) regardless of the control for other pollutants.

A more recent small-area (ecological) study in Scotland (Lee et al. 2022) described the effects of air pollution on hospitalisations and deaths over a longer time frame than the US studies (between 1 March 2020 and 31 July 2021), and with a much finer spatial resolution for exposure estimates. The study reported a statistically significant increased risk of hospitalisation (8 to 9%) and an increased risk of death (3 to 10%) for a 1 µg/m^3 increase in $PM_{2.5}$, which was sometimes statistically significant, depending on the model used. However, no statistically significant increased risk was found for NO_2. An ecological study in England (ONS, 2020), using a non-standard design that was prone to a number of biases, found associations between $PM_{2.5}$ concentrations and COVID-19 mortality rates, but these lost statistical significance when controlling for ethnicity. However, no statistically significant impact of $PM_{2.5}$ on COVID-19 deaths was found once ethnicity was controlled for. We note that a subsequent recently published ONS study[2], with an improved design and using individual-level data for London, also did not find significant associations between air pollution and COVID-19 deaths after adjustment for ethnicity and other confounders.

Individual-level studies

Most studies reviewed used administrative testing data on infection by SARS-CoV-2, and/or administrative data on hospitalisation and mortality from COVID-19 infections. In some studies, this data was linked into existing cohort databases. All of the studies with individual-level data that we examined adjusted for age, sex and, at either the individual or area level, at least one indicator of socioeconomic status. Many also adjusted for additional factors such as ethnicity, smoking, BMI and co-morbidities. We provide a visual summary of findings in forest plots (Figures 1 to 4).

We did not identify any studies investigating the effect of air pollution exposure on persistent symptoms post COVID-19 (‘long COVID’).

The only purpose-designed prospective population cohort study to investigate air pollution and COVID-19 was Kogevinas et al. 2021 This recruited ~9000 individuals in north-eastern Spain between June to November 2020. The majority were aged 40 to 65 years. Unlike other studies reliant on reverse transcriptase/polymerase chain reaction (PCR) antigen tests, which identify current infection only, the study included both clinical history for all individuals, and blood antibody tests (used as a measure of any past infection) in ~4100 individuals. Of the subset with antibody tests, 743 (18%) had positive tests, of whom 40% had had asymptomatic infections. Ambient air pollution at place of residence 2018 to 2019 was assigned using well-evaluated ELAPSE European air pollution models at high (100 m) resolution.

[2] Office for National Statistics (ONS) 2023. Coronavirus (COVID-19) mortality and long-term outdoor air pollution in London: September 2020 to January 2022

Air pollution levels were significantly associated with COVID-19 disease, with higher relative risks for more severe disease, but were not statistically significantly associated with infections. Adjusted relative risks[3] for COVID-19 disease in the full study population were 1.14 (95% CI:1.00,1.29) for NO_2 and 1.17 (95% CI:1.03,1.32) for $PM_{2:5}$ per interquartile range (IQR) corresponding to 11.62 µg/m^3 NO_2 and 1.86 µg/m^3 $PM_{2.5}$. In participants with antibody testing, RRs[3] for serologically confirmed SARS-CoV-2 infection were not statistically significant: 1.23 (95% CI 0.96, 1.56) and 1.19 (0.93, 1.52) for NO_2 and $PM_{2.5}$, respectively, possibly as a result of a lack of statistical power. This is potentially one of the most informative studies to date providing evidence on associations between air pollution exposure and COVID-19 outcomes. Strengths include a prospective cohort design, careful proactive ascertainment of outcomes that avoids selection issues inherent in use of administrative data, good confounder control and good quality air pollution exposure assessment. Limitations of the study are that it is relatively small, participation rate was 62%, it relates to earlier SARS-CoV-2 variants and was pre-vaccination. The study did not adjust for ethnicity, but almost all participants were of white ethnic origin.

Studies of long-term exposure association with SARS-CoV-2 infection

Seven studies using individual-level data investigated the link between long-term air pollution exposure and SARS-CoV-2 infection (Sheridan et al. 2022; Veronesi et al. 2022; Chadeau-Hyam et al. 2020; Travaglio et al. 2021; Casey et al. 2022; Kogevinas et al. 2021; Zhang et al. 2021). Four of these studies (Travaglio et al. 2021; Chadeau-Hyam et al. 2020; Zhang et al. 2021; Sheridan et al. 2022) relate to the UK; all used data from the UK Biobank cohort at sequential time points, that had been linked to government COVID-19 test data. The studies respectively included ~1450 participants who had been tested for COVID-19, of which 664 were COVID-19 cases (Travaglio et al. 2021); ~4500 individuals who had been tested for COVID-19, of which 1325 were cases (Chadeau-Hyam et al. 2020); ~7300 participants who had been tested for COVID-19, of which 1485 were cases (Zhang et al. 2021); and ~11,000 cases from a population of ~425,000 (only some of whom had been tested for COVID-19) (Sheridan et al. 2022). The most recent UK Biobank study (Sheridan et al. 2022) has been included in the forest plots (Figures 1 to 4).

Of the 4 UK Biobank studies, 2 (Sheridan et al. 2022; Travaglio et al. 2021) found statistically significant positive (adverse) associations between modelled $PM_{2.5}$ and NO_2 exposure and a SARS-CoV-2 positive test result, one study only found associations with NO_2 (Zhang et al. 2021), while one study (Chadeau-Hyam et al. 2020) did not find associations for either pollutant.

[3] The relative risks (RRs) for COVID-19 disease and infection were adjusted for the same set of core confounders as those in the forest plots (figures 1,3 and 4), with those in the forest plots additionally adjusted for smoking and physical activity. The RRs for COVID-19 disease and infection without additional adjustment have been included in the text for comparison with those for disease severity presented by Kogevinas et al (Kogevinas et al. 2021) without additional adjustment.

The 4 UK Biobank studies have potential misclassification bias in exposure assessment. Sheridan et al. 2022, Zhang et al. 2021 and Chadeau-Hyam et al. 2022 used European Study for Cohorts and Air Pollution (ESCAPE) air pollution concentrations modelled for 2010 applied to residential address at enrolment in 2006 to 2010 (10 to 15 years prior to infection) and did not account for changes in residential address (~25% of UK Biobank participants have moved). Travaglio et al. 2021 used both an average of 2018 and average of 2014 to 2018 air pollution measurements based on 1 km^2 modelled background concentrations. In addition, the association with infection is also likely to be biased in studies relying on data from the early phase of the pandemic when testing in the UK was only for symptomatic cases (Travaglio et al. 2021; Chadeau-Hyam et al. 2020; Zhang et al. 2021), an issue that may also apply in other countries.

Of the other 3 studies, a general population study in a northern Italian city (Veronesi et al. 2022) found statistically significant associations of SARS-CoV-2 infection with $PM_{2.5}$, PM_{10}, NO_2 and NO. A US study of pregnant women found statistically significant associations of SARS-CoV-2 infection with $PM_{2.5}$ in subgroup analyses only (Casey et al. 2022), while the prospective cohort study in Spain (Kogevinas et al. 2021), discussed above, found non-significant associations in analyses of all participants and in those with serology. The Italian study (Veronesi et al. 2022) linked citizens by residential address to modelled average annual exposure to air pollution ($PM_{2.5}$, PM_{10}, NO_2, NO and O_3) on a 1 km^2 grid and to regional health authority data on PCR testing for SARS-CoV-2 infection. After adjustment for confounders, all pollutants (with the exception of O_3) were associated with COVID-19 incidence in single pollutant models; the association being slightly weaker for NO_2 and NO compared to $PM_{2.5}$ and PM_{10}. The study by Casey et al. 2022 investigated the link between modelled $PM_{2.5}$ exposure in 2018 to 2019 on a 300 m^2 grid resolution and the risk of a positive PCR test for SARS-CoV-2 infection among pregnant women screened at delivery at Columbia University Medical Centre, in New York City (USA), with links to electronic health records for prior PCR test results. No association was reported between a 1 $\mu g/m^3$ increase in $PM_{2.5}$ exposure and ever testing positive for COVID-19; however, an increased risk (OR 1.62; 95% CI 1.04, 2.53) was observed for those using Medicaid (a measure of low SES).

