STUDY

Requested by the ENVI committee

European Parliament

Air pollution and COVID-19

Including elements of air pollution in rural areas, indoor air pollution, vulnerability and resilience aspects of our society against respiratory disease, social inequality stemming from air pollution

Policy Department for Economic, Scientific and Quality of Life Policies
Directorate-General for Internal Policies
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PE 658.216 - January 2021

EN

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Including elements of air pollution in rural areas, indoor air pollution and vulnerability and resilience aspects of our society against respiratory disease, social inequality stemming from air pollution

Abstract

This study is about the effects of air pollution on health, notably COVID-19. The COVID-19 pandemic continues to wreak havoc in many areas of the world. The infection spreads through person-to-person contact. Transmission and prognosis, once infected, are potentially influenced by many factors, including air pollution. Studies have suggested that air pollution increases the incidence and the severity of the disease. However, the current data are too limited to be certain. Especially the quantitative contribution of air pollution to the disease is still very uncertain.

This document was provided by the Policy Department for Economic, Scientific and Quality of Life Policies at the request of the committee on the Environment, Public Health and Food Safety (ENVI).

This document was requested by the European Parliament's committee on Environment, Public Health and Food Safety.

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LINGUISTIC VERSIONS
Original: EN

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Manuscript completed: December 2020
Date of publication: January 2021

This document is available on the internet at:
http://www.europarl.europa.eu/supporting-analyses

For citation purposes, the study should be referenced as: Brunekreef, B, et al., *Air pollution and COVID-19. Including elements of air pollution in rural areas, indoor air pollution and vulnerability and resilience aspects of our society against respiratory disease, social inequality stemming from air pollution,* study for the committee on Environment, Public Health and Food Safety, Policy Department for Economic, Scientific and Quality of Life Policies, European Parliament, Luxembourg, 2021.

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LIST OF ABBREVIATIONS

AAQD	EU Ambient Air Quality Directives 2008/50/EC and 2004/107/EC
ACE-2	Angiotensin-converting enzyme 2
ACS	American Cancer Society
ALRI	Acute Lower Respiratory Infections
APHEA	Air Pollution and Health: a European Approach
BC	Black Carbon
BMI	Body Mass Index
CI	Confidence Interval
CO2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CTM	Chemical Transport Model
DALY	Disability Adjusted Life Years
ECDC	European Centre for Disease Prevention and Control
EEA	European Environment Agency
EPA NAAQS	Environmental Protection Agency National Ambient Air Quality Standard
ESCAPE	European Study of Cohorts for Air Pollution Effects
EU	European Union
EU LV AQD	European Union Limit Value from Air Quality Directive
GBD	Global Burden of Disease
ICU	Intensive Care Unit
IQR	Interquartile range
LMIC	Low- and Middle-Income Countries

MSI	Mobility Scale Index
NEC	National Emission Ceiling, directive 2016/2284
NH3	Ammonia
NMVOC	Non-Methane Volatile Organic Compounds
NO,NO2,NOx	Nitrogen Monoxide, Nitrogen Dioxide, Nitrogen Oxides
O3	Ozone
OECD	Organisation for Economic Cooperation and Development
PM2.5, PM10	Particulate matter of 2.5/10 microns in diameter or smaller
R0	Basic reproduction number
RR	Relative Risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Corona Virus 2
SO2	Sulphur Dioxide
TROPOMI	Tropospheric Monitoring Instrument
UFP	Ultrafine particle
UK	United Kingdom
US, USA	United States of America
VOC	Volatile Organic Compounds
WHO	World Health Organisation
WHO AQG	World Health Organisation Air Quality Guidelines

LIST OF SCIENTIFIC TERMS

Ace-2	Angiotensin-converting enzyme 2, the protein that provides the entry point for the coronavirus to hook into and infect a wide range of human cells
Airbase	The European air quality database maintained by the European Environment Agency (EEA) through its European topic centre on Air pollution and Climate Change mitigation
Alveolar Macrophages	The primary defence cells of the innate immune system, clearing the air spaces of infectious, toxic, or allergic particles that have evaded the mechanical defences of the respiratory tract, such as the nasal passages, the glottis, and the mucociliary transport system
Case Fatality Rate	Percentage of infected cases who die from the disease
Cellular Signalling	Cells typically communicate using chemical signals, proteins or other molecules produced by a sending cell, often secreted from the cell and released into the extracellular space where they can float – like messages in a bottle – over to neighbouring cells
Cohort Study	A study in which a group of individuals is followed over time, measuring exposure to air pollution, other risk factors and disease or death at the individual level
COVID-19	Coronavirus disease 2019, the contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Ecological Study	In ecological studies the unit of observation is the population or community, not the individual. Disease rates and exposures are measured in each of a series of populations and their relation is examined. Often the information about disease and exposure is abstracted from published statistics and therefore does not require expensive or time-consuming data collection
Epidemiology	The study of the distribution of health and disease and their determinants in human populations
Exposome	The totality of exposures to environmental pollutants throughout the life course, including from prenatal development to end-stage disease and mortality
Hypercholesterolemia	A very high blood cholesterol level
Mucociliary Clearance	Defence mechanism of the lungs in which mucus and potentially harmful foreign substances contained in it are moved out of the lung by an escalator-like movement

OMICS- platforms	Collective technologies that measure the characteristics of the various types of molecules making up the cells of an organism, named from the suffix '-omics', as in 'genomics'
One Health Studies	A specific category of studies that explore transmission of infectious disease such as Corona Virus Disease 2019 (COVID-19) from animals to humans or from humans to animals
Oxidative Stress	Phenomenon caused by an imbalance between production and accumulation of oxygen reactive species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products
Q Fever	'Query fever' is an infectious disease caused by infection with *Coxiella burnetii*, an obligate intracellular bacterial pathogen
R0	Basic reproduction number. It denotes how many persons in average are infected by each infected case in the population. If it is above one, the infection will spread exponentially; if it is below one, the infection will gradually diminish or even disappear
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2, the virus that causing coronavirus disease 2019
Time Series Studies	Studies that investigate whether on relatively high pollution days the number of (respiratory, cardiovascular etc.) deaths or hospital admissions is higher than on low pollution days
Zoonoses	Diseases transmitted from wild or domestic animals to humans

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EXECUTIVE SUMMARY

The ongoing COVID-19 pandemic is an acute public health crisis the world has seldom seen before. More than a million deaths have already occurred worldwide, and many countries are now forced to deal with a second or even third wave of infections, after the first wave hit in early 2020. The scientific community is trying to understand where, why and how this pandemic exactly started and unfolded, what treatments might be available, and what external risk factors may be contributing to the spread and severity of the disease.

Air pollution is one of many factors that has received some attention in recent months as a factor which may facilitate the spread, severity and prognosis of the disease. Many reports have appeared, quite often as pre-publications which were not (yet) peer reviewed. The purpose of this study is to discuss the potential effects of air pollution on COVID-19 in the context of what is known about health effects of air pollution in general, and about state-of-the art methods to study such effects.

Sources and concentrations of air pollution

In Europe, many sources contribute to air pollution. These include energy production from fossil fuel or biomass combustion, road traffic, shipping emissions, home and utility building heating, industrial production, agricultural emissions, and others. These sources not only produce pollutants directly (primary emissions), but they also produce so-called precursor gases which, through atmospheric reactions, produce secondary pollutants. Examples are fine particles produced from ammonia from farming, sulphur oxides from burning of sulphurous fossil fuel and nitrogen oxides from road traffic; and ozone produced from nitrogen oxides and hydrocarbons under the influence of sunlight and elevated air temperatures. Concentrations of most pollutants have fallen over the last decades; ozone is an exception due to the rising hemispheric background concentrations resulting from worldwide increases in precursor gases as well as global warming. Yet, most of Europe is still not in compliance with World Health Organisation Air Quality Guidelines (WHO AQG) for fine particles and – to a lesser extent – ozone.

As people spend most of their time indoors, and most of that time in the home, exposure to pollution indoors is also important. Next to outdoor pollution penetrating indoors, several indoor sources exist such as (cigarette) smoking, cooking, candle burning and woodstoves and fireplaces.

Health effects of air pollution

Much of what we know about the health effects of air pollution comes from epidemiological studies. Epidemiology is the 'science of public health'. We study human populations as they go about their daily lives and try to quantify what levels of air pollution they are exposed to – next to a range of other factors that may influence health, such as diet and occupation. Air pollution epidemiology uses sophisticated methods to estimate exposure at the home address and even personal level. Increasingly, such methods combine field observations with chemical transport models, satellite images and land use data. To study the health effects of these exposures, large population cohorts are followed for periods of years to decades, to precisely document the association between air pollution and development of chronic diseases such as heart disease, asthma, Chronic Obstructive Pulmonary Disease (COPD), lung cancer and diabetes. With the advent of 'big data' facilities, we increasingly also utilise multi-million population data bases from censuses, mortality and hospital

admission databases, electronic patient data bases and so forth. Such studies have made it possible to document health effects of low-level air pollution occurring in rural areas where, until recently, populations were not studied. Collectively, long-term studies of air pollution have shown convincing evidence of effects of fine particles (PM2.5) on all-cause mortality, and on morbidity and mortality from cardiovascular and respiratory disease as well as diabetes and lung cancer. Furthermore, nitrogen dioxide (NO_2) and ozone (O_3) are associated with respiratory disease and mortality.

Apart from studies of long-term effects, there is also a long tradition of studying effects of short-term variations in air pollution concentrations. Grounded in the studies of dramatic episodes of very high pollution in, for example, the Meuse valley (Belgium) in 1930 and London (UK) in 1952, these so-called time series studies have convincingly demonstrated effects on mortality and hospital admissions starting from very low levels of exposure.

In comparison, there have been fewer studies on the health effects of indoor pollution, and of the direct effects of air pollution from farming. Indoor studies have primarily been focused on effects of environmental tobacco smoke, gas cooking emissions, home dampness and, more recently, phthalates and other complex chemicals. Studies on air pollution from farming include a focus on the role of specific microbial farm pollutants which may be relevant in specific locations and potentially during human disease outbreaks traceable to farm animals (zoonoses). Studies in rural communities have demonstrated, in rare instances, transmission of zoonotic infections such as avian influenza from poultry, or Q fever from goats and sheep infected with *Coxiella burnetii*. In addition, lower lung function and more pneumonia have been shown in residents living close to intensive livestock operations. Interestingly and conversely, living in farming communities has also been shown to confer some protection against allergy and asthma.

Against this 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. COVID-19 is an incredibly difficult endpoint to study. The spread of the disease is highly dynamic in both time and space simply because the virus is transmitted from person to person. Infected persons differ vastly from each other in how much virus they shed, and clusters of cases often occur while the shape of the pandemic waves is driven by so-called superspreading events. Methods that work well to study associations between long-term exposure to air pollution and chronic disease development are limited when investigating such a fast-moving target. Also, time series methodology to assess short-term air pollution effects was developed primarily to study long, multi-year daily observations of time-varying exposures and health effects in otherwise stable populations. With COVID-19, the time series studies so far were necessarily very short, which makes them vulnerable for uncontrolled errors. A clear and intuitive example is that the time courses of air pollution as well as COVID-19 were both influenced by a whole variety of (COVID-19) preventive lockdown measures which created artificial correlations between declines in air pollution and COVID-19 over time.

These reservations should not be interpreted as suggesting that air pollution may not have some detrimental effect on COVID-19, both in incidence and severity. Air pollution clearly increases the prevalence of cardiovascular and respiratory disease. Patients suffering from these diseases have an increased risk of mortality from COVID-19 compared to healthy subjects. Also, air pollution has been shown to increase the occurrence of respiratory infections from a variety of pathogens, likely by reducing host defences. 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-characterised exposure to air pollution and other risk factors and well-characterised disease manifestations.

Environmental justice and policy recommendations

Meanwhile, the global burden of disease from air pollution is very large. In Europe alone, fine particulate matter is estimated to account for some 400,000 premature deaths every year. The worldwide number is well over 4,000,000. These effects are more likely to occur in disadvantaged populations with higher exposures and/or increased susceptibility to air pollution effects on health and/or higher baseline rates of cardiovascular and respiratory disease. WHO is currently revising its Air Quality Guidelines, and the EU has pledged to follow the new guidelines for its policies regarding abatement of air pollution. If, and when effects of air pollution on COVID-19 have been more clearly established, this will be a further stimulus to aggressively pursue such policies.

KEY MESSAGES

1. Air pollution causes chronic diseases such as asthma, COPD, lung cancer, heart disease and diabetes. Many of these conditions predispose to COVID-19 hospitalization, ICU admission and death. For this reason alone, there is serious concern about the negative impacts of air pollution on the COVID-19 pandemic.

2. Air pollution has been shown to reduce respiratory resistance against bacterial and viral infections other than Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). However, evidence is emerging that people living in high pollution areas might be more frequently infected by SARS-CoV-2, and more likely to develop COVID-19 once outbreaks occur. Almost all studies used aggregate data, i.e. data on COVID-19, air pollution and other risk factors averaged over areas such as municipalities and counties. Outbreaks as well as air pollution are related to population density and other spatial variables. It has been very difficult until now to disentangle any independent effects of air pollution from effects of other causes of the disease outbreaks. This has likely resulted in an overestimation of the effect of air pollution on COVID-19 occurrence and severity in studies available to date.

3. Methods are available to do much more refined studies of air pollution and COVID-19 but such studies are more demanding in terms of obtaining the necessary data and dealing with privacy issues. In one or a few years' time, the research community will be able to apply all the advanced tools of the trade to investigate effects of air pollution in large cohorts and administrative databases with excellent opportunities to include individual level data. To explore whether air pollution influences SARS-CoV-2 infection and COVID-19 outcomes, high resolution temporal and spatial data are required, preferably supported by virus sequencing data.

4. A significant fraction of COVID-19 survivors has been burdened by adverse long-term conditions affecting the heart, lungs and other organ systems. Concerns are raised as these conditions can be worsened by long-term air pollution exposure and because short-term exposure to air pollution has been shown to increase hospital admissions for respiratory and heart conditions.

5. The overall impact of air pollution on heart and chronic lung disease is more than large enough to motivate aggressive reduction policies. Such policies that protect the population from the effects of air pollution are likely to protect as well against COVID-19 deaths possibly attributable to air pollution.

1. INTRODUCTION

The ongoing COVID-19 pandemic is an acute public health crisis the world has seldom seen before. Close to 50 million cases and more than a million deaths have occurred worldwide already (WHO, 2020c), and – after initial successes in containing the first wave during the first half of 2020 - there now are rapidly accelerating second and third waves in many countries including those within Europe. The scientific community is striving to understand when, why and how this pandemic exactly started and unfolded, what treatments might be available, and what external risk factors may be contributing to the spread and severity of the disease.

Air pollution is one of many factors that has received some attention in recent months as a factor which may facilitate the spread and severity of the disease. Many reports have appeared, quite often as pre-publications which were not (yet) peer reviewed. Given the extent of the pandemic, the need to understand who are at most risk of severe disease, and the known associations between air pollution and respiratory and cardiovascular disease, the question whether the occurrence and prognosis of COVID-19 disease can in part be influenced by environmental pollution is a valid one. However, despite some early claims, the current evidence needs to be reviewed with caution. First, there are methodological aspects to consider.

Almost all studies published so far have used a so-called ecologic design. This refers to a study design which uses *aggregate* data, and not *individual* data. Units of aggregation include municipalities, provinces, counties, health regions etc. Populations included in these units varied widely within and between unit categories. A limitation of this design is that associations at the aggregate level may not reflect the true relationship between exposure and disease at the individual level. As an example, studies have looked at the association between county mortality rates from COVID-19 and average pollution levels in these counties, across the United States, without having access to information on causes of death, age, lifestyle habits, air pollution at the home address etc. at the individual level. At the aggregation level, associations between air pollution and COVID-19 are then analysed, taking into account other factors such as area-level population size and density, socio-economic status, neighbourhood connections, etc. At best, these studies should be seen as 'hypothesis generating', and further studies with detailed individual information about exposure, disease, age, sex, diet, socio-economic status etc. are needed to shed more light on causal connections between air pollution and COVID-19.

