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Investigating links between air pollution, COVID-19 and lower respiratory infectious diseases

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Key Findings

Air pollution has harmful effects on the lungs. When COVID-19, a disease which infects the airways of the lungs, became a global pandemic it raised the question - does air pollution increase the chance of catching COVID-19 or worsen health outcomes if you do contract it?

In a remarkably short time hundreds of papers have been published about COVID-19 and air pollution. These papers have varied widely in quality and content. This report provides a comprehensive overview of the most credible evidence for the links between air pollution and COVID-19 (since November 2020) and other lung infections (since 2011). It should be noted that as the pandemic is so recent research into air pollution and COVID-19 is not as mature as other research areas, and further research will be necessary to strengthen these emerging findings.

- The review found that long-term exposure to air pollution before the pandemic increased the risk of hospitalization in people already infected with COVID-19 in a small number of good-quality studies. Inconsistent results were found for studies of long-term exposure to air pollution and the number of COVID-19 cases.
- There is evidence that long-term exposure to air pollution increases susceptibility to worse outcomes from COVID-19. This may be due to the already well-established link between air pollution and lung and heart disease, which are known to make people more vulnerable to adverse outcomes from COVID-19.
- There is evidence that exposure to air pollution might increase the likelihood of contracting COVID-19 if you are exposed to the coronavirus. This comes from a few studies that found, once inhaled into the lungs of animals, pollutants increase amounts of the protein that allows the coronavirus to attach to the lung cells.
- There is already a well-established link between air pollution and a range of infections in the lower part of the lung, (such as acute bronchitis and pneumonia). This is often overlooked in developed countries. A review in this report found several studies from 2011-2021 showed a link between air pollution and hospital admissions for lung infections although the studies were spread across different age groups and disease definitions.
- Particulate matter does not appear to play any important part in transporting COVID-19 in the environment, as had been suggested by some earlier studies.
- The evidence for a link between short term exposure to pollution and COVID-19 is unclear at this stage, and difficult to evaluate on the available evidence.

Historically, air pollution has been most associated with “non-communicable” diseases that can't be directly transmitted between people. For example, there is extensive and growing evidence on the impact of air pollution on heart and lung diseases. Until now, the role air pollution plays in infectious respiratory diseases has been overlooked and underestimated in the UK. This review shows that there is some increasing evidence of links between exposure to air pollution and susceptibility to hospital admissions from COVID-19 and, whilst this study highlights that more research is needed in this area, it is already clear that tackling air pollution is important in reducing the vulnerability of the population to COVID-19, and other infections like it.

1.0 Executive Summary

Transport for London (TfL) and the Greater London Authority (GLA) commissioned researchers from the Environment Research Group (ERG) at Imperial College London to investigate the links between air pollution, COVID-19 and other infectious diseases.

The approach taken in this report is based on a rapid evidence review of COVID-19 and air pollution and a parallel evidence review of lower respiratory infections and air pollution preceding the COVID-19 time-period. For the former, the choice was made to classify the evidence, which is now rapidly growing, according to the underlying hypothesis on the exposure, the potential mechanism and the health outcome considered.

This report builds on the preceding work by Brunekreef et al (2021), which reviewed some key studies reported before November 2020 and found that although the hypothesis that exposure to air pollution may affect COVID-19 outcomes (mortality at the time of the Brunekreef review) is plausible, based on older evidence and possible mechanisms, the evidence base was still sparse and more work was needed to provide solid evidence. The review in this report provides an update with more recent studies with an additional focus on considering studies separately according to the possible pathways by which air pollution exposure could affect infection with COVID-19 and the severity of disease outcomes.

1.1 Epidemiological evidence on air pollution and COVID-19

Since the start of the pandemic, a range of ideas have been put forward for possible relationships between air pollution and COVID-19. For the purposes of this report we have split these into four broad categories:

- (i) Effects of long-term exposure to pollutants on COVID-19 severity and outcomes as well as transmissibility
- (ii) Effects of short-term exposures, happening concurrently with exposure to SARS-CoV-2 or COVID-19 disease, on COVID-19 transmissibility and severity
- (iii) Studies on whether the virus can be transmitted via ambient particles due to urban air pollution
- (iv) Changes in air pollution levels and mixtures because of measures taken (e.g. lockdown) to reduce COVID-19 transmission

Evidence in each of these categories is summarised below.

- (i) *Effects of long-term exposure to pollutants on COVID-19 severity and outcomes as well as transmissibility*

Exposure to air pollution is well known to be associated with an increase in the incidence of chronic respiratory diseases which render the population more vulnerable to COVID-19. As a consequence, researchers have been exploring the plausible hypothesis that long-term exposure to pollutants would therefore increase the number and severity of COVID-19 cases since the start of the pandemic.

Our search identified thirty-four papers of sufficient quality to assess in detail. Of these 29 papers applied an ecological approach, analysing aggregated data over the area or its population (with a spatial resolution ranging from country to neighborhood or small administrative unit level), and 5 used individual data.

From the **ecological studies** we conclude that there are indications in appropriately conducted, and analysed, studies that long-term exposures to pollutants, mainly ambient PM and NO₂, are associated with the extent of COVID-19 infections and severity. Some of the ecological studies reviewed provide evidence to support the hypothesis that pre-existing long-term exposure to air pollution would increase the severity of COVID-19 due to an increase in the proportion of vulnerable individuals in polluted areas.

In terms of the number of cases, the evidence and its interpretation is less clear; this is because the ecological approach doesn't show whether there are just more cases or if the increased disease severity, noted above, has led to more cases being reported.

The ecological studies reviewed cover different areas of the world with more studies from the US and Italy. They also used a range of exposure and outcome definition methods and different analytical approaches. While they provide evidence to support the hypothesis that long-term exposure to air pollution is associated with severity of COVID cases, no quantitative estimates can be derived at this stage.

Of the five **studies including individual data** and analyzing cohorts, four were trying to evaluate a causal association between exposure to pollutants and COVID-related health outcomes. Two studies evaluated the risk of hospitalization among COVID-19 cases in the U.S. (Mendy et al, Bowe et al) and found that higher long-term exposure to PM_{2.5} was associated with a pronounced increase in the probability of hospitalization. Two studies included mortality among cases as the health outcome: one found no evidence of an effect based on 459 deaths (Elliott et al) and the other found an association but it is unclear on how many cases it was based (Lopez-Feldman).

Overall, the evidence is persuasive, but the quantitative estimates differ. It is not possible to assess at this point whether the quantitative differences are a result of differences in populations (e.g. the age distribution, health aspects), random variation, or differences in exposure to air pollution.

(ii) *Effects of short-term exposures, happening concurrently with exposure to SARS-CoV-2 or COVID-19 disease, on COVID-19 transmissibility and severity*

For short-term studies 27 papers were identified and reviewed. There was considerable variation in the results of these studies, and all of them should be treated with caution for the following reasons: low statistical power due to short study periods; no proper adjustment for confounders, such as public holidays (and changes in holiday travel) or meteorology and presence of confounding from lockdown measures changing both levels of air pollution and rates of COVID-19 infections. Publication bias may be another reason for caution, especially if one takes into account the urgency for some results that could have been used to inform policies during the pandemic.

Six studies report no consistent associations for all pollutants that they included in the analysis, while at least 3 studies report statistically significant negative associations, implying that air pollution may have a protective effect on COVID-19 health endpoints.

Other studies report strong positive associations for specific pollutants, some of which are interpreted as causal and go up to 34.8% (95% CI: 29.3%– 40.4%) increase in the daily confirmed COVID-19 cases for a unit increase in daily NO₂. These results should be treated with caution as there might be serious flaws in their analysis, such as residual confounding or even no control for confounding, while various machine learning methods applied show associations which are interpreted as causal without clear justifications. Finally, the lack of consistent findings for specific pollutants seems to hold for all exposures that have been examined, including PM₁₀, PM_{2.5}, NO₂, O₃, SO₂, CO and papers using a combined air quality index.

(iii) *Studies on whether the virus can be transmitted via ambient particles due to urban air pollution.*

It was suggested early on in the COVID-19 pandemic that the virus could ‘hitch a ride’ on particulate air pollution and travel further distances than if the virus was only in droplets from infected individuals. Recent studies have not supported this. While it is still theoretically possible, particulate air pollution is considered unlikely to be a significant contributor to the risk of transmission in the environment. Enzymes that break down viral RNA are likely to be the major factor determining environmental persistence of the virus.

(iv) *Changes in air pollution levels and mixtures because of measures taken (e.g. lockdown) to reduce COVID-19 transmission.*

Understanding the changes in air pollution as a result of lockdown measures could lead to greater understanding of the contribution of different sources to air pollution levels. The UK Air Quality Expert Group (AQEG) produced a [report](https://uk-air.defra.gov.uk/research/aqeg/publications)¹ on changes in the UK in July 2020, which suggested a consistent drop in NO₂ levels but a more mixed pattern for other pollutants.

Our search also identified a large number of studies on this issue from all over the world, particularly in Asia. As well as looking at changes in the amount of pollution, there are studies examining changes in PM composition, including changes in oxidative potential, which is thought to be an important factor in how particles affect health.

There are also several health impact assessment studies – these need examining in detail to understand if they have taken into account how changes in individual behaviour during lockdowns change exposure patterns and also other factors like the major changes in baseline rates for mortality and respiratory disease due to COVID-19.

In addition, there are a number of studies noting smaller numbers of asthma exacerbations due to the general reduction in respiratory infections during lockdowns, a point relevant for interpretation of air pollution and health studies in this period.

¹ <https://uk-air.defra.gov.uk/research/aqeg/publications>

Understanding all of these changes is relevant to interpreting epidemiological studies of air pollution done during the pandemic. A list of these exposure and health impact assessment studies is provided but the numbers are sufficiently large that detailed examination of them would justify a separate project.

1.2 Toxicological evidence on air pollution and COVID-19

Understanding how exposure to air pollution might affect how the body responds to a virus like SARS-CoV-2 is an important area in its own right, but it is also helpful in understanding why the effects seen in the epidemiological studies have occurred.

Experiments to explore the mechanisms by which air pollutants enhance susceptibility to, or severity of, COVID-19 require considerable time to develop and perform. As a result, several hypotheses are presented in the literature but peer-reviewed validations of these ideas remain scarce. These hypotheses are considered plausible because they build from existing understanding of the interplay between air pollutants and other respiratory infections. They include:

- (i) Increased expression of proteins required for host cell entry
- (ii) Impaired antimicrobial function of immune cells
- (iii) Increased incidence of underlying health conditions

Several studies demonstrate that inhaled pollutants increase expression of ACE2, the receptor in cells to which the virus spike protein binds, and other genes which can make the host more susceptible to the virus. These effects are observed in both alveolar epithelial cells (cells that line the air sacs of the lungs) and macrophages (specialised immune cells involved in the detection and destruction of harmful micro-organisms), thus promoting susceptibility to infection. However, further experimentation is required to confirm whether the same exposures impact host immune cell defences in the context of SARS-CoV-2.

1.3 Evidence on air pollution and hospital admissions for lower respiratory infections

Reviews by WHO, the US Environmental Protection Agency and others describe multiple studies demonstrating that exposure to a range of outdoor and indoor air pollutants predisposes people to, and worsens the outcomes from respiratory infections, including acute upper and lower respiratory infections, bronchitis, bronchiolitis, pneumonia and influenza.

Previously, the UK Department of Health funded a systematic review of time-series (short-term exposure) studies on air pollution and health, including respiratory infections, up to 2011. This report focusses on additional work that has been done since then on hospital admissions for lower respiratory infections.

This report found an increased number of studies on PM_{2.5} published since 2011 which provide evidence for an association with hospital admissions for lower respiratory infections. The results for PM₁₀ (at least since 2011) are more mixed and only small numbers of studies examining NO₂ and O₃ are available.

These papers included studies in adults, the elderly and all ages, which is more relevant to providing plausibility to effects of air pollution on COVID-19, as COVID-19 fortunately has much less serious effects in children.

For all pollutants, results are scattered across different disease definitions and age groups, such that there are insufficient numbers of studies in each disease definition/age group combination for a meta-analysis of studies published since 2011, although this might be possible if added to pre 2011 studies. Overall, this section of the report highlights what is an often-overlooked health impact of exposure to air pollution.

1.4 Strengths and Limitations

For studies on air pollution and COVID-19, it is inevitable that the research area is not as mature as some other areas of the literature on air pollution and health. Not only has the time period available to study any relationship been short but COVID-19 itself is not well understood. It may be that further research will indicate other confounders that should be taken into account in these studies. In addition, particularly early in the pandemic, data collection was either absent or under-developed and definitions related to data collection have been changing.

The authors of this report include expertise in epidemiology, toxicology and health impact assessment. This allowed us to examine the interplay between studies of mechanisms and epidemiological studies to the degree possible given the early stages of research on air pollution and COVID-19. Some other reviews adopt results from studies in other fields uncritically e.g. reviews of mechanisms take epidemiological study results at face value even though some of them are only correlation analyses.

While we have done full literature searches in selected areas and put these into the context of the different possible pathways involved in the effects of air pollution on COVID-19, this was a short project. We considered studies on air pollution and COVID-19 published after the review by Brunekreef et al (2021) based on studies up to November 2020, rather than describing all studies published since the start of the pandemic in detail. Similarly, for the more general literature on air pollution and respiratory infections, we were only able to consider one part of this subject area in detail (air pollution and hospital admissions for lower respiratory infections) and that only for studies published since a previous systematic review based on studies published prior to 2011.

Despite the continually evolving nature of the research in this area, we believe it is useful to provide a current summary of the research, particularly as some studies are of very poor quality and this needs to be identified and taken into account in summarizing the research.

1.5 Conclusions

The conclusions of our review work are summarized on the Key Findings page. It is clear from this that some areas of research are strengthening, such as the publication of studies on long-term exposure to air pollution and hospital admissions for COVID-19 with individual data. In addition to being a more robust type of study, these also showed consistent effects of air pollution on COVID-

19 hospital admissions. The number of studies is still small and insufficient to use for quantifying the size of the risk, but this suggests research to establish this relationship further would be useful.

In contrast, earlier concerns that the virus was carried on particulate air pollution, and might travel further as a result, have not been confirmed. While the presence of virus on air pollution particles remains a theoretical possibility, and there are challenges in studying this issue fully, it is already clear that there are far more significant factors determining transmission of the virus in the environment that are a higher priority for research at the present time.

The situation for short-term exposure is less clear cut. The review work on short-term exposure to air pollution and hospital admissions for lower respiratory infections in general, provides plausibility for an effect of short-term exposure to COVID-19 (and provides justification for more research and policy attention in its own right). The emerging toxicological findings on air pollution and increased expression of the ACE2 receptor also provides some plausibility. On the other hand, the epidemiological studies of short-term exposure to air pollution and COVID-19 provide no conclusive answers. These types of studies are always going to be difficult to do against a background of rapidly changing rates of infections and lockdowns.

While it is important to continue to monitor this evolving area of research, it is already known that reducing air pollution improves health. The importance of this has been further emphasized by the fact that diseases caused or worsened by air pollution also lead to increased vulnerability to severe outcomes to COVID-19, including hospital admissions.

2.0 Introduction

Transport for London (TfL) and the Greater London Authority (GLA) commissioned researchers from the Environmental Research Group (ERG) at Imperial College London to investigate the links between air pollution, COVID-19 and other infectious diseases in London.

The COVID-19 pandemic reached the UK in Spring 2020 and has had several waves of serious numbers of cases, hospital admissions and deaths in Spring 2020, Autumn 2020 and early 2021. Vaccination has been rolled out across the UK population since December 2020 and is now providing some protection against hospital admissions and deaths. Nonetheless, there remains concern about improving understanding of the factors that may pre-dispose people to catching COVID-19 and experiencing more serious outcomes after infections.

Air pollution is well known to be associated with several diseases that provide susceptibility to COVID-19, including respiratory and cardiovascular disease (WHO, 2013).

Lockdown measures to control the pandemic also reduce levels of air pollution (AQEG, 2020). Reductions in air pollution benefit health but this also complicates interpretation of effects of short-term exposure to air pollution, where pandemic measures may mean reductions in both pollution and COVID-19 cases, creating a correlation between the two that is related to the pandemic measures rather than necessarily a biological link.

All these general factors will be considered in this report.

Transport for London (TfL) and the Greater London Authority (GLA) commissioned this work to investigate links between air pollution and COVID-19 and other infections through

- (i) An evidence review of COVID-19 and air pollution
- (ii) An evidence review of other infections and air pollution
- (iii) Mapping the correlation between exposure to ambient air pollution and reported infection rates and outcomes from COVID-19 in London.

This report provides an expert commentary on the evidence on air pollution and COVID-19 and on air pollution and other infections i.e. the first two parts.

How we approached the project:

- We considered possible reasons why air pollution and COVID-19 might be linked (see start of section 4.0)
- We considered past evidence on air pollution and lower respiratory infections to inform plausibility of some aspects of these mechanisms (section 3.0 of the report)
- We structured the consideration of the literature on air pollution and COVID-19 in the context of these potential mechanisms (section 4.0)

While we have performed literature searches in specific areas as described below, and members of the project team have discussed the inclusion and exclusion of some papers between them, it has not been possible in the time available to do a formal systematic review with duplicate sifting and data-extraction. In addition, to constrain the work into the time available, we have only included studies published since a previous review of studies up to November 2020. Good systematic

reviewing practice has been followed in other respects, but we would describe the work as an expert commentary rather than a full systematic review.

3.0 Evidence on air pollution and lower respiratory infections

3.1 Introduction

The COVID-19 pandemic is serious and globally disruptive but only recent. While there has been an explosion of research on COVID-19, and some research on the effects of air pollution on infection with or worsening of the disease, it takes some time for new research areas to mature. However, there is information on the effect of air pollution on other respiratory infections. A broad overview of this literature is provided in section 3.2 below to see whether this evidence lends plausibility to the possibility of an effect of air pollution on COVID-19.