Studies of long-term exposure association with COVID-19 hospitalisation and disease severity

We considered 10 studies of long-term exposure based on individual data that investigated the link between air pollution and hospitalisation and/or intensive care unit (ICU) admission (based on records of admission or treatment in hospital) for COVID-19 (Bowe et al. 2021; Bozack et al. 2022; Chen, Wang, et al. 2022; Chen, Sidell, et al. 2022; Mendy et al. 2021a; Mendy et al. 2021b; Kogevinas et al. 2021; Marquès et al. 2022; Chen et al. 2021; Sheridan et al. 2022). We set aside an early Spanish study (Marques et al. 2022) of 2112 patients with SARS-CoV-2 infection admitted to 515 Catalan hospitals April to June 2020 because air pollution concentrations were assigned to hospital of admission (not place of residence), effectively giving only 111 exposure measurements, leading to exposure misclassification. In addition, there was limited confounder adjustment. Of the remaining studies, 8, relating to 7 separate

datasets, reported at least one statistically significant association between air pollutant exposure and COVID-19 hospitalisation, while one study using UK Biobank (Sheridan et al. 2022) found no association. The forest plots for these studies are shown in Figures 1, 3 and 4.

There were 6 studies from the US relating to 4 datasets, all studying and finding associations of hospitalisation with $PM_{2.5}$. Two also considered other pollutants. One study (Bowe et al. 2021) used a US veterans database to create a cohort of ~170,000 COVID-19-positive veterans (identified from laboratory tests and clinical notes) with modelled $PM_{2.5}$ for 2018 linked to zip code of residence. They reported a 10% (RR 1.10; 95% CI 1.08, 1.12) increase in the risk of hospitalisation per IQR increase in $PM_{2.5}$ (1.9 μg/m^3). Two studies (Chen Z et al. 2021; Chen Z et al. 2022) used the same dataset, a retrospective cohort of ~75,000 COVID-19 cases identified (by positive PCR or diagnosis code for COVID-19 in March to August 2020) from the Californian Kaiser Permanente healthcare system. Air pollution exposure in the year before diagnosis was identified by inverse square weighting of air pollution monitoring data to place of residence. The one-year averaged exposures to both $PM_{2.5}$ and NO_2 were associated in single pollutant models with COVID-19 related hospitalisation, intensive respiratory support (IRS), and intensive care unit (ICU) admissions for COVID-19 infected patients (Chen Z et al. 2022). COVID-19 severity was also associated with NO_x concentrations arising from non-freeway traffic but not total NO_x or freeway NO_x (Chen Z et al. 2021). Another US study (Mendy et al. 2021a) investigated ~15,000 COVID-19 patients diagnosed 13 March 2020 to 30 September 2020 in the University of Cincinnati healthcare system linked through zip code of patients' residence with modelled $PM_{2.5}$ exposure at a 0.01° x 0.01° grid for 2009 to 2018. It found an association between long-term average concentrations of $PM_{2.5}$ and hospital admissions (OR 1.18; 95% CI 1.11, 1.26 per 1 μg/m^3). An earlier study using the same database, for 13 March 2020 to 5 July 2020 (Mendy et al. 2021b), using data for 1128 COVID-19 patients, only found significant associations between hospitalisations and $PM_{2.5}$ in those with pre-existing respiratory disease. A further study used data from 7 New York City hospitals (Bozack et al. 2022) to construct a patient cohort of 6,542 adults hospitalised with PCR-confirmed SARS-CoV-2 infection. This investigated associations between modelled $PM_{2.5}$, NO_2 (2018 to 2019) and black carbon (BC) (2017 to 2018) as assigned to a 100m^2 grid containing residential address, and severity. A borderline statistically significant association was reported between $PM_{2.5}$ and an increased risk of ICU admissions (RR 1.13; 95% CI 1.00, 1.28 per 1 μg/m^3 increase), while no such association was found for the risk of intubation. Neither NO_2 nor BC were associated with ICU admissions or intubation. Finally, in analyses stratified by ethnicity, significant associations with $PM_{2.5}$ were only seen for those of Hispanic ethnicity.

There was one study from Canada (Chen C et al. 2022) that used laboratory confirmed SARS-CoV-2 infection and hospitalisation administrative data in Ontario. Approximately 151,000 individuals, ≥ 20 years old and not residing in long-term care, with laboratory confirmed SARS-CoV-2 infection were studied. These were linked with modelled $PM_{2.5}$, NO_2, and O_3 at postcode of residence 2015 to 2019. The study included several individual and contextual covariates in the analyses. A statistically significant association was found between long-term exposure to $PM_{2.5}$ and hospital admissions (OR 1.06; 95% CI 1.01, 1.12) while there was a non-significant

association between intensive care unit (ICU) admissions (OR 1.09; 95% CI 0.98, 1.21) and $PM_{2.5}$ (per IQR 1.7 μg/m^3). Ozone was also associated with a statistically significant increased risk for both outcomes (hospital admissions, and ICU admissions), but no associations were observed for NO_2.

There were 2 European studies included in our considerations, after Marquès et al. 2022 was removed for the reasons described above. The Spanish Catalan prospective cohort described above (Kogevinas et al, 2021) reported a positive and statistically significant association between pre-pandemic $PM_{2.5}$ exposure and severe COVID-19 disease in the full cohort (RRR 1.51; 95% CI 1.06, 2.16 per IQR of 1.86 μg/m^3 $PM_{2.5}$.)[4], defined as where the patient was either admitted to hospital or required oxygen therapy. In contrast, a non-significant association was found for NO_2 with COVID-19 severity (RRR 1.26; 95% CI 0.89, 1.79 per IQR of 11.62 μg/m^3). In the participants with antibody testing allowing serological confirmation of SARS-CoV-2 infection, RRRs of 2.03 (95% CI 0.99, 4.17) and 1.84 (95% CI 0.94, 3.58) were reported for $PM_{2.5}$ and NO_2, respectively.

The only UK study to look at hospitalisations (Sheridan et al. 2022) used data from the UK Biobank cohort to evaluate the association of modelled air pollution ($PM_{2.5}$, PM_{10}, NO_2 based on 2010 data and place of residence, the limitations of which are discussed above) and COVID-19 outcomes over the pre-vaccination time period. After adjusting for confounders and COVID-19 risk factors, no association was found between $PM_{2.5}$ or NO_2 and COVID-19 hospitalisations, with a relatively small sample size (n=1,598 hospital admissions).

Studies of long-term exposure association with COVID-19 mortality

Eight of the individual-level studies looked at associations between long-term exposure to air pollution and COVID-19 mortality. We set aside a study (Marquès et al. 2022) of patients in 15 Spanish hospitals due to the limitations in the study design relating to case identification and statistical analyses (as noted above in paragraph 44). Of the remaining studies, 5 (relating to 4 separate datasets) (Bozack et al. 2022; Chen Z et al. 2021; Chen Z et al. 2022; Chen C et al. 2022; Lopez-Feldman et al. 2021), reported statistically significant associations of at least one pollutant with COVID-19 mortality. Two other studies, both using UK Biobank data, found no significant association with COVID-19 mortality (Elliott et al. 2021; Sheridan et al. 2022). The forest plots can be seen in Figures 1,3 and 4 below, and details of the studies are included in following paragraphs. We have excluded Lopez-Feldman et al. 2020 from the forest plots as limitations with the air pollution exposure assessment in the study design make direct comparisons with the other studies difficult (discussed in paragraph 50). Both Lopez-Feldman et al. 2020 and Elliott et al. 2021 only looked at mortality as an outcome. However, 5 studies (relating to 4 datasets) looked at hospitalisation as well as mortality (Bozack et al. 2022; Chen Z

[4] This association is based on multinomial regression models that estimate RRRs, with 3 categories for the dependent variable: (i) non-cases, (ii) mild cases (people with prior positive diagnostic test for SARS-CoV-2 infection or with ≥ 4 COVID-19 related symptoms combined with being in contact with a diagnosed COVID-19 case), and (iii) severe cases (hospitalisations or ICU admissions or oxygen therapy without admission.

et al. 2021; Chen Z et al. 2022; Chen C et al. 2022; Sheridan et al. 2022), with findings concordant in 3 of these 4 datasets in terms of showing significant associations (Bozack et al. 2022, Chen Z et al. 2021, Chen Z et al. 2022) or no significant associations (Sheridan et al. 2022) across both hospitalisation and mortality.