As a further complication, COVID-19 is an incredibly difficult endpoint to study. The spread of the disease is highly dynamic in both time and space. The virus is transmitted from person to person, with infected persons differing vastly from each other in how much virus they shed, and clusters of cases often occur. There is considerable heterogeneity in transmission, and most transmission is caused by a limited number of superspreading events. These, in turn, are related to human behaviour, socio-economic and demographic factors (such as household size and multi-generation households) and compliance to control measures (Chang et al., 2020). Methods that work well to study associations between long-term exposure to air pollution and chronic disease development are not necessarily suitable to investigate such a fast-moving target. Also, time series methodology was developed primarily to study long, multi-year daily observations of time-varying exposures and health effects in otherwise stable populations. With COVID-19, the time series studies so far were necessarily very short, which makes them vulnerable to uncontrolled errors.

The purpose of this study is to discuss the potential effects of air pollution on COVID-19 in the context of what is known about the health effects of air pollution in general, and about state-of-the art methods to study such effects. We will first discuss sources and concentrations of the major outdoor

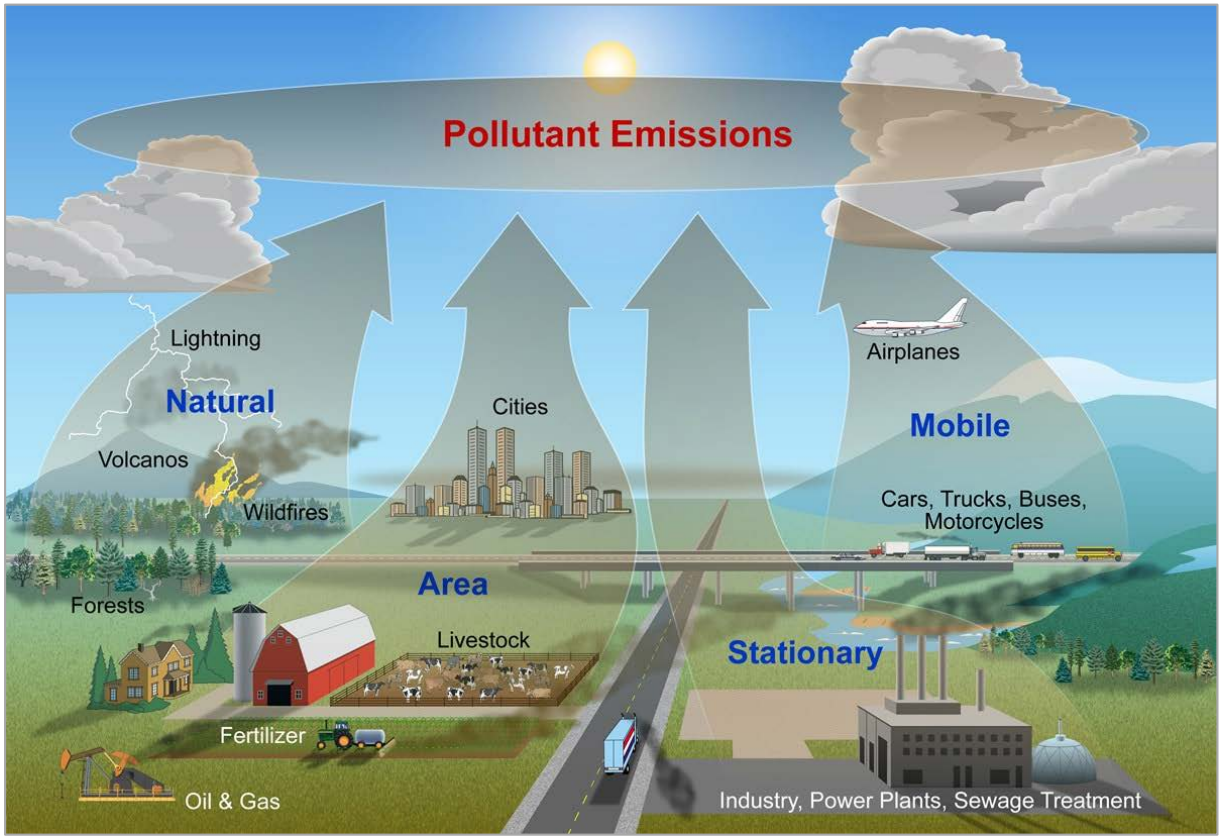
air pollutants in Europe today. Then we will briefly discuss sources and concentrations of indoor air pollution (chapter 2). Chapter 3 starts with a brief overview of current methods that are used to study the health effects of air pollution, followed by summaries of the main health effects of outdoor and indoor air pollution. We will discuss specifically what is known about effects of outdoor and indoor air pollution on respiratory infections. A separate section is devoted to methods which are suitable to study environmental determinants of COVID-19, followed by a review of studies on associations of outdoor air pollution and COVID-19. We are not aware of studies on indoor air pollution as a determinant of COVID-19. Chapter 4 deals with vulnerability, environmental justice and societal resilience. There has been a fair amount of work on this in the air pollution field, some of which may be relevant for COVID-19. Chapter 5 discusses emerging evidence of effects of COVID-19 containment measures on air pollution concentrations and on health effects of air pollution. Finally, in chapter 6, we will examine EU air pollution policies and in chapter 7, we make some recommendations.

2. SOURCES AND CONCENTRATIONS OF AIR POLLUTION

2.1. Outdoor air pollution in urban and rural areas in Europe

Sources of air pollution in urban and rural areas are many, as shown in figure 1 below:

Figure 1: Sources of air pollution



Source: National Park Service, US available at https://www.nps.gov/subjects/air/sources.htm

The sources include energy production from fossil fuel or biomass combustion, road traffic, shipping emissions, home and utility building heating, industrial production, agricultural emissions and others. These sources not only produce pollutants directly (primary emissions) but they also produce so-called precursor gases which, through atmospheric reactions, produce secondary pollutants. Examples are fine particles produced from ammonia from farming, sulphur oxides from burning of sulphurous fossil fuel and nitrogen oxides from road traffic; and ozone produced from nitrogen oxides and hydrocarbons under the influence of sunlight and elevated air temperatures. Concentrations of most pollutants have fallen over the last decades; ozone is an exception due to the rising hemispheric background concentrations resulting from worldwide increases in precursor gases as well as global warming. Yet, most of Europe is still not in compliance with WHO Air Quality Guidelines for fine particles and – to a lesser extent – ozone.

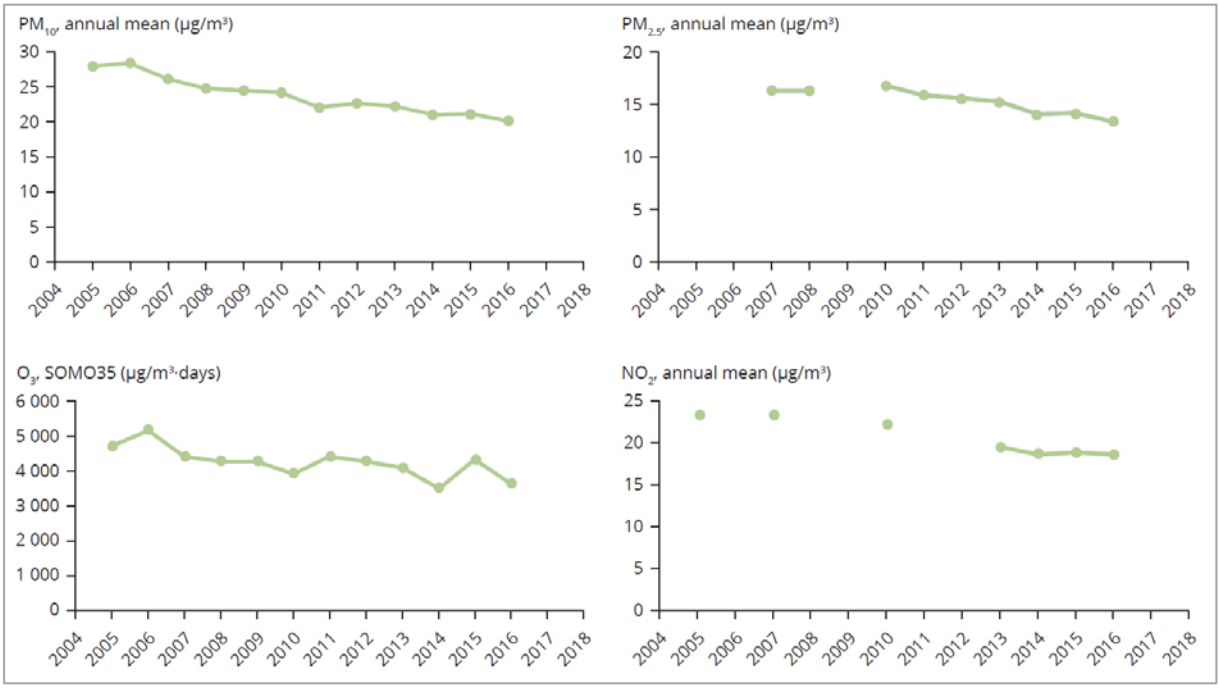
Secondary particles often contribute up to half of the particle mass in any area in Europe. Fine particles have a very long atmospheric lifetime. They are transported over long ranges and in smaller EU countries, imported particles may account for up to or more than half of the particle mass people are exposed to.

Over the last decades, air pollution exposures in Europe have gradually decreased in response to tighter regulations at the EU, national and regional levels (figure 2). Despite those reductions, large

parts of the European population are still exposed to PM and ozone concentrations well above World Health Organisation Air Quality Guidelines (table 1).

In rural areas, especially those with much livestock farming, agriculture is a source of air pollutants, including both coarse and fine particles, odorous gases, microbial toxins, and potentially pathogenic viruses and bacteria. Primary PM from livestock houses is mainly of organic nature, but livestock farming is also an important contributor to secondary particles, which are formed by gaseous ammonia from livestock production, and combustion-based gases. As a result, agricultural ammonia emissions have been identified as major contributors to the particle mass in urban and rural areas. Yet, ambitions at the EU level to reduce especially ammonia emissions are seen as insufficient (see also Chapter 6 and 7) (Harrison et al., 2014).

Figure 2: Changes in air pollution over time



Note: SOMO35: Sum of Ozone Means Over 35 ppb.

Source: European Environment Agency, available at https://www.eea.europa.eu/publications/air-quality-in-europe-2019

Table 1: Percentage of urban population exposed to air pollutants above certain limits

Pollutant	EU reference value [a]	Urban population exposure (%)	WHO AQG [a]	Exposure estimate (%)
PM_{10}	Day (50)	13-19	Year (20)	42-52
$PM_{2.5}$	Year (25)	6-8	Year (10)	74-81
0_3	8-hour (120)	12-29	8-hour (100)	95-98
NO_2	Year (40)	7-8	Year (40)	7-8
BaP	Year (1)	17-20	Year (0.12) RL	83-90
S02	Day (125)	<1	Day (20)	21-31
Key	<5%	5-50%	50-75%	>75%

Source: European Environment Agency, available at https://www.eea.europa.eu/publications/air-quality-in-europe-2019

2.2. Indoor air pollution in urban and rural areas in Europe

2.2.1. Relevance of indoor air pollution

People spend the majority of their time indoors, either at homes, workplaces, shops, schools or other enclosed spaces such as cars, buses and trains. Therefore, the quality of indoor air is highly important to personal health (Environmental Protection Agency, EPA, 2020; WHO, 2010). There are a variety of sources of indoor air pollution, which generally emit and/or are present at varying frequencies. The relative importance of any single pollution source is dependent upon how much of a given pollutant it emits and how hazardous that pollutant is. Individual building characteristics, including age, material, and level of maintenance are also important contributors to the degree and makeup of indoor air pollution.

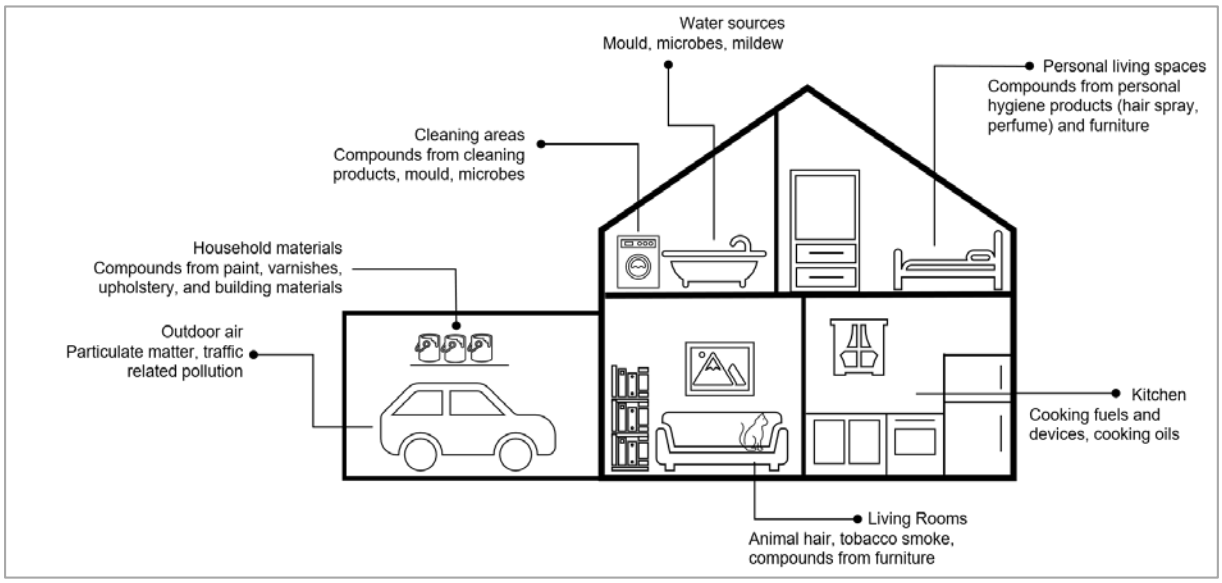
2.2.2. Sources of indoor air pollution

Not all sources of indoor air pollution are emitted or present at equivalent levels or frequencies. Some sources (e.g. furnishings, building materials) passively generate pollutants at a relatively stable rate whereas other compounds are only introduced through active contributions such as smoking, cleaning, or heavy traffic on roads near the home. Example sources of indoor air pollution are illustrated in Figure 3 and described below.

2.2.3. Outdoor air pollution

Owing to natural exchanges of indoor and outdoor air, air pollution from outdoor sources migrates indoors. This is especially relevant for buildings in proximity to roadways where traffic derived air pollution (e.g. particulate matter, benzene, NO_2) may be high, and is transported indoors by passive or active ventilation. The degree of infiltration is highly variable, depending on a myriad of factors including building design, season, meteorology, and naturally, intensity of outdoor air pollution.

Figure 3: Sources of indoor air pollution



Source: George Downward (author's own elaboration).

2.2.4. Fuel combustion

The residential combustion of solid fuels (wood, coal etc.) is a common practice in resource-poor settings globally, especially low-income and low-middle-income countries. In these settings, the household air pollution generated results in several million deaths per year. Within Europe, the indoor burning of solid fuels has become relatively uncommon, with a recent European Commission report indicating that household solid fuel combustion represents approximately 2.6% of the total energy consumption within the EU. However, as this is a highly inefficient method of generating energy, it produces higher emissions of particulate matter than road transport. These emissions contribute to both indoor and outdoor air quality with the relative proportion to each dependent upon multiple factors such as stove quality, stove maintenance, and correct stove usage. In one case report, an old wood stove was reported to generate indoor pollution at levels equivalent to a heavily trafficked road.