Consideration of the evidence on air pollution and respiratory infections is important in its own right. It is an area that has not had wide attention in the UK, although it is a large issue in developing countries. In addition to the above overview, we wished to consider one area in more detail and chose to update the literature on air pollution on hospital admissions for lower respiratory infections, to see if there was sufficient evidence to use for quantification in health impact assessment. (As a small project, it was not possible to cover a wider number of areas). The reasons for this choice are explained in section 3.3 below.

3.2 Overview of evidence on air pollution and respiratory infections

The ENVI report by Brunekreef et al (2021) provides an overview of effects of outdoor and indoor air pollution on respiratory infectious disease other than COVID-19. The report notes that there are multiple studies demonstrating that exposure to both outdoor and indoor air pollution predisposes to and worsens the outcomes of respiratory infections. There is mechanistic evidence as to how this might occur (Ciencewicki et al 2007) including an earlier emphasis on toxicological evidence on nitrogen dioxide and susceptibility to infection in animals (IPCS 1997). Pooling results across 10 birth cohorts in Europe showed an effect of air pollution on pneumonia in children (MacIntyre et al 2014). This has also been found in a birth cohort in the Czech Republic for pneumonia (Hertz-Picciotto et al 2007) and for bronchiolitis in two case-control studies in infants (Karr et al 2007; Karr et al 2009). There are panel studies on air pollution and acute bronchitis in children (Hoek et al 2012), that have been recommended for use in quantification by WHO (WHO 2013). Air pollution is associated with increases in hospital admissions for Chronic Obstructive Pulmonary Disease (COPD) (Atkinson et al 2014; Mills et al 2015, Walton et al 2014, Moore et al 2016). COPD exacerbations are often caused by respiratory infections.

The [US EPA Integrated Science Assessments](#) have reviewed evidence on air pollutants and infections – their conclusions from the most recent versions of the reports for each pollutant are in the paragraphs below. Note that the studies reviewed can be from 2 or 3 years before the final publication dates of 2019, 2016 and 2020 for particulate matter, NO₂ and O₃ respectively.

For PM_{2.5}, the Integrated Science Assessment report noted the generally positive associations between short-term exposure and hospital admissions and emergency department visits for combinations of respiratory infections (with more limited and inconsistent evidence for specific respiratory infections, such as pneumonia) in a section on the evidence in support of the ‘likely to be causal’ determination for short-term exposure to PM_{2.5} and respiratory effects. It was pointed out that potential co-pollutant confounding remained unexamined in studies of respiratory infection. There was considered to be limited evidence from toxicological studies at relevant

concentrations, but the evidence did show altered host defence and greater susceptibility to bacterial infection.

It was considered that recent epidemiological studies did not indicate a clear relationship between long-term PM_{2.5} exposures and respiratory infection in infants or adults. While the limited number of studies reviewed generally reported associations between PM_{2.5} and at least some of the examined respiratory infection outcomes, there was limited overlap in endpoints across studies. Where the same endpoint was examined across multiple studies, large birth cohort studies found some evidence of an association between PM_{2.5} and infant bronchiolitis but the results were not entirely consistent.

The US EPA ISA on particulate matter did not cover PM₁₀.

For NO₂, it was concluded by the US EPA that studies in animals and humans collectively demonstrated that NO₂ exposure (including at ambient levels) impaired host defence. Responses in humans included reduced activity of the mucociliary escalator (which clears pathogens up and out of the airways) and altered humoral² and cell-mediated immunity, while responses in experimental animals included changes in alveolar function and SP-D³ nitration. Epidemiological studies were inconsistent.

For O₃, conclusions were only given in the Integrated Science Assessment for respiratory effects overall but the evidence from experimental studies in animals and humans that ozone caused respiratory tract inflammation was noted to potentially lead to altered host defence, which is linked to increased respiratory infections. Epidemiological studies showed associations between exposure to ozone and markers of respiratory tract inflammation, and ED visits and hospital admissions for respiratory infection. Together with other proposed pathways, this was considered to provide plausibility for epidemiological evidence of the respiratory health effects of ozone.

Household air pollution in developing countries has been shown to be linked to acute respiratory infections in children under 5. Dherani et al (2008) performed a systematic review and meta-analysis of studies of indoor air pollution from unprocessed solid fuel use and pneumonia risk in children under 5. They reported an odds ratio of 1.78 (95% confidence interval, CI: 1.45-2.18) for 'higher vs lower exposure'. They acknowledged that this was based on studies of varying design, indirect measures of exposures (e.g. 'sometimes carries child while cooking') and varying disease definition from maternal recall to diagnosis based on clinical tests. Pneumonia severity also varied and only some studies examined mortality. Many sensitivity analyses were performed to account for these challenges in the evidence base and the overall conclusion was that there was sufficient evidence to strengthen the need for interventions to provide alternative cooking fuels or stoves.

A randomized clinical trial found a significant reduction in physician-diagnosed pneumonia with a reduction in pollution (using CO as a marker) as a result of changing from a three stone fire to a chimney wood stove (Smith et al 2011). This trial, along with other evidence on short-term and long-term studies on ambient air pollution and lower respiratory infections (Mehta et al 2013) and evidence from effects of second hand smoke on acute lower respiratory infection risk (US Surgeon-general's report, 2006) were considered sufficiently robust to be used in developing an integrated exposure response function (a modelled exposure response function spanning estimated PM_{2.5}

² Immunity mediated by non-cellular factors such as antibodies.

³ Surfactant-protein D – a protein in the lung lining fluid maintaining appropriate surface tension in the lung and contributing to microbial clearance.

exposures across sources from ambient air pollution to smoking) (Smith et al 2014). This integrated exposure response function approach was subsequently extended to lower respiratory infections in adults (Cohen et al 2017) with the addition of information on active smoking and increased risk of mortality from pneumonia in adults e.g. Pirie et al (2013).

3.3 Collation of evidence on short-term exposure to air pollution and hospital admissions for respiratory infections since 2011

As discussed in the above overview, there are established concentration-response functions for PM_{2.5} and lower respiratory infection mortality in children under 5. To provide a contribution in this area, we wished to address an area of the literature that was not already well summarized into an established concentration-response function but nonetheless would be suitable for use in health impact assessment and relevant to interpretation of the literature on air pollution and COVID-19. We chose to examine short-term exposure to air pollution and hospital admissions for lower respiratory infections. A previous UK Department of Health funded systematic review and meta-analysis had provided weak evidence for an effect of ozone based on a small number of studies (Walton et al 2014) and had not summarized results for NO₂ (Mills et al 2015) or PM_{2.5} (Atkinson et al 2014). We chose hospital admissions rather than mortality because these may occur in larger numbers than deaths, at least in developed countries. In addition, the relevance to assessing plausibility for an effect of air pollution on COVID-19 outcomes is better for hospital admissions (where patients will previously have been exposed to air pollution at home and in the ambient environment) compared with mortality where the majority of patients will be in a hospital setting. We examined papers published since 2011, the literature search cut-off in the previous systematic review.

Literature searching and sifting

We based the search string on those used in the UK Department of Health funded systematic review of time-series studies up to 2011 (Atkinson et al, 2014; Mills et al 2015, Walton et al 2014). The full search string is given in the Appendix section 6.1. The update search was on air pollution and lower respiratory infection admissions on PubMed, from 2011 to the present.

The initial 434 hits in the search were narrowed down to 19 relevant papers (see section 6.1 for details of exclusions). A further 2 of the 19 were excluded on the basis of poor quality. Pothirat et al (2019) does not control for season or long-term time trend and Sahin et al (2021) was just a correlation analysis with no control for confounders. Wang et al (2021) was for bronchiectasis with LRI – this was excluded as it relates to exacerbation of a chronic disease. Nhung et al, 2019 has been excluded because it addressed length of hospital stay rather than counts of hospital admissions. One was on acute upper respiratory infections only (Trianti et al 2017). This left a final total of 14 papers.

We retained two papers on lower respiratory infection mortality for comment, although as mortality was not in the search terms this will not be the complete set of post 2011 papers on mortality.

There were 11 papers on PM_{2.5} and hospital admissions, 4 on PM₁₀, 3 on NO₂ and 2 on O₃. The two papers on mortality both covered PM₁₀ and one covered O₃. There was no study from Europe (there are more before 2011, but European researchers have concentrated more on the effects of long-term exposure more recently). There are 4 papers from North America from 2 locations, as in

Europe, more of the studies in the US and Canada were done pre-2011. The number of studies from Asia was the largest (7), a region with rather few studies before 2011. These included studies from China, South Korea, and Vietnam.

The papers covered a range of different age groups and a range of different definitions of lower respiratory infections, or specific diagnoses within the lower respiratory infection umbrella. This is discussed in more detail in the section on whether a meta-analysis is possible. First, a more general description of the studies is given.

Most of the studies are standard time-series studies – studies that examine whether day-to-day variation in air pollution is related to day-to-day variation in hospital admissions. Unlike the air pollution and COVID-19 studies discussed later, the confounding factors that need to be considered are well established and widely used. A good quality study should control for daily variations in temperature and for long-term time trends. Other factors controlled for include day of the week, relative humidity and flu epidemics. Studies should be at least a year long, preferably longer, to have sufficient statistical power.

There were also a few case-crossover studies where the number of hospital admissions on a particular day with a known level of air pollution is compared with other days, often on the same day of the week, a set short period (e.g. 2 weeks) before and after the specified day. These days will be similar in most respects but probably have a different air pollution level. This type of study should control for temperature but does not need to control for season and long-term time trends as the comparisons made are usually within the same season/short time period. It has been shown that case-crossover studies are equivalent to time-series studies (Lu and Zeger, 2008) so we have considered them together.

In summarizing the papers, studies on broad groupings of lower respiratory infections are described first, followed by studies on more specific diagnoses. It should be noted that the ICD⁴ codes are not necessarily the same for all studies examining lower respiratory infections – some exclude influenza and pneumonia, some include pneumonia but not influenza etc. We use the categorization of the authors but note the ICD codes.

Studies do not necessarily use the same categories of age grouping either. We have grouped studies by young children (combinations under 5 years), children (combinations including ages over 5 years), adults and all ages. Young children and children were separated because the diseases and their consequences are different in young children while their airways are small. There tend to be more studies in young children, perhaps because the numbers of events are greater in young children. It should be noted, however, that studies in all ages, adults or the elderly are more relevant to interpreting the possibility that air pollution might be related to COVID-19 outcomes. All age group combinations are considered here because there is an interest in whether it would be possible to quantify an effect of air pollution on hospital admissions from lower respiratory infections as a question in its own right.

The results described are for single pollutant models. This means that only one pollutant was considered at a time. In reality, due to the close correlations between pollutants, individual pollutant results may be partly reflecting effects of other pollutants. Some studies do aim to

⁴ International Classification of Diseases

disentangle the effects from other pollutants. These results may be mentioned when of interest but a thorough consideration of this issue would need further work.

All studies gave results for 'all year' but some also considered results by season. These are not described here but are worth future consideration as part of the overall evidence base.

A summary of the findings is given below, with fuller descriptions of the studies in the Appendix sections 6.2-6.6.

Results from studies of air pollution and hospital admissions for lower respiratory infections

The results for PM_{2.5} generally showed positive and statistically significant associations in young children (Horne et al 2018, Luong et al 2020), children (Horne et al 2018, Zheng et al 2017) and adults (Horne et al 2018). The result for Kim et al (2020) in all ages was not statistically significant and Xia et al (2017) only found a positive and statistically significant result in all ages above a threshold of 80 µg/m³. However, Yao et al (2020) did find a positive and statistically significant association.

There are fewer studies for PM₁₀ (although there are more pre-2011) and the results are mixed. Le et al (2012) found no association in young children but Zheng et al (2017) found a positive and significant association in children. Positive and significant associations were found for all ages (Yao et al (2020), Xia et al (2017)) but for Xia et al (2017) this was only found above a threshold of 100 µg/m³, at the upper end of the range of concentrations.

There was only one study for NO₂ showing a positive and statistically significant association only above 60 µg/m³ for all ages (Xia et al 2017) and one for ozone showing a negative association in young children (Le et al, 2012).

Results from studies of air pollution and hospital admissions for pneumonia

Some studies looked at diagnoses within the lower respiratory infections grouping. There were fewer studies for pneumonia admissions and the results were mixed. For PM_{2.5}, results were not statistically significant in young children (Luong et al, 2020) or all ages (Kim et al, 2020). For adults a positive and significant association was found in one study (Croft et al, 2019) but not in another (Pirozzi et al, 2018). The latter did however find an association in the elderly.

There were no studies using PM₁₀ since 2011, although there are several before then e.g. a study in 36 cities by Medina-Ramon et al (2006).

Pirozzi et al (2018) found no association for NO₂ and O₃ in adults. Unlike for PM_{2.5}, no results are presented for the elderly.

Results from studies of air pollution and hospital admissions for influenza/bronchiolitis and mortality from lower respiratory infection/pneumonia

The small number of studies on air pollution and hospital admissions for influenza and bronchiolitis are also discussed in the Appendix section 6.4-6.5, as are a few studies on mortality from LRI or pneumonia (section 6.6).

The number of studies on hospital admissions in these categories is too small to come to conclusions, at least since 2011.

While there may be other studies on mortality since 2011, the publication of a multi-city study of PM₁₀ and O₃ and lower respiratory infection mortality in children in South America is notable (Romieu et al 2012). Positive and statistically significant associations were found but not in all of the 3 cities studied. Sun et al (2019) found a positive but non-significant association with PM₁₀ and pneumonia mortality in all ages.

Comparison with pre 2011 evidence

The most obvious changes in evidence before and after 2011 is the increase in studies on PM_{2.5} and the increase in studies in Asia. Atkinson et al (2014) did not include admissions for lower respiratory infections in their meta-analysis of PM_{2.5} time-series studies, probably because the studies were scattered across different age groups and disease definitions. There are now more studies on PM_{2.5} showing evidence of associations. While the studies were still scattered across different age groups and disease definitions, with insufficient studies in each category for meta-analysis, meta-analysis might now be possible in combination with the pre 2011 evidence (this would need investigation).

Atkinson et al (2014) did not cover PM₁₀ but there are larger numbers of PM₁₀ studies pre-2011, particularly in the elderly (in the US hospital admission data is easier to obtain in the elderly due to Medicare records). The small number of studies with mixed results found post 2011 could be added to this information.

A systematic review and meta-analysis by Mills et al (2015) did not cover NO₂ and lower respiratory infections. There are fewer studies than for PM₁₀ and studies are again scattered across different age groups and disease definitions. It is unclear whether the small number of studies published since 2011 would mean a meta-analysis was now possible.

Walton et al (2014) did provide meta-analysis summary estimates for ozone and admissions for lower respiratory infections for both children 1.26% (-0.13, 2.66) increase per 10 µg/m³ and the elderly 0.57% (-0.14, 1.28) increase per 10 µg/m³ daily 8-hour maximum ozone. Only one study for ozone and admissions for lower respiratory infections has been published since 2011, showing a negative association in young children (Le et al, 2012). Thus, the evidence remains unconvincing, with the caveat that effects of ozone can be masked by negative correlations with other pollutants.

Although further searching for studies on short-term exposure to air pollution and mortality from lower respiratory infections or pneumonia, would be needed, the publication of a new multi-city study suggests a meta-analysis might be possible. PM₁₀ was not considered in the previous UK Department of Health funded systematic review and meta-analysis and there are several pre 2011 studies on PM₁₀. For ozone, a positive and statistically significant association of 1.18% (0.46, 1.91) increase per 10 µg/m³ daily 8-hour maximum ozone was found in the previous meta-analysis (Walton et al 2014), and the new study will add to this.

Nhung et al (2017) did a systematic review and meta-analysis of studies of air pollution and pneumonia admissions in children published before early 2017, finding positive and statistically significant associations across pollutants. However, this meta-analysis combined hospital admissions and emergency room visits and different age groups of children. This is reasonable when considering a qualitative conclusion of whether there is evidence for an effect. For quantitative use

in health impact assessment for policy purposes, it is less accurate because emergency room visits as defined in the US do not have a health care equivalent in the UK (they are similar to a combination of GP and A & E visits). They can still be used for a rough estimate of the 'size of the problem' (Williams et al 2019) but not for precise comparisons of costs and benefits in policy analysis. For this purpose, further work investigating meta-analysis of hospital admissions alone (combining pre and post 2011 evidence) would be worthwhile.

Conclusions for post 2011 evidence on air pollution and hospital admissions for lower respiratory infections

The increased number of studies on PM_{2.5} published since 2011 provide evidence for an association with hospital admissions for lower respiratory infections. The results for PM₁₀ (at least since 2011) are more mixed and only small numbers of studies examining NO₂ and O₃ are available. For all pollutants, results are scattered across different disease definitions and age groups, such that there are insufficient numbers of studies in each disease definition/age group combination for a meta-analysis of studies published since 2011. Nonetheless, this might be possible in combination with pre 2011 studies, as further work.

This area of evidence does lend some plausibility to an effect of air pollution on hospital admissions with COVID-19.

4.0 Evidence on air pollution and COVID-19

4.1 Introduction

Many of the publications on air pollution and COVID-19 fail to account for other explanations for apparent correlations between air pollution and COVID-19. There have already been debates in the literature on these issues (Brunekreef et al 2021, Villeneuve and Goldberg 2020).