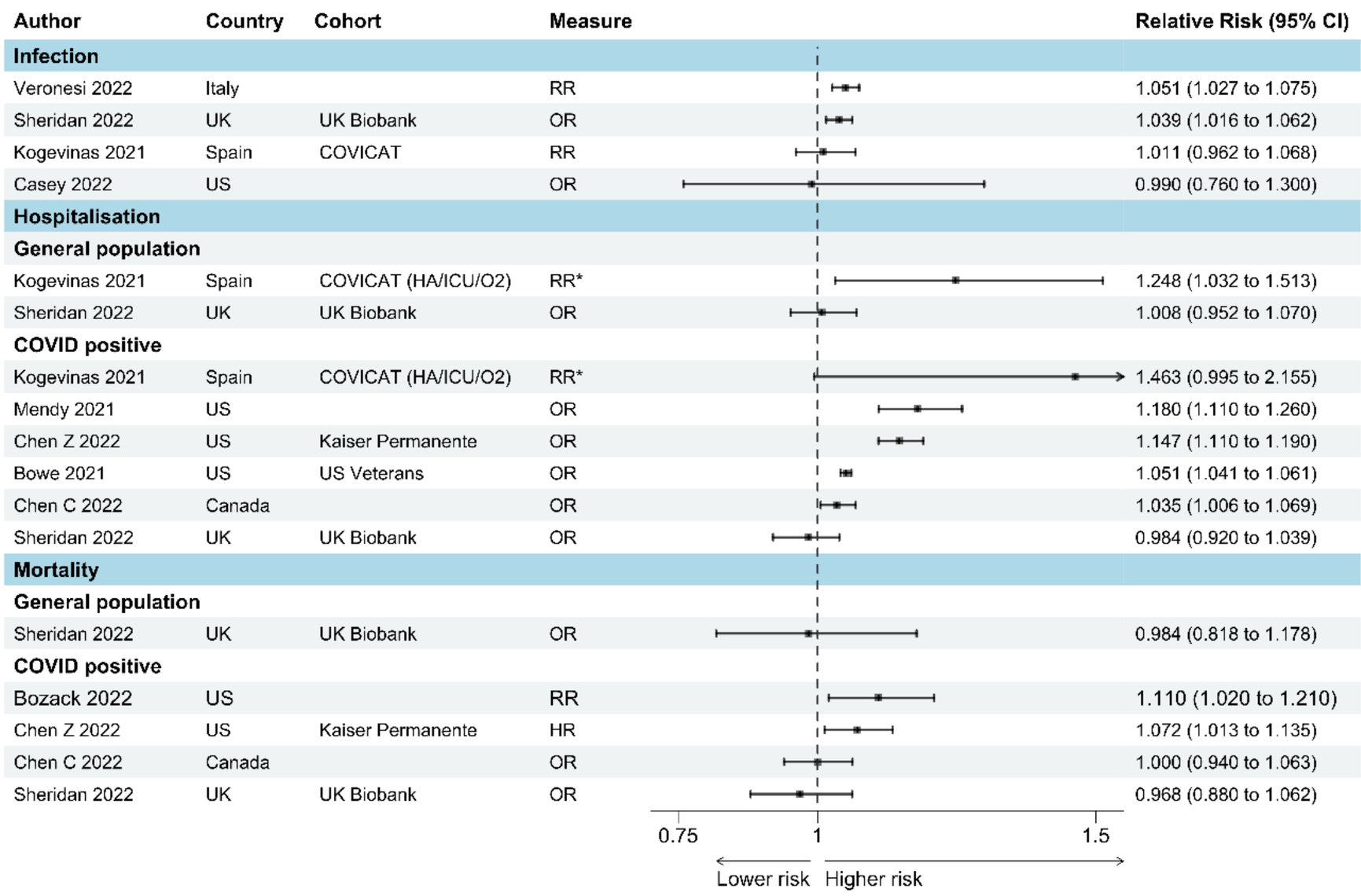
A study from Mexico relating to early in the pandemic (Lopez-Feldman et al. 2020) used Ministry of Health data on confirmed COVID-19 cases in Mexico City linked to mortality data up to 7 October 2020. Total number of deaths is not stated. There will have been selection bias in case identification – it was noted that the number of COVID-19 tests performed was very low, due to a decision by the government not to perform widespread testing. Also, the case fatality was 10 to 11% (high), suggesting more severe cases are more likely to have been tested. The main analysis used a global dataset of modelled $PM_{2.5}$ air pollution estimates averaged to one of 76 municipalities for 2000 to 2018, which will be prone to some exposure misclassification (exposure was not assessed at the residential address-level and did not account for residential history). Analyses found that an increase of 1 $\mu g/m^3$ $PM_{2.5}$ long-term exposure was associated with a 0.77% increase in the probability of dying.
Elliott et al. 2021, using data from the UK Biobank, also in the earlier part of the pandemic, examined associations between 459 COVID-19 deaths between 31 January and 21 September 2020 (from linked mortality data) and modelled $PM_{2.5}$, PM_{10} and NO_x concentrations in 2010 at place of residence at enrolment. The study found associations between COVID-19 mortality and age, male sex and Black ethnicity, as well as comorbidities and oral steroid use, but not air pollution in multivariate models. A previously discussed UK Biobank study (Sheridan et al. 2022) considered March to December 2020 with 568 COVID-19 deaths. The study did not find associations of mortality with $PM_{2.5}$, PM_{10} or NO_2 air pollution after adjusting for individual-level covariates (including age, sex, income and ethnicity), area-level deprivation and urbanicity. The pattern of loss of statistical significance after adjustments was similar for both hospitalisation and mortality outcomes.

The remaining 6 studies also investigated hospitalisations and details are given above. Two US California studies (Chen Z et al. 2021; Chen Z et al. 2022) used data from the Californian Kaiser Permanente health care system. Chen Z et al. 2022 found a statistically significant association between one-year average exposure to $PM_{2.5}$ and the risk of mortality in a single pollutant model (HR 1.11; 95% CI 1.02, 1.21 per 1-SD 1.51 $\mu g/m^3$) and in a two-pollutant model (HR 1.14; 95% CI 1.02, 1.27 per 1-SD 1.51 $\mu g/m^3$), adjusted for NO_2. No associations were seen for annual averages of NO_2 or ozone. COVID-19 mortality was associated with NO_x concentrations arising from non-freeway traffic but not total NO_x or freeway NO_x (Chen Z et al. 2021).

The study of patients hospitalised with PCR-confirmed SARS-CoV-2 in New York (Bozack et al. 2022) found a statistically significant association between a 1 $\mu g/m^3$ increase in $PM_{2.5}$ and increased risk of mortality (RR 1.11; 95% CI 1.02, 1.21). Neither NO_2 nor BC were associated with mortality. The study (Chen C et al. 2022) of a cohort in Ontario with confirmed SARS-CoV-2 infection found a statistically significant association between long-term exposure to ozone and mortality (consistent with results for hospitalisation from the same study), but not for $PM_{2.5}$

(inconsistent with results for hospitalisation). No significant associations were seen for either mortality or hospitalisation with NO_2.