2.2.5. Tobacco smoke

The impact of tobacco smoke on health is well documented and numerous public health measures have been implemented around the world to limit exposure to "second-hand" tobacco smoke in public places and businesses. However, no such protections typically exist for private residences meaning that residential tobacco usage represents a notable source of indoor air pollution in households with one or more smokers.

2.2.6. Building materials and furnishings

Regardless of age, building materials and furnishings represent a diverse source of indoor air pollutants. Varnishes, glues, upholsteries, and paints all contain compounds (e.g. VOCs, Volatile Organic Compounds) which will gradually be emitted into the indoor space with the passage of time. Additionally, within older buildings, the deterioration of building components containing asbestos, either as part of normal wear and tear or as part of part of an acute event (e.g. a major renovation), will result in the release of this well-known carcinogen into the household (Alpert et al., 2020).

2.2.7. Household cleaning/maintenance

Many compounds used for household cleaning result in the emission of particulate matter. For cleaning materials which are embedded on a surface, the release of indoor pollutants occurs at a relatively stable rate. However, other short-term activities (e.g. painting, use of adhesives) can result in a short-term increase in indoor pollutants. Interestingly, vacuuming can have the unintended consequence of actively disturbing dust and may in some situations agitate indoor air pollution (Knibbs et al., 2012).

2.2.8. Moisture

The accumulation of indoor moisture encourages the growth of mould, mildew, and dust mites, all of which can contribute to poor indoor air quality. Further, the infiltration of moisture into household products (e.g. wood, metal) may result in a more rapid degradation of those products and accelerate the rate at which other pollutants are released.

2.2.9. Rural versus urban settings

There are several differences in sources, constituents, and concentrations of indoor air pollution between urban and rural settings. For example, in urban communities, traffic derived pollution is more likely to contribute to indoor air pollution than rural communities, where farming related sources (e.g. pesticides, animal waste) are more likely.

2.2.10. Methods to improve indoor air quality

In principle, the most effective method to improve indoor air quality is to remove/replace the individual emission sources. A reduction in outdoor air pollution will reduce indoor pollution as a flow-on effect. Taking actions to reduce indoor/outdoor ventilation (e.g. closing windows) may play a role in reducing indoor pollution levels; however, household ventilation is a useful strategy for removing indoor pollutants so it is important to remember that this will also prevent the out-flow of pollution generated indoors and as such is a limited solution.

The role of proper ventilation of indoor spaces as a means to reduce exposure to SARS-CoV-2 has received considerable attention (Morawska & Cao, 2020; Morawska & Milton, 2020). Existing ventilation standards are mostly designed to prevent high CO_2 concentrations from happening in indoor spaces. CO_2 is produced by normal breathing and has long served as an indicator for perception of stale air caused by human body odours, personal care products and the like. It is unclear whether existing ventilation standards are sufficient to prevent SARS-CoV-2 infections from spreading as this also depends on how many infected persons are present and how much virus is being shed by them.

There are several commercial air purifiers available for purchase, many of which are relatively effective at removing particulate material from the indoor space. In regions where high levels of pollution are unavoidable (e.g. heavily polluted areas in Low and Middle Income Countries (LMIC) or regions prone to high outdoor pollution from wildfires) these devices may play an important role in improving indoor air quality (Fazli et al., 2019; WHO, 2020a). However, the effectiveness of these devices varies widely by design and type and are generally unable to clear gaseous compounds from the air, limiting their overall role in public health. Indeed, the recent WHO report on personal interventions concluded that such individual level interventions were the least desirable in the hierarchy of interventions, especially when compared to public policies focussed on emission reduction.

3. HEALTH EFFECTS OF AIR POLLUTION

3.1. Methods in air pollution epidemiology

Much of what we know about the health effects of outdoor and indoor air pollution comes from epidemiological studies. Epidemiology is the 'science of public health'. We study human populations as they go about their daily lives and try to quantify what levels of pollution they are exposed to – next to a range of other factors that may influence health, such as smoking, diet and occupation.

Epidemiological studies compare the health of individuals with high and low air pollution exposures, taking into account other risk factors. We distinguish studies of long-term exposure (e.g. high annual averages) and short-term exposure (e.g. high pollution days). These two types of studies use different designs and exposure assessment methods.

Air pollution epidemiology studies of long-term exposure use sophisticated methods to estimate exposure at the home address and even personal level. Increasingly, such methods combine air pollution measurements with chemical transport models, satellite observations and land use data. To study the health effects of these exposures, large population cohorts are followed for periods of years to decades, to precisely document the association between air pollution and development of chronic diseases such as heart disease, asthma, COPD, lung cancer and diabetes. With the advent of 'big data' facilities, we increasingly also utilise multi-million population data bases from censuses, mortality and hospital admission databases, electronic patient data bases and so forth. Such studies have made it possible to document the effects of low-level air pollution occurring in rural areas where, until recently, populations were not studied. Studies have assessed a wide range of health effects, ranging from physiological changes to mortality and morbidity from respiratory and cardio-metabolic diseases. The most informative studies are those which evaluate individual exposure and health, allowing the inclusion of individual risk factors such as smoking habits, diet and occupation. Earlier studies used a so called 'ecological' design, comparing the frequency of disease and the average air pollution concentrations in different areas such as neighbourhoods or municipalities. These studies are difficult to interpret because they lack data on individual disease, exposure and other risk factors. For this reason, in the recent evaluation by the World Health Organization of studies on outdoor air pollution, ecological studies were excluded from the assessment (Chen et al., 2020; Huangfu et al., 2020).

In recent years, major advances have also been made in the development of the so-called Exposome concept. This concept attempts to grasp the totality of exposures to environmental pollutants throughout the life course, including from prenatal development to end-stage disease and mortality. The development of various environmental and lifestyle sensors, comprehensive screening of biological effects (OMICS- platforms), combined with big data approaches have made such studies increasingly possible. The European Union is currently funding a series of coordinated large studies in this area which will increase our understanding of lifetime pollution exposures and health effects considerably. These studies will contribute significantly to characterise health effects of air pollution in conjunction with other external (e.g. noise, green space) and internal (e.g. metabolic factors) Exposome factors.

Apart from studies of long-term exposure effects, there is also a long tradition of studying effects of short-term variations in air pollution concentrations. These studies are grounded in the studies of dramatic episodes of very high pollution in, for example, the Meuse valley (Belgium) in 1930 and London (UK) in 1952, comparing morbidity and morbidity on episode days with days before and after the episode. Since the 1990s, so-called time series studies have assessed associations between

daily variation of air pollution and daily mortality and hospital admissions at much lower concentrations. These studies investigate whether on relatively high pollution days the number of (respiratory, cardiovascular etc.) deaths or hospital admissions is higher than on low pollution days. Time series studies need to correct for other factors that may result in increased daily numbers of deaths or hospital admissions, such as heatwaves and cold spells but also occurrence of influenza epidemics, long-term trends and seasonality (mortality is typically higher in winter). Time series are most informative if continuous observations from multiple years are included in the study.

Exposure to air pollutants in time series studies is usually estimated from continuous outdoor air pollution monitoring stations operating in the area of the population under study. Several studies have documented that the temporal variation in outdoor concentrations of especially fine particles is well correlated with the temporal variation in personal exposure. This supports the use of outdoor air pollution concentrations as a metric of exposure in time series studies (Janssen et al., 2000; Janssen et al., 1998; Janssen et al., 1999).

In comparison, there have been fewer studies on the health effects of indoor pollution, and of direct effects of air pollution from farming. Indoor studies have been most focused on effects of environmental tobacco smoke, gas cooking emissions, home dampness and, more recently, phthalates and other complex chemicals. In comparison to studies of the health effects of outdoor air pollution, studies of indoor air pollution more often use questionnaires as a principal tool to assess exposure to indoor pollutants. This is because it is not possible to measure air pollution in a large number of homes for any prolonged period of time. In addition to questionnaires, investigators use validation studies to measure the validity of questionnaires in terms of the accuracy and precision with which they represent measurements of environmental tobacco smoke and other indoor pollutants.

Studies in rural communities have demonstrated, in rare instances, transmission of zoonotic infections such as avian influenza from poultry, or Q fever from *Coxiella burnetii* infected goats and sheep. In addition, lower lung function and increased pneumonia incidence have been shown in residents living close to intensive livestock operations (Smit et al., 2017). Interestingly, living in farming communities has also been shown to confer some protection against allergy and asthma. Interestingly, living in farming communities has also been shown to confer some protection against allergy and asthma. Until recently, there have been few studies of health effects of air pollution in rural communities. This is because air pollution was not routinely measured in such areas, with the exception of measurements conducted at a few background sites not located near urban areas of other large sources of pollution. Advances in air pollution exposure modelling have made inclusion of rural populations in nationwide studies possible. However, dedicated exposure measurement and modelling campaigns are still needed in studies focused on specific rural exposures related to pesticide use, specific microbial emissions from intensive livestock farming etc.

3.2. Health effects of outdoor air pollution

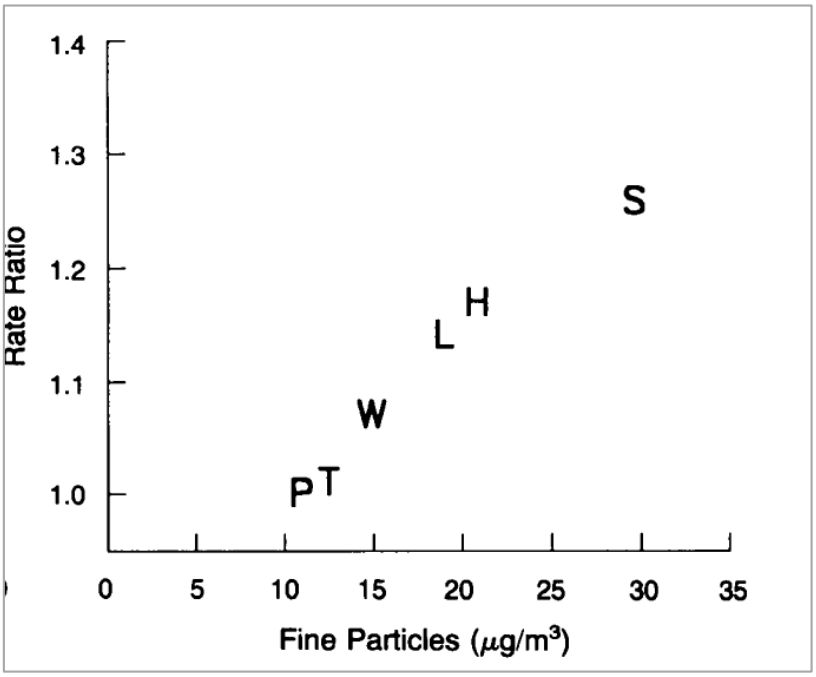
3.2.1. Studies of long-term effects

There is great interest in long-term effects occurring after years or even decades of exposure to high pollution levels. Fifty years ago an association was published between the 1960 mortality rates and air pollution levels comparing 114 metropolitan areas in the USA (Lave et al., 1970, 1972). Another analysis focused on 1980 metropolitan-area average mortality and air pollution in the USA again found a positive relationship (Ozkaynak et al., 1987). However, because both studies did not analyse

individual data but area-wide, group averages (ecological studies), they were not considered as providing sufficient evidence for setting air pollution standards or guidelines.

This changed when in 1993, a landmark study was published that followed a cohort of almost 9,000 subjects, living in six US cities, for about 14 years (Dockery et al., 1993). This study is referred to as the Six Cities Study. In this study, detailed data on individual characteristics such as smoking, and education were collected. In each city, data on several air pollutants including fine particulate matter with a diameter of less than 2.5 µm (PM2.5) was collected over many years. At relatively low concentrations, a strong association between PM2.5 and mortality was found (figure 4) after adjustment for other risk factors such as smoking.

Figure 4: Associations between fine particles and mortality in the Six Cities Study



Note: On the Y-axis, the 'Rate Ratio' reflects the risk of death relative to the cleanest community, Portage. P=Portage, Wisconsin; T=Topeka, Kansas; W=Watertown, Massachusetts; L=St. Louis, Missouri; H=Harriman, Tennessee; S=Steubenville, Ohio.

Source: Dockery et al., 1993.

These findings were supported in 1995 by the results of another very large US cohort study, the so-call American Cancer Society (ACS) study (Pope et al., 1995). This study followed about half a million individuals over a seven-year period. Based on these two studies, the US Environmental Protection Agency established an annual average PM2.5 standard of 15 µg/m^3 in 1997. This standard generated vigorous debate from various stakeholders. A unique re-analysis project was carried out to investigate the replicability of the findings by a team of independent investigators (Krewski et al., 2003). In the process, new techniques for spatial analysis of associations between air pollution and health were developed. The original findings were found to be solid, and a new analysis of the ACS

study was published in 2002 (Pope et al., 2002) showing monotonous increases in cardiopulmonary and lung cancer mortality starting from annual average concentrations as low as 10 µg/m^3 PM2.5.

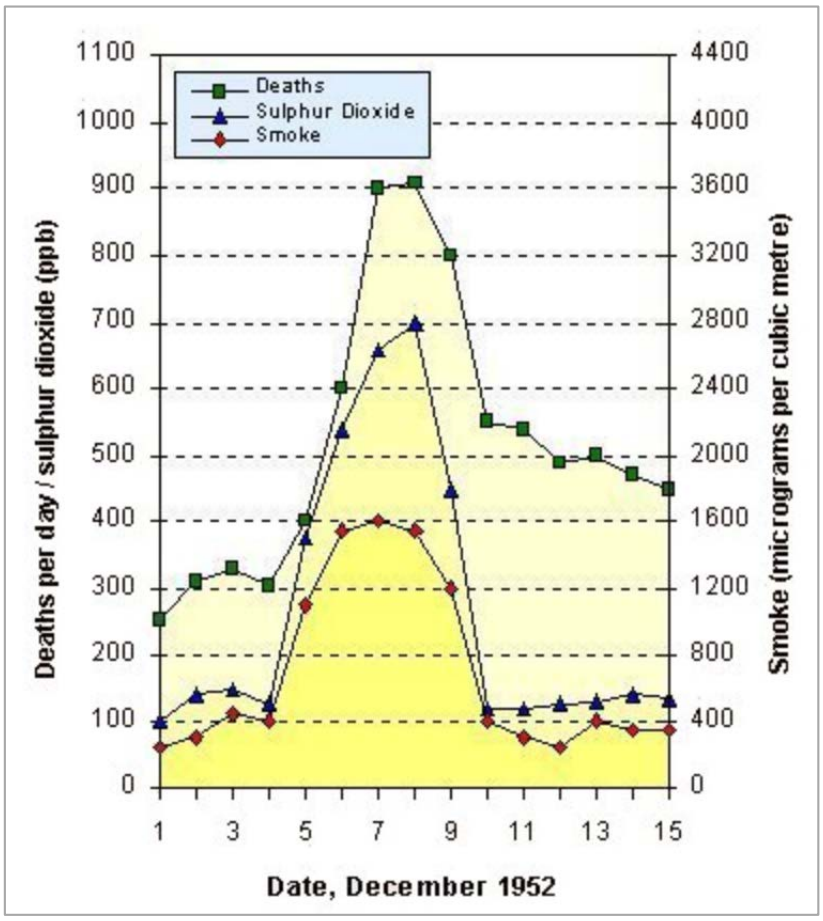
In Europe, no comparable studies of long-term effects of air pollution were available at the time. When the Air Quality Directive was revised in the 2005-2008 period, the absence of European studies on long-term effects of especially PM2.5 was used as an argument to set a relatively lax annual average PM2.5 limit value of 25 µg/m^3 which has not been revised since. However, a large EU funded collaborative study, the European Study of Cohorts for Air Pollution Effects (ESCAPE) and several other large studies have since demonstrated that air pollutants such as PM2.5, Black Carbon (BC) and nitrogen dioxide (NO_2) are associated with multiple effects on health ranging from low birthweight, early childhood pneumonia, child and adult lung function to lung cancer and total, non-accidental mortality (Adam et al., 2015; Beelen et al., 2014; Crouse et al., 2015; Di et al., 2017; Gehring et al., 2013; MacIntyre et al., 2014; Pedersen et al., 2013). These associations were found at concentrations well below EU limit values for PM2.5 and NO_2. The World Health Organization is currently in the process of updating the Global Air Quality Guidelines published in 2005 (WHO, 2005).