In the ENVI report by Brunekreef et al 2021 (literature cut-off November 2020), there is a description of study designs and the text provides caution for the results of ecological data. The report notes that against the background of well-established methods and findings from air pollution epidemiology studies, investigations on effects of air pollution on COVID-19 are still in their infancy. It continues highlighting the difficulties of investigating air pollution and COVID-19 outcomes and the fact that “lockdown” or restriction measures affect both COVID-19 health outcomes and the levels of air pollution acting as strong confounders. However, the report correctly points out that the hypotheses concerning possible pathways through which high air pollution exposures could interact with COVID-19 transmission and severity are plausible.

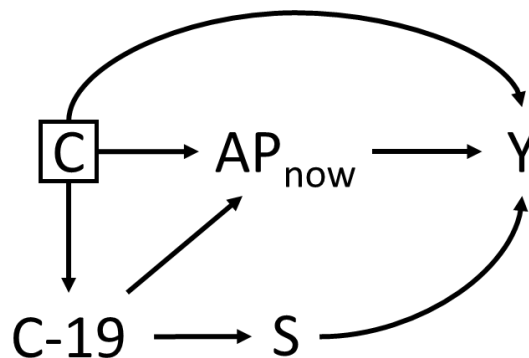
Our expert commentary provides an overview of the studies published since the cut-off date for the Brunekreef review, prioritising descriptions of the better-quality studies.

There are several potential causal pathways between air pollution and COVID-19:

- Long-term exposure to air pollution leading to more susceptible groups (e.g. respiratory and cardiovascular disease) in the population and hence more severe consequences from COVID-19 (these could include susceptible groups that are easily identifiable and those that are not)
- Long-term exposure to air pollution leading to immune system changes or other changes that increase the chance of catching COVID-19
- Short-term exposure to air pollution leading to more severe consequences once people already have COVID-19
- Short-term exposure to air pollution leading to immune system changes that increase the chance of catching COVID-19
- Air pollution increasing exposure to COVID-19 (particles as a carrier)

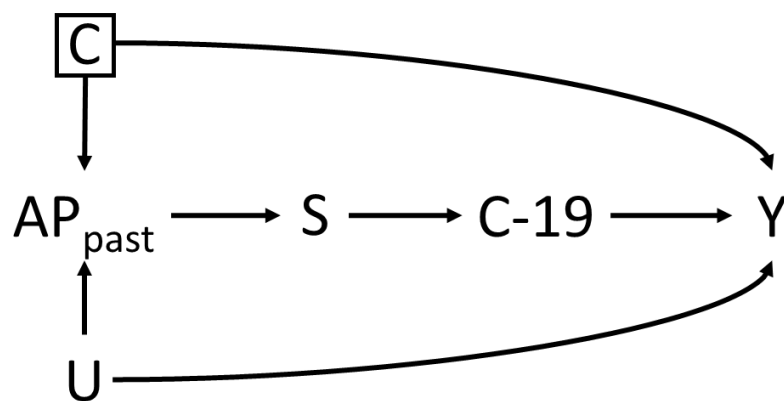
These can be summarized in the following two diagrams,

Figure 1 - Directed Acyclic Graph (effects of short-term exposure to air pollution in the presence of Covid-19).



AP: Air pollution, C: Other risk factors (e.g. race, age, SES, etc.), S: Susceptibility, i.e. diagnosed disease leading to worse prognosis if infected, C-19: Covid-19 infection, Y: Health outcome (e.g. death).

Figure 2 - Directed Acyclic Graph: effects of long-term exposure to air pollution in the presence of Covid-19.



AP: Air pollution, C: Other risk factors (e.g. race, age, SES, etc.), U: unmeasured confounders, S: Susceptibility, i.e. AP affecting immune system, C-19: Covid-19 infection, Y: Health outcome (e.g. death).

We organise the description of studies according to these potential pathways below.

4.2 Approach

We performed an update search on PubMed to add to the studies of air pollution and COVID-19 of which we were already aware. The search was from the cut-off date of Brunekreef et al 2021 in November 2020.

The search strings and numbers of papers excluded at each stage is given in Appendix 6.0.

We also discussed the issues with Professor Marta Blangiardo and Dr Garyfallos Konstantinoudis (Imperial College, London) and Professor Anna Hansell, (University of Leicester), academics who have worked/are working on air pollution and COVID-19 studies (Konstantinoudis et al 2021).

4.3 Short-term exposure on air pollution and COVID-19

Table 1 Studies evaluating associations between short-term exposure to air pollution and COVID-19 (cases, hospital admissions or mortality)

Reference	Study Area/ Design	Exposure Assessment	Outcome
Zhou J et al, Environ Sci Pollut Res Int, June 2021	China, 120 cities/ ecological time-series	O ₃ , NO ₂ , SO ₂ , CO, PM _{2.5} as daily means in each city	Daily confirmed case counts collected from the official website of Harvard University
Ye T et al, Toxics, February 2021	Italy/ case-crossover	Daily averages of PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ , and CO and 8-hour maximum of O ₃	Daily all-cause mortality (stratified by age and gender)
To T et al, Environ Res, January 2021	Ontario, Canada/ ecological time-series	Daily UV and O ₃ data (January to June 2020) averaged across each Ontario PHU (n = 34) from the Environment and Climate Change Canada and the Ontario Ministry of the Environment, Conservation and Parks	Daily incidence or time-varying reproductive number [R _t] from an open dataset compiled by the Ontario Ministry of Health and Long-Term Care based on information reported by local public health agencies
Stufano A et al, Environ Res, July 2021	Lombardy, Italy/ ecological time-series	Daily means of PM ₁₀ , PM _{2.5} , NO ₂ , SO ₂ and O ₃ as collected by the monitoring stations of the Regional Environmental Protection Agency	Total daily numbers of new COVID-19 confirmed cases for each province of Lombardy retrieved from the website of the 'Dipartimento di Protezione Civile' (Italian civil defense body)
Sahoo MM, Environ Sci Pollut Res Int, February 2021	India, 32 states and Union Territories/ ecological time-series	Daily and hourly PM _{2.5} , PM ₁₀ , NO ₂ and SO ₂ from an online platform (www.openaq.org)	Daily notified infected cases from 30 th Jan 2020 to 23 rd Apr 2020 collected from the reports updated by Ministry of Health and Family Welfare, Government of India.

Reference	Study Area/ Design	Exposure Assessment	Outcome
Pei L et al, Environ Sci Pollut Res Int, July 2021	China, 325 cities/ ecological time-series	Daily AQI, PM _{2.5} , PM ₁₀ , NO ₂ , O ₃ and meteorology (up to lag 21) from the China National Environmental Monitoring Centre (CNEMC)	Daily COVID-19 confirmed incidence (to exclude the influence of the population density for COVID-19 confirmed cases)
Moshhammer H et al, Wien Klin Wochenschr, May 2021	City of Vienna, Austria/ ecological time-series	Daily PM ₁₀ and NO ₂ concentrations	Number of new cases per number of already infectious cases, assuming that each COVID-19 case was infectious starting 1 day before diagnosis and remained infectious for another 4 days
Meo SA et al, Sci Total Environ, February 2021	California, USA, 10 counties/ ecological time-series	Daily PM _{2.5} , CO and O ₃ levels obtained from three meteorological sites	Daily cases and daily deaths due to the COVID-19 pandemic collected from the Web
Mele M et al, Environ Res, March 2021	Paris, Lyon and Marseille, France/ ecological time-series	Daily NO ₂ from the monitoring network	Confirmed deaths (total and daily), resuscitations (daily), and hospitalizations (daily) due to COVID-19
Mehmood K et al, Chemosphere, May 2021	Punjab, Sindh, Khyber Pakhtunkhwa, Pakistan/ ecological time-series	Data on daily PM _{2.5} were collected from the US consulate offices	Daily confirmed COVID-19 cases
Magazzino C et al, J Environ Manage, May 2021	New York, USA / ecological time-series	Daily NO ₂ and PM _{2.5} concentrations	Daily COVID-19 deaths
Ma Y et al, Environ Sci Pollut Res Int, April 2021	Shanghai, China/ ecological time-series	Daily AQI and mean concentrations of NO ₂ , SO ₂ , PM _{2.5} , PM ₁₀ , CO, and O ₃ obtained from the China National Environmental Monitoring Center	Daily confirmed COVID-19 cases
Lu B et al, Environ Sci Pollut Res Int, May 2021	China, 41 cities/ ecological time-series	Daily 24-h average levels of ambient PM _{2.5} , PM ₁₀ , SO ₂ , NO ₂ and CO as well as daily 8-h mean levels of O ₃ for each city obtained from https://www.aqistudy.cn/	Daily newly confirmed COVID-19 cases

Reference	Study Area/ Design	Exposure Assessment	Outcome
Lorenzo JSL et al, Environ Res, June 2021	Singapore/ ecological time-series	Daily averages of NO ₂ , SO ₂ , CO, O ₃ , pollutant standards index (PSI), PM _{2.5} and PM ₁₀	Daily confirmed number of COVID-19 cases
Liu Q et al, Environ Sci Pollut Res Int, March 2021	China, Japan, Korea, Canada, America, Russia, England, Germany, and France and 27 municipalities in China/ ecological time-series	PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ and O ₃ collected from real-time air quality index of Air Pollution in the World database (http://aqicn.org). Municipal level data was collected from the National Health Commission of the People's Republic of China.	Daily newly confirmed COVID-19 cases
Kutralam-Muniasamy G et al, Environ Sci Pollut Res Int, July 2021	Nuevo Leon, Veracruz, Tabasco and Yucatan, Mexico/ ecological time-series	Daily AQI from PM _{2.5} and PM ₁₀ levels from 15 air monitoring stations. Also, chronic daily intake (CDI) was estimated for assessing the human health risk upon exposure to PM through the inhalation pathway. Risk assessment for the carcinogenic and non-carcinogenic risk of PM was calculated using the parameter called hazard quotient	Daily COVID-19 cases and deaths during Saharan dust event
Isphording IE and Pestel N, J Environ Econ Manage, July 2021	Germany/ ecological time-series	3-day average of PM ₁₀ and O ₃ based on measurements	Number of confirmed cases and deaths from COVID-19 by county by sex and age group
Hoang T et al, Trop Med Int Health, April 2021	South Korean/ ecological time-series	Daily means of PM _{2.5} , PM ₁₀ , O ₃ , NO ₂ , CO and SO ₂ (seven days lags)	Daily confirmed cases COVID-19

Reference	Study Area/ Design	Exposure Assessment	Outcome
Gujral H and Sinha A, Environ Res, March 2021	California LA and Ventura, USA, Two counties/ ecological time-series	Monitoring site measurements of PM _{2.5} , PM ₁₀ and O ₃ (daily maximum concentration and median concentrations of the monitoring stations for the county-level data were used)	Daily incidence and mortality from the Johns Hopkins database
Díaz-Avalos C et al, Int J Environ Res Public Health, December 2020	New York, USA, 9 counties in the southernmost region/ ecological time-series	Daily PM _{2.5} and O ₃ from the EPA network	Number of COVID-19 “daily infected ratios” from the DoH NY State.
Dales R et al, Environ Res, July 2021	Santiago, Chile, 32 communities and 2 adjacent urban comunas/ ecological time-series	Daily means of NO ₂ , CO, O ₃ and PM _{2.5} from 9 sites, one per sector	COVID-19 daily deaths
Bigdeli M et al, Int J Environ Sci Technol (Tehran), January 2021	Iran, 31 provinces/ ecological time-series	Satellite data for CO, NO ₂ , O ₃ and SO ₂	Density of number of confirmed COVID-19 cases daily in each province (i.e. divided by population)
Pegoraro V et al, BMC Public Health, 2021	Italy/ ecological time-series	PM ₁₀ daily concentration data from air quality monitoring stations for the period January 2020 – June 2020	Pneumonia due to COVID-19
Fernández D et al, Environ Pollut, February 2020	Denver, USA, Barcelona, Spain and Milan, Italy/ ecological time-series	Daily average of PM _{2.5} , PM ₁₀ and O ₃ from the World Air Quality Index project	COVID-19 cases and deaths (daily and total) and time since the last reported case spanning January 21 st to May 18 th , 2020, based on the most recent publicly available population-level information (per country), as reported by WHO

Reference	Study Area/ Design	Exposure Assessment	Outcome
Coccia M, Environ Sci Pollut Res Int, April 2021	Italy, 55 provincial capitals/ ecological time-series	Total days exceeding the limits set for PM ₁₀ or for O ₃ in 2018.	Number of infected individuals in March and April 2020 and number of deaths until May 2020
Ben Maatoug A et al, Environ Sci Pollut Res Int, April 2021	Riyadh, Jeddah, Makkah, Saudi Arabia/ ecological time-series	Daily values of PM ₁₀ , NO ₂ and O ₃ in 3 cities	Daily number of COVID-19 cases and deaths
Ali Q et al, Int J Environ Sci Technol (Tehran), March 2021	Punjab, Sind, Khyber Pakhtunkhwa and Islamabad Capital Territory, Pakistan/ ecological time-series	Daily PM _{2.5} data obtained from the Air Quality Open Data Platform	Infection rate (no of cases/days of COVID-19 infection (outbreak)). Daily COVID-19 statistics from March 10, 2020, to October 04, 2020 obtained from the Government of Pakistan

27 papers were identified as studies looking at short-term exposure to air pollution and COVID-19 incidence and/or mortality (Table 1). These studies were located in Europe, North and South America and Asia, but we could not find any papers from Africa or Oceania. Most of the identified studies conducted standard time-series analysis, while we identified studies that applied machine learning algorithms, simple correlation analysis or geographical weighted regression, and one time-stratified case-crossover study (Ye et al 2021).

Studies that did not perform a proper epidemiological analysis, as described in various textbooks and papers (Baker & Nieuwenhuijsen 2008, Bhaskaran et al 2013), and only present graphs or simple correlation coefficients or did not control for previously known confounders, e.g. temperature and humidity, were not relied upon for overall conclusions as they were regarded as potentially misleading to identify the correct exposure-response associations. All studies identified in our review suffer from a very short time-period, as most of them include time-series data for one to two months. This significantly reduces the statistical power to detect an exposure-response association and might even create spurious associations as just a few influential data-points might create a false positive relationship.

Outcome:

The vast majority of studies looked at the daily confirmed COVID-19 cases to increase statistical power, as this health outcome occurs more frequently than COVID-19 mortality. They did not use cumulative cases, as daily incidence is available at city level, even though ascertainment bias may highly impact these outcomes. Some studies also looked at COVID-19 mortality, although deaths

have significantly lower number of counts than cases. Other outcomes that have been examined include all-cause mortality during the pandemic period (Ye et al 2021). Moreover, other endpoints that have been examined are resuscitations and hospitalisations due to COVID-19 (Mehmood et al 2021), daily infected ratios (Díaz-Avalos et al 2020), time-varying reproductive number [Rt] (To et al 2021) and daily confirmed COVID-19 incidence per number of already infectious cases (Moshammer et al 2021). For the latter, it was assumed that each COVID-19 case was infectious starting 1 day before diagnosis and remained infectious for another 4 days which might be questionable as this period might differ based on various factors, such as the variant of the virus, the lockdown phases, meteorology and others.

Confounding:

Proper control for confounding is important in any epidemiological study, and this becomes even more profound in air pollution epidemiological studies with COVID-19 health endpoints, as apart from the traditional confounders in time-series analyses (e.g. meteorology and seasonality), there are other factors that can distort the exposure-response associations, such as COVID-19 measures, lockdown stages, population mobility and density. Only a few studies have actually managed to take this into account in their statistical analysis (Sahoo 2021, Stufano et al 2021, To et al 2021), while failing to control for these factors might create false positive associations between air pollution and COVID-19 mortality and cases. There is a considerable number of published papers that either have not properly adjusted for important confounders in their analysis or they failed to mention control for confounding in their methods (Bigdeli et al 2021, Meo et al 2021, Mele et al 2021, Magazzino et al 2021, Liu et al 2021). In addition, most studies include only meteorological factors as potential confounders, such as temperature, relative humidity and wind speed. These variables are important and have generally been included in time-series studies over the last decades along with temporal/seasonal trends and day of the week (Bhaskaran et al 2013), which, surprisingly, are not included in most of the identified studies. In addition, the factors that are missing from most of the studies but are potential confounders, are indicators about the COVID-19 measures taken to decrease contacts, mobility and population density. These factors are associated both with the exposure to air pollution, since people's mobility, including the use of the car fleet, or lockdowns and their different stages (full/partial/local) can affect outdoor concentrations, and the health outcome, as these measures prevent the spread of the virus.

Exposure Assessment:

The associations between COVID-19 related outcomes and a wide range of different pollutants have been examined, including PM₁₀, PM_{2.5}, NO₂, O₃, SO₂ and CO. Some studies have also used the Air Quality Index (AQI) as the exposure of interest (Pei et al 2021, Ma et al 2021, Lorenzo et al 2021, Kutralam-Muniasamy et al 2021). The averaging time is 24-hour averages for all pollutants, except ozone for which daily 8-hour maximum is used. The air pollution concentrations are generally obtained from fixed monitoring stations and the number of sites used depends on the density of the monitoring network within each city. There was one study that used satellite data for their exposure assessment (Bigdeli et al 2021). As explained above, the duration of the studies is short, with air pollution concentrations for a time period as low as less than one month.