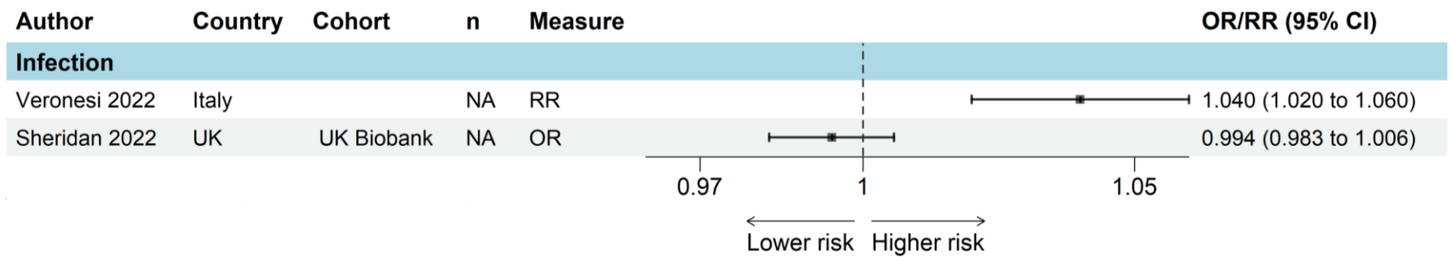
Figure 1. Forest plot showing association of $PM_{2.5}$ exposure and risks of SARS-CoV-2 infection, and COVID-19 hospitalisation and mortality



All estimates are per 1 μg/m^3 increment. All estimates are from single-pollutant models except those from Chen Z 2022, where estimates from both single-pollutant and two-pollutant models (highlighted in dark blue) are included. RRR stands for risk ratios ratio. Coefficients used in the forest plots are from analyses that are most directly comparable and are not necessarily exactly the same as the text.

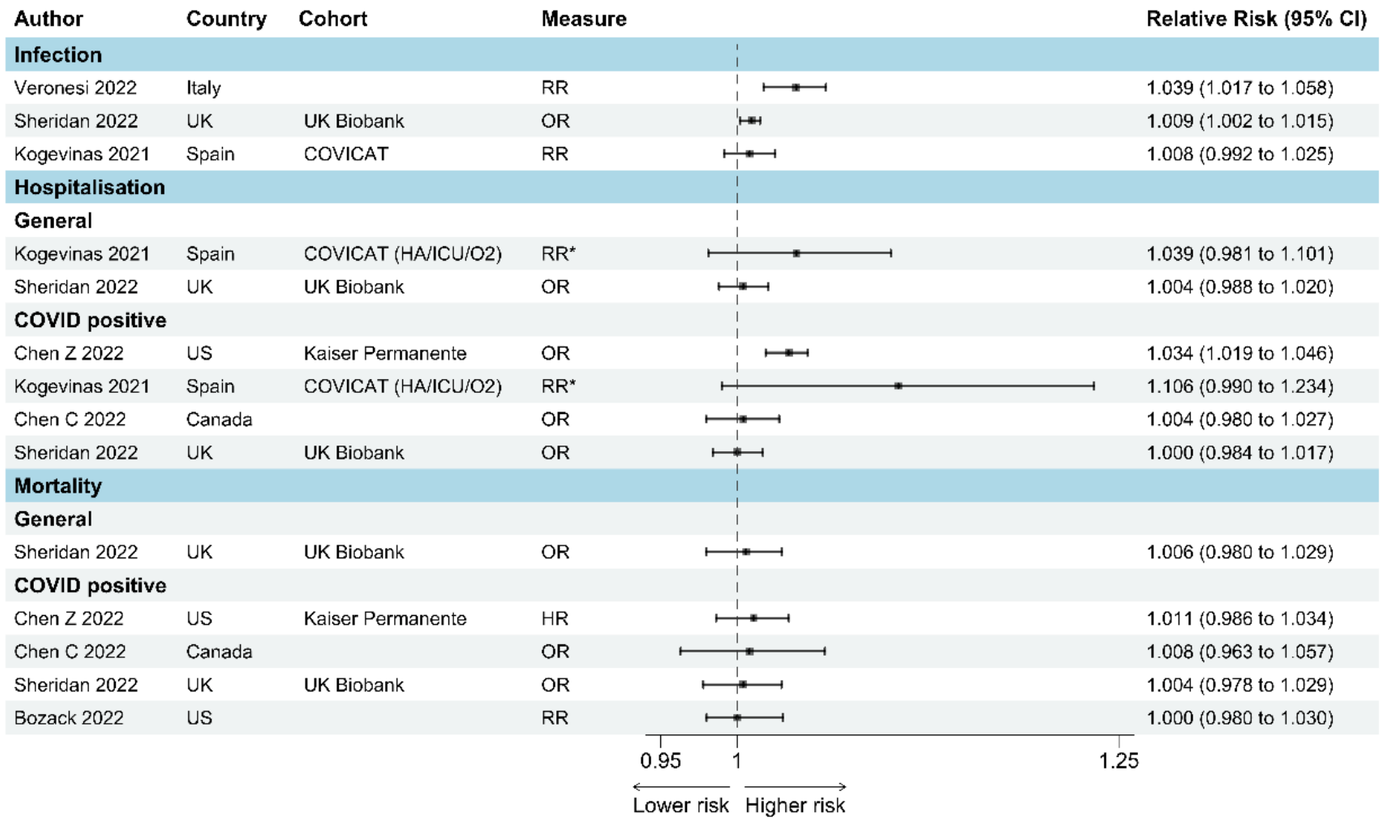
*This association is based on multinomial regression models that estimate risk ratios ratio (RRR), with 3 categories for the dependent variable, that is, non-cases or mild cases (people with prior positive diagnostic test for SARS-CoV-2 infection or with ≥ 4 COVID-19 related symptoms combined with being in contact with a diagnosed COVID-19 case or severe cases (hospitalisations or ICU admissions or oxygen therapy without admission). Since the severe cases are those people that have been hospitalised and it is compared with those that have not been infected (including mild cases), this is equivalent to an RR.

Figure 2. Forest plot showing association of PM_{10} exposure and risks of SARS-CoV-2 infection



All estimates are per 1 μg/m^3 increment and are from single pollutant models. Coefficients used in the forest plots are from analyses that are most directly comparable and are not necessarily exactly the same as the analyses commented on in the text.

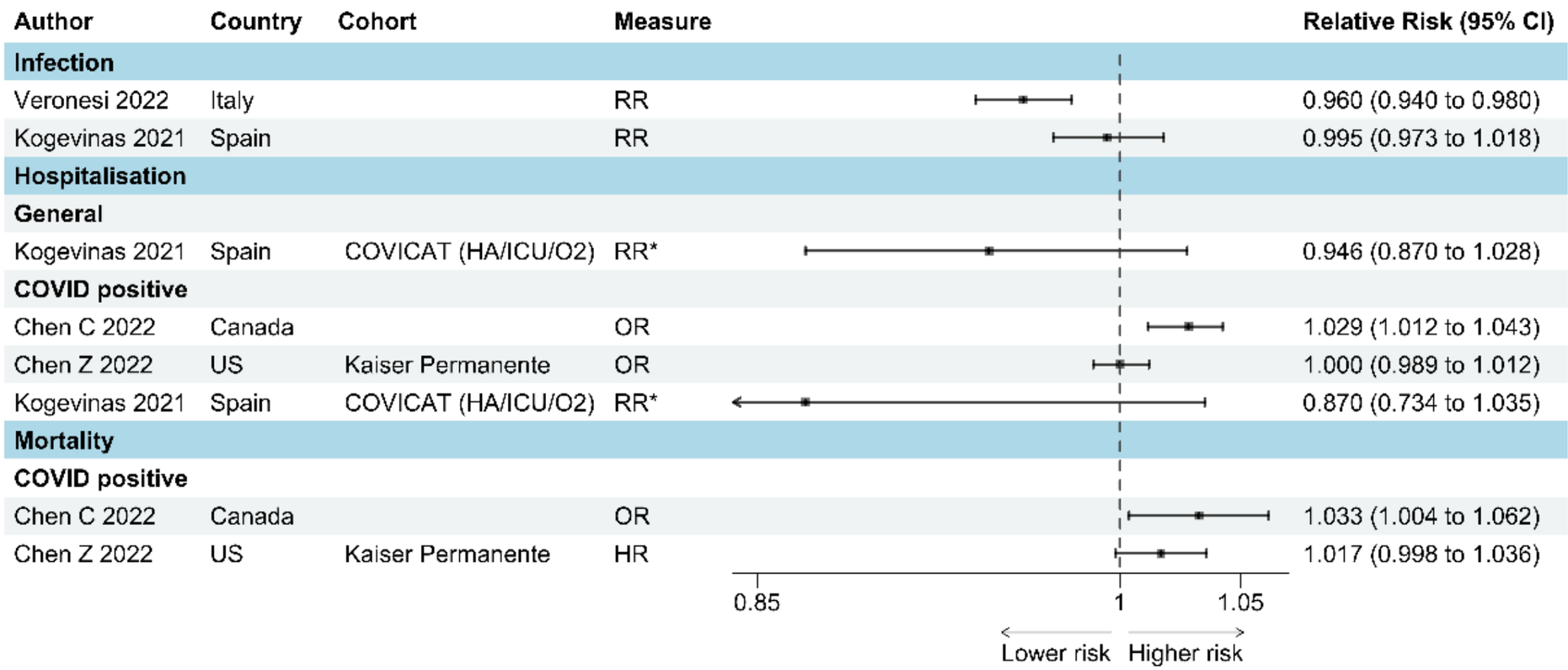
Figure 3. Forest plot showing association of NO_2 exposure and risks of SARS-CoV-2 infection, and COVID-19 hospitalisation and mortality