In the last decade, methods have been developed to estimate outdoor concentrations of the major outdoor air pollutants PM2.5, BC, O_3 and NO_2 with fine spatial resolution for the whole planet. These methods use not only data from monitoring stations but also chemical transport models, land use data and satellite observations as mentioned in section 3.1. This has facilitated studies of very large populations, not restricted to urban areas where most of the monitors are. Examples include studies using national mortality statistics, national censuses and Medicare data on all elderly living in the US. Recently, estimates of long-term average outdoor air concentrations on non-regulated air pollutants are becoming increasingly available, including ultrafine particulates and chemical composition of fine particles. Studies have shown that perhaps some of the previously observed health effects of PM2.5 might be due to these very small particles (<100 nm) (Downward et al., 2018).

3.2.2. Studies of short-term effects

In the first half of the 20th century several air pollution episodes occurred with dramatic immediate effects on mortality: Meuse valley, Belgium in 1930; Donora, PA, USA in 1948; and the most dramatic of all, London, UK, 1952. These episodes were all produced by a combination of high local pollution emissions and stagnant weather conditions preventing atmospheric dispersal of the pollution. The London 1952 episode resulted in some 4,000 additional deaths in the first week, and some 8,000 more in the following 2 months. The immediate effects are shown in figure 5. The dramatic changes in pollution and deaths left little doubt about the causal nature of the effect.

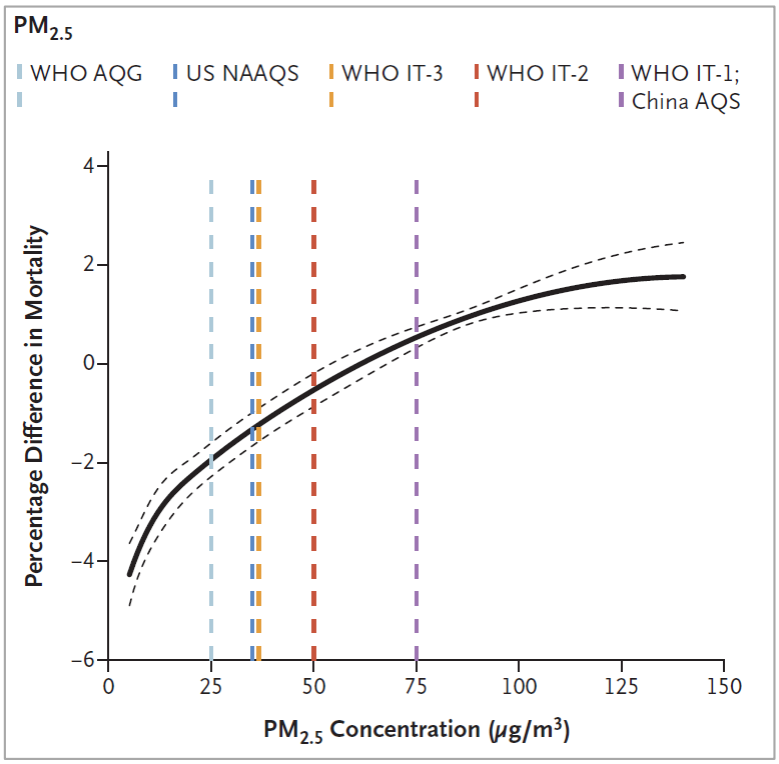
Figure 5: Air pollution and mortality in the London smog of 1952



Source: Enviropedia, UK available at http://www.air-quality.org.uk/03.php

The London Smog of 1952 gave rise to air pollution reduction policies that gradually decreased pollutant concentrations over time. Yet, concern remained about effects of day-to-day changes in air pollution on daily mortality, hospital admissions, etc. At lower concentrations, the effects of air pollution on deaths and hospital admissions are, obviously, much smaller than during high pollution episodes, and time series analysis methods have been developed to analyse the temporal relationships between air pollution and health. Such methods filter out temporal patterns related to long-term trends, season, flu epidemics etc. before linking air pollution to health. For such methods to work well, typically time series of a few to several years are necessary (section 3.1). A recent study has jointly analysed time series data from no less than 652 cities from all over the world (C. Liu et al., 2019). The results in Figure 6 show a monotonous concentration-response curve for PM2.5 and mortality which is even clearly visible at very low concentrations well below the current WHO short-term, 24-hour Air Quality Guideline of 25 µg/m^3.

Figure 6: Pooled concentration-response curve for PM2.5 and mortality



Note: The y axis represents the percentage difference from the pooled mean effect (as derived from the entire range of PM concentrations at each location) on mortality. Zero on the y axis represents the pooled mean effect, and the portion of the curve below zero denotes a smaller estimate than the mean effect.

Source: C. Liu et al., 2019.

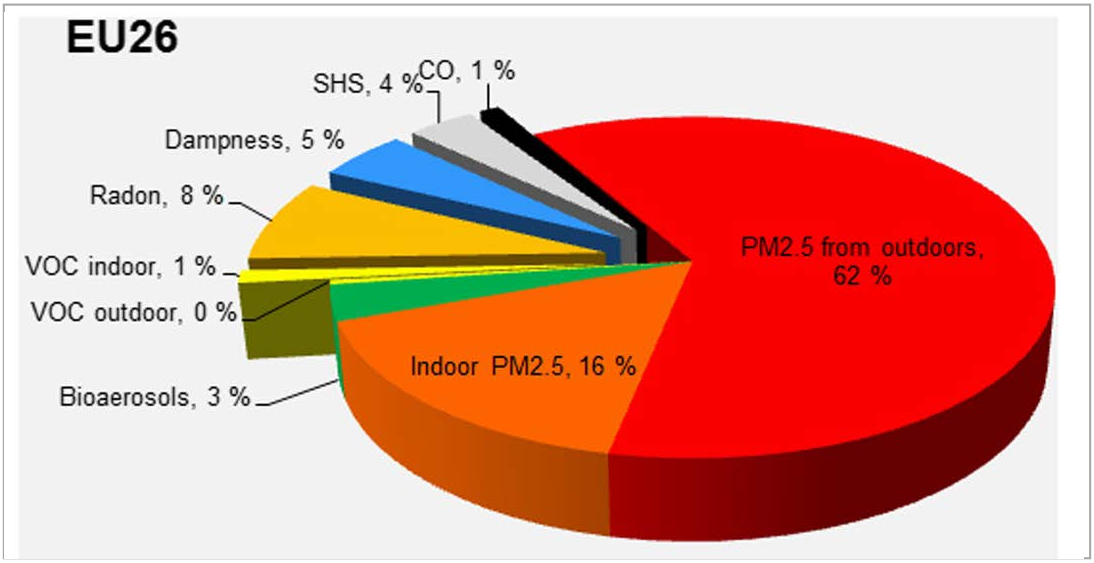
Many time series studies of acute effects of air pollution have been published over the last 25 years. A major contribution to the field was the EU funded APHEA study (Air Pollution and Health: a European Approach). This study looked at the acute effects of air pollution on mortality and cardiovascular and respiratory hospital admissions. Robust associations were documented for many pollutant-outcome pairs, notably all-cause and cause-specific mortality in relation to fine particles, NO_2 and sulphur dioxide (SO_2) which was still a major pollutant in Europe in the 1990s (Katsouyanni et al., 1997; Samoli et al., 2006; Samoli et al., 2005).

Time series studies address acute effects. As it may take some time after exposure until a hospital admission or a death occurs, time series studies typically allow for such delays by modelling lagged effects, with lags considered up to one week or, in rare circumstances, 2 weeks.

3.3. Health effects of indoor air pollution

As indoor air pollution represents a combination of infiltrated outdoor air with indoor sources, there is some overlap between the health effects of outdoor and indoor air pollution. However, owing to the unique indoor sources of pollution combined with the high amount of time spent indoors, there is a separate burden of disease attributable to sources of indoor air pollution, which is estimated at a loss of over 700,000 healthy life-years within the EU (Asikainen et al., 2016). This burden is even higher in low-resource settings (e.g. LMIC) where higher absolute levels of exposure combine with poorer health infrastructures to compound this effect.

Figure 7: Burden of disease due to indoor pollution



Note: Based on 26 EU countries (no data were obtained for Croatia and Malta) (2.1 M Disability Adjusted Life Years (DALY)/year).

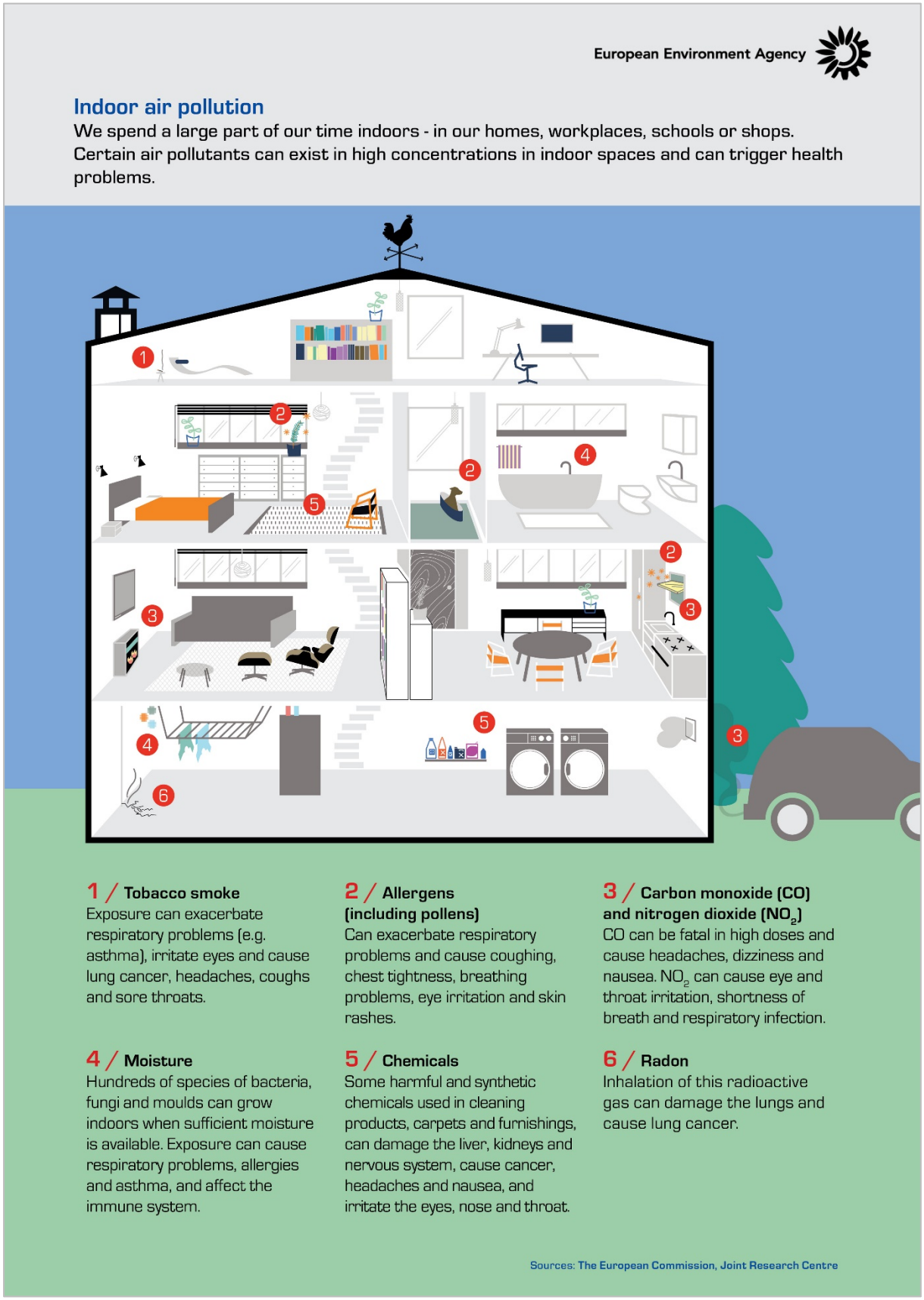
Source: Asikainen et al., 2016.

The specific health risks associated with indoor air pollution vary depending on the agent in question. Some examples are described in Figure 8. These health effects can be acute or chronic. Typical acute effects include eye irritation, dizziness, fatigue, and respiratory symptoms. The individual likelihood of having such an acute reaction to indoor pollution is dependent on many factors including pre-existing conditions and the type and concentration of pollutant(s).The treatment of acute effects can in some cases be as simple as removing the exposure. However, in other cases, such as the aggravation of disease, urgent medical care and potentially hospitalization may be needed.

Most of the literature on indoor air pollution does not consider human beings themselves as a source of pollution. Yet, in the case of the current COVID-19 pandemic, human-to-human transmission is of key importance. This was stressed before when we briefly discussed the ongoing debate about the importance of proper ventilation of indoor spaces to reduce transmission.

In contrast to acute effects, other health effects may arise years after long-term (or repeated) exposures (chronic effects). The chronic effects of indoor air pollution include major diseases such as cancer, heart disease, and respiratory disease all of which have the potential to be severely debilitating and/or fatal. In many cases the disease caused by chronic exposure can also be acutely aggravated. For example, asthma is a chronic respiratory disease which affects both adults and children (Tiotiu et al., 2020). Exposures to sources of indoor air pollution have been identified as risk factors for asthma and have been linked to an increased likelihood of severe asthma attack.