Main Findings:

There is considerable heterogeneity in the study findings as was expected due to the various limitations that have been described above. Short time-periods, no proper adjustment for confounders and the fact there have been significant changes due to the lockdown measures might well explain this heterogeneity. More specifically, a number of studies report no consistent associations for all pollutants that they included in the analysis (Stufano et al 2021, Ma et al 2021,

Bigdeli et al 2021, Meo et al 2021, To et al 2021, Hoang et al 2021). Others report strong positive associations for specific pollutants, some of which are interpreted as causal and go up to 34.8% (95% CI: 29.3%– 40.4%) increase in the daily confirmed COVID-19 cases for a unit increase in daily NO₂ (Ye et al 2021, Sahoo 2021, Zhou et al 2021, Mehmood et al 2021, Magazzino et al 2021, Lu et al 2021, Lorenzo et al 2021, Dales et al 2021). We think that these results should be treated with caution as there might be serious flaws in their analysis, such as residual confounding or even no control for confounding, while various machine learning methods applied show associations which are interpreted as causal without clear justifications. On the other hand, there are studies that report statistically significant negative associations, implying that air pollution may have a protective effect on COVID-19 health endpoints (Sahoo 2021, Lorenzo et al 2021, To et al 2021). These are less in number compared to those that report adverse effects, but publication bias may be a possible explanation, especially if one takes into account the urgency for some results that could have been used to inform policies during the pandemic. We feel that these findings should also be interpreted with caution, as these associations might be a result of confounding, especially from lockdown measures which, as stated in Brunekreef et al 2020, *“have created artificial correlations between declines in air pollution and COVID-19 over time”*. Finally, there are no consistent findings for specific pollutants and these conclusions seem to hold for all exposures that have been examined, including PM₁₀, PM_{2.5}, NO₂, O₃, SO₂, CO and AQI.

Toxicological commentary on short term exposure and worsening COVID 19 outcomes

SARS-CoV-2 can generate mild or strong pathological responses, with excessive inflammation and ‘cytokine storms’ associating with more severe disease states (Tang et al 2020). In particular, very high quantities of the pro-inflammatory cytokine, IL-6, have been detected in the blood of patients with severe COVID-19 (Mehta et al 2020). Short term exposure to PM₁₀ has also been associated with increased circulating IL-6 levels in the general adult population (as well as other pro-inflammatory cytokines, IL-1 β and TNF- α) (Tsai et al 2012) with cell culture and rodent models strongly supporting a link between air pollutants and cytokine secretion (Gerlofs-Nijland et al 2019, Schwarze et al 2013, Ayygari et al 2004).

As such it has been hypothesised that a heightened inflammatory state may occur when the already inflamed lungs of patients are exposed to inflammatory air pollutants (or vice versa) (Lai et al 2021, Signorini et al 2021). This additive inflammatory effect of SARS-CoV-2 and air pollution is yet to be validated experimentally, but, with cytokine storms predicted as a major determinant of COVID-19 severity (Tang et al 2020) it is important to identify and mitigate against contributing factors for disease progression.

The mechanisms by which cytokine storms cause severe COVID-19 include excessive and dysregulated immune cell activity. Pro-inflammatory cytokines recruit immune cells (neutrophils and monocytes) to the alveoli where they release proteases (protein digesting enzymes) and reactive oxygen species as a component of their anti-microbial arsenal. While intended to destroy pathogenic proteins, these molecules do not act selectively, and so excessive quantities, as produced during severe inflammation, can damage the alveolar walls, impairing gas exchange and leading to respiratory failure (Moldoveanu et al 2009). Many cytokines also promote thrombosis, leading to the development of microthrombi in blood vessels. Development of microthrombi in the cardiac vessels is associated with cardiac injury and failure in patients that develop severe COVID-19 (Pellegrini et al 2021).

Acute Respiratory Distress Syndrome (ARDS) often associates with mortality during severe COVID-19 infection (Hsu et al 2021). Studies of hospital admissions and emergency ambulance dispatches

demonstrate significant, positive associations between ARDS cases and acute spikes in ozone, PM₁, PM_{2.5} and PM₁₀ concentrations (Rhee et al 2019, Rush et al 2017 and Lin et al 2018), indicating another pathway by which pollutant exposure might accelerate COVID-19 progression. Due to the dry cough that accompanied early cases of SARS-CoV-2 infection, it was postulated that COVID-19 related ARDS is perpetuated by epithelial barrier dysfunction rather than endothelial damage (which creates alveolar exudates) (Li and Ma 2020). Damage to the pulmonary epithelium has been observed following PM exposure *in vitro*, with PM₁₀ and diesel exhaust particles disrupting tight junctions and inducing occludin internalization (Caraballo 2013).

Toxicological commentary on short-term exposure and increased infection with COVID-19

Some general mechanisms suggested for explaining a link between air pollution and lower respiratory infections has been discussed in Section 3.0. Since the start of the pandemic, there has understandably been intense research into the mechanisms by which the SARS CoV-2 virus infects the human body. The first step for the virus to enter a cell, in order to replicate, involves the Angiotensin-converting enzyme-2 (ACE2) receptor to which the virus spike protein binds (Figure 3). This is followed by cleavage (cutting) of the spike protein by trans-membrane protease serine 2 (TMPRSS2). This in turn allows the virus to fuse with the cell membrane and enter the cell. (The process of receptor binding followed by removing part of the amino acid chain to 'activate' the binding protein is a common one in biology, that is taken advantage of by the virus in this case). In health, ACE2 maintains blood pressure, facilitating activation of angiotensin I and II (Burrell *et al.* 2004). Although TMPRSS2 is strongly implicated in viral infection and prostate cancer, its function in health requires further investigation.

Infection of the host cell by SARS-CoV-2 is described here in some detail because we identified several papers that examined whether air pollution increases the expression of the ACE-2 receptor and/or TMPRSS2. Presenting early results from experimentation into the impacts of very acute exposure (2h) to PM₁₀ collected from Marylebone Road, London, Miyashita *et al* (2020) measured ACE2 expression *in vitro* using flow cytometry. In cultures of A549 human alveolar epithelial cells, significant, dose-dependent increases in ACE2 signal were detected (relative to particle-free controls) following exposure to 10 and 20 µg/ml PM₁₀. These changes were consistent with the cellular response to 5% cigarette smoke which was used as a putative positive control for heightened ACE2 expression. The 10 µg/ml PM₁₀ exposure also caused increased ACE2 expression in human primary nasal epithelial cells but data for the higher dose was not presented (Miyashita *et al* 2020). Together these data demonstrate that real-world, urban particles have potential to alter expression of host susceptibility proteins in the upper and lower airways.

Focusing *in vivo*, Sagawa *et al* (2021) exposed mice for 24h to 500µg PM_{2.5} or PM₁₀ from Yokohama, Japan using intratracheal instillation. Employing immunohistochemical techniques, they identified increases in ACE2 and TMPRSS2 protein expression in the alveolar region of the lungs. As well as the overall amount of protein, the number of cells expressing ACE2 and TMPRSS2 was significantly higher after PM exposure than it was for control mice. Importantly, these changes were most predominant in the areas surrounding particle deposition. Using markers specific for type II epithelial cells (AT2) and macrophages, Sagawa *et al.* found that ACE2 and TMPRSS2 over-expression occurred predominantly in type II epithelial cells but also in macrophages (Sagawa et al 2021).

Alveolar macrophages are the primary players of the innate immune system, secreting a wide range of inflammatory cytokines and antimicrobial molecules when stimulated by toxic material. They also undergo a process called phagocytosis, whereby they engulf and attempt to destroy the particle or pathogen. Cell culture experiments demonstrate that SARS-CoV-2 infection does stimulate THP-1

monocytes and macrophages to release cytokines and deplete the virus (Boumaza et al 2021). However, experiments have not been performed to determine whether this continues to occur if the cell has been pre-exposed to PM. The ability of pollutants to impair clearance of other respiratory pathogens has long been documented (Lundborg et al 2006, Kaan and Hegele 2003, Selley et al 2020, Duffney et al 2020, Rylance et al 2015a) so it is plausible to consider that PM exposure could reduce clearance of SARS-CoV-2 from the alveoli, thus enabling infection to take hold.

In a letter to the editor of *Zoological Research*, Zhu *et al.* (2021) described the first experiments to directly measure the impact of PM exposure on viral infectivity. Human alveolar epithelial cells were exposed to urban PM (NIST 1648) for 24h (50 or 200µg/ml) then inoculated with SARS-CoV-2. As well as expressing greater levels of ACE2 and TMPRSS2, the PM-exposed cells contained more viral spike protein than particle-free cells (Zhu et al, 2021), indicating that PM exposure enhanced viral entry into the cells. The authors exposed ACE2 humanised mice (mice that are bred to express human ACE2) to NIST 1648 (400µg) via intranasal inoculation and then to SARS-CoV-2 after 3 days. Consistent with the cell culture experiments, PM-exposed mice expressed more ACE2 and TMPRSS2 than control mice and had higher viral loads both 1 and 3 days post-infection. PM-exposed mice also displayed more severe congestion than the control mice and had higher expression levels of COVID-19 related inflammatory cytokines. The authors suggest that PM exposure may have worsened the severity of disease, but without results from a longer post-exposure period, it is difficult to confirm this. Such experiments may be limited by ethical factors.

Together these studies suggest that by up-regulating ACE2 and TMPRSS2 expression, air pollution could increase susceptibility to infection of airway cells by SARS-CoV-2. It is important to note however, that not all of the studies examine specifically whether air pollution increases the infectivity of SARS CoV-2. These are challenging experiments to do given the risks of working with the virus and means that the effect of air pollution on infectivity is often inferred rather than demonstrated directly. In addition, the pollutant doses used were considerably higher than those experienced during usual human exposures, meaning that caution should be taken when extrapolating the results to human populations.

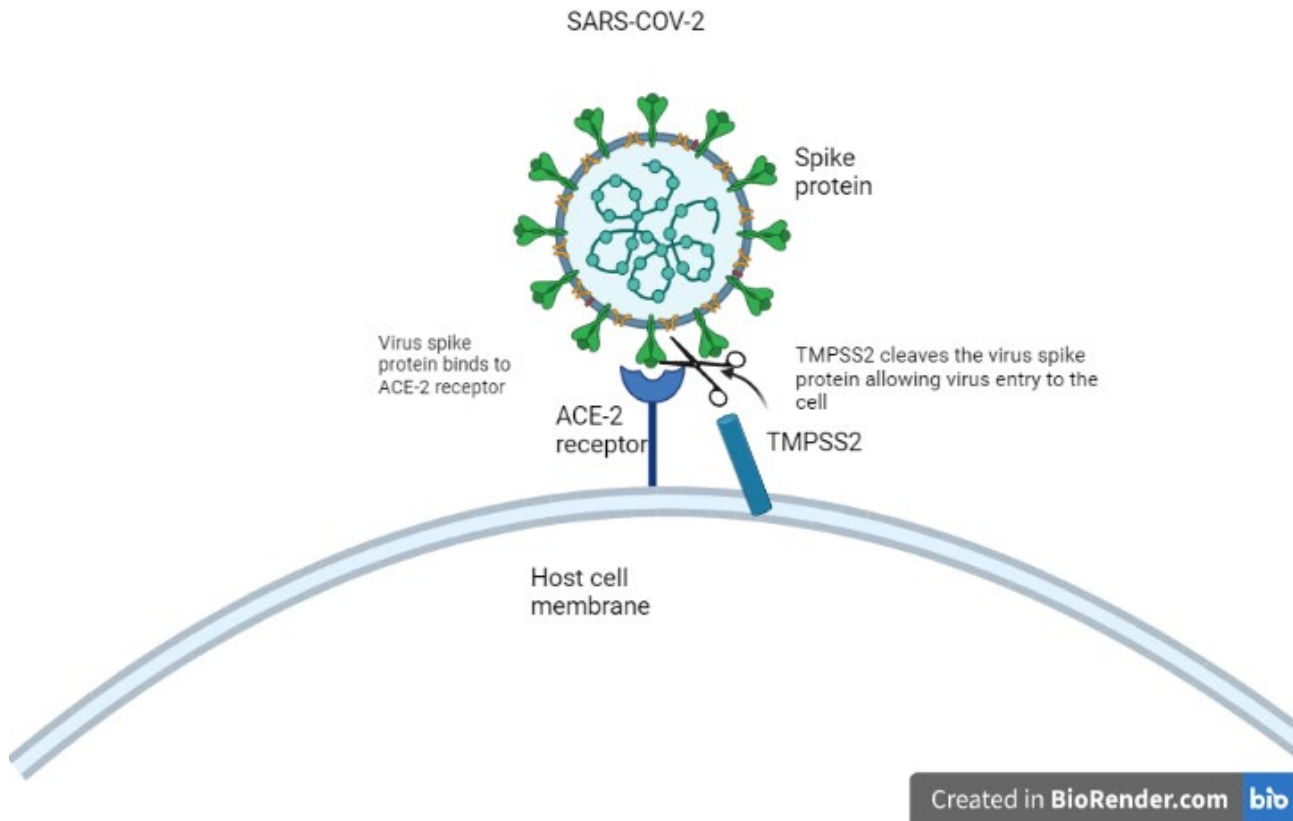


Figure 3 ACE-2 angiotensin converting enzyme-2 TMPRSS2 Trans-membrane protease serine 2

4.4 Long-term exposure on air pollution and increase in susceptible groups at risk of severe consequences of COVID-19

Literature search results

Thirty-four papers were identified from the search. Table 2 shows the reference, area of study, study design, exposure and health outcome used.

Of these, 29 papers applied an ecological approach, analysing aggregated data by spatial unit (with a spatial resolution ranging from country to neighborhood or small administrative unit level), and 5 used individual data.

Table 2 Studies evaluating associations between long-term exposure to air pollution and COVID-19 (cases, hospital admissions or mortality)

Reference	Study Area/Design	Exposure assessment	Health outcome
Zheng P et al, Environ Pollut, May 2021	324 cities in China/ ecological	Daily data PM _{2.5} , PM ₁₀ , SO ₂ , CO, NO ₂ and O ₃ for each city, from air quality stations across China from January 2015 to March 2020. For each city, the average concentration for each pollutant before the COVID-19 outbreak (January 2020) was calculated across the entire available period	Confirmed COVID-19 cases, Severe COVID-19 cases, COVID-19 deaths
Zhang Y et al, Mech Ageing Dev, Mar 2021	UK Biobank cohort/ individual	Exposure data were collected by the Small Area Health Statistics Unit as part of the BioSHaRE-EU Environmental Determinants of Health Project (http://www.bioshare.eu/). PM _{2.5} , PM ₁₀ , NO ₂ and Nox	COVID-19 infection
Zaldo-Aubanell Q et al, IJERPH, April 2021	Catalonia, by basic health area/ ecological	2016 NO ₂ and PM ₁₀ annual average using exposure modelling from the General Direction of Environmental Quality and Climate Change of the Catalan Government and an annual weighted average for each BHA was calculated	COVID-19 Cases and Deaths
Tripepi G et al, Eur J Pub Health, Feb 2021	Italy, 107 provinces/ ecological	O ₃ as effect modifier (no more details)	SARS-CoV-2 cases (including active cases, recovered/discharged patients and deceased) on 21 March 2020 in Italian provinces were obtained via a public data repository of Padua University, Department of Public Health, which acquires the data from the National Civil Protection Department.
Tian T et al, Infect Dis Pov, Jan 2021	U.S. 3125 counties/ ecological	Average daily PM _{2.5} (µg/m ³) from Environmental Public Health Tracking Network	Number of cumulative confirmed cases and deaths from March 1 to August 27, 2020, for counties in the United States from the New York Times

Reference	Study Area/Design	Exposure assessment	Health outcome
Rodriguez-Villamizar LA et al, Sci Total environ, Feb 2021	Colombia, 1122 municipalities/ ecological	PM _{2.5} from Copernicus Atmospheric Monitoring Service CAMS Reanalysis (CAMSRA) and CAMS Near Real-Time (CAMSNRT) Monthly average gridded data at a 0.125-degree resolution from January 2014 to December 2018. PM _{2.5} concentrations at the centroid of each municipality by mathematical interpolation from the nearest four retrieved CAMSRA* concentrations. Additionally, in order to evaluate the responsiveness of CAMS-based estimation of PM _{2.5} concentrations, as a support for data validation, exposure data were evaluated for the quarantine period (between March 1 and August 31, 2020) using CAMSNRT	Data related to the number of confirmed cases and deaths for COVID-19 and the number of RT-PCR tests to confirm positive cases of infected people from the National Institute of Health (INS) website
Pansini R & Fornacca D, Front Pub Health, Jan 2021	Chinese prefectures/ ecological	PM _{2.5} , PM ₁₀ , O ₃ , NO ₂ , SO ₂ , CO from ground monitoring stations for 2014 to 2016, while UV Aerosol Index, CO, HCHO, NO ₂ , O ₃ , SO ₂ in 2019 were also assessed using satellite data	COVID-19 infection and fatality figures for every prefecture of the People's Republic of China (2 nd administrative divisions, equivalent to U.S. counties) from the Chinese government health commission COVID-19 cases and deaths analyzed in this study captured the first and unique wave of SARS-CoV-2 infection for this country (19 December 2019–23 May 2020).
Naqvi HR et al, Remote Sens Appl, April, 2021	India, by region/ ecological	Air Quality Index (AQI), PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ , O ₃ monthly average data for pre-lockdown (February 25 th , 2020 and March 24 th , 2020) and post-lockdown (March 25 th , 2020 and April 24 th , 2020) periods from the Central Pollution Control Board (CPCB) portal (https://cpcb.nic.in/) & remote sensing data from Copernicus Sentinel-5 to determine the average monthly spatial variations in tropospheric NO ₂ concentrations	COVID-19 mortality (as of 1 June 2020) from different portals handled by the Ministry of Health & Family Welfare & investigation was performed after 2 weeks (as of 15 th June 2020) of updated COVID-19 mortalities to assess the variations in the relationship between these variables.