All estimates are per 1 μg/m^3 increment. All estimates are from single-pollutant models except those from Chen Z 2022, where estimates from both single-pollutant and two-pollutant models (highlighted in dark blue) are included. RRR stands for risk ratios ratio. Coefficients used in the forest plots are from analyses that are most directly comparable and are not necessarily exactly the same as the text.

*This association is based on multinomial regression models that estimate risk ratios ratio (RRR), with 3 categories for the dependent variable, that is, non-cases or mild cases (people with prior positive diagnostic test for SARS-CoV-2 infection or with ≥ 4 COVID-19 related symptoms combined with being in contact with a diagnosed COVID-19 case or severe cases (hospitalisations or ICU admissions or oxygen therapy without admission). Since the severe cases are those people that have been hospitalised and it is compared with those that have not been infected (including mild cases), this is equivalent to an RR.

Figure 4. Forest plot showing association of O_3 exposure and risks of SARS-CoV-2 infection, and COVID-19 hospitalisation and mortality



All estimates are per 1 μg/m^3 increment and are from single pollutant models. Coefficients used in the forest plots are from analyses that are most directly comparable and are not necessarily exactly the same as the text.

*This association is based on multinomial regression models that estimate risk ratios ratio (RRR), with 3 categories for the dependent variable, that is, non-cases or mild cases (people with prior positive diagnostic test for SARS-CoV-2 infection or with ≥ 4 COVID-19 related symptoms combined with being in contact with a diagnosed COVID-19 case or severe cases (hospitalisations or ICU admissions or oxygen therapy without admission). Since the severe cases are those people that have been hospitalised and it is compared with those that have not been infected (including mild cases), this is equivalent to an RR.

Studies of vaccine effectiveness

There is limited evidence of the influence of exposure to air pollution on the efficacy of the SARS-CoV-2 vaccine. A small study (Zhang et al. 2022) looked at daily exposures to air pollution ($PM_{2.5}$, PM_{10}, SO_2, NO_2, O_3 and CO) and plasma neutralising antibody (Nab) titres of an inactivated SARS-CoV-2 vaccine in vaccinated healthcare workers. It reported that daily exposure doses of air pollutant were significantly negatively associated with plasma Nab, suggesting that exposure to air pollution may inhibit Nab expression and reduce immunity. Another population-based cohort study (Kogevinas et al. 2023, originally reported as a International Society for Environmental Epidemiology conference abstract in 2022) in Catalonia in May to June 2021 measured immunoglobulin antibodies in blood samples against 5 viral target antigens and estimated pre-pandemic air pollutant exposure at place of residence. Among 927 vaccinated adults not infected with SARS-CoV-2, higher exposure to $PM_{2.5}$, NO_2 and black carbon before the pandemic was associated with a lower vaccine antibody response, with an inverse pattern for ozone. This plausible effect on vaccine immune response and protection against future infection and severity requires further investigation.

Transmission of SARS-CoV-2 by particulate air pollution

The SARS-CoV-2 virus is recognised as spreading from an infected person's mouth or nose in small aerosolised droplets following coughing, sneezing, or breathing. These particles range in size from larger respiratory droplets to smaller aerosols. It has been suggested that particles in the air may act as carriers of virus-laden respiratory particles, enabling the virus to travel further in more polluted areas. Walton et al. 2021 concluded that, unlike studies early in the pandemic, more recent studies appear to support the conclusion that air pollutants do not have an important role in transporting the virus in the environment. This conclusion is supported by a review (Ishmatov et al. 2022) suggesting that transmission of the virus in this way is misconceived and has resulted from misinterpretation of data, terminology, and skewed citation practices in the literature.

Air pollution and other respiratory infections

There is evidence that exposure to indoor and outdoor air pollutants can predispose people to, and worsen the outcome from, respiratory infections other than SARS-CoV-2, such as acute upper and lower respiratory infections, bronchitis, bronchiolitis, pneumonia and influenza (Walton et al. 2021)

Building on a previous systematic review and meta-analyses (Walton et al. 2014), the review by Walton et al. 2021 also reviewed studies of the association between short-term exposure to air pollution and hospital admissions for lower respiratory infections published since 2011. It

reported an increased number of studies for $PM_{2.5}$ providing evidence for an association with hospital admissions for lower respiratory infections. The results for PM_{10} were more mixed and only a limited number of studies examining NO_2 and O_3 were available. This evidence lends plausibility to an effect of air pollution on COVID-19 outcomes.

Pickford et al. 2021 also investigated the associations between air pollution and viral respiratory infections other than SARS-CoV-2. In studies of short-term exposure, statistically significant positive (adverse) associations were seen between NO_2 and influenza-like illness, influenza and respiratory syncytial virus (RSV) combined. For $PM_{2.5}$ only influenza showed a small significant association (the analysis being dominated by one study).

The review by Bourdrel et al, 2021 concluded that evidence for other respiratory viruses supports the hypothesis that air pollution exposure may facilitate COVID-19 infection via pathways involving decreased immune responses and viral entry into cells.

Mechanistic evidence

Experimental evidence of how air pollution might affect how the body responds to the SARS-CoV-2 virus was considered in reviews by Walton et al. 2021 and Bourdrel et al. 2021. There is a biologically plausible mechanism, suggested by results of experimental studies which show that exposure to air pollutants increases the expression of the ACE2 and TMPRSS2 receptors, which are known to allow the virus to attach and enter lung cells. Studies of differences in ACE2 expression in human cohorts have shown an association with the higher rates of infection and disease severity seen in patients with pre-existing disease, males and older populations (Patel and Verma, 2020; Silva et al. 2023; Zheng et al. 2022). However, there was no evidence in the period reviewed directly demonstrating this mechanism for SARS-CoV-2 – it was inferred from studies without exposure to the virus or from in-vitro studies. Changes in the expression of ACE2 and TMPRSS2 in response to air pollution might be uniquely relevant to SARS-CoV-2 but similar up-regulation of a receptor used by pneumococci to adhere to and infect airway cells has also been reported in experimental studies following exposure to PM_{10} (Miyashita et al. 2022).

Pollution and immune function

The immune response has 3 main ways of tackling infection: limiting or preventing pathogen access into the body; rapid response from innate immune cells; and a later more specific response from adaptive immune cells (lymphocytes) that specifically destroy the pathogen, as well as producing neutralising antibodies to prevent infection. More detail on mechanisms of these immune responses in relation to SARS-CoV-2 and other respiratory infections, can be seen in Annex B.

There are several points at which both short-term and long-term air pollutant exposure could impact on immune function and modify the susceptibility of an individual to worsened disease outcomes.

Viral entry and recognition

Air pollution, including $PM_{2.5}$, ozone and NO_2, has been shown to damage the lung barrier, including epithelial cells (Leni et al. 2020; Lelieveld et al. 2021; Marczynski et al. 2021) and impair the mucus layer and the underlying ciliated cells (Cao et al. 2020) affecting mucociliary clearance. In addition, acute pollutant challenge with PM_{10} has been shown to upregulate the expression of viral receptors including ACE2 and TMPRSS2 in epithelial cells and also other receptors that mediate entry of respiratory pathogens (Miyashita et al. 2022). Collectively, this damage to the barrier and higher expression of viral receptors could promote viral infection and affect susceptibility to infection following exposure.