Figure 8: Potential health effects of indoor air pollution

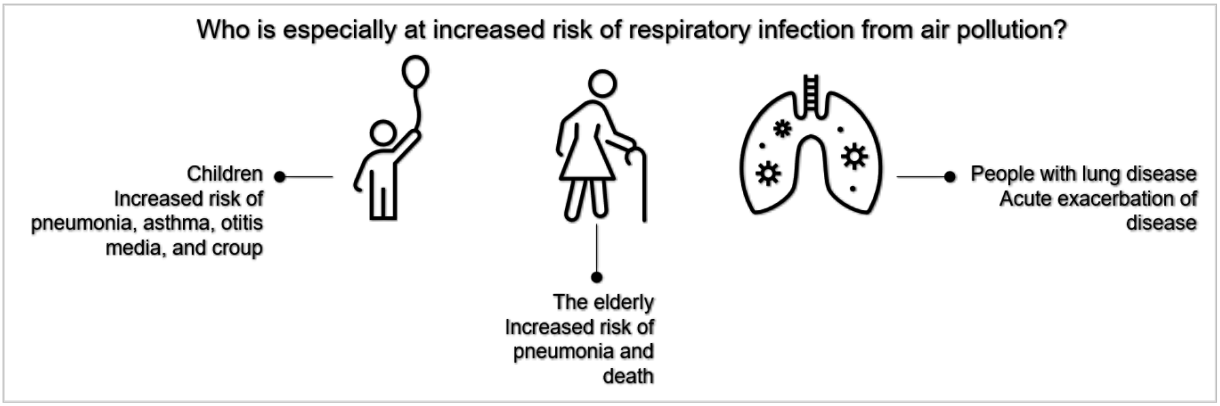


Source: European Environment Agency available at https://www.eea.europa.eu/signals/signals-2013/articles/indoor-air-quality

3.4. Effects of outdoor and indoor air pollution on respiratory infectious disease other than COVID-19

Multiple studies have demonstrated that exposure to both outdoor and indoor air pollution predisposes to and worsens the outcomes of respiratory infections. One of the first well recognised studies of this phenomenon dates back to the 1952 London smog, during which deaths from pneumonia increased threefold, with children and the elderly being particularly at risk (Logan, 1953). Since then, both short-term and long-term effects of air pollution on respiratory infections have been studied multiple times in time series and cohort studies. Mechanistic studies have suggested already many years ago that pollutants such as NO_2 and particulate matter may decrease resistance to respiratory bacterial or viral infections (Ciencewicki et al., 2007; Samet et al., 1990). This may occur through damaged airway epithelium, reduced ability of macrophages to phagocytize or inactivate viruses, oxidative stress and other mechanisms. The results of the epidemiological studies have consistently found that high levels of air pollution are associated with acute lower respiratory infections (ALRI), especially among children (Q. Liu et al., 2017). The most important pathogens in ALRI are bacteria (*Streptococcus pneumoniae*, *Haemophilus influenza*), and viruses (influenza, respiratory syncytial virus). However, in most epidemiological studies on air pollution and respiratory infection, the viral and bacterial aetiology is unknown.

Figure 9: Risk groups for respiratory infections from air pollution

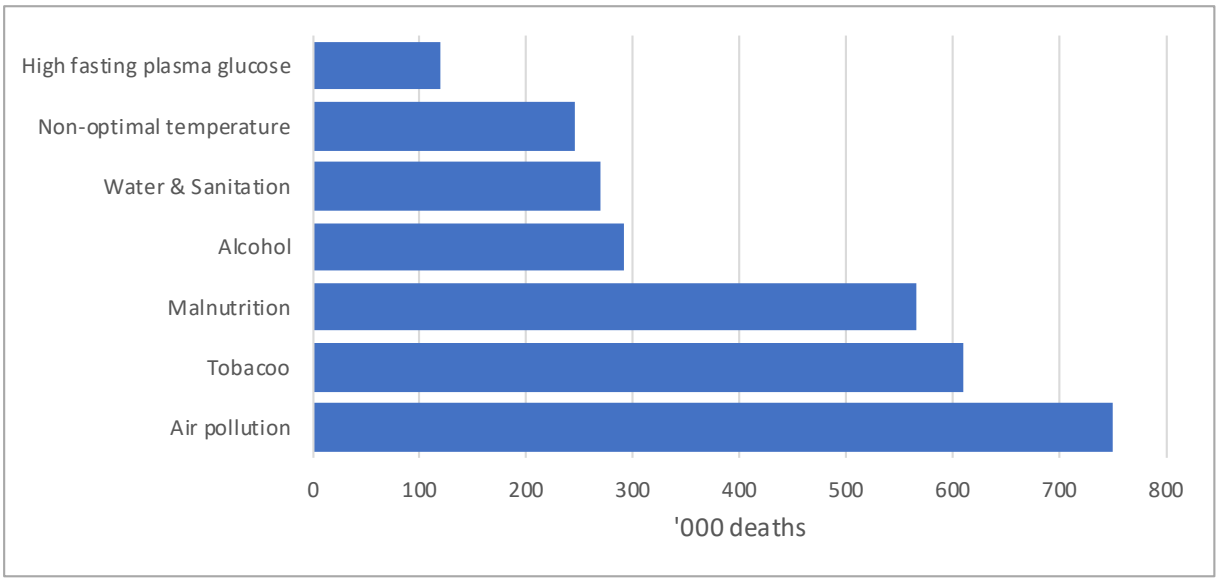


Source: George Downward (author's own elaboration).

3.4.1. Paediatric respiratory infections

Globally, ALRI represents a leading cause of death and disability in children, causing approximately 800,000 deaths per year, especially in LMIC (Vos et al., 2020). Within Europe, the role of air pollution on the respiratory health of children has been well established. A study of 10 birth cohorts from around Europe reported an elevated and statistically significant relationship between individual components of air pollution and childhood respiratory infectious diseases such as pneumonia, otitis media, and croup (MacIntyre et al., 2014). An important feature of note is that in addition to the risk of death, recurrent respiratory infections among children may have long-term consequences including delays in growth, development, and academic performance.

Figure 10: Global deaths in 2019 from respiratory infections attributed to different risk factors



Source: Institute for Health Metrics and Evaluation, available at http://ihmeuw.org/5aoy

3.4.2. Adult respiratory infections

Children are not the only group at risk of air pollution related respiratory infections. Of the approximately 2 million deaths per year due to respiratory infection, approximately one third are attributable to air pollution, more than those attributable to tobacco smoke (Figure 10). The elderly are especially susceptible to respiratory infection, where multiple medical co-morbidities combine to produce a high rate of mortality and frequently, among survivors, reduced independence and quality of life. Air pollution plays an important role in this risk factor where older persons exposed to higher levels of air pollution are more likely to be hospitalised with pneumonia than those exposed to lower levels (Neupane et al., 2010).

An additional sub-group of adults who are particularly at risk of respiratory infections are those with chronic obstructive pulmonary disease (COPD), a chronic lung disease typically caused by smoking. COPD is a gradually progressive disease which is prone to acute "exacerbations" of illness, frequently caused by infection, which can be life threatening and often require hospitalization. A recent systematic review and meta-analysis reported that increases in air pollution were positively associated with COPD exacerbations, resulting in hospitalizations, and increasing the underlying burden of disease (J. H. Li et al., 2016).

3.4.3. Rural versus urban areas

Urban and rural environments, which have different compositions and intensities of air pollution, will likely also have different relationships between air pollution and respiratory infections. Living in rural areas within Europe typically results in lower absolute levels of some forms of air pollution, which may therefore be linked to lower rates of respiratory infection (Gandini et al., 2018). However, exposure to relatively larger particles generated by livestock movement, windblown dust etc. may be larger in rural areas. Also, inhabitants of intensive livestock farming regions are at higher risk of pneumonia and zoonotic infections. In particular, living close to poultry or goat farms is associated with community-acquired pneumonia with unknown aetiology (Poulsen et al., 2018, Smit and Heederik, 2017). Non-infectious agricultural air pollutants may play a role (such as endotoxins from

manure), by predisposing to respiratory infections through chronic airway inflammation and subsequent host immune responses. Similarly, increased ammonia concentrations in the air – a marker for livestock related air pollution – are associated with acute deficits in lung function in adults, in particular in COPD patients, and in asthmatic children living in livestock-dense areas (Borlée et al., 2017) (van Kersen et al., 2020) (Loftus et al., 2015).

3.4.4. Discussion of potential mechanisms

There are two main ways by which air pollution can be linked to respiratory infections. The first is through *predisposing* individuals to infection (and worsening of infection) through such mechanisms as injuring the lungs and suppressing the normal immune response. The second way is through *transmission* of the disease itself for example by being transported within particulate matter or through the spread of aerosol droplets. These mechanisms can act in concert (i.e. both predisposing and transmitting) with the combined role of these agents being dependent on the content and concentration of the air pollution and the nature of the pathogen in question.

3.4.5. Predisposition to infection

The respiratory system is one of the first lines of defence against infectious and foreign agents and as such has a complicated array of defences available to protect the body against infection, ranging from mucociliary clearance to alveolar macrophages (see list of terms for explanation). Tobacco smoke, which can be considered an extreme form of personal exposure to very high levels of air pollution is well known to suppress many of these natural defences and directly damage the lungs, predisposing the individual to respiratory infections.

Similar to tobacco smoke, air pollution has long been recognised as an inhibitor of mucociliary function (Wolff, 1986), impairing the lung's ability to remove foreign (and infectious) agents. Further, the small components of air pollution, such as PM2.5 and ultra-fine particles penetrate deep into the lung, bypassing protections which typically catch larger materials. The relatively large surface area to mass ratio of these smaller particles can result in high levels of deposition directly onto alveolar surfaces where the toxic compounds contained within them are deposited to and absorbed by the underlying tissue (Losacco et al., 2018). This process has a variety of physiological responses including cellular signalling, inflammatory responses, and oxidative stress which can lead to multiple diseases, including chronic obstructive pulmonary disease, sufferers of which (as noted above) are predisposed to respiratory infections. The immune function of pulmonary defences can also be suppressed via disruptions to the production of defensive proteins (cytokines) and by suppressing the ability of immune cells to "eat" invading organisms (phagocytosis).

3.4.6. Transmission of disease

A typical method of transmission of respiratory disease is the spread of droplets containing an infectious agent from an infected person to an uninfected person. SARS-CoV-2 has spread primarily through respiratory droplet transmission within a short range. Under uncommon circumstances, and mainly indoors, airborne transmission of SARS-CoV-2 appears to have occurred over long distances or times. Obviously, air is the vehicle through which the agents spread, meaning that particulate material may be able to function as a carrier for infectious agents. One study detected SARS-CoV-2 RNA in PM10 collected in Bergamo, Italy (Setti et al., 2020). Whether SARS-CoV-2 particles adsorbed to outdoor PM remain viable for a prolonged period of time is unknown, but given the epidemiology of COVID-19, it is unlikely that outdoor air pollution is a significant route of transmission. A study from Italy was unable to demonstrate the presence of SARS-CoV-2 on airborne particulate matter

collected in two areas that were heavily affected and non-affected, respectively, in the early phases of the outbreak in the spring of 2020 (Chirizzi et al., 2020).

3.5. Methods to study environmental determinants of the COVID-19 pandemic

Whether air pollution affects the spread and/or impact of an infectious disease depends on multiple factors and very little is known about possible mechanisms. Patients with SARS-CoV-2 infection expel virus-laden droplets of different sizes, and most (indoor) transmission is associated with droplets, but with a less well understood role for short- and long-range aerosols that do not settle as readily and therefore are less controlled by physical distancing measures. Indoor air pollution and the association of viruses with particulate matter could affect the relative contribution of droplets and aerosols. A higher fraction of virus laden small particles that reach the lower airways could lead to increased frequency of more severe disease.

Chronic exposure to air pollution may lead to overexpression of the receptor for SARS-CoV-2, (ACE2) and for other airway infections (Paital et al., 2020). Such increased expression has been associated with increased susceptibility to COVID-19. Upon infection, patients develop a range of symptoms that are relatively mild during the first week. Most patients recover, but a small fraction shows rapid deterioration starting around the second week of illness. This phase is characterised by a hyperinflammatory syndrome. The pro-inflammatory state that has been observed in persons with chronic air pollution exposure may thus lead to earlier and enhanced frequency of severe disease. Immuno-suppressive effects of air pollution may lead to delayed viral clearance and therefore increased opportunity for secondary spread and delayed recovery. These and other potential mechanisms could play a role but there currently is no evidence for or against such associations.

Against a background of well-established methods and findings from air pollution epidemiology studies, investigations on the effects of air pollution on COVID-19 are still in their infancy. COVID-19 is an incredibly difficult endpoint to study. The spread of the disease is highly dynamic in both time and space simply because the virus is transmitted person to person, infected persons differ vastly from each other in how much virus they shed and clusters of cases often occur; methods that work well to study associations between long-term exposure to air pollution and chronic disease development are not suitable to investigate such a fast-moving target. Also, time series methodology was developed primarily to study multi-year daily observations of time-varying exposures and health effects in otherwise stable populations. With COVID-19, the time series studies so far were necessarily very short, which makes them vulnerable for uncontrolled errors. Even more problematic is that the short-term time trends of air pollution as well as COVID-19 incidence were both influenced by a whole variety of lockdown measures which created artificial correlations between declines in air pollution and COVID-19 over time.

Air pollution epidemiological studies make use of different study designs that associate disease occurrence with long-term or short-term air pollution exposure. Section 3.1 describes such common designs. For effects of long-term exposures, cohort studies with individual data on exposure, disease and covariates are preferred over case-control studies and cross-sectional studies even when these have valid data on exposure, disease and covariates. Ecological studies which do not have data at the individual level are generally mainly used for hypothesis generation, see for instance (Chen et al., 2020).

Studying associations between air pollution and COVID-19 requires careful consideration of important issues, briefly summarised in this section.

3.5.1. Definition of health endpoints

A major issue is the definition of the health endpoints and frequency measures to characterise and measure COVID-19 in the population (Pearce et al., 2020) (Villeneuve et al., 2020) (Heederik et al., 2020). Correct diagnosis of COVID-19 related morbidity, and assessing COVID-19 mortality as well as the reported number of positive SARS-CoV-2 tests is dependent on the available test capacity (which has been highly variable in the first phase of the pandemic) and access to the test. In particular, population data on positive cases was and continues to be influenced by this and may result in underdiagnosis and misclassification of disease and/or COVID-19 associated mortality which may have been differential across population groups. Also, estimates based on reporting of laboratory diagnosed cases are extremely challenging owing to differences in test algorithms which need to adapt to market mechanisms in assay development, distribution chains disturbed by international travel and trade restrictions, and regional collapse in production capacity. Similarly, hospital and ICU admissions are monitored as part of most national pandemic response plans but are not internationally standardised and are affected by the organization of health systems and health care practices. To provide a more uniform measure of pandemic impact, many countries are planning population-wide antibody surveys to obtain an independent measure of infection rate. The World Health Organization has developed a framework to harmonise studies in order to allow pooled analysis (WHO, 2020b). In addition, analyses based on mortality statistics are being pursued to obtain a second measure that is less dependent on the healthcare system functioning (Vestergaard et al., 2020). Such studies may provide a starting point for true scientific analysis of potential interactions between COVID-19 incidence, severity and air pollution.

3.5.2. Epidemiological study designs

Another important issue is what study design to use to investigate the association between air pollution and COVID-19. As mentioned, in air pollution epidemiology, 'ecological' designs using aggregate data are generally not seen as providing valid concentration-response relationships but instead seen as hypothesis generating. Almost all of the studies presented so far have used this design in which no individual-level data was available on both COVID-19 mortality, morbidity, air pollution exposure and key confounding factors. 'Confounding factors' in this context are variables that can distort associations between air pollution and COVID-19 because they are or may be correlated with both, air pollution and COVID-19. Such variables include age, gender, underlying co-morbidity, but also more intractable variables such as the number of interactions with other people. Ideally these confounding factors should be adjusted for using statistical techniques. It is well known that imperfect adjustment often occurs in ecological studies, because these factors are not available on the individual level, but only on the aggregate level of a municipality, county, province etc. This can lead to finding an association that does not exist in real life or to not finding an association where one does exist.

Misclassification of exposure can lead to unexpected results in the context of ecological studies. Non-differential misclassification of exposure (i.e. the same exposure misclassification occurs in cases and controls) will generally lead to underestimation of associations between air pollution and disease. However, in ecological studies, specific problems exist which in the field of health and disease geography are known as the 'Modifiable Areal Unit Problem' and the 'Uncertain Geographic Context Problem'. Recent contributions from this field have cautioned against naïve use of ecological study designs to investigate air pollution and COVID-19 (Helbich et al., 2020, Wang and Di, 2020). The 'Modifiable Areal Unit Problem' is a problem that arises when aggregating data over different levels, different associations between exposure and disease may occur. In a contribution from China it was shown that in Hubei province, the association between daily NO_2 concentrations

and COVID-19 deaths could be positive, negative or absent depending on the level of aggregation (city vs. province) and aggregation strategy. The 'Uncertain Geographic Context Problem' describes misspecification of the geospatial context that manifests in the over- and underestimation of the "true" exposure to environments, and ultimately results in inferential errors. These authors conclude that individual rather than aggregate data are needed to obtain unbiased results.