Reference	Study Area/Design	Exposure assessment	Health outcome
Mendy A et al, Respir Med, Mar 2021	Cincinnati Metropolitan area/ individual	0.01°×0.01° grid from Van Donkelaar et al 2019, 10-year average	Hospitalization, defined as admission for a duration of ≥24h to a hospital or clinic within the UC healthcare system for COVID-19 following the diagnosis of the infection.
Liu S & Li M, Rev Panam salud Publica, Nov 2020	U.S by county/ ecological	O ₃ , NO ₂ , CO, SO ₂ and PM _{2.5} at county-level from EPA website	County-level total COVID-19 deaths up until 14 May 2020 as a percentage of the county's total 2019 population estimate.
Lipsitt J et al, Environ Int, Mar 2021	U.S. LA county by neighborhood	LUR model (30m resolution) using data from 2016	COVID-19 incident case rate, mortality rate and case-fatality rate, and hypertension and diabetes (potentially associated with COVID-19 severity)
Lembo R et al, Acta Biomed, Feb 2021	Europe / ecological	Six air pollution agents (PM ₁₀ , PM _{2.5} , NH ₃ , SO ₂ , non-methane volatile organic compounds and NO ₂) up to 2017	Number of SARS-CoV-2 positive and COVID-19 deaths per country (11 th February to 17 th May 2020). Cases and deaths normalized for population aged over 65 years old
Konstantinoudis G et al, Environ Int, Jan 2021	England, 32844 LSOAs/ ecological	2014-2018 average NO ₂ and PM _{2.5} concentration in England from the Pollution Climate Mapping (PCM) which produces annual estimates during 2001–2018 for NO ₂ and 2002–2018 for PM _{2.5} at 1x1km resolution for the UK. Exposures were weighted using a combination of population estimates.	COVID-19 deaths with a laboratory confirmed test as reported to Public Health England (PHE) by June 30, 2020 (38,573 in total).
Kim H & Bell ML. Am J Respir Crit Care Med, May 2021	New York, 177 neighbourhoods/ ecological	Annual average PM _{2.5} levels from December 2008 to December 2018 and summer (June-August) average O ₃ levels from 2009 to 2018 in 300m raster	COVID-19 confirmed mortality from February 29, 2020 to January 5, 2021.
Hutter HP et al, IJERPH, Dec 2020	Austria, Vienna by district/ ecological	2019 annual average levels of NO ₂ and PM ₁₀ based on daily mean values from sites with at least 75% data availability run by EEA. As not all districts had a site, “a binary variable equal or above versus below the upper quartile of all districts (20µg/m ³ for PM ₁₀ , 30µg/m ³ for NO ₂)” was used	Daily reported COVID-19 cases and deaths, 28 Feb 2020 to 21 Apr 2020

Reference	Study Area/Design	Exposure assessment	Health outcome
Huang G & Brown PE, Spat Spat, Mar 2021	Germany, county level/ ecological	PM _{2.5} , PM ₁₀ , NO ₂ , SO ₂ and benzene, arsenic, cadmium and nickel: modelled population-weighted exposure using 2016–2018 data from EEA monitoring sites and fine gridded population density	Accumulated COVID-19 cases up to 13 th September 2020 at county level
Hou CK et al, J Med Virol, May 2021	China, 14 major cities/ ecological	1- , 3-, and 5-year averages for Air quality index (AQI), PM _{2.5} , PM ₁₀ , SO ₂ , NO ₂ and O ₃	The number of confirmed cases, deaths, and discharges during the epidemic period (until 28 April 2020). Case fatality rate was calculated (number of deaths/(number of deaths + number of discharges)))
Hassan MS et al, Environ Monit Assess, Jan 2021	Bangladesh, Dhaka, by small unit/ ecological	PM _{2.5} , NO ₂ , aerosol optical thickness (AOT), SO ₂ , CO, water vapor and O ₃ of the period 2010–2020 . Also, annual average of high-resolution atmospheric data from different satellites was analyzed.	Daily Thana (small administrative unit of Bangladesh) wise COVID-19 infection rate
Elliott J et al, Eur J Epidemiol, Mar 2021	UK, UK Biobank cohort/ individual	Modelled Nox, PM ₁₀ , PM _{2.5} , PM _{2.5} absorbance at residential address, Kees et al 2013	COVID-19 mortality
Dettori M et al, Environ Res, Apr 2021	Italy, 107 provinces/ ecological	Annual PM ₁₀ , PM _{2.5} and NO ₂ averages from fixed monitoring sites	Standardised Mortality Rate from COVID was used which indirectly standardizes for age
Deguen S & Kihal-Talantikite W, IJERPH, Feb h2021	France, Department/ ecological	NO ₂ from monitors located within each department.	Total number of hospitalized persons due to COVID-19 infection, total number of severe COVID-19 cases in the intensive health care in the hospital, total number of deaths at the hospital caused by COVID-19 infection, and total number of hospitalized patients recovered and returned back home.
De Angelis E et al, Enviro Res Apr 2021	Italy, Lombardy, 1439 municipalities/ ecological	PM _{2.5} , PM ₁₀ and NO ₂ 2016-19 averages from chemical transport model with 4 km ² grid validated against measurements. Weighted mean concentration per municipality was calculated.	Incidence of COVID-19 from 20/2/2020 to 16/4/2020 and excess in all-cause mortality from 1/3/2020 to 30/4/2020

Reference	Study Area/Design	Exposure assessment	Health outcome
Correa-Agudelo E et al, IJERPH, Apr 2021	U.S. 3142 counties/ ecological	Surface annual particulate matter satellite PM _{2.5} images for 2000-2018	COVID-19 deaths, ratio of observed over expected, per county
Chakraborty J, Environ Res, Feb 2020	U.S. 3108 counties/ ecological	187 hazardous air pollutants from EPA report 2018 NATA, combined in respiratory hazard index. One county excluded for not having the index value.	COVID-19 incidence, number of confirmed cases by county per 100,000 population, Jan 22 to Nov 13 2020
Cascetta E et al, IJERPH, Jan 2021	Italy, 107 provinces/ ecological	PM _{2.5} and PM ₁₀ annual average from ARPA	Number of hospitalized residents and number of positive tests for COVID-19 from March to July 2020 Data were taken from the Civil Protection
Barnett-Itzhaki Z & Levi A, Environ Res, Apr 2021	36 OECD countries/ ecological	Percentage of population exposed to PM _{2.5} levels above WHO guidelines from World Bank website	Number of confirmed cases, number of deaths, rate of mortality among cases, mortality in the population, all country level between 12/1/2020 and 7/6/2020
López-Feldman A et al, Sc Total Environ, Feb 2021	Mexico city/ individual	Average of PM _{2.5} satellite and WHO measurements (Hammer et al 2020) in 1.1km ² grids for 2000-2019. Short-term exposures from ground measurements and weighted averages based on distance for 76 municipalities in Mexico City.	COVID-19 deaths among cases
Fiasca F et al, JERPH, Dec 2020	Italy 62 provinces/ ecological	Average weekly levels of PM _{2.5} and NO ₂ from EEA, stratified by provinces and metropolitan cities. Average concentrations across three periods: 2016–2020 years, to evaluate historical data, March–May 2020, to assess current concentrations during the months of the first wave of coronavirus, and March-October 2020, to analyze pollutant levels for the entire epidemic period.	Number of COVID-19 cases, stratified by provinces, updated on 24 June 2020, for the first wave of coronavirus infection, and on 3 November 2020, to consider the entire epidemic period.
Solimini A et al, Sci Rep, Mar 2021	International, 63 countries, 730 regions/ ecological	PM _{2.5} and PM ₁₀ from the Copernicus Atmosphere Monitoring Service	Cumulative number of COVID-19 cases in the 14 days following the date when more than 10 cumulative cases were reported.

Reference	Study Area/Design	Exposure assessment	Health outcome
Sharma GD et al, Environ Sci Pollut Res Feb 2021	International, 10 countries/ ecological	PM _{2.5}	COVID-19 deaths and cases
Hu H et al, Sci Total Environ, May 2021	U.S. by county/ ecological	Several environmental data at county level obtained from various sources. In total 377 variables, including 6 pollutants; 7 PM _{2.5} components; 164 air toxicants; 98 food environment and 19 vacant land	COVID-19 mortality until October 2020.
Filippini T et al, Sci total Environ, Mar 2021	Italy, Veneto & Emilia Romagna, 15 provinces/ ecological	Satellite Copernicus data for NO ₂ from 1 to 24 February at 7 km ² grid.	Mortality rate by province
Bowe B et al, Environ Int, Apr 2021	US Veterans Cohort/ individual	PM _{2.5} exposure model for 2018 at 1 km ² resolution. Coordinates of residential address assigned the appropriate grid value.	COVID-19 hospitalization: first admission 7 days prior to 15 days after testing positive.
Chakrabarty RK et al, Sci Total Environ Mar 2021	U.S. by State/ ecological	Modelled long-term exposure averages of PM _{2.5} and components for 2012-2017. Based on correlation analysis, PM _{2.5} mass and Sulfate-Nitrate-Ammonium was included in the epidemiological analysis.	State-wise R ₀ values obtained by fitting the prediction of a susceptible-exposed-infected-recovered (SEIR) model to confirmed COVID-19 cases

Ecological studies

Ecological analyses seek to provide evidence that higher long-term population exposure to one or more air pollutants or an air pollution index, is associated by an increase in COVID-19 related health outcomes, such as the number or rates of confirmed cases, or hospitalizations, or deaths. The underlying hypothesis, which is plausible, whether stated explicitly or implied, is that exposure to air pollution either increases the group of susceptible individuals to severe COVID outcomes (hospitalization, death) or even increases transmissibility. The ecological approach is relatively cheap and quick to apply as the data needed are usually collected for other purposes, thus providing a good opportunity to get an initial impression of what may be the association hypothesized. To assess long-term effects that data need to be aggregated by geographical area. However, a major problem with this type of analysis, as identified in most basic Epidemiological handbooks (Baker & Nieuwenhuijsen 2008), is the so called “ecological fallacy”, resulting from the fact that geographical areas do not only differ by air pollution levels but also by many other factors (other environmental, socio-economic, demographic and even genetic). This leads to the possibility that relationships identified at an ecological level cannot be identified at the individual level (the fallacy). Researchers attempt, with varying success, to adjust for these potential confounding factors. In order to apply an adjustment, data is needed for the confounding variables at the same spatial resolution. Additionally, both exposure to pollution and confounders are expressed at an area level in this type of analysis, assigning the same exposure to the whole population, thus incorporating a varying degree of measurement error with consequences for the estimates of association.

In the ENVI Report (end of 2020) (Bruneekreef et al 2021), no separate sections are devoted to studies of short- and long-term exposures, maybe because the database of studies was much smaller and the quality less good at the end of 2020 compared to mid-2021, but there is a description of study designs and the text provides caution for the results of ecological data. The Report notes that *“Against the background of well-established methods and findings from air pollution epidemiology studies, investigations on effects of air pollution on COVID-19 are still in their infancy”* (p.13). It continues highlighting the difficulties of investigating air pollution and COVID-19 outcomes and the fact that “lockdown” or restriction measures affect both COVID-19 health outcomes and the levels of air pollution acting as strong confounders. However, the Report correctly points out that the hypotheses concerning possible pathways through which high air pollution exposures could interact with COVID-19 transmission and severity are plausible and concludes that *“Such effects are possible and even likely for COVID-19 as well, but further, careful research is needed to quantify such effects reliably preferably involving the study of individuals with well-characterized exposure to air pollution and other risk factors and well characterized disease manifestations”*.

We think that ecological analyses with good and careful adjustment of confounders can provide useful evidence even when residual confounding may not be excluded. Also, since the beginning of 2021 further studies have been reported providing a larger database of reports and somewhat better adjustment for confounders.

Among the ecological studies (n=29) presented in Table 2, 10 have no real consideration for confounding effects. These studies either present only simple correlations or apply geographical association models or identify clusters or areas which among other characteristics have higher air pollution levels or just apply large scale association methods or have major methodological problems (Tripepi et al; Tian et al; Pansini & Fornacca; Naqvi et al; Liu & Li; Hou et al; Hassan et al; Deguen & Kihal-Talantikite; Hu et al; Hutter et al). These will not be further considered in this review but are included in Table 2 to allow the reader access to complete information.

Four studies include pollution and health data at country level: Lembo et al analyze data for 33 European countries; Barnett-Itzhaki & Levi data on 36 OECD countries; Solimini et al data from 730 regions in 63 countries; and Sharma et al data from 10 countries. Considering the fact that within country variability in air pollution levels is large in most countries and adjustment for confounders is necessarily very crude, the meaning of higher pollution concentrations and what these may reflect in terms of other environmental, SES and demographic characteristics, leads to considering the results from such studies as showing non-causal associations.

Among the other 15 ecological studies, 5 use data from the U.S., 1 from China, 8 from European countries among which 5 are using national or regional data from Italy and 1 from Colombia.

Chakraborty (2020) addressed the association of “Hazardous Air Pollutants” (HAP) and socioeconomic and other vulnerability factors with the prevalence of COVID in all counties (n=3108) in the continental U.S. The COVID-19 cases were downloaded on Nov 13, 2020 and the number of confirmed cases per 100,000 population was calculated and used for the analysis. The HAPs were 187 substances considered as hazardous for health and their concentration per county was recorded from the E.P.A. NATA database (2018). The Cumulative Respiratory Risk from HAP exposure was used. The analysis attempted to identify whether socially disadvantaged groups are overrepresented in counties where higher COVID-19 exposure spatially coincides with higher HAP respiratory risk. Several SES, health and spatial variables were taken into account. Counties were

classified into categories according to high or low COVID-19 and HAP respiratory risk and the various categories described in terms of SES, age, population density and other variables. Further analysis indicated which of these variables is a predictor for a county to belong to the high-high category. Thus, the association of long-term exposure to HAPs was not assessed, but the results identified that counties belonging to the high-high category were more likely to be in the southeastern U.S. and in California, whilst a higher proportion of non-hispanic blacks, adults without high-school education, socioeconomically deprived residents, people with disabilities, those without health insurance is a predictor of belonging to the high-high category. Although the results cannot be used to assess the role of air pollution in COVID-19 related health outcomes, they give us evidence on the potential confounders that must be taken into account.

Chakrabarty et al (2021) estimated the State-wise time-averaged R_o between March 2 and April 30, 2020 using state-of-the-art methodology. $PM_{2.5}$ long-term, 2012-2017, exposure levels by State were based on observations from ground-level measurements, GEOs-Chem model outputs and satellite data. Generalised additive models (GAM) were used to examine the association between $PM_{2.5}$ level and R_o . Forty-three State level potential confounders were considered including the age distribution of the population, SES variables, characteristics of the health care system, variables related to the testing procedures, family size and other pollutants and meteorological variables. The results indicate that for $PM_{2.5}$ levels below $6 \mu g/m^3$, an increase by 1 unit in long-term exposure is associated with a 0.25 increase in the R_o . However, there is no association in counties with $PM_{2.5}$ concentrations above $8 \mu g/m^3$, a result not discussed by the authors, which appears hard to explain.

Correa-Agudelo et al also analyzed data in the U.S. by county and assessed (among other characteristics) the association of $PM_{2.5}$ long-term exposure (2000-2018) with the ratio of observed over expected -based on population size- COVID-19 deaths between 22 January and 1 September 2020. They accounted for several confounders: age distribution, ethnicity, SES, air hub and road connectivity, population health, health care system. The results show that the COVID-19 mortality rate was higher by 14% in counties with higher $PM_{2.5}$ by $1 \mu g/m^3$ and it was associated with several other population, SES, connectivity, health and ethnicity characteristics.

Lipsitt et al analyzed the incidence case rate for COVID-19 cases, the mortality and case-fatality rates in the Los Angeles County in the U.S., by neighborhood statistical area, in relation to long-term NO_2 exposure based on a Land-Use-Regression model. Potential confounders considered included demographic characteristics, age, race, SES variables, population, smoking, obesity, hypertension, diabetes, health care system related variables and spatial misalignment of the data was taken into account. The results indicate that an increase in long-term NO_2 concentrations equal to an IQR (8.7 ppb) was associated with a 1.5-1.8 increase in the case-rate and a 1.7 to 1.9 increase in the mortality rate but was not associated with the case-fatality rate. The results remained robust in sensitivity analyses.

Kim and Bell conducted an analysis of the association between long-term exposure to $PM_{2.5}$ (2008-2018) and summer ozone (2009-2018) in 177 neighborhoods of NY city and COVID-19 confirmed mortality from February 29, 2020 to January 5, 2021. They adjusted for several confounders, including number of tests, confirmed number of cases, age, population density, SES, health care system characteristics and health related variables. The results indicated an increase in COVID-19 mortality associated with increased ozone but not with $PM_{2.5}$.

Filippini et al explored the association between COVID-19 province (n=16) specific mortality rates and NO₂ exposure in two Italian regions (Veneto and Emilia Romagna) between February and April 2020. NO₂ was retrieved from the Copernicus satellite for a grid of 7km² from which a population weighted spatial average for each province was computed. The data were validated against measurements and missing values were imputed. Temperature and humidity, population mobility, the presence of airports, population density and age were adjusted for. Results were compatible with a non-linear increase in COVID-19 mortality rates for levels of NO₂ >100 µmol/m³.

De Angelis et al analysed the association of COVID-19 incidence (February 20 to April 16, 2020) and mortality (March 1 to April 30, 2020) with PM_{2.5}, PM₁₀ and NO₂ long-term concentrations in Lombardy, Italy, at Municipality level (n=1439). The authors accounted for several confounders including time since first reported case, population size and density, age, sex, family size, SES variables, mobility, health care and population health related variables as well as for temperature and humidity. The results indicated that an increase of 10µg/m³ in PM_{2.5} and PM₁₀ (2016-2019) was associated with an increase of 58% and 34% in COVID incidence respectively. NO₂ was inversely associated with COVID incidence. A similar increase in PM_{2.5} levels was associated with a 23% excess increase in all-cause mortality (COVID-19 specific mortality results were not reported).