Innate defence

Particulate matter exposure drives enhanced production of cytokines such as IL-6 by epithelial and other innate immune cells (Rückerl et al. 2007; Shears et al. 2020). Endogenous particles and exogenous nanoparticles have been shown to impact trained immunity in innate immune cells namely macrophages (Muñoz-Wolf and Lavelle, 2021; Crişan et al. 2017; Crișan et al. 2016; Ma et al. 2020). Innate trained immunity is the ability of a prior inflammatory insult to influence and worsen subsequent responses to a later adverse encounter and is known to occur in epithelial cells and innate immune cells, such as monocytes and macrophages (Bekkering et al. 2021).

Adaptive immunity

Much less has been explored in the context of adaptive lymphocyte responses to air pollution, however, there are possible impacts on B cell development or function associated with $PM_{2.5}$, black carbon and carbon monoxide exposure (Raqib et al. 2022). Similarly, particulate matter has been shown to drive the maturation of dendritic cells in the airway, that act as a bridge between the innate and adaptive immune response, with subsequent activation of T cells, which play a variety of roles in the elimination of virally infected cells (Pfeffer et al. 2018; Mann et al. 2017). Given the importance of adaptive immunity in resistance to infection, and in vaccine responses, this will be an important area for future research.

Vascular responses

In addition to the acute and sustained pulmonary inflammatory responses to SARS-CoV-2 infection, evidence of systemic effects are often apparent, characterised by activation of the endothelium (viewed as being secondary to the loss of barrier function in the lung), inflammation (increased circulating levels of IL-6, IL-1β, and IL-18 and complement activation) and the development of a prothrombotic state (characterised by increased D-dimer levels, due to

impaired fibrinolysis and platelet activation) (Flaumenhaft et al. 2022; Martínez-Salazar et al. 2022). Combined, these events may contribute to the formation of blood clots within the body. Previous experimental studies of human volunteers exposed to diesel exhaust (Unosson et al. 2021; Mills et al. 2011; Lucking et al. 2011) have demonstrated the capacity of inhaled combustion aerosols to drive systemic inflammation, endothelial dysfunction and changes in blood coagulation, suggesting that acute exposures could potentially exacerbate the changes occurring due to COVID-19. This needs to be investigated.

Potential contribution of air pollution to the systemic effects of SARS-CoV-2 infection are of concern as COVID-19 can have particularly adverse impacts on individuals with underlying cardiovascular conditions. Even relatively mild infection with SARS CoV-2 has been shown to cause cardiovascular complications (Wang et al. 2022; Puntmann et al. 2022; Krishnan et al. 2013; Lucking et al. 2011) with the formation of associated microclots (Grobbelaar et al. 2021) in tissues and within the circulation, which have been associated with features of long COVID (Prasannan et al. 2022; Kell, et al. 2022; Pretorius et al. 2021; Pretorius et al. 2022).

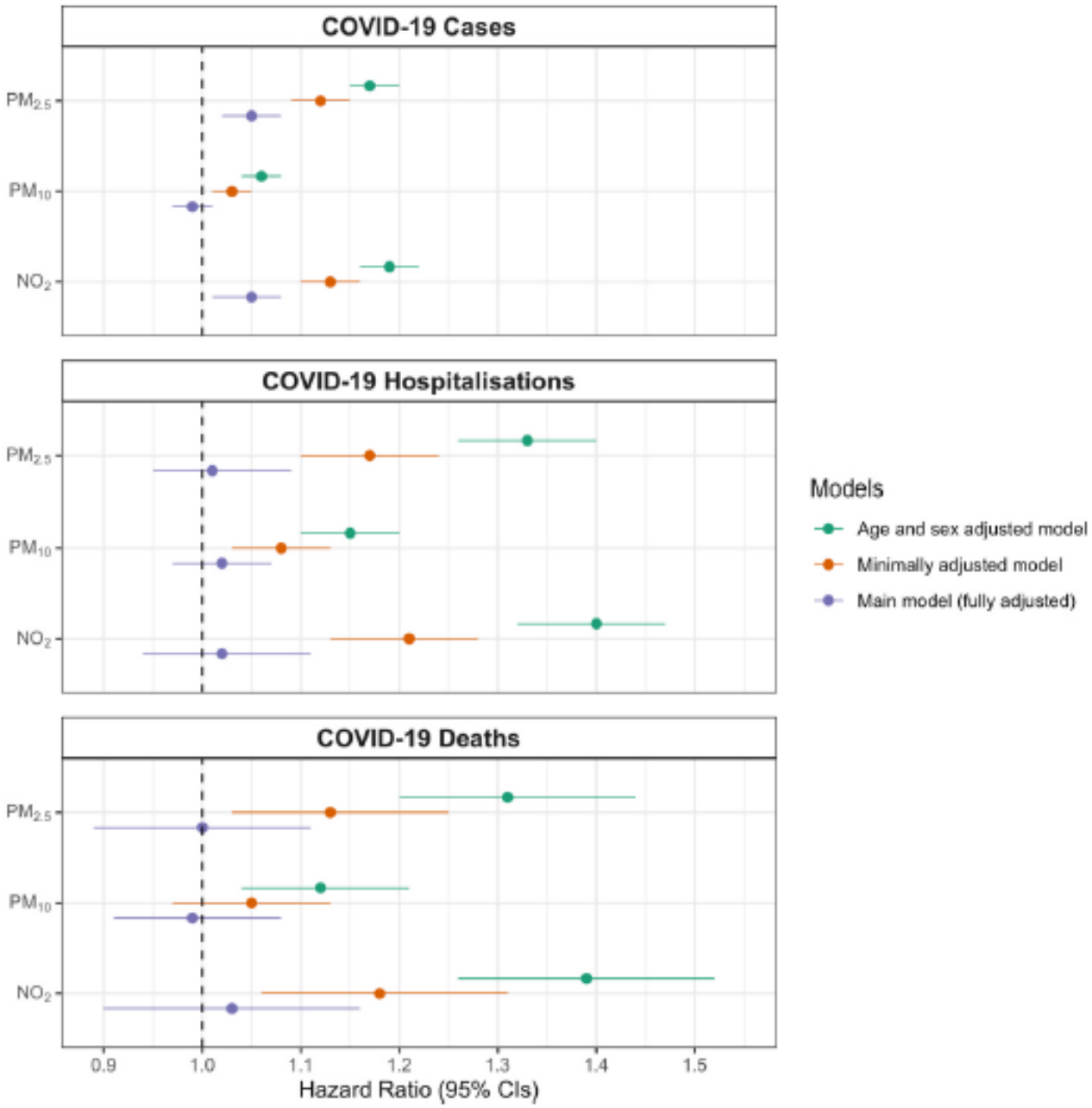
Discussion

The potential impact of air pollution on SARS-CoV-2 infection and COVID-19 disease is a rapidly evolving area of research, with new individual-level epidemiological studies using more robust methodologies continuing to be published. Most, though not all, individual-level epidemiological studies report associations of $PM_{2.5}$ with COVID-19 hospitalisation. There is less evidence that air pollution increases susceptibility to infection with the SARS-CoV-2 virus, although some studies have found a greater association with infection than severity. The evidence on mortality is less clear, with fewer studies available. Mechanistic evidence to date supports a potential effect of air pollution on infection and severity. Overall, we consider that the available studies on COVID-19, together with evidence of effects of air pollution on lower respiratory infections more generally, suggest that exposure to air pollution may worsen the symptoms of COVID-19 disease.

An assessment and graphical representation of the potential causal relationship between long-term exposure to $PM_{2.5}$ and infection with COVID-19, COVID-19 severity and mortality is presented in a separate working paper. COMEAP is trialling this approach as a method of providing a visual representation of the strength of the available epidemiological and experimental evidence, and their integration to come an overall view on the evidence for causality. This is based on the framework described in a report by the Joint COT and COC Synthesis and Integration of Epidemiological and Toxicological Evidence subgroup (SETE), which aims to review approaches for synthesising and integrating epidemiological and toxicological evidence (SETE, 2022). This approach was considered for other pollutants, however, most of the mechanistic studies reported in this statement looked at $PM_{2.5}$ exposure and there was less evidence for other pollutants.