3.5.3. COVID-19 population dynamics

COVID-19 outbreaks are highly dynamic in space and time. The number of individuals affected by SARS-CoV-2 in a country or region depends on different factors which need to be taken into account in the analysis of the data. First, an initial introduction of the infection is needed. Without introduction there is no further spread. The fact that some regions or cities had initially higher frequencies of COVID-19 cases had to do with early introduction and early stage superspreading events (Althouse et al., 2020). Similarly, further spread is thought to be driven by superspreading events, where 80% of transmissions result from 20% of the infected population. The likelihood and frequency of opportunity for superspreading events is in part related to population density and age structure, the level of urbanization and/or social contact patterns and other factors. The dynamics of an epidemic further depend on transmissibility of the infectious agent, contact rates, duration of infectiousness and host susceptibility. Together, these features are summarised in the basic reproduction number or R_0. R_0 denotes how many persons are infected by each infected case in a population where all individuals are susceptible (no vaccination or immunised individuals because of prior disease): if it is above one, the infection will spread exponentially; if it is below one, the infection will gradually diminish or even disappear. As the spread of infection is influenced by many factors, comparisons between regions or comparisons within a region over time are challenging. Changes in R_0 can occur over time as a result of the natural history of the epidemic; exhaustion of susceptible individuals (for instance resulting from development of immunity, vaccination or because of underlying genetic factors). Changes also happen because infection control measures are being implemented (including going from some form of physical distancing to complete lock down measures). This was shown by the levelling off of the epidemic curves in many countries where physical distancing and lock down measures were implemented in the spring and early summer of 2020. In particular, the reproduction number can be high and variable in space and time in early stages of an epidemic when disease recognition and control measures are still very limited. Comparison across regions is further compromised by the lack of standardization in choice and timing of control measures. Thus, to study the effect of air pollution on the spread of COVID-19 requires knowledge about the timing of the virus introduction and the dynamics of the outbreaks in the study area(s). When comparing different study areas, the local outbreak size needs to be accounted for. A specific question is whether the effects of long-term air pollution exposure could have an impact on viral loads in infected persons. Studies have shown that the amount of virus shed differs greatly between infected individuals, and modelling studies estimate a strong skewing in the contribution of individuals to transmission towards persons with extremes in viral load ('super-spreaders').

3.5.4. Other factors that influence SARS-CoV-2 infection and COVID-19 in the population

We do not yet have a precise catalogue of risk factors for the occurrence of COVID-19 incidence, hospitalization rates, mortality rates and case fatality rates (the case fatality rate is the % of infected cases who die from the disease). An evaluation of over 17 million general practitioner records in the UK identified being male, having a higher age and deprivation, having diabetes, severe asthma,

and/or CVD as risk factors for one or more of these four metrics of COVID-19 occurrence (Williamson et al., 2020).

To sum up, a major challenge in studying associations between air pollution and COVID-19 morbidity and mortality lies in the complexity of the infection's dynamics and the limited insight into the pathogenesis of how air pollution and other risk factors influence COVID-19. Without a well-established list of external risk factors for the dynamics of the disease, it is hard to rule out confounding or other types of bias as an alternative explanation of associations with air pollution seen in ecological studies so far.

3.5.5. How do we make progress?

Where do we look for progress? Studies at the individual level are urgently needed in which the incidence, progression and remission of COVID-19 is investigated in large, well characterised cohorts in Europe. There is a long tradition of EU funded research collaborations that have already created the necessary infrastructure and expertise to conduct such studies. This expertise does not only include traditional cohort studies such as in the ESCAPE study (Beelen et al., 2014) (Raaschou-Nielsen et al., 2013). It also includes analyses of very large populations in administrative databases generated by censuses or disease and death registries (Fischer et al., 2015). To make such studies most valuable, it is of utmost importance to precisely define and standardise metrics for studying COVID-19 infection incidence and prevalence in the population. It would be important also to perform studies in populations of well-defined and clinically characterised patients, which are followed over time to explore the prognosis of COVID-19 morbidity and mortality in relation to air pollution and other risk factors at the individual level. The effect of air pollution on disease prognosis can be studied using more conventional approaches among individuals with COVID-19 infection. For example, by following up confirmed patients in different regions with different levels of air pollution. However, even this type of study might be complicated as disease severity and testing policies may differ between regions and treatment centres. Also, the quality of care delivered by health care systems may vary across regions depending on the size of the local outbreak. These scenarios are more classical examples of biases for which a range of solutions may be considered based on established methods in environmental epidemiology.

The use of test-negative designs has been proposed in which risk factors are compared between subjects that present themselves for SARS-CoV-2 testing and then appear test positive or test negative to SARS-CoV-2 (Vandenbroucke et al., 2020). Both populations have the same incentives to present themselves for testing and it is assumed that the same selection mechanisms act in both populations. Then, associations are explored between test positivity or test negativity with a range of potential determinants. An example is discussed in section 3.6 (Chadeau-Hyam et al., 2020). Such a design can eliminate some of the aforementioned concerns (access to testing etc.), but it has other limitations, mainly related to shared risk factors for being tested regardless of the outcome (e.g. presence of respiratory disease). In general, it can be said that to explore whether air pollution influences SARS-CoV-2 infection and COVID-19, high resolution temporal and spatial data are required, preferably supported by virus sequencing data. Especially for COVID-19, the landscapes of tests and testing strategies within and between regions and countries are changing fast, and this needs to be taken into account.

3.5.6. One Health studies

A specific category are studies that explore transmission of COVID-19 from animals to humans or from humans to animals. Since April, SARS-CoV-2 has been found on mink farms in an increasing number of countries, with increasing evidence for subsequent spillback to humans. Here,

transmission through the air might have taken place. However, these studies explore transmission between different reservoirs (human, animal, and environment) and make use of other sources of scientific evidence than more classical air pollution epidemiology studies. They are sometimes referred to as 'One Health' studies, 'One Health' being a concept linking health of companion animals (cats, dogs etc.), animals kept for food or fur production (pigs, chicken, mink etc.) to the health of human populations. Such studies may answer questions such as whether SARS-CoV-2 virus exposure through indoor or outdoor air can be a route of transmission. To explore associations between emissions of contaminated particles and disease occurrence around farms, studies can be done by using classical epidemiological techniques, possibly strengthened with spatial analysis and dispersion modelling. However, an additional layer of information that is available nowadays involves the complete sequencing of the viral genetic information from viruses that have been sampled from animals and humans. Sequencing studies can show the genetic relatedness, and this is a powerful molecular approach that contributes to evaluating whether associations are likely causal. Molecular approaches combined with contextual epidemiological data may give information about the directionality of an association (transmission from humans to animals or animals to humans). As a result, even relatively small-scale epidemiological studies or population surveys can result in strong conclusions about causality and directionality. For instance, through systematic sequencing of a proportion of viruses from the first wave in the Netherlands, it could be established that the virus had been introduced into mink farms on 5 separate occasions and then continued to spread among farms, with subsequent zoonotic transmission to humans living or working on the farms, but no evidence of spill-back to inhabitants of nearby villages was found (Oude Munnink et al., 2020). In Denmark, however, introduction of the virus on mink farms has led to spread among mink and a subsequent spill-back to the community sparking a local outbreak.

3.6. Effects of outdoor air pollution in urban and rural areas on COVID-19

The well-established associations between short-term and long-term air pollution exposure and respiratory outcomes, including infectious diseases, has led many researchers to hypothesise a link between air pollution and worsening of COVID-19 symptoms and prognosis. As discussed in section 3.5, we need tailor-made methods to study associations between exposure to air pollution and a pandemic viral infection that is spread by person-to-person transmission. Environmental epidemiologists have already expressed their concerns about the surge of studies that do not fulfil quality criteria and are not sufficiently informative, while receiving worldwide (social) media attention (Heederik et al., 2020; Villeneuve et al., 2020). Two reviews of the literature available as preprint or peer-reviewed journal article have already been published (Bhaskar et al., 2020; Copat et al., 2020). Both show a literature dominated by preprints of ecological studies, reporting a wide variety of associations – sometimes negative – between air pollution and COVID-19 outcomes. In this section, a concise, non-systematic overview of the current literature (updated to November 2020) will be presented, highlighting the strengths and limitations of the different approaches taken. Challenges and recommendations to study outdoor air pollution in connection with COVID-19 will be discussed, building on the methodological remarks made in the previous section 3.5.

3.6.1. Literature overview

We conducted a literature search until November 8, 2020 and we used the following terms in PubMed: (air pollution OR PM2.5 OR NO_2 OR Ozone) AND (COVID-19 OR COVID-19 incidence OR COVID-19 mortality). This search led to 452 hits. We do not provide a systematic review of this vast and quickly evolving literature. Rather, we selected a small number of papers on COVID-19 and air pollution to illustrate key points which we think are important to appraise the current flock of studies

(summarised in Table 2). Priority criteria for inclusion were geographic location, i.e. studies conducted in EU Member States, studies published in scholarly journals after peer-review, and variation in study designs. The studies available so far were conducted using publicly available COVID-19 incidence or mortality statistics aggregated at different administrative levels, e.g. city, municipality, county, or region. Daily or long-term air pollution data were obtained from fixed-site monitoring stations and/or previously developed prediction models. The studies evaluated both the incidence of COVID-19 cases as well as mortality (or case-fatality) in relation to current levels of air pollution (short-term studies) or in relation to long-term (annual or multi-year) concentrations recorded in the past. Almost all studies had an ecological study design, i.e. air pollution data were averaged over the same level of spatial aggregation as the COVID-19 data in order to regress the reported COVID-19 incidence, deaths, and/or case fatality rates against average air pollution concentrations and other determinants of the disease. Some studies have used area-level covariates in the statistical analysis to adjust for potential confounding. A few studies applied a time-series design that regresses daily case counts against moving average air pollution concentrations observed in the days or weeks before the case counts. Individual-level studies are not yet available, except for an analysis in a subset of the UK Biobank population that assesses risk factors for testing positive for SARS-CoV-2, conditional on being tested, including residential air pollution concentrations (Chadeau-Hyam et al., 2020). One important aspect of the available studies is the possibility to control for several potential confounders related to COVID-19 occurrence, including population density and mobility, multi-pollutant exposures, and, most importantly, spatial autocorrelation. Studies that did not present statistics other than scatter plots or simple correlation coefficients were excluded from this literature review as those are completely inadequate to assess the potential relationship (e.g. (Accarino et al., 2021; Conticini et al., 2020; Fattorini et al., 2020; Frontera et al., 2020; Fronza et al., 2020; Ogen, 2020; Setti et al., 2020; Travaglio et al., 2021). Out of three time-series studies conducted in China (Jiang et al., 2020; B. Wang et al., 2020; Zhu et al., 2020), we considered only the last one (B. Wang et al., 2020) as the most complete investigation. We also included a time series study from the USA (Adhikari et al., 2020).

Table 2: Overview of selected studies on air pollution and COVID-19

Reference	Publication date (all 2020)	Study design	Location and level of aggregation	Air pollution	Main results
Studies in EU Member States					
(Cole et al., 2020)	4 Aug	Ecological	The Netherlands, nationwide, 355 municipalities	Long-term PM2.5, NO_2 and SO_2 (2015-2019)	Range of effects: 13.0-16.6% increase in mortality per 1 ug/m^3 PM2.5. Many area-level covariates included but often without justification as to why these would be related to COVID-19

Reference	Publication date (all 2020)	Study design	Location and level of aggregation	Air pollution	Main results
Studies in EU Member States					
(Coker et al., 2020)	4 Aug	Ecological	Italy, nine Northern regions and analysis at municipality level	Long-term PM2.5 (2015-2019)	One µg/m^3 increase in PM2.5 associated with a 9% (95% CI 6–12%) increase in COVID-19 mortality. Results adjusted for socio-demographics, meteorology, distance from an airport as a proxy of mobility and spatial autocorrelation. Potential residual confounding from intensity of social interaction
(Chadeau-Hyam et al., 2020)	20 Aug	Test-negative case-control	UK Biobank population, 4,509 tested English subjects, individual level	Long-term NO_x, PM10, PM2.5, soot, at residential address (2010)	PM2.5 associated with testing positive compared with testing negative (RR=1.16, 95%CI1.0-1.33 per 1 µg/m^3). Associations with PM attenuated after adjustment for individual-level confounders. Exposure to soot was higher in all subjects tested versus those who were not tested, suggesting a potential bias in the decision to test for COVID-19.
(Saez et al., 2020)	12 Sep	Ecological	Spain, Catalonia, 372 Basic Health Areas and 42 regions	Long-term PM10 and NO_2 (2011-2019)	Daily incident positive cases are associated with NO_2, and to a lesser extent with PM10. Results were adjusted for population density and socio-economic variables. Authors speculate that air pollutants have actually been surrogates of the mobility of residents in the small area.
Studies outside EU					
(Adhikari et al., 2020)	5 June	Time Series	Queens, New York	Daily maximum eight-hour O_3, daily average PM2.5	Daily incident positive cases are associated with O_3 (10.51% increase (7.47–13.63)) but a strong negative relation between PM2.5 and new cases was found. No associations were found for mortality. Results were adjusted for meteorological variables and temporal autocorrelation. Study of limited size with poor control of temporal factors.

Reference	Publication date (all 2020)	Study design	Location and level of aggregation	Air pollution	Main results
Studies outside EU					
(Stieb et al., 2020)	26 Aug	Ecological	Canada, nationwide, 111 health regions	Long-term PM2.5 data for 2000–2016	PM2.5 exposure is associated with COVID-19 incidence (RR 1.07, 95% CI 0.97–1.18 per 1 µg/m^3) after controlling for province, temperature, demographic and health characteristics, days since peak incidence in the region, and spatial autocorrelation. In view of large difference between unadjusted and adjusted effect estimates, authors interpret findings as indicative of residual confounding.
(Liang et al., 2020)	8 Oct	Ecological	USA, nationwide, 3122 counties	Long-term (2010–2016) county-level exposures to NO_2, PM2.5, and O_3	County-level average NO_2 associated with COVID-19 case-fatality rate and mortality rate. Adjusting for co-pollutants, per interquartile-range (IQR) increase in NO_2 (4.6 ppb), COVID-19 case-fatality rate and mortality rate were associated with an increase of 11.3% (95% CI 4.9%–18.2%) and 16.2% (95% CI 8.7%–24.0%). No association between case-fatality rate and lPM2.5 or O_3, although per IQR increase PM2.5 (2.6 µg/m^3) was marginally associated, with a 14.9% (95% CI 0.0%–31.9%) increase in COVID-19 mortality. Results controlled for spatial trends and test positive rate, health care capacity, phase of epidemic, population mobility, population density, socio-economic status, race and ethnicity, behavioural risk factors, and meteorology. The authors are cautious about the interpretation as NO_2 represents the intensity of anthropogenic activity, especially traffic, but they cannot exclude the possibility that NO_2 might be a proxy of "urbanicity", i.e. factors related to the spread of the infection.