Fiasca et al analysed data from 62 and 67 Italian provinces respectively for PM_{2.5} and NO₂ obtained from the EEA database (2016-2020) in relation to the incidence of COVID-19 until June 24, 2020 and until November 2, 2020. The authors accounted for age and population density. The results indicate that an increase of PM_{2.5} and NO₂ by 1µg/m³ is associated with an increase in COVID-19 incidence by 1.56 and 1.24 per 100,000 persons. However, the adjustment for confounding is inadequate for a reliable estimate.

Dettori et al analyzed data on COVID-19 and the association with PM₁₀, PM_{2.5} and NO₂ concentrations based on fixed site measurements in 107 Italian provinces. They report results on the fact that high COVID-19 Standardized Mortality Ratios (SMR) coincide with areas (Milano, Po valley) of high PM₁₀ pollution. In multiple linear regression models PM₁₀ is associated with SMR but not NO₂ or PM_{2.5}. The methods applied are not so clear and provide only indications of a positive association between COVID mortality and PM₁₀ pollution.

Cascetta et al also analyze data from the 107 Italian provinces and emphasize the proximity to sea, PM_{2.5} levels and altitude in association with the number of hospitalized patients from 21 February to 27 July 2020 (adjusted for number of positive tests). The authors accounted for age (proportion over 50 years) but no other potential confounders. They report an increase in COVID-19 hospitalization rate with increasing PM_{2.5} concentrations but the adjustment for confounding may be considered inadequate.

Zaldo-Aubanell et al explore the association of long-term exposure to NO₂ and PM₁₀ with COVID-19 incidence and mortality by Basic Health Area (BHA) in Catalonia, Spain (n=372). They account for confounders including demographics (sex, age >65 years), SES and co-morbidity data. They report an increase in COVID-19 mortality associated with an increase in NO₂ and PM₁₀ (Odds ratios 1.013 and 1.048 respectively per unit increase in the pollutants) and an increase in incidence only associated with PM₁₀ (OR 1.003). NO₂ increases were inversely associated with incidence.

Konstantinou et al investigated the association of COVID-19 deaths by June 30, 2020 and NO₂ and PM_{2.5} long-term (2014-2018) average levels by Lower Super Output Area (n=32,844) in England. After adjusting for demographics, SES, residence type, health, health care, and population

characteristics, an increase in COVID deaths, which, however, does not reach the nominal level of statistical significance, was reported.

Huang and Brown analysed data from Germany by county (n=401) investigating the association between accumulated COVID-cases up to 13 September 2020, and PM_{2.5}, PM₁₀, NO₂, and a few other pollutants. They accounted for temperature and population density as potential confounders. The results indicate that an increase in NO₂ concentrations by 1µg/m³ is associated with an increase in COVID 19 incidence rate by 5.58% but no association was reported with the other pollutants.

Zheng et al analysed data from 324 cities in China (excluding Wuhan) and explored the association between confirmed cases, severe cases and deaths from COVID-19 and long-term exposure to NO₂, PM_{2.5}, PM₁₀ and a few other pollutants based on measurements from monitoring sites. The authors accounted for several confounders including travel from Wuhan, travel within city, SES, age and health related characteristics. An increase of 10µg/m³ in NO₂, PM_{2.5} and PM₁₀ was found associated with 37.8%, 32.3% and 14.2% increases in the number of COVID cases respectively. The same increase in pollutants was found associated with a 26.3%, 15.7%, and 6.43% increase in severe COVID cases respectively. However, when cities were stratified by population size most associations lost statistical significance.

Rodriguez-Villamizar explored the association of COVID-19 mortality and long-term levels of PM_{2.5} (2014-2018) in Colombia, at Municipality level (n=772). The results do not indicate an association between long-term exposure to PM_{2.5} and mortality from COVID after adjusting for confounders.

From the above ecological studies, we may conclude that there are indications in appropriately conducted and analysed studies that long-term exposures to pollutants, mainly ambient PM and NO₂, are associated with the extent of COVID-19 infections and severity. The underlying mechanisms are different for the COVID-related health outcomes considered. If we hypothesize that long-term exposure to pollution increases the proportion of the susceptible population, which is reasonable, based on previous evidence, then we should expect more severe outcomes of COVID-19 cases. Some of the above studies indeed provide evidence to support this. However, if the health outcome analyzed is the number of cases, the underlying mechanism is not clear from epidemiological evidence (toxicological evidence is discussed below). It may be that the same number of cases leads to a larger number of confirmed cases if the cases are generally more severe, which brings us to the previous hypothesis about the association of long-term pollution and COVID-19 case severity. If, however, long-term pollution is hypothesized to be associated with higher transmissibility, this issue is related to the discussion on the role of PM in the SARS-CoV-2 transmission which is not clear yet.

The above studies cover different areas of the World with more studies from the US and Italy. They also represent various exposure and outcome definition methods and different analytical approaches. So, at this point, they provide evidence to support the hypothesis that long-term exposure to air pollution is associated with severity of COVID-19 cases, but no quantitative estimates can be derived.

Studies with individual data

In the next paragraphs the 5 studies with individual data are presented and discussed. Having individual data leads to the possibility for better control of confounding. But often, at the same time, there is a loss of statistical power due to the smaller number of cases analyzed and there may be a

larger magnitude of measurement error in exposure assessment leading possibly to an underestimation of effects.

Two of the studies utilized the UK based cohort “UK Biobank” which includes individual data for about 500,000 persons across the UK. Elliott et al analyzed factors associated with all-cause mortality (n=2,626) and COVID mortality (n=459) between January and September 2020. They found that several SES, occupational and health related variables were associated with COVID-19 mortality, but air pollutant concentrations were not after accounting for confounding. Zheng et al used data for only 7,362 participants (1,485 COVID-19 positive and 5,877 non-COVID) from the UK Biobank who had COVID testing and exposure and genetic data. The authors included many exposure variables (17 behavioral; 9 metabolic risk factors; 11 disease related variables; 4 SES variables; 102 single-nucleotide polymorphisms) including exposure to PM_{2.5}, PM₁₀, NO₂ and NO_x based on previous models. All associations have been explored and 15 exposure factors were found associated with COVID-19 including NO₂ concentration. However, this type of analysis does not consider the causality of the association and in this case NO₂ may be an indicator of a set of correlated variables related to the urban setting or to high traffic exposures which NO₂ concentrations indicate.

Mendy et al analysed 1,128 COVID-19 hospitalizations between March 13 and July 5, 2020, using individual data from the Cincinnati health care system in the US. Hospitalization was defined as admission with a duration of equal or more than 24 hours and there were 310 patients hospitalized and 818 not hospitalized. PM_{2.5} exposure was based on a previously developed and validated model (2008-2017). Sociodemographic and health variables were accounted for. The results from a logistic regression model indicated that PM_{2.5} exposure was associated with the risk of hospitalization only among persons with pre-existing asthma or COPD, in which the odds of hospitalization increased by 62% with a 1µg/m³ increase in PM_{2.5} exposure. An inverse association was observed among patients without pre-existing disease.

Bowe et al used individual data from a US cohort of Veterans and included all individuals who tested positive for COVID-19 between March 2, 2020 and January 31, 2021 (n=174,661). Exposure to PM_{2.5} was based on modelled data for 2018 at 1km². The appropriate grid value was assigned to the residential address. There were 25,422 hospitalizations. One IQR increase in PM_{2.5} (1.9µg/m³) was associated with a 10% increase in the risk of hospitalization after accounting for confounders. Models of non-linear exposure–response suggested an increased risk at PM_{2.5} concentrations below the national standard 12 µg/m³. Formal effect modification analyses suggested a higher risk of hospitalization associated with PM_{2.5} in Black people compared with White people (p = 0.045), and in those living in socioeconomically disadvantaged neighborhoods (p < 0.001).

Lopez-Feldman et al analysed data from a COVID-19 cases cohort on mortality from COVID-19 using individual data for confirmed cases in Mexico City Metropolitan Area and PM_{2.5} exposure data from 2000 to 2018. They assessed case fatality. They also evaluated short-term effects separately in the same models, accounting for individual level and municipal level covariates. The results provide evidence of a positive relationship between pollution and mortality that significantly grows with age and that appears to be mostly driven by long- rather than short-term exposure. Specifically, an increase of 1µg/m³ in PM_{2.5} long-term exposure is associated with a 0.77% increase in the probability of dying.

Of the five studies including individual data and analyzing cohorts, four were trying to evaluate a causal association between exposure to pollutants and COVID-related health outcomes. Two studies

included mortality among cases as the health outcome: one found no evidence of an effect based on 459 deaths (Elliott et al 2021) and the other found an association but it is unclear on how many cases it was based (Lopez-Feldman et al 2020). Two studies evaluated the risk of hospitalization among COVID-19 cases in the U.S. (Mendy et al 2021, Bowe et al 2021) and found that higher long-term exposure to PM_{2.5} was associated with a pronounced increase in the probability of hospitalization. The evidence is persuasive, but the quantitative estimates differ. It is not possible to assess at this point whether the quantitative differences are a result of differences in populations (e.g. the age distribution, health aspects), random variation, differences in exposure etc.

Preliminary conclusions based on studies for long-term effects

Studies with individual data provide evidence that persons exposed to PM_{2.5} before the pandemic had more severe COVID-19 outcomes, specifically had a higher hospitalization rate. This evidence is not so clear for mortality. From the ecological studies, which cover a wider range of locations but account less well for confounders, there are more indications about an association with long-term exposure to PM and NO₂ and mortality from COVID-19. This is still not entirely consistent, but there is also some evidence that exposure to the same pollutants is associated with higher incidence or transmission (as indicated by Ro in one study) of COVID-19.

Toxicological commentary on long-term exposure

Individuals with existing pulmonary or cardiovascular conditions, diabetes or compromised immune function are shown to be especially susceptible to severe COVID-19 (Lee et al, 2021, Rogado et al 2020, Yang et al 2020, Leung et al 2020). Chronic exposure to air pollution exacerbates and possibly induces many of these conditions (Thurston et al 2020, Li et al 2016, Rajagopalan et al 2018), potentially contributing to the high incidence of severe COVID-19 cases, hospitalisations and deaths in polluted regions.

Due to the concentrated presence of redox-active molecules, oxidative stress is an outcome common to air pollutant exposures (Kelly, 2003). This occurs when the levels of reactive oxygen species (ROS) produced in the lung by inhaled pollutants outweigh the availability of endogenous antioxidants, leading to cellular dysfunction, tissue damage and induction of inflammatory signalling cascades (Kelly, 2003). In the lungs, prolonged and excessive oxidative stress and inflammation can lead to destruction of alveolar walls (as seen in emphysema and chronic obstructive pulmonary disease), wheezing and bronchial constriction (associated with asthma) and pulmonary fibrosis (scarring). As discussed in section 4.3, existing pulmonary inflammation could contribute to progression of COVID-19 severity, through contributions to cytokine storms. Additionally, phagocytosis of pathogens is impaired in the macrophages of patients with COPD and severe asthma (Belchamber et al 2019, Liang et al 2014), further increasing susceptibility to respiratory infections. Air pollution has multiple effects on the immune system as reviewed by Glencross et al (2020).

As recently reviewed by Bevan *et al.* (2021), chronic air pollution exposure may contribute to the development of cardiovascular conditions through promotion of atherosclerosis (development of fatty plaques on blood vessel walls) (Bevan et al 2021). As with the pulmonary effects of pollutant exposure, initiation of plaque formation is caused primarily by oxidative stress and inflammatory mediators that arise within the lungs. As well as pro-inflammatory cytokines, these mediators include activated immune cells, oxidized lipids and vasoconstrictors. Together, these act to dysregulate vascular endothelial barrier function, promote thrombosis, drive ischemic damage and increase blood pressure (Bevan *et al.* 2021).

Our literature searches did not yield any publications that have directly explored the effects of long-term air pollutant exposure on COVID-19 infectivity. However, one study by Vo et al (2020) explored the impact of sub-chronic ozone exposure on the expression of genes that are known to facilitate cellular infection by SARS-CoV-2. Here, mice were exposed to ozone (0.8ppm) for 3 weeks (5 nights/week, 4h/night). Using immunohistochemistry, the authors identified heightened TMPRSS2 protein expression in the lungs which, consistent with the effects of acute PM exposure, localised to alveolar epithelial cells and macrophages as well as epithelial cells from non-alveolar airway regions. RNA sequencing showed that considerable dysregulation occurred for 32 genes that associate with host susceptibility to SARS-CoV-2 infection. Again, these changes occurred primarily in the lung parenchyma (alveoli and respiratory bronchioles) and the macrophages (Vo et al 2020).

We interpret these data to indicate that changes in the expression of host susceptibility genes continue to occur in the longer-term presence of pollutants. As a maintained response, rather than as an initial, transient reaction. We therefore consider it plausible that people experiencing regular exposure to air pollution have increased susceptibility to infection by SARS-CoV-2.

A limitation of this study (for our purpose) is that the authors do not present a full, untargeted analysis of the RNA sequencing data. With this, it might be possible to assess the likelihood of prolonged ozone exposure impacting antimicrobial activities in the macrophages. Impaired immune cell function is often hypothesised to explain the association between air pollution exposure and respiratory tract infections (detailed in Section 3.2). Unfortunately, publications detailing the impact of chronic exposure on the antimicrobial behaviours of immune cells are scarce. However, dampened oxidative burst and inflammatory cytokine secretion have been observed in the alveolar macrophages of healthy individuals who are exposed chronically to cooking smoke (Rylance et al, 2015b). This suggests that impaired immune function as a result of chronic air pollution exposure is a possibility.

4.5 Air pollution increasing exposure to COVID-19

Various studies have examined transmission by the presence of the virus through airborne particles or droplets in the ambient air, especially for occupational exposures. Interest in this area was sparked by a paper that was published earlier than the time period after the Brunekreef review literature cut-off date (Setti et al 2020). Many studies include this as a reference (highlighting for example the fact that Setti et al mention that COVID-19 transmission could be further augmented by particulate matter beyond the social distance of 2m up to 10m). This section considers whether this proposal has been confirmed by later studies.

This overview concentrates on studies on transmission of the virus where the link with particulate air pollution is studied. There is a wider literature on transmission of the virus through aerosols and droplets in general. For example, Yarahmadi et al 2021 collected bioaerosol samples and reported that COVID-19 may be detected in the air and affect health care workers. They also report that intensive care units (ICU) wards with confirmed cases of COVID-19 had higher airborne emission of COVID-19 compared to other ICU wards and reaerosolisation of SARS-CoV-2 particles into the atmosphere of ICU wards may be possible due to the mobility of the health care workers. However, these types of studies are not considered further here.

A recent review by Ram et al 2021 suggested that there is evidence that SARS-CoV-2 can be transmitted by inhaling droplet nuclei and/or by virus attached to a susceptible host particle which

may be ambient PM. However, they report that previous studies showed that SARS-CoV-2 virus has not been detected on surfaces and air vents, and therefore, airborne transmission is not expected in the ambient air.

Nor et al 2021 and Pivato et al 2021 investigated PM and whether it can act as a carrier of the virus by looking for SARS-CoV-2 RNA in particles which have a longer lifetime in the ambient air compared to respiratory liquid droplets. Pivato et al reported that there is a very low probability of detecting RNA of the virus in PM, while Nor et al 2021 concluded that SARS-CoV-2 RNA is present within sampling of the ambient air but there is no direct link between PM and COVID-19.

Similar conclusions were reached from Linillos-Pradillo et al 2021 who measured PM₁₀, PM_{2.5} and PM₁ and examined the presence of SARS-CoV-2 RNA in ambient air. More specifically, they measured PM concentrations in May 2020, 5-6 weeks after the peak in COVID-19 cases and deaths, and two Sahara dust outbreaks occurred during this period. No presence of the virus was detected, and the authors claim that this may be attributed to the reduced human activity due to COVID-19 measures, high temperature and the atmospheric conditions.

These findings suggest that ambient PM measurements may not provide any information about the viral load and PM concentrations cannot act as an indicator of SARS-CoV-2 diffusion or an early indicator for another wave of the pandemic.

On the other hand, Baron 2021 supported that PM is strongly related with COVID-19 infection and transmission, while the changes in the air pollution concentrations may have contributed to the evolution of the virus. He suggested that the cities that were not highly affected by the pandemic in the first wave share common geographical characteristics, as they are close to the sea. Ambient salinity increases atmospheric humidity which in turn makes the environment more hostile for the hydrophobic N-terminal peptide of the virus. However, Baron forms the hypothesis that in the second wave coastal cities were affected by the pandemic probably because Clade G displaced Clade D and the mutation affects the hydrophobic properties of the virus. This paper contains some unusual ideas that are inferred rather indirectly – thus more investigation would be needed.

In order to assess whether PM can affect the transmission of the virus and its diffusion rapidity, Collivignarelli et al have performed a correlation analysis between the PM concentrations and seeding time⁵ and doubling time at province level in Italy. Similarly, Aabed and Lashin 2021 assess the relationship between CO₂ and COVID-19 incidence in 188 countries and seek to predict the spread of the virus in Italy, Spain and China using various environmental factors as inputs. However, we think that this kind of analysis is not appropriate to answer the complex research question of COVID-19 transmission and PM, as there is no control for potential confounders and the proposed associations might be prone to confounding bias. As mentioned in sections 4.3 and 4.4, the same reservations about simple correlation analyses hold for the epidemiological studies on COVID-19 related outcomes for both short- and long-term exposure.

In conclusion, in comparison to papers published early in the pandemic, more recent papers do not support any strong influence of particulate air pollution on transmission of the virus.

⁵ Seeding time is the time that elapses between the first case identified in each province and reported by official data and the achievement of a number of cases equal to the median of the cumulative cases reported up to the day before the rise of the curve.