There are a number of methodological issues which make studies of interactions between air pollution and COVID-19 outcomes difficult to conduct and interpret. In particular, there may be difficulties to adequately adjust for confounders. These methodological challenges have been described in the literature, for example Villeneuve and Goldberg, 2020 and Hansell and Villeneuve, 2021. The types of confounders adjusted for in the studies reviewed varied (see Annex C). However, we also note that high levels of correlation between a number of confounders and air pollution may exist (for instance, air pollution may be higher in inner city areas, with higher levels of deprivation, over-crowding and proportion of ethnic minorities), raising the potential for over-adjustment, that is, adjustment for multiple confounders highly correlated with air pollution obscures some of the effects due to air pollution. To illustrate this concern we show Figure 5 reproduced from Sheridan et al. 2022, which shows associations between air pollution and infections, hospitalisations, or mortality sequentially adjusted for age and sex; individual characteristics (such as ethnicity, household income, smoking, BMI, care home residency, and number of COVID tests taken); and area-level characteristics (area-level deprivation and urbanicity). Most associations lose statistical significance after full adjustment, but adjustment for factors such as urbanicity may partially also adjust for air pollution exposures.

Figure 5. Changes in effect estimates between air pollutants and infections, hospitalisations, or mortality of sequentially adjusting models for confounders



Reprinted from Sheridan C and others. Associations of air pollution with COVID-19 positivity, hospitalisations, and mortality: Observational evidence from UK Biobank Environmental Pollution 2022: volume 308, page 119,686
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The reported size of associations differs between studies and between countries. This may relate to heterogeneity in study design and confounder adjustment, but may also reflect real differences between populations, such as in COVID-19 susceptibility. We note that the exposure-response coefficients reported for associations between air pollutants and COVID-19 outcomes are often higher per unit concentration than those for other outcomes associated with

air pollutants, such as cardiovascular and chronic respiratory disease incidence, hospitalisation and mortality. It is difficult to produce a summary estimate of the size of the risk due to the small number of studies that use individual data and well-characterised exposures, outcomes and adjustment for other risk factors. More studies of this type are required to enable meta-analyses to be performed and derive reliable overall effect estimates. Members are aware of a number of new individual-level studies from various countries in various stages of submission for publication, which should help address this.

There are several plausible mechanisms by which air pollution may impact on SARS-CoV-2 infections and COVID-19 disease, but there are few mechanistic studies available to date. In particular, the established links between long-term exposure to air pollution and heart and lung disease suggest that long-term exposure could make individuals more susceptible to severe COVID-19 symptoms, as individuals with these conditions are already at greater risk of developing severe COVID-19. There is some experimental evidence suggesting that air pollution can up-regulate cell-surface receptors which allow SARS-CoV-2 to enter cells. In addition, there is evidence that air pollution can impair innate host defences against respiratory infections, for example, reducing the effectiveness of the barrier function of the respiratory tract epithelium, enhancing viral entry and immune dysfunction.

Reducing air pollution-induced susceptibility of the population to COVID-19 seems appropriate from a public health perspective. The weight of the available evidence points to long-term air pollution exposure increasing the likelihood and severity of COVID-related disease, and hence strengthens the already powerful case for enhanced measures to reduce air pollution exposures in the interests of public health. This statement has not attempted to quantify the effect such reductions might have on COVID-19.

Conclusions

Based on evidence reviewed up to the end August 2022, there is epidemiological evidence from a number of large, well conducted individual-level studies that previous long-term exposure to $PM_{2.5}$ is associated with an increased risk of severe disease and hospitalisation with COVID-19 following infection. There is also some evidence for an increased risk of death from COVID-19 but this is less clear, which may be due to a smaller number of studies and those studies having less statistical power due to mortality being a rarer event than hospitalisation.

Epidemiological associations of severe disease, hospitalisation and mortality with other pollutants are less convincing, in part due to a smaller number of studies available.

There is limited and inconsistent epidemiological evidence to date that long-term exposure to air pollution increases the risk of infection with the SARS-CoV-2 virus and more studies.

There are a number of potential plausible mechanisms by which air pollution may increase risk and severity of respiratory infections. However, the effect of air pollution is often inferred rather than measured directly and there are very few mechanistic studies directly examining air pollution and SARS-CoV-2 infection available to date.

To date, there is extremely limited evidence, either epidemiological or mechanistic, on the influence exposure to air pollution may have on recovery from SARS-CoV-2 infection.

Similarly, there is extremely limited evidence investigating whether air pollution exposure might affect the efficacy of the SARS-CoV-2 vaccine or longer-term persistence of symptoms following infection.

Currently, there is a lack of convincing evidence that ambient air pollution plays an important role in transporting viable SARS-CoV-2 virus in the environment.

Recommendations for future research

General

The COVID-19 pandemic has highlighted a lack of epidemiological or mechanistic work on air pollution and respiratory infections. Future research should also consider other respiratory pathogens of public health importance such as influenza and Respiratory Syncytial Virus (RSV).

Epidemiological studies: air pollution and COVID-19

More well-conducted cohort studies (with individual-level data and adjustment for confounders) investigating whether prior long-term exposure to air pollution makes individuals more susceptible to severe COVID-19 symptoms would be valuable. We are aware of other studies that are being undertaken using individual level data in the process of publication.

Updated systematic reviews and meta-analyses of the epidemiological evidence identified would be useful and we are aware of ongoing work on this.

Study designs that try to distinguish between associations with past or current air pollution exposures and COVID-19 outcomes would be useful, as the policy implications are different.

We note that evidence currently available mainly relates to earlier phases of the pandemic. Further research should consider SARS-CoV-2 variant(s) and vaccination status if possible, where these may influence the impact of air pollution on infection and severity.

Mechanistic studies: air pollution and COVID-19

Experimental studies on effects of air pollution exposure on ACE2 and TMPRSS2 expression and the infectivity of the virus would be informative. However, such experiments will be challenging. Human studies might include exposure of volunteers to roadside pollution, perhaps with and without masks in order to distinguish effects of particulate and gaseous pollutants, for example. Another approach might be to measure ACE2 and TMPRSS2 receptor levels in a human population, both in the nasal cavity and lungs, and assess whether this influences subsequent infection with the virus.

Research on the mechanisms by which air pollution alters immune function and increases susceptibility to respiratory infections including, but not restricted to, SARS-CoV-2, and specifically whether different variants are particularly impacted, would be valuable. The impact of environmental pollution on immune fitness in the nasal cavity requires further research. Most studies of SARS-CoV-2 focus on the lung and peripheral blood, whereas the initial infection response and viral load is largely dictated by immunity and efficacy of barrier function within the nasal cavity. The effects of pollution on development of microclots and dysregulated immune function in COVID-19 and long COVID warrants study. Further research on the impacts of pollution on the kinetics and magnitude of the immune response in diverse groups to account for age, comorbidities and pre-existing lung conditions, such as COPD, is warranted.

Research is needed to assess the impacts of air pollution on the immune response to vaccination and the development of effector and memory immune responses, accounting for SARS-CoV-2 variant(s) where these may influence the impact of air pollution on infection and severity.

Effects of lock-down (and re-opening) on air quality

Timely research would be facilitated by the compilation and release of emissions data as soon as possible after abnormal changes occur, as in the COVID-related lockdowns. Much of the initial analysis of the impacts of lockdowns on air quality relied on monitoring data. Lockdowns imposed major changes to the daily routines of most individuals, with a consequent change to the balance between home, workplace and outdoor exposures to air pollutants, as well as affecting indoor concentrations. There is a need to better quantify these changes, and to take them into account in short-term studies of air pollution effects upon COVID-19 as they are likely to impact heavily upon the outcome of time series epidemiological studies. Given logistical challenges of conducting personal monitoring during lock-downs or similar large-scale societal changes, we would recommend greater use of models. For estimating outdoor air quality exposure of individual subjects in cohort studies, high resolution spatial modelling is likely to provide better estimates of outdoor concentrations at the location of residence than monitoring data.