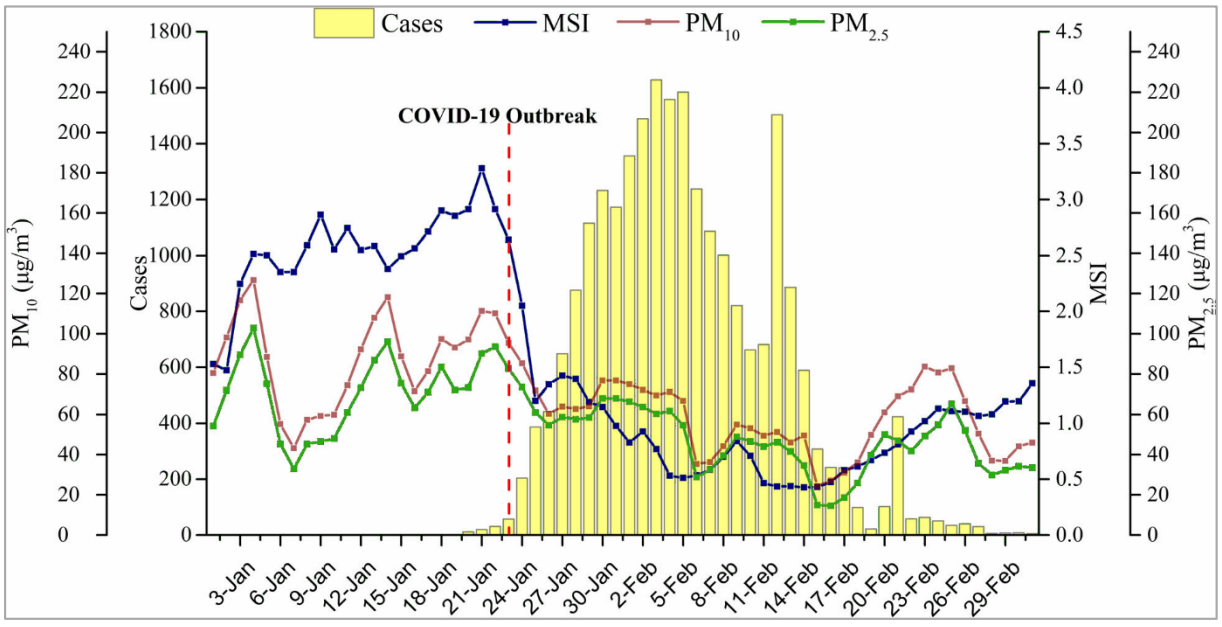
Reference	Publication date (all 2020)	Study design	Location and level of aggregation	Air pollution	Main results
Studies outside EU					
(B. Wang et al., 2020)	21 Oct	Time Series	China, 63 cities	Daily concentrations of PM2.5 and PM10 (national air quality monitoring system)	Each 10 μg/m^3 increase in the concentration of PM10 and PM2.5 was positively associated with the incident cases of COVID-19, RRs (both at lag 7) were 1.05 (95% CIs: 1.04, 1.07) and 1.06 (95% CIs: 1.04, 1.07), respectively. Results adjusted for ambient temperature, absolute humidity, and population mobility scale index. Population mobility was the strongest risk factor for confirmed cases. The study did not control for public health intervention and estimated population mobility alone may not fully account for that. Residual confounding is likely.
(X. Wu et al., 2020)	4 Nov	Ecological	USA, nationwide, 3089 counties	PM2.5 concentration estimates at the county level and then averaged across the period 2000–2016	An increase of 1 ug/m3 in the long-term average PM2.5 is associated with 11% (95% CI, 6 to 17%) increase in the county's COVID-19 mortality rate. Results were adjusted for 20 county-level covariates including density, days since the first COVID-19 case was reported, median household income, percent of owner-occupied housing, percent of the adult population with less than high school, education, age distribution, and percent of Black residents that were the most important predictors of mortality. Although the set of confounders included several socio-economic factors and health care resources and activities, there was no control for proxies of intensity of social interactions and population mobility. In addition, control for spatial correlation might have been inefficient (adjustment for the longitude and latitude of the centroid of each county) to account the clustering effect and non-linear relationships.

Source: author's own elaboration.

Several aspects of the review need to be considered. We considered three published studies conducted in the EU and six published studies conducted elsewhere. There were two time series studies on incidence of the disease in relation to short-term exposure (Adhikari et al., 2020; B. Wang et al., 2020), six ecological studies on long term exposure on three different outcomes (incidence, case-fatality, and mortality) - all based on some aggregation at geographical/administrative level (municipalities (Coker et al., 2020; Cole et al., 2020), health regions (Saez et al., 2020; Stieb et al., 2020) or counties (X. Wu et al., 2020) (Liang et al., 2020), and only one study based on individual data (Chadeau-Hyam et al., 2020).

The time-series studies were conducted in 63 cities in China (B. Wang et al., 2020) and in a single New York area (Adhikari et al., 2020) in the USA; only the Chinese study provided some indications of positive associations of PM10 and PM2.5 exposure with incidence of the disease (at a long lag of 7 to 14 days) whereas the New York study did not show an effect for PM (even a negative association). While the New York study had limitations due to the size and adjustment for temporal factors, the Chinese study was large and carefully adjusted for temporal factors but one, namely public health interventions that were taken in the specific cities to limit the epidemic (Figure 11, the dashed line indicates when lockdown measures were started). Such interventions were taken as a consequence of the epidemic and failure to adjust for those factors (even having considered a mobility index) could have introduced a bias. The additional factor that limits the interpretation of time-series studies is that, unlike usual time-serious studies on air pollution considering several cities and several years, only very short periods of no more than a few months have been studied thus limiting the contrasts and the possibility to evaluate seasonal patterns.

Figure 11: Daily PM and COVID-19 cases in 63 cities in China



Note: Trends of daily PM levels, MSI, and confirmed COVID-19 cases in 63 cities of China from January 01 to March 02, 2020. The mobility scale index (MSI) reflects the scale of the population mobility in a city.

Source: B. Wang et al., 2020.

All the ecological studies used regression analyses to evaluate whether air pollution exposure at the aggregate level is associated with incidence (Cole et al., 2020; Saez et al., 2020; Stieb et al., 2020), case-fatality (Liang et al., 2020), and COVID-19 mortality (Liang et al., 2020) (Coker et al., 2020; X. Wu et al., 2020) (Cole et al., 2020). Positive associations were seen for PM2.5 exposure in relation to incidence and mortality in the Netherlands (Cole et al., 2020) and in Canada (Stieb et al., 2020), and mortality in Italy (Coker et al., 2020) and in the USA (X. Wu et al., 2020). It is remarkable that all the effect estimates from

these studies were very high (reaching 11% for an increase of 1 ug/m^3 in the USA, and 17% in the Netherlands). This is up to 20 times the effect estimates for all-cause mortality reported from the Medicare cohort (Di et al., 2017) and in a recent meta-analysis (Chen et al., 2020). However, the findings of the USA study on mortality (X. Wu et al., 2020) were not replicated in a study that used a similar data set and study design but with a more aggressive control of confounding variables and spatial autocorrelation (Liang et al., 2020). The latter study found an association of NO_2 but not PM2.5 with both case-fatality and mortality. A similar association was found between NO_2 exposure and incidence of positive cases in Spain (Saez et al., 2020). It is difficult to draw a conclusion from these studies as they had different outcomes, implying different denominators (general population for incidence and mortality, cases for case-fatality), different predictors, implying different potential confounding variables, and inconsistent results. The issue of confounder control is of great relevance here as no study was able to control at aggregate level for proxies of population levels of social contacts and mobility, two important predictors of the epidemic.

The only study so far based on individual data from the UK Biobank (Chadeau-Hyam et al., 2020), with regard to both exposure at residential address and data about testing results, provides conflicting results with respect to air pollution exposure. The elevated relative risks found were attenuated when various individual confounders were considered in the model. At the same time, the study detected a clear association between air pollution exposure (especially black carbon) and the probability of being tested. Such an association indicates that studies in the general population should consider that the probability of being tested (and then the probability of being positive) could be related to air pollution exposure and adjustment for such a potential bias is necessary.

Box 1: Can we quantify the percentage of COVID-19 deaths attributable to PM2.5?

Can we quantify the excess COVID-19 deaths that could be avoided if the population were exposed to lower counterfactual PM2.5 levels? In the first place, one needs strong evidence that PM air pollution is causally related to COVID-19 mortality. Despite the lack of such evidence, a recent study estimated the fraction of worldwide COVID-19 mortality attributable to PM2.5 exposure to be 15% (95%CI 7%-33%) (Pozzer et al., 2020). The basis of this estimate was a concentration response function developed by the authors using data from two ecological studies. One is discussed here (X. Wu et al., 2020), the other is a simple, unadjusted, correlation analysis that compared case fatality ratios – not mortality rates- of the 2003 SARS epidemic and estimated, not measured PM2.5 air pollution levels in just five Chinese cities (Cui et al., 2003). The Wu et al. study was based on much the same data as the Liang et al. study (Liang et al., 2020), discussed in this section, which did not find a significant relationship with PM2.5. A new study on case fatality ratios from China was published just before the Pozzer at al. study was submitted (Yao et al., 2020). This study is also discussed in this section, and was using data on COVID-19, case-fatality and pollution data from dozens of cities in China and actual measurements of PM2.5. Although still a study on case-fatality ratios and not on mortality rates, this study would have been far more suitable than the Cui et al. 2003 paper. These observations make the estimated attributable fraction highly questionable. **Because of the reservations we expressed here about the available ecological studies on COVID-19 and air pollution, we think the current evidence base does not allow estimates of the percentage of worldwide COVID-19 deaths attributed to PM2.5 to be made with any precision.**

Source: author's own elaboration.

A remarkable feature of most of the quoted studies is that they used historic, long-term average air pollution concentrations as exposure variables: 2000-2016 in (Stieb et al., 2020) and (X. Wu et al., 2020), 2010-2016 in (Liang et al., 2020), 2015-2019 in (Cole et al., 2020), 2011-2019 in (Saez et al., 2020). If

exposures up to 20 years before the pandemic hit are important drivers of the observed associations, reducing air pollution now would possibly have an effect on the disease 5-20 years from now. There is very little discussion of this in the literature, but one implication would be that there is no urgent need to investigate the association between air pollution and COVID-19 in the shortest possible time, using less than ideal methods. In one or a few years' time, the research community will be able to apply all the advanced tools of the trade to investigate effects of air pollution in large cohorts and administrative databases with excellent opportunities to include individual level data. The reason why this takes a while is because such individual level data take time to process, and careful procedures need to be developed and applied to comply with privacy regulations.

3.6.2. COVID-19 and air pollution in rural areas

Most published studies were conducted in urban regions, and nationwide analyses that included both urban and rural areas did not explicitly distinguish between sources of urban and rural air pollution. The study in The Netherlands discusses the role of intensive livestock farming which can be an important contributor to PM2.5 by emitting large quantities of ammonia (NH_3) and secondary inorganic aerosol formation (Cole et al., 2020). The suggested correlation between agricultural air pollution and COVID-19 incidence in the south-eastern part of the Netherlands has, however, not been substantiated as the spatial pattern of the second wave of the infection, starting in the late summer of 2020, was quite different from the initial outbreak.

3.6.3. Discussion

As already indicated, the general approach of the available studies has been an ecological regression analysis where group level data (i.e. counties in the USA, regions in Canada, municipalities in Italy and The Netherlands) has been used as the unit of analysis. Such an approach has been recently advocated (X. Wu et al., 2020) as it allows a quick evaluation of the available data, can be useful for hypothesis generation and to make suggestions for policymaking. This could be the spirit of these initial investigations in terms of time-series analyses of current air pollution exposure and COVID-19 incidence, or long-term exposure and case-fatality rates or mortality rates in the general population. However, the limitations of the ecological approach in comparison with studies with individual data are widely recognised as they may present an ecological fallacy (Robinson, 2009). This fallacy can manifest associations in ecological regression that do not exist or are even in the opposite direction of true associations at the individual level.

Several potential confounders have been considered in the ecological analyses, with extensive sensitivity analyses conducted in some studies (Liang et al., 2020) (X. Wu et al., 2020). However, there was a general lack of variables that could be a good surrogate of the main factor responsible for spread of the disease, human-to-human interactions and the local outbreak size. Any possible indicator reflecting human-to-human transmission could serve for the purpose, but it has been neglected in current research (Bontempi et al., 2020). It has been indicated, for instance, that parameters involving commercial exchanges (accounting for human-to-human transmission mechanisms), should be considered (Bontempi, 2020). In addition, population mobility data could serve as an additional proxy of social contacts as a study in the USA (X. J. Li et al., 2020) provides evidence that reductions in population mobility may act to constrain the growth rate in COVID-19 cases, particularly in urban settings. In summary, if regression analysis should be considered for further studies it is essential to account for indicators of person-to-person contacts and social interactions like economic activities and

population mobility in addition to population density, and the response of health care and public health measures to limit the COVID-19 diffusion.

The reservations about studies conducted so far should not be interpreted as suggesting that air pollution may not contribute to the occurrence or severity of COVID-19. After all, air pollution has clearly been shown to increase respiratory infections from a variety of pathogens, probably by reducing host defences. Such effects are possible and even likely for COVID-19 as well, but further, careful research is needed to quantify such effects reliably, involving the study of individual-level data on COVID-19 health outcomes, together with population data on residential addresses, air pollution exposure, demographics, and individual-level confounders. Such studies should also incorporate indicators of person-to-person contacts and social interactions to avoid bias in the analyses. In Europe there is long-term excellent experience in utilizing large cohorts and, more recently, very large administrative database cohorts to study health effects of air pollution.

For a non-specialist summary of the issues surrounding studies on air pollution and COVID-19, we refer the reader to (Nicole, 2020).

4. VULNERABLE GROUPS IN THE COVID-19 PANDEMIC

At present, our knowledge regarding risk factors for COVID-19 is limited. However, socio-economically disadvantaged groups and minorities have been reported to be more severely affected by the pandemic in different parts of the world (Burstrom et al., 2020; Dorn et al., 2020; Z. Wang et al., 2020). These observations make it reasonable to assume that, even though there is currently a lack of specific studies, social determinants of health including health and health care, social and community context, neighbourhood and built environment, education, and economic stability contribute to these inequalities (Singu et al., 2020). These determinants can contribute to the social inequalities in COVID-19 through differential exposure to the virus and differential vulnerability to and prognosis of the infection (Burstrom et al., 2020).

Higher exposure to the SARS-CoV-2 virus (and thus higher likelihood of infection) among socio-economically disadvantaged groups is likely as avoiding physical proximity to other people might be more difficult among these groups for several reasons. For example, households of socio-economically disadvantaged groups tend to have more occupants while also being smaller, making it relatively difficult to isolate infected household members (WHO, 2019) . This can result in an increased risk of respiratory infections as has been shown for viruses other than SARS-CoV-2 (WHO, 2018). Also, lower paid workers are more likely to be exposed to the virus as they are over-represented among "essential workers" such as health and social care workers, shop assistants, etc. and thus cannot work from home to avoid physical proximity to other people (OECD, 2020). Socio-economically deprived people may also be more dependent on public transport to get to work or lack protective equipment, which may further increase exposure to the virus (Burstrom et al., 2020). Low health literacy is another problem as it may result in a lower likelihood of following recommendations such as social distancing during the pandemic (Singu et al., 2020).

Older age and underlying health conditions such as cardiovascular disease, diabetes, or chronic lung disease, hypertension and cancer have been suggested to be associated with adverse prognosis in SARS-CoV-2 infected people (Petrilli et al., 2020; Simonnet et al., 2020; Z. Wu et al., 2020). The higher prevalence of these underlying health conditions among socially disadvantaged groups may contribute to higher vulnerability (Sommer et al., 2015). Underlying diseases may explain part of the greater vulnerability of the elderly, but less social support may also contribute to observed age differences in COVID-19 outcomes (OECD, 2020). Limited access to health care due to lack of facilities nearby or financial barriers such as lack of health insurance and health expenditures like prescription drug spending are other factors that may increase vulnerability to COVID-19 (Dorn et al., 2020; Z. Wang et al., 2020).