4.6 Pandemic measures reducing concentrations of air pollution

Examining the changes in air pollution as a result of lockdown measures could lead to greater understanding of the contribution of sources to air pollution levels. It is also relevant to interpreting epidemiological studies of air pollution done at this time. The UK Air Quality Expert Group (AQEG) produced a [report](#) on changes in the UK in July 2020 (AQEG 2020). This suggested a consistent drop in NO₂ levels but a more mixed pattern for other pollutants. The scope of the work was not intended to cover the effect of pandemic measures on levels of air pollution. Nonetheless, we note that our search identified a large number of studies on this issue from all over the world, particularly in Asia. There are studies examining changes in PM composition, including changes in oxidative potential. A list of these studies is provided in an accompanying document (Annex 1 at <https://www.imperial.ac.uk/school-public-health/environmental-research-group/research/air-pollution-epidemiology/air-pollution-and-covid-19/>) but the numbers are sufficiently large that detailed examination of them would justify a separate project.

Some of these studies included health impact assessments of the reductions in air pollution. Any health impact assessment done at this stage would be difficult to interpret – if past concentration-response functions are used these are likely to be inaccurate because the relationship between outdoor air pollution concentrations and personal exposure is likely to be very different during lockdowns. In addition, the baseline rates for respiratory disease (in particular) and cardiovascular disease (to some extent) are very atypical during a pandemic. In addition, there are a couple of studies noting smaller numbers of asthma exacerbations due to the general reduction in respiratory infections during lockdowns, a point relevant for interpretation of air pollution and health studies in this period.

Some short-term exposure studies examined all-cause mortality. This is an important relationship that needs to be re-examined during this period as both the distributions of the air pollution concentrations and daily deaths might have changed dramatically and this might be reflected in changes in the concentration-response functions used in health impact assessment and the number of estimated air pollution-attributable deaths or life-years lost.

5.0 Discussion

Early in the pandemic, very little was known about COVID-19 and there was a strong drive for researchers in all fields to help in some way. Initially, there were many poor-quality papers which simply looked at correlations between air pollution and COVID-19 cases or deaths without any control for the factors that could lead to an apparent relationship, without it being true in reality. Examples of this include the fact that major cities with high population density, areas with high household density and areas with national and international travel links are likely to have higher COVID-19 incidence as well as higher air pollution. In addition, lockdown measures reduce COVID-19 cases and air pollution which appears to give a strong relationship between the two which is unlikely to be real. What is needed are studies that account for these other factors first and then see if air pollution contributes to the remaining variation in COVID-19 cases or mortality.

As time has gone on, the quality of studies available has improved to some extent. Expert epidemiologists knew that these studies needed to be done carefully and would take time to set up, and some of these more careful studies have now been published. Nonetheless, the research is still at a fairly early stage, not least because there is more to learn about COVID-19 itself.

This report has outlined the status of the literature on air pollution and COVID-19 at this time (to May 2021). It has also provided a reminder that there is a literature on air pollution and respiratory infections in general, that has received relatively little attention in developed countries. This report has also examined how this literature on respiratory infections in general contributes to the plausibility of an effect of air pollution on COVID-19.

5.1 Summary of evidence on air pollution and lower respiratory infections

There is general evidence for an effect of air pollution on respiratory infections across varying designs of studies and from epidemiology as well as toxicology. While the results can be somewhat mixed at the detailed level e.g. within specific pollutant, age group and infection definition categories, the overall message does provide some plausibility for an effect of air pollution on COVID-19. There are some biological mechanisms common to many types of infections e.g. the importance of macrophages in clearing infections and others that are more specific to particular infections or groups of infections. From the perspective of quantifying an effect of air pollution on hospital admissions from lower respiratory infections, the literature since 2011 included evidence of associations in several studies, particularly for PM_{2.5} but the results were scattered across age groups and disease definitions such that there were insufficient studies for meta-analysis in any particular category. Nonetheless, meta-analysis might be possible in combination with pre-2011 studies and/or with investigation of whether it would be appropriate to combine some of the age group/disease categories e.g. disease categories with small numbers of hospital admissions may make little difference if included or excluded from ICD10 code groups.

5.2 Summary of evidence on air pollution and COVID-19

One of the aims of our approach was not only to see if the quality of studies had improved since the review by Brunekreef et al (2021) but also to discuss the new studies in the context of the different potential pathways for an effect of air pollution on COVID-19.

Short-term exposure and increased cases of COVID-19

This is particularly challenging to study because it requires a good understanding of the potential alternative reasons for short-term variations in cases of COVID-19. This can include many aspects such as variations in amount of testing, changes in pandemic measures at different times, different travel connections becoming key at different times as the pandemic evolves across the world and many others. The short-term exposure to air pollution and COVID-19 studies are generally not of good quality – some are simple correlation analyses, some are good quality from the air pollution perspective with control for temperature and season but do not include the necessary additional confounding factors. Inevitably, studies are shorter than would normally be the case because the pandemic has not been in existence as long as the standard duration of time-series studies (at least 1 or 2 years). Overall, this area of literature is not conclusive. There is some plausibility from the toxicological evidence on increased expression of ACE2 receptors after air pollution exposure and from the general literature on the effects of exposure of macrophages to air pollutants. However, this area of research is still evolving, concentrations may be high and there is only one study of direct interaction with the SARS-Cov-2 virus rather than inference from effects on relevant pathways. It is not clear how the effect of air pollution on ACE2 receptor expression compares with the effect of other environmental chemicals or other factors (e.g. medicines) i.e. even if it does increase ACE2 receptor expression, it may or may not be a significant driver of receptor levels in the context of other factors.

Short-term exposure and more severe COVID-19 outcomes

There are also challenges with studies examining the pathway of short-term exposure to air pollution and worsening of COVID-19 outcomes. One advantage is that outcomes of hospital admissions and deaths are better defined than cases. Nonetheless, the quality of the studies was not sufficient to give conclusive results. From the toxicological perspective, the evidence that air pollution can increase levels of inflammatory cytokines circulating in the blood adds plausibility to days with higher levels of air pollution leading to a pro-inflammatory state, and maybe increasing the likelihood of worsening COVID-19 (although this has not been demonstrated directly). Should better quality epidemiological studies of short-term exposure show an association with COVID-19 hospital admissions, there would be some toxicological evidence to support it. This argument is less cogent for deaths where exposure to air pollution might be expected to be lower for those patients who die in hospital.

Long-term exposure and increased cases of COVID-19

Long-term exposure studies have different challenges than the short-term exposure studies. Modelling air pollution exposure is well-established and long-term exposure pre-pandemic is not affected by lockdown measures. At least on the air pollution exposure side, there is an option for a longer duration of data than for the short-term exposure studies. For cases, there are still challenges in accounting for the level of testing, but some of the effect of the early lack of testing can be minimized by using cumulative totals over the time of the pandemic. The data on long-term exposure to air pollution and number of cases is not entirely consistent. There is relatively little known about long-term exposure to air pollution and susceptibility to infection by SARS-CoV-2 – increased expression of the ACE2 receptor and TMPRSS2 is better established as a short-term response that is reversible, although sub-chronic exposures to ozone and PM show increased ACE2 expression suggesting repeat exposures can continue to maintain the response over time. It is therefore unclear whether there might be a long-term effect or whether any apparent long-term

effect might be a reflection of higher long-term exposure acting as a surrogate for the probability of higher short-term exposures. There could be some long-term effect of air pollution on macrophage function, impairing clearance of the virus. However, studies of this are scarce. There is also a possibility that any association with long-term exposure to air pollution and cases is in fact a result of increasing severity of response, rather than an increase in infectivity of the virus. For example, if long-term exposure increases the numbers of people in susceptible groups and these groups are then less likely to be asymptomatic, then they would be more likely to take a test.

Long-term exposure and worsening outcomes from COVID-19

In many ways this is the most plausible pathway, because it is already known that air pollution increases the numbers of people with respiratory and cardiovascular disease, and these people are more likely to experience worse outcomes from COVID-19. Previously while some ecological studies (studies analysing area level information) had suggested this, studies with individual data were lacking (Brunekreef *et al* 2021). Now there are a small number of studies with individual data, with the clearest result for an association with hospital admissions for COVID-19. Nonetheless, with the small number of studies, and the variation in the size of the results, quantifying the size of this relationship is not appropriate at the current time. Studies are also likely to improve further in quality over time, as COVID-19 becomes better understood and ways to consider additional confounding factors are developed. The toxicological evidence linking air pollution and respiratory and cardiovascular disease is reasonably well established, at least for some pollutants. It is also possible that long-term exposure to air pollution leads to a baseline pro-inflammatory state that increases the severity or likelihood of the cytokine storm leading to the more severe consequences of COVID-19.

Air pollution increasing exposure to COVID-19

A paper early in the pandemic suggested that particulate matter could carry the virus and thus be a factor in transmission of the virus. More recent studies have not supported this. Although the presence of virus on particulate matter remains a theoretical possibility, and there are analytical challenges in testing for it, it seems unlikely to be a significant contributor to risk. One of the main factors determining persistence of virus in the environment is the presence of RNAases (proteins that break down viral RNA).

5.3 Strengths and limitations

We have done full literature searches in selected areas and put these into the context of the different possible pathways involved in the effects of air pollution on COVID-19. The authors include expertise in epidemiology, toxicology and health impact assessment. (Some other reviews adopt results from studies in other fields uncritically e.g. reviews of mechanisms take epidemiological study results at face value even though some of them are only correlation analyses). Thus, the interplay between studies of mechanisms and epidemiological studies is addressed to the degree possible given the early stages of research on air pollution and COVID-19.

This was, however, a short project. We considered studies on air pollution and COVID-19 published after the review by Brunekreef *et al* (2021) based on studies up to November 2020, rather than describing all studies published since the start of the pandemic in detail. Similarly, for the more general literature on air pollution and respiratory infections, we were only able to consider one part

of this subject area in detail (air pollution and hospital admissions for lower respiratory infections) and that only for studies published since a previous systematic review based on studies published prior to 2011.

For studies on air pollution and COVID-19, it is inevitable that the research area is not as mature as some other areas of the literature on air pollution and health. Not only has the time period available to study any relationship been short but COVID-19 itself is not well understood. It may be that further research will indicate other confounders that should be taken into account in these studies. In addition, particularly early in the pandemic, data collection was either absent or under-developed and definitions related to data collection have been changing.

Nonetheless, we believe it is useful to provide a current summary of the research, particularly as some studies are of very poor quality but may nonetheless receive wide press coverage.

From a policy perspective, the evidence described in this report increases the importance of reducing air pollution, maintaining and extending policies already in place. If the effects of long-term exposure to air pollution and hospital admissions for COVID-19 are mediated by increases in numbers of people with respiratory and cardiovascular disease, then this is covered by shielding policies. While there may be some additional people who are susceptible by virtue of an effect of air pollution on the immune system, this is not sufficiently established to have an impact on COVID-19 policy at this stage.

5.4 Further work

For consideration of quantification of effects of air pollution and hospital admissions for lower respiratory infections, the next step would be to consider whether combining the post-2011 literature with the pre-2011 literature would allow meta-analysis or updates of previous meta-analyses. Interpretation of these results would also be aided by assessing the results of multi-pollutant model and seasonal results in these studies. Fuller examination/updating of time-series literature on air pollution and lower respiratory infection mortality would also be useful.

There is a view that enough time-series studies have been done already, and there is maybe some truth in this for broad categories such as all-cause mortality or all respiratory admissions in Europe and the US. But this is not necessarily the case for all pollutants and all sub-diagnoses. As PM_{2.5} monitoring has only been established more recently, there is no large body of recent studies in Europe and the US, with most studies from Asia. And the number of studies on NO₂ and O₃ is still small, as is the number of studies that assessed the health effects of PM components. The studies are also scattered across age groups and disease definitions, so additional studies in each of these categories would help.

In terms of the methodological aspects of these short-term exposure studies of air pollution and COVID-19, there are some certain challenges related to COVID-19 health outcomes due to the nature of the disease. This is apart from the known issues of time-series analysis, such as the proper control for meteorological and seasonal trends and the potentially unstable or unreliable estimates from short time periods, e.g. less than a year. Regarding the study duration, we believe that using only a few months of data do not adequately account for the complex characteristics of the disease, such as the infection and incubation period or potentially prolonged health deterioration that may result in death or other health outcomes. Thus, longer time-series analyses that will take into

account the different stages of the lockdown measures, the restrictions in mobility, the waves of the pandemic and the differential testing capacity are needed in order to draw better conclusions for the health effects of short-term exposure to pollution. What is also unknown is which air pollutants have stronger associations with COVID-19 outcomes. Since most of the pollutants share common sources, they are usually highly correlated which renders the identification of their independent effects a very challenging process. Multi-pollutant model analysis that accounts for multicollinearity in the exposures should be used to identify the most harmful pollutants. Moreover, the natural experiment of the pandemic allows the application of methodologies such as interrupted time series, regression discontinuity design and difference-in-differences analysis in order to assess the causal effects of air pollution on health taking into account the changes in the exposures and our everyday life due to the pandemic. Finally, as suggested also by Villeneuve and Goldberg (2020), a case-crossover design with individual data would allow researchers to investigate the acute effects of air pollution on COVID-19-related outcomes, such as mortality and morbidity, adjusting for individual level confounders and selection bias for the testing capacity across the study area.

While there have now been studies of long-term exposure to air pollution and COVID-19 with information from individuals, the number of studies is still quite small. For mortality and case-fatality, there are insufficient studies to be conclusive so more studies of these outcomes with individual data would be useful. It is recognized that these further studies may not be easy to bring off, particularly for prospective studies, because the different waves of cases at different times and the increases in vaccination makes statistical power difficult to predict.

There is a need for better baseline data. For diseases that have been established for many years, there is a stable baseline of diagnosis. While some cases might be missed, there is often some idea of the proportion of these missing cases. Particularly early in the pandemic, definitions of cases and deaths were changing. Some of this is stabilizing but consistent identification of cases is still a challenge, given that those that are asymptomatic may still pass on the virus. It is possible that modelling on the health outcome side as well as the exposure side could help, i.e. approaches to model the true case rate using a variety of information sources. Prospective studies of the transmission of COVID-19 in general could also be used to determine how air pollution is associated with this transmission (Villeneuve and Goldberg, 2020).

There are strong reasons for better understanding of transmission of COVID-19 in any case, including the role of RNAases in destroying the virus in the environment, and the exact size fractions of exhaled infectious particles. This is a higher priority at the present time than work on the role of particulate air pollution in carrying the virus, if any, but this wider work will help put any future work on the latter issue in context.

For further toxicological work it would be useful to have models to explore exactly which pollutants impact ACE2 expression and to look at the effect of pollution on phagocytosis of SARS-CoV-2 specifically.

The large number of studies on changes in exposure due to lockdowns were not reviewed here but would be worth evaluating in separate work. The health impact assessment studies should also be explored – it seems likely that new approaches to health impact assessment will need to be developed using concentration-response functions that take into account changes in how ambient concentrations act as a proxy for personal exposure and considering which baseline rates (before or during the pandemic).

5.5 Conclusions

Studies of air pollution and COVID-19 remain challenging. Many poor-quality studies are still being published but there are now more better-quality studies available, including a small number with individual data, suggesting effects of air pollution on hospital admissions for COVID-19 (probably via increasing numbers of people with respiratory and cardiovascular disease). More recent studies do not support any significant role for particulate matter in transmission of COVID-19, although it remains a theoretical possibility. The toxicological evidence is in the early stages, although there are suggestions of effects on increased expression of the receptors and some other host proteins involved in viral entry to the cell. The literature on air pollution and respiratory infections provides some plausibility for an effect of air pollution on COVID-19 and is an important issue in its own right, although more work is needed to develop approaches to quantification of these risks.

Overall, this provides additional support for the importance of reducing levels of air pollution and thus reducing the susceptibility of the population to infectious agents.

The references to the main report and to the Appendix in section 6.0 are given in section 7.0 at the end of the report.

6.0 Appendix

6.1 Search strings for air pollution and respiratory infections

The search string used was based on that used for the previous report on air pollution and asthma admissions in London (Walton et al 2019) which was in turn based on a previous Department of Health funded systematic review (Atkinson et al 2014; Mills et al 2015; Walton et al 2014). The search was performed in June 2021.

((((((((((air pollution) OR pollution) OR ozone) OR nitrogen dioxide) OR nitrogen oxide*) OR particulate matter)) AND (((timeseries) OR time series) OR time-series) OR daily) OR casecrossover)) AND (((((((hospital admission*) OR admission*) OR emergency room) OR visit*) OR attendance*) OR a AND e) OR (a and e)) OR (accident and emergency)) OR emergency department*)) AND ("2011"[Date – Publication] : "3000"[Date - Publication])) AND lower respiratory infection)

There were 434 hits. The title sift narrowed the number down to 121 papers, excluding 313 papers that were not on air pollution. An abstract sift narrowed this down further to 58 time-series papers (exclusions included 18 papers on household air pollution and 20 on health impact assessment, as well as papers on asthma treatment, COVID-19, study designs other than time-series, studies on smoking, studies on temperature and toxicology studies). A first full paper sift excluded studies on diseases other than lower respiratory infections, studies that were not on hospital admissions or emergency room visits or mortality and studies that were not on the key pollutants PM_{2.5}, PM₁₀, NO₂ or O₃, leaving 40 studies. A further detailed full paper sift removed studies that consider emergency room visits only (some emergency room visit studies separate visits into those that resulted in admission to hospital and those that did not, the former were included as hospital admission studies). This left 19 studies.

A further 2 of the 19 were excluded on the basis of poor quality. Pothirat et al (2019) does not control for season or long-term time trend and Sahin et al (2021) was just a correlation analysis with no control for confounders. Wang et al (2021) was for bronchiectasis with lower respiratory infection (LRI) – this was excluded as it relates to exacerbation of a chronic disease. Nhung et al, 2019 has been excluded because it addressed length of hospital stay rather than counts of hospital admissions. This left a final total of 15 papers.