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Annex A

Literature search used for Imperial College London MSc dissertation 'Investigating links between long-term exposure to air pollution and COVID-19 health outcomes in cohort studies with individual-level data: A systematic review and meta-analysis' by Abigail B. Schneider (Schneider, 2022).

A.1 Search strategy

Studies were identified through an online search of the following databases on 1 July 2022: EMBASE, Ovid MEDLINE, Scopus, and Web of Science. Preliminary searches to ensure the proper literature was being identified were conducted on 30 May 2022 and 9 June 2022. The following search string was used to obtain the relevant literature: "air pollution" OR "particulate matter" OR "PM2*" OR "criteria pollutants" OR "NO2" OR "nitrogen dioxide" OR "nitrogen oxide" OR "PM10" OR "O3" OR "ozone" OR "SO2" OR "sulfur dioxide" OR "sulphur dioxide" AND "covid-19" OR "coronavirus" OR "sars-cov-2" OR "covid" AND "cohort stud*" OR "cohort study" OR "prospective stud*" OR "longitudinal stud*" OR "longitudinal study" OR "individual data" AND "long term." The modified search strategy by database can be found below (A.2). Assistance was sought from a medical librarian at Imperial College London to narrow down the search strategy and identify relevant key terms. Search terms were curated to identify keywords in titles and abstracts, and papers in any language except English were excluded. Papers retrieved were timebound by the length of the COVID-19 pandemic, with the start date being March 2020 and the end date being 11 July 2022. Studies were limited to human only outcomes. A total of 502 studies were retrieved via this process. Studies were also retrieved from 2 additional sources: the Walton et al 2021 report and reference list searching of studies selected for inclusion, from which an additional 3 studies were selected for inclusion.

A.2 Search strategy by database

Database	Search string	Total number of papers identified
EMBASE	"air pollution" OR "particulate matter" OR PM2* OR "criteria pollutants" OR NO2 OR "nitrogen dioxide" OR "nitrogen oxide" OR PM10 OR O3 OR ozone OR SO2 OR "sulfur dioxide" OR "sulphur dioxide" AND covid-19 OR coronavirus OR sars-cov-2 OR covid AND "cohort stud*" OR "cohort study" OR "prospective stud*" OR "longitudinal stud*" OR "longitudinal study" OR "individual data" AND "long term"	50
Ovid Medline	"air pollution" OR "particulate matter" OR PM2* OR "criteria pollutants" OR NO2 OR "nitrogen dioxide" OR "nitrogen oxide" OR PM10 OR O3 OR ozone OR SO2 OR "sulfur dioxide" OR "sulphur dioxide" AND covid-19 OR coronavirus OR sars-cov-2 OR covid AND "cohort stud*" OR "cohort study" OR "prospective stud*" OR "longitudinal stud*" OR "longitudinal study" OR "individual data" AND "long term"	363
Scopus	"air pollution" OR "particulate matter" OR PM2* OR "criteria pollutants" OR NO2 OR "nitrogen dioxide" OR "nitrogen oxide" OR PM10 OR O3 OR ozone OR SO2 OR "sulfur dioxide" OR "sulphur dioxide" AND covid-19 OR coronavirus OR sars-cov-2 OR covid AND "cohort stud*" OR "cohort study" OR "prospective stud*" OR "longitudinal stud*" OR "longitudinal study" OR "individual data" AND "long term"	44
Web of Science	"air pollution" OR "particulate matter" OR PM2* OR "criteria pollutants" OR NO2 OR "nitrogen dioxide" OR "nitrogen oxide" OR PM10 OR O3 OR ozone OR SO2 OR "sulfur dioxide" OR "sulphur dioxide" AND covid-19 OR coronavirus OR sars-cov-2 OR covid AND "cohort stud*" OR "cohort study" OR "prospective stud*" OR "longitudinal stud*" OR "longitudinal study" OR "individual data" AND "long term"	44

Annex B

Additional information on relevant immunological mechanisms

Viral entry and recognition

There are several barriers present in the respiratory tract to prevent infection. These include the production of anti-microbial factors that can kill or prevent the uptake of viruses, including biological barriers such as mucus, surfactant, anti-microbial defensins and the sweeping action of the cilia on the epithelial cells that line part of the respiratory tract (Kudryashova et al. 2022). Any breaches in these defences will help viruses enter the body more readily. It is notable that ageing (Bailey et al. 2022) and chronic conditions such as COPD (Bhowmik et al. 2009) are linked with altered barrier function that may enhance susceptibility to COVID-19. SARS CoV-2, the virus that causes COVID-19, enters via the airways and latches onto and infects cells that express ACE2, with the associated protease TMPRSS2 also playing a significant role. Studies have indicated that variance in expression of ACE2 is associated with resistance to infection – lower expression in children may contribute to better resistance (Bunyavanich, Do, and Vicencio, 2020), whereas higher expression in men compared with women (Gagliardi et al. 2020) may drive differential susceptibility to infection.

Innate defence

Immune cells that reside in the lung airways, such as macrophages, natural-killer cells and others, deal with infection early on, repair damage and recruit other cells to the site. Multiple studies have shown that how macrophages contribute to these responses is important. Dysregulated development (Mann et al. 2020), activation (McGonagle et al. 2020), and responses resulting in enhanced production of proinflammatory cytokines such as IL-6 (D'Agnillo et al. 2021) is important in susceptibility to COVID-19. The virus can also evade the action of critical anti-viral cytokines, most notably interferons (Hadjadj et al. 2020), which has been linked to severe disease.

Adaptive immunity

Air pollution can impact dendritic cell maturation, with consequential effects on T cell maturation and adaptive immunity (Whitehouse et al. 2020). COVID-19 infection causes changes in both B (which produce antibodies) and T cells lymphocytes, both acutely associated with elevated production of pro-inflammatory cytokines such as IL6, with impacts most apparent and over the longer term in those with severe COVID-19 (Shuwa et al. 2021). Alterations in the ratio of T lymphocytes are also associated with enhanced susceptibility to infection (Mann et al. 2020).

Annex C

Table showing individual confounders considered in studies

		Fixed characteristics			**Lifestyle**	**Medical factors**			**Socio-economic characteristics**				**Household factors**		**Medical Centre**	**Stage of pandemic**
	Study	Age	Sex	Ethnicity	Smoking	BMI	Medical history	Comorbidity	Education	Employment/essential worker	Income	Insurance status	Housing	Care home residency	Medical centre	Onset time/date of diagnosis
Long-term exposure studies	Bowe, B, et al., 2021	✓	✓	✓	✓											
	Bozack A, et al., 2022	✓	✓	✓								✓			✓	✓
	Casey JA, et al., 2022	✓		✓												
	Chadeau-Hyam M, et al., 2020	✓	✓	✓	✓	✓	✓		✓	✓			✓			
	Chen C, et al., 2022	✓	✓					✓		✓						✓
	Chen Z, et al., 2021	✓	✓	✓	✓	✓		✓				✓			✓	
	Chen Z., et al., 2022	✓	✓	✓	✓	✓		✓				✓			✓	
	Elliott J., et al., 2021	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓			
	Kogevinas M, et al., 2021	✓	✓	NA	✓	✓	✓	✓	✓	✓						
	Lopez-Feldman A. et al., 2020	✓	✓		✓	✓		✓								✓
	Marquès M, et al, 2022	✓	✓		✓	✓	✓	✓								
	Mendy A. et al., Res. Med., 2021	✓	✓	✓	✓	✓		✓								
	Mendy, A., Res, 2021	✓	✓	✓				✓								
	Sheridan C, et al., 2022	✓	✓	✓	✓	✓	✓	✓			✓			✓		
	Travaglio M, et al., 2021	✓	✓					✓								
	Veronesi G, et al., 2022	✓	✓				✓	✓						✓		
	Zhang Y., et al.,2021	✓	✓	✓					✓	✓			✓			

Key: NA = not applicable; blank = not adjusted for