We retained two papers on lower respiratory infection mortality for comment, although as mortality was not in the search terms this will not be the complete set of post 2011 papers on mortality.

6.2 Hospital admissions for lower respiratory infections

In the text below figures in brackets after the estimate of effect size are 95% confidence intervals.

PM_{2.5} and hospital admissions for lower respiratory infection in young children

Horne et al (2018) performed a case-crossover study in the Wasatch Front, a region between the Wasatch mountains and the Great Salt Lake in Utah. They found positive and statistically significant associations between PM_{2.5} and hospital admissions for acute lower respiratory

infections (respiratory syncytial virus, influenza, viral pneumonia and bronchiolitis, ICD10 codes B97, J09-J11, J12, J21) in children ages 0-2 years for various lag times after exposure, up to an odds ratio of 1.15 (1.11 – 1.19) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ for a cumulative lag of 0-27 days.

Luong et al (2020) also found an association between $\text{PM}_{2.5}$ and hospital admissions for acute lower respiratory infection (pneumonia or bronchiolitis, J13-J18 and J21), in children under 5 years, in a time-series study in HoChi Minh City, Vietnam. For a lag of 3 days, there was a 3.51% (0.96 – 6.12) increase in hospital admissions per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. When split into age groups <1 year, 1-2 years and 2-5 years, associations remained positive but were only statistically significant in the 1-2 year-old age group.

$\text{PM}_{2.5}$ and hospital admissions for lower respiratory infection in children

Horne et al (2018) also considered children aged 3-17, finding an odds ratio of 1.32 (1.20–1.44)-per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ for a cumulative lag of 0-27 days. The two other studies in this age group were time-series studies. Oh et al (2020) is a multi-city study in 7 Korean cities examining effects in children (age not specified). They found a 1.20% (95% CI: 0.71, 1.71)⁶ increase in hospital admissions for lower respiratory infection (acute bronchitis, bronchiolitis and unspecified lower respiratory infection, ICD 10 code J20-J22) for a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ for a cumulative lag of 0-7 days.

The other study by Zheng et al (2017) in Ningbo, China defined acute lower respiratory infection as ICD 10 code J12-J18, which would be better described as pneumonia. Whatever the exact health outcome definition, this study also found a positive and statistically significant association of a 1.50% (0.35, 2.66) increase in relative risk per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ for a cumulative lag of 0-2 days, in children under 14.

$\text{PM}_{2.5}$ and hospital admissions for lower respiratory infection in adults

Only one study was available. Horne et al (2018) again found an increased odds ratio in adults 18+ as well as in children (OR 1.19 (1.09 - 1.31) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ for a cumulative lag of 0-27 days.

$\text{PM}_{2.5}$ and hospital admissions for lower respiratory infection, all ages

There are three time-series studies covering all ages. Kim et al (2020) studied 15 regions in Korea using modelled hourly $\text{PM}_{2.5}$ concentrations at a 3 x 3 km scale before averaging by region and 24-hour period. A difference in difference approach was taken taking both spatial and temporal information into account. Acute lower respiratory infection was defined as pneumonia, acute bronchitis, bronchiolitis and other lower respiratory infection (ICD10 J12-J18, J20-22). The association was positive but just lacked statistical significance RR 1.014 (0.999, 1.029) up to lag day 7 at 30 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ compared with a reference of 20 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$.

Another time-series study from Shenzhen, China (Xia et al 2017) defined acute lower respiratory infections as acute bronchitis, bronchiolitis and other lower respiratory infection (ICD J20-22). They found a 34.1% (21.0-48.6) increase in risk per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ over 14 days of lag, but only above a threshold of 80 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$. This threshold was above the 75th percentile of

⁶ The authors described this as a % increase in odds ratio but as Poisson regression was used, this should be a % increase in relative risk.

concentrations in Shenzhen and would be a relatively high concentration in many other locations as well.

The time-series study from Yichang, China (Yao et al, 2020) defined acute lower respiratory infections as pneumonia, acute bronchitis, bronchiolitis and unspecified lower respiratory infections (ICD 10 code J12-18, J20-22). There was a positive and statistically significant association at lag 1 day (results only shown graphically).

PM₁₀ and hospital admissions for lower respiratory infection in young children

Le et al (2012) performed both a time-series and case-crossover study in Ho Chi Minh City in Vietnam in children aged 28 days to 5 years. Acute lower respiratory infections were defined as pneumonia and bronchiolitis (ICD 10 J13-16, J18, J21). No association was found for PM₁₀ for average lag 1-6 (a non-significant 0.26% (-0.94 to 1.47) increase in the time-series analysis and a non-significant decrease (-1.10% (2.31 to 0.12)) in the case-cross over analysis, per 10 µg/m³ increase in PM₁₀).

There are also pre 2011 studies on PM₁₀ and lower respiratory infections admissions in children (Mehta et al, 2013).

PM₁₀ and hospital admissions for lower respiratory infection in children

Zheng et al (2017) performed a time-series analysis in Ningbo, China. Acute lower respiratory infection was described as ICD 10 codes J12-J18 (pneumonia), so this study can also be considered in the pneumonia section. An excess risk of 1.45 (0.63, 2.27) was found for a cumulative lag 0 to 1 day.

PM₁₀ and hospital admissions for lower respiratory infection in all ages

The study by Xia et al (2017) from Shenzhen described above found a 22.8% (16.5, 29.3) increase per 10 µg/m³ increase in PM₁₀ over 14 days of lag, but only above a threshold of 100 µg/m³ PM₁₀. As with PM_{2.5}, this is above the 75th percentile of concentrations in Shenzhen.

The time-series study from Yichang, China (Yao et al, 2020) found a positive and statistically significant association at lag 1 day (results only shown graphically) for PM₁₀ as well as PM_{2.5}.

NO₂ and hospital admissions for lower respiratory infection in young children

Le et al (2012) considered NO₂ as well as PM₁₀. There was stronger evidence for an association than there was for PM₁₀ in the case-crossover analysis with a 4.32% (0.04 to 8.79) increase per 10 µg/m³ increase in 24-hour average NO₂ (lag 1-6). The time-series results were quite different (- 1.08% (-5.14 to 3.17) increase for the same pollutant increment and lag) but the two types of analysis both showed strong effects of NO₂ in the dry season rather than the all-year results just described.

NO₂ and hospital admissions for lower respiratory infection in all ages

Xia et al (2017) also examined 24-hour average NO₂. While the results seem convincing (a 32.1% (20.5, 44.9) increase per 10 µg/m³ increase in NO₂ over 14 days of lag), this was above a threshold of 60 µg/m³, again suggesting no effect over most of the concentration range.

O₃ and hospital admissions for lower respiratory infection in young children

Only one study of ozone and lower respiratory infections admissions has been published since 2011 (although there were studies before that time, Walton et al 2014). This was the study in Ho Chi Minh city by Le et al (2012). This showed negative associations in both types of analysis, significantly so in the case-crossover analysis (-1.96% (-3.25 to -0.64) increase per 10 µg/m³ increase in O₃ (averaging time unclear) for average lag days 1-6). The equivalent result in the time series analysis was -0.98% (-2.30 to 0.35).

6.3 Hospital admissions for pneumonia

Of the papers on hospital admissions for pneumonia, two were excluded on the basis of poor quality. Sahin et al (2021) was just a correlation analysis with no control for confounders. Pothirat et al 2019 was a time-series analysis with control for temperature but no control for season or long-term time trend. One study (Chang et al 2017) analysed inpatient and outpatient visits combined so has not been covered here.

PM_{2.5} and hospital admissions for pneumonia in young children

The one study available (Luong et al (2020)) found no significant association between PM_{2.5} and hospital admissions for pneumonia (ICD 10 J13- J18), in children under 5 years, in a time-series study in Ho Chi Minh City, Vietnam. For a lag of 3 days, there was a 3.13% (-0.81 - 7.22) increase in pneumonia hospital admissions per 10 µg/m³ increase in PM_{2.5}.

PM_{2.5} and hospital admissions for pneumonia in adults

A case-crossover study in New York State found a 2.1% (0.1 to 4.2) increase in hospital admissions for bacterial pneumonia (ICD10 code J13-J16) per interquartile range (IQR) of 5 µg/m³ PM_{2.5} (lag 0-6) in adults (Croft et al (2019)). The relationship for culture-negative pneumonia (ICD 10 code J18) was more robust with narrower confidence intervals (2.4% (1.6 to 3.1) per 5 µg/m³ PM_{2.5}). This was probably because total numbers of admissions are greater in this category. A subsequent study by Croft et al (2020) using a similar dataset to examine PM components and culture negative pneumonia, did not find a statistically significant association with PM_{2.5} but the number of admissions in the dataset was a lot smaller.

Pirozzi et al (2018) performed a case-crossover study in subjects with a mean age of 58 years (IQR 41-75) in the Wasatch Front, Utah. The ICD code was not given but described as a primary diagnosis of pneumonia or a secondary diagnosis of pneumonia subsequent to respiratory failure/sepsis. No association was found in the overall group (OR 1.00 (1.00 – 1.01) (lag 1) per 10 µg/m³ above 12 µg/m³ PM_{2.5} but a significant increase in the odds ratio was found in the elderly (>65 years) OR 1.33 (1.12 - 1.58) (lag 1).

PM_{2.5} and hospital admissions for pneumonia, all ages

The study by Kim et al (2020) in 15 regions in Korea was described previously under PM_{2.5} and lower respiratory infections. For pneumonia (ICD10 J12-J18), no association was found RR 0.990 (0.973, 1.00829) at 30 µg/m³ PM_{2.5} compared with a reference of 20 µg/m³ PM_{2.5} up to lag day 7.

PM₁₀ and hospital admissions for pneumonia

No studies for PM₁₀ and hospital admissions for pneumonia were found, probably because more recent studies use PM_{2.5} instead. There are older studies on PM₁₀ and pneumonia admissions e.g. Medina-Ramon et al 2006.

NO₂ and hospital admissions for pneumonia in adults

Pirozzi et al (2018) also examined 24-hour average NO₂ in the study in Utah. The association was positive but not statistically significant OR 1.02 (0.96 - 1.07) per 10 ppb NO₂.

O₃ and hospital admissions for pneumonia in adults

Daily 8-hour maximum ozone was also an exposure examined by Pirozzi et al (2018). No association was found (OR 0.96 (0.91 - 1.02) per 10 ppb ozone).

6.4 Hospital admissions for influenza

PM_{2.5} and hospital admissions for influenza in adults

The case-crossover study in New York State (Croft et al (2019)) looked at associations with influenza (ICD 10 code J09-J11) as well as with pneumonia, but found no association (excess risk – 0.6% (-3.8 – 2.6) per IQR of 5.5 µg/m³ PM_{2.5} (lag 0-6) in adults. A subsequent study by Croft et al (2020) using a similar but smaller dataset to examine PM components, also found no association (excess risk 6.7% (-5.1, 20.0) per IQR of 6.78 µg/m³ PM_{2.5} (lag 0-6).

6.5 Hospital admissions for bronchiolitis

PM_{2.5} and hospital admissions for bronchiolitis in young children

Luong et al (2020) found a non-significant association between PM_{2.5} and hospital admissions for bronchiolitis, (ICD 10 code J21), in children under 5 years, in a time-series study in HoChi Minh City, Vietnam. For a lag of 3 days, there was a 1.92% (-4.17 - 8.39) increase in hospital admissions for bronchiolitis per 10 µg/m³ increase in PM_{2.5}.

6.6 Lower respiratory infection and pneumonia mortality

While the search did not include mortality as a search term, it nonetheless picked up some time-series studies on air pollution and mortality which are mentioned here.

PM₁₀ and lower respiratory infection mortality in young children and older children

In the multi-city study by Romieu et al (2012), the effect of ambient PM₁₀ concentrations on infant and child mortality from lower respiratory infection (LRI, J10-J22) was studied only for Mexico City, Santiago, and São Paulo. Significant increased mortality risk in infants under 1 year was observed in Mexico City (1.38% (0.09 to 2.69) increase per 10 µg/m³ increase in PM₁₀) but not Santiago (-1.54% (-3.10 to 0.04)) or Sao Paolo (-2.53% (-4.65 to -0.36)). In older children aged 1-14, a significant increased mortality risk was observed in Santiago (1.28% (0.80 to 1.76) but the positive

associations did not reach statistical significance in Mexico City 3.10% (-0.20 to 6.51) or Sao Paolo 1.40% (-2.05 to 4.98) per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} .

O_3 and lower respiratory infection mortality in young children and older children

For O_3 , an increased mortality risk was observed in Mexico City (in infants 0.85% (0.37 to 1.33) per 10 $\mu\text{g}/\text{m}^3$ increase in O_3 and older children 1.76% (0.54 to 3.00)) (Romieu et al 2012). Associations were not significant in infants in Santiago (-0.51% (-1.33 to 0.31) or Sao Paolo 1.52% (-0.16 to 3.23) and in older children in São Paulo (-1.00% (-3.37 to 1.41). There was a significant negative association in older children in Santiago -1.17% (-2.1 to -0.23).

PM_{10} and pneumonia mortality all ages

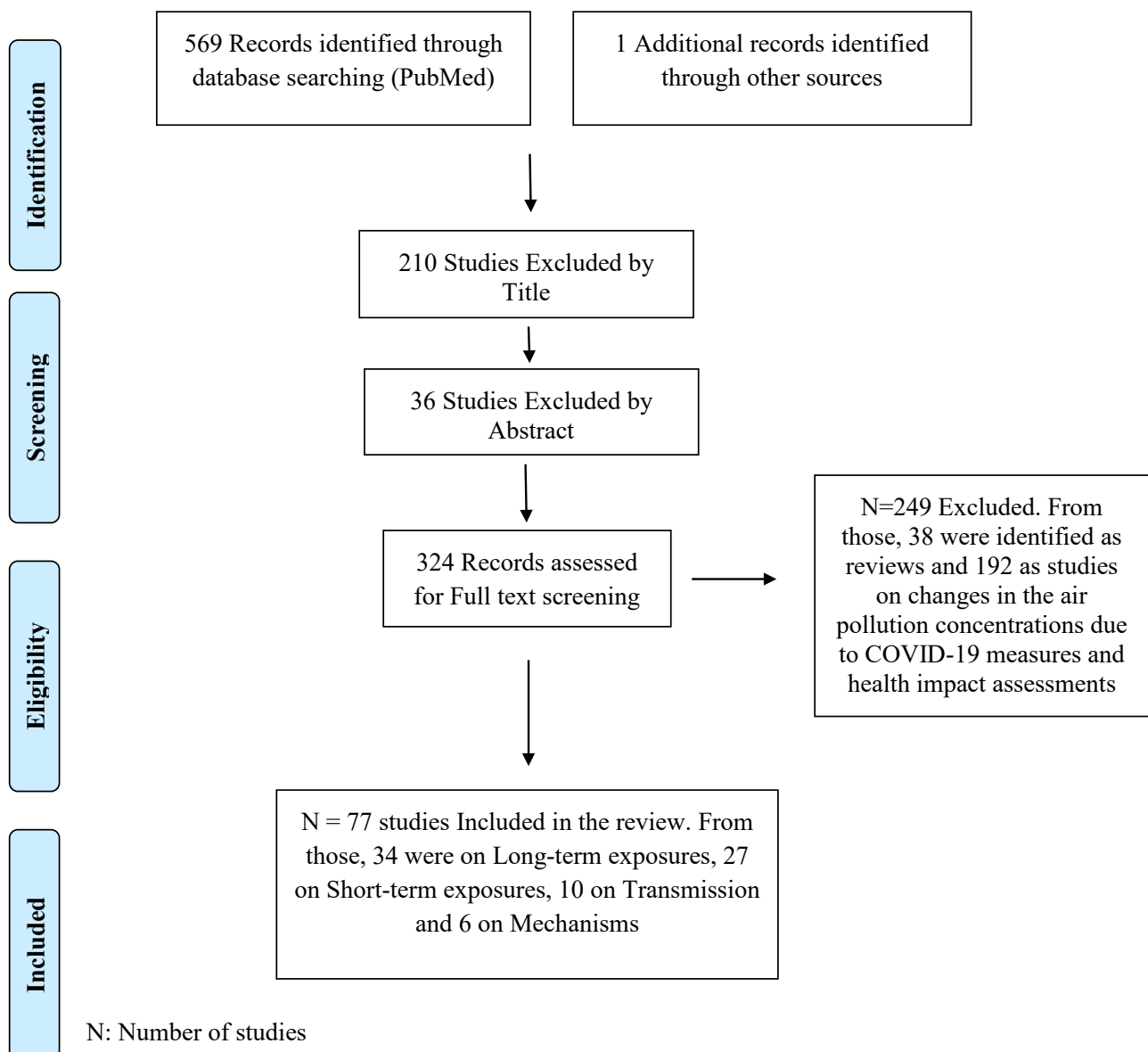
Sun et al (2019) performed a time-series study of mortality from pneumonia (ICD 10 code J12-J18) in all ages in Hong Kong. A positive but non-significant association was found per IQR of 41.1 $\mu\text{g}/\text{m}^3$ increase in PM_{10} but this was only shown in graphical form.

6.7 Literature searching for air pollution and COVID-19

The search string was (air pollution OR PM2.5 OR NO2 OR Ozone) AND (COVID-19 OR COVID-19 incidence OR COVID-19 mortality) from 01/11/2020 until 14/05/2021 (same search string as Brunekreef et al, 2021 which was up to 08/11/2020).

The flow diagram with the number of studies excluded at each stage and the final number of studies that were included in the review is below:

Figure 4 - Flowchart for the systematic literature search on air pollution exposure and COVID-19



7.0 References to Main Report and Appendix

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