Exposure to air pollution has been hypothesised to increase vulnerability to COVID-19 due to its negative impact on the immune system and relationship with the health conditions that have been found to be associated with increased COVID-19 risks (Cohen et al., 2017) (Burnett et al., 2018) (Glencross et al., 2020). See also chapter 3.6. Therefore, higher levels of exposure among disadvantaged groups can increase social inequalities in the COVID-19 pandemic. In addition, a higher vulnerability of disadvantaged groups resulting in more adverse health effects may further increase social inequalities. In the subsequent paragraphs, we provide a summary of the evidence for differences in exposure and vulnerability to air pollution between socio-demographic groups, focussing on the European situation.

4.1. Social inequalities in air pollution exposure

While it is often assumed that socio-economically disadvantaged groups are exposed to higher levels of air pollution, this is not always the case in Europe (Fairburn et al., 2019; Hajat et al., 2015). Some

studies found positive associations between socio-economic status and air pollution while others have found no or negative associations. The studies that have been published so far, vary with regard to the pollutants considered, the definition of socio-economic status and the geographical scale.

For example, in a Europe-wide analysis of PM10 concentrations in 2004-2008 at the level of sub-national regions, higher PM10 concentrations were found in lower income regions across Europe (Richardson et al., 2013). This association, however, was found to reflect primarily East-West inequalities and was not found when Eastern and Western Europe were considered separately. In fact, some of the most polluted regions in Western Europe were also among the richest (i.e. Lombardy and Emilia Romagna from Northern Italy, and Flemish Brabant and Wallonia Brabant from Belgium). At the same time, improvements in PM10 concentrations over the study period were greatest in the highest income regions.

At the national level, PM10 and NO_2 concentrations were highest in the most deprived areas of England and the Netherlands (Fecht et al., 2015). These disparities were consistent between regions of the two countries and between cities, except for the cities of Bristol (England) and Rotterdam (the Netherlands). Also, NO_2 concentrations were consistently higher in areas with higher percentages (> 20%) of non-Whites, while for PM10 higher concentrations were found for some neighbourhoods of East of England, Yorkshire, Leeds and Amsterdam with ≤ 20% non-Whites. In the Swiss National Cohort, the proportions of foreign nationals and people living in old and unrenovated buildings were higher among those exposed to the highest PM10 concentrations (Huss et al., 2010). In contrast, in a Dutch nation-wide cohort study, participants living near a major road had higher education and were less likely to work in blue-collar jobs than other residents (Hoek et al., 2002). No differences in NO_2 concentrations at the home address have been found for participants of a cohort study from Oslo with low and high socio-economic status measured by education and occupation (Nafstad et al., 2004). Associations between NO_2 and socio-economic status were inconsistent in a Spanish birth cohort, with no differences between socio-economic groups in two of the three study areas (Gipuzkoa and Sabadell) and highest NO_2 concentrations among unskilled manual workers in the third area, Valencia (Vrijheid et al., 2012).

At the city level, in London, concentrations of nitrogen oxides were generally higher for areas and individuals with lower socio-economic position/greater deprivation, with the exception of central London (UK) where concentrations were higher for more affluent groups (Goodman et al., 2011). In Rome (Italy) people with higher incomes and a higher socio-economic status were more likely to live towards the central area of the city where traffic emissions are higher, while more disadvantaged groups were more likely to live in the suburbs where traffic emissions are lower (Forastiere et al., 2007). In Strasbourg (France) a non-linear association was found between NO_2 levels and deprivation index with midlevel deprivation levels having the highest NO_2 concentrations (Havard et al., 2009).

As people spend most of their time indoors, and most of that time in the home, exposure to pollution indoors is also important (sections 2.2, 3.3 and 3.4). Next to outdoor pollution penetrating indoors, several indoor sources exist such as smoking, gas cooking, candle burning and fireplaces. The contributions of outdoor air pollution and air pollution from indoor sources depends on building characteristics and ventilation. Reductions in building permeability and ventilation have been shown to decrease the relative impact of outdoor air pollution and to increase the relative importance of the impact of indoor sources on indoor air quality (Hamilton et al., 2015). While social inequalities have been intensively studied for outdoor air pollution, the evidence on social inequalities in indoor air pollution is much more limited (Ferguson et al., 2020). A lower socio-economic position has been found to be associated with a higher residential exposure to environmental tobacco in children in Germany (Bolte et al., 2009). Higher levels of NO_2 and PM2.5 have been reported for homes of disadvantaged groups in the US and France (Baxter et al., 2007; Brown et al., 2015). Cooking time, gas stove usage and

occupant density, were identified as important contributors to air pollution levels. Smoking is another important source of particulate matter and is associated with socio-economic status. Children of socio-economically disadvantaged families are more likely to be exposed to smoking at home (Bolte et al., 2009) and are more likely to become a smoker themselves, and less likely to quit smoking (Currie et al., 2012; Schaap, 2010).

4.2. Social inequalities in susceptibility to air pollution

Socio-economically disadvantaged groups may not only experience more health problems from air pollution because of their higher exposures, but also as a direct or indirect result of their social position. O'Neill et al. (O'Neill et al., 2003) propose a framework for how air pollution and socio-economic factors may interact to influence health differentiating between direct and indirect consequences of low socio-economic position. Direct consequences of a low socio-economic position include lack of access to, or income to pay for healthy food and health care. In addition, increased psychosocial stress among disadvantaged groups is proposed as a pathway for increased susceptibility among these groups. Another proposed pathway includes co-exposure to other pollutants in the workplace. Indirect pathways include increased susceptibility due to underlying conditions, traits and behaviour.

Reviews by the American Heart Association suggest that susceptible populations to the effects of air pollution include the elderly; individuals with diabetes; patients with pre-existing coronary heart disease, chronic lung disease, or heart failure; and individuals with low education or socio-economic status (Brook et al., 2004; Brook et al., 2010). Evidence for stronger associations in smokers is more mixed and little evidence was found for effect modifications by race, hypercholesterolemia or blood pressure. In a more recent analysis of 367,251 participants from 22 European cohort studies, no effect modification by smoking status, education level, fruit intake, or BMI has been found (Beelen et al., 2014).

5. EFFECTS OF COVID-19 CONTAINMENT ON AIR POLLUTION AND ON HEALTH EFFECTS OF AIR POLLUTION

5.1. COVID-19 containment and air pollution

A representative sample of the literature on COVID-19 lockdowns and air pollution was selected to illustrate the current state of affairs (summarised in Table 3). Priority criteria for inclusion were geographic location, i.e. studies conducted in EU Member States, and studies published in scholarly journals after peer-review. The studies available so far evaluated air pollution estimates based on ground-level air measurements as routinely collected for regulatory purposes (e.g. AirBase), tropospheric measurements through satellite measurements (e.g. TROPOMI), or through a combination of methods including chemical transport models (CTM). To estimate the impact of the lockdown measures on air pollution levels two approaches have been used. The first approach is to compare air pollution levels during the lockdown period to comparable periods in previous years (e.g. 3 to 5 years prior to 2020) or by comparing pre- and post- lockdown air pollution levels to levels during the lockdown period. Both analyses require a correction for meteorological conditions to improve the validity of the comparison: some of the differences between 2020 pollution levels and those measured in other years could be due to differences in wind direction, atmospheric stability etc. Several studies have noted that incomplete correction for meteorological conditions could lead to biased results (Xiang et al., 2020).

Studies published to date provide a relatively consistent picture, with NO_2 levels decreasing by 30 to 50% during lockdown periods in Europe. The PM2.5 decrease was less pronounced (5 to 20%), while PM10 concentrations were only marginally decreased. In contrast, O_3 increased slightly during the lockdown periods likely through the fact that O_3 is not titrated out by NO to form NO_2. Reductions in air pollution related to COVID-19 lockdowns are thus the most pronounced for traffic related pollutants. These reductions correspond to mobility data (APPLE, 2020) indicating that in most European countries traffic (i.e. driving) reduced by about 60% during the lockdown periods (February – May) (See Figure 12).

COVID-19 containment, air pollution and health effects

Several studies have attempted to quantify the beneficial health impacts due to the reduction in air pollution as a result of COVID-19 containment (Giani et al., 2020; Venter et al., 2020). Giani et al. computed the short-term and long-term health impacts of air pollution reductions from COVID-19 lockdowns Europe using approaches similar to the Global Burden of Disease (GBD) project. Based on an assumed PM2.5 reduction of 2.2 $\mu g/m^3$ (17%) across Europe an estimated 2190 (1960-2420) premature deaths were averted in Europe during the COVID-19 containment measures in February – May 2020. Long-term avoided premature fatalities due to reduced PM 2.5 concentrations could range from 13 600 to 29 500 for Europe, depending on the assumed future of the pandemic and exit strategies scenarios (Venter et al., 2020). The analyses by Giani et al., and Venter et al. should be regarded as preliminary lessons from the COVID-19 pandemic. Actual impacts on the burden of disease should account for the totality of the lockdown-induced changes such as changes in lifestyle behaviours (e.g. physical activity, dietary changes), stress and mental health, economic changes, and delayed treatments for disease. These changes could well offset or surpass the observed reductions in burden of disease due to reduced air pollution levels during the COVID-19 lockdown periods. As such there is no silver lining of the COVID-19 pandemic but these analyses are indicative of the health benefits from air pollution that could be achieved due to large emission reductions from lowered human and industrial activities.

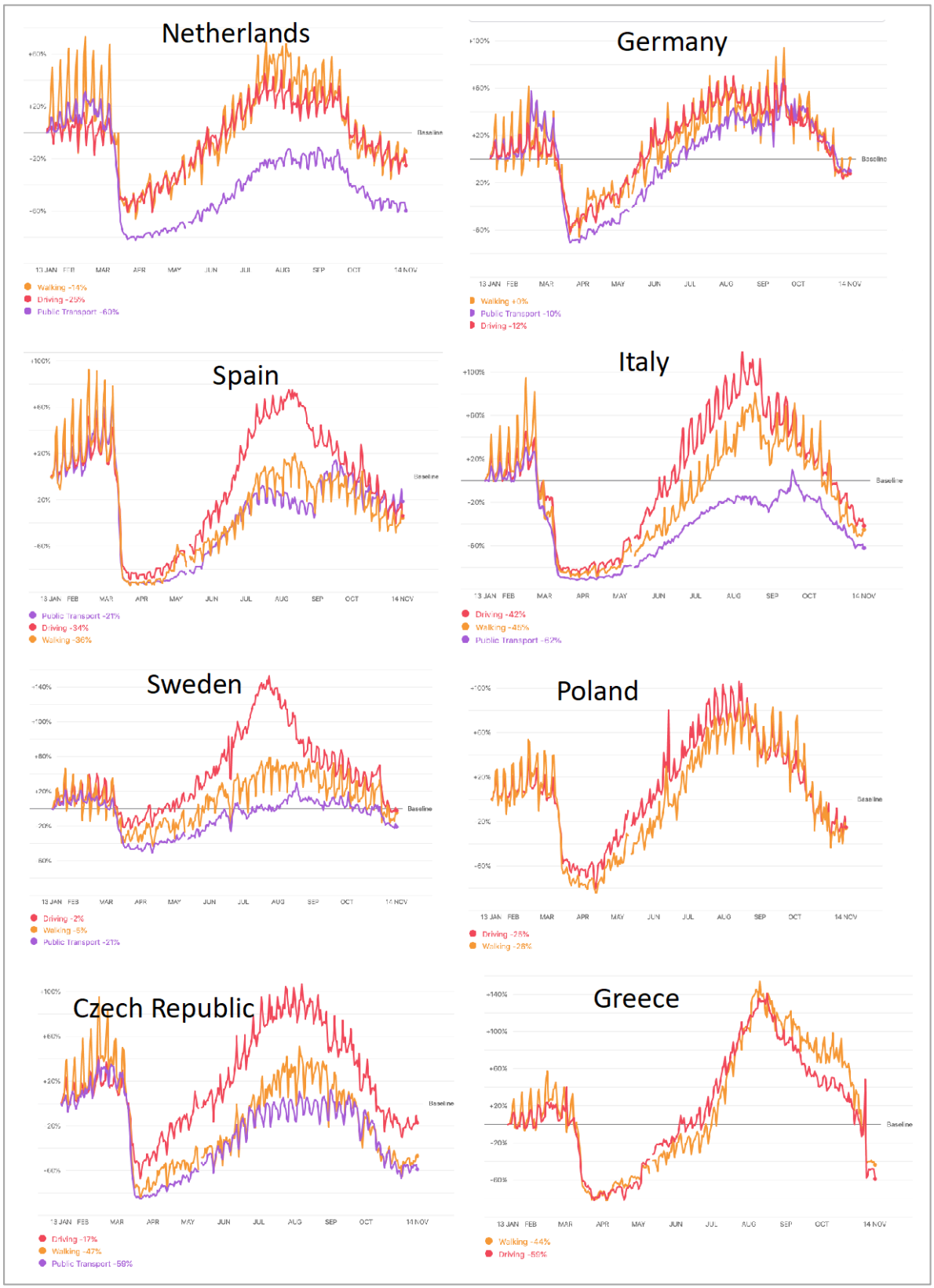
Table 3: Effect of COVID-19 mitigation measures on air pollution and on health effects from air pollution

First Author	Lockdown period (All 2020)	Air pollution data sources	Area	Air pollution measures	Main results
Studies in EU Member States					
(Dobson et al., 2020)	March/April	Ground-level reference monitoring sides	Scotland	PM2.5, NO_2	PM2.5 decreased marginally (<1 ug/m^3); 6% as compared to previous years). NO_2 decreased by 10 µg/m^3 (40%).
(Giani et al., 2020)	Feb/May	Ground level measurement data and CTM	Europe	PM2.5	Population weighted PM2.5 decreased by 2.2 µg/m^3 (17%)
(Putaud et al., 2020)	Feb/March	Ground level measurement data	Northern Italy	NO_2, PM10	NO_2 reduced by 30 and 40% at urban and regional sides. PM10 were not significantly affected by lockdown measures.
(Hörmann et al., 2020)	March/May	Ground level measurement data	Graz, Austria	NO_2, NO, PM10, CO	No effect on CO and PM10. Significantly effect of lockdown on NO_2 and NO. In particular, mean NO_2 levels were reduced by 35–41%.
(Ordonez et al., 2020)	March/April	Ground level measurement data (airBase)	Europe	NO_2, O_3	Daily maximum NO_2 decreased consistently over the whole continent, with relative reductions ranging from 5% to 55% with respect to the same period in 2015–2019 for 80% of the sites considered (10th – 90th percentiles). O_3 showed a variable pattern. With some areas showing increases in O_3 concentrations.
(Menut et al., 2020)	March	The WRF 3.7.1, and CHIMERE models v2017r	Western Europe	NO_2, PM10, O_3	Decreases in NO_2 concentrations ranging from −30% to −50% in all western Europe countries. The effect on PM2.5 concentrations has been less pronounced (−5 to −15%). O_3 provided variable results with increases in some areas.

First Author	Lockdown period (All 2020)	Air pollution data sources	Area	Air pollution measures	Main results
Studies in EU Member States					
(Venter et al., 2020)	Jan/May	Ground level measurement data and TROPOMI satellite data	Global including Over 15 European countries	NO_2, PM2.5, O_3	During lockdown dates, ground-level NO_2 concentrations were, on average, 60% (population-weighted mean with 95% CI: 48 to 72%) lower. PM2.5 declined by 31% (17 to 45%), whereas O_3 increased by 4% (−2 to 10). In absolute terms 11 µg/m³ (9 µg·m³ to 14 µg/m³) decline in NO_2 and a 12 µg/m³ (7 µg/m³ to 18 µg/m³) decline in PM2.5. A 4 µg/m³ increase in O_3 (1 µg/m³ to 8 µg/m³)
Studies outside EU					
(Goldberg et al., 2020)	March/April	TROPOMI satellite data	20 cities US	Tropospheric NO_2	NO_2 decreases ranged between 9.2% and 43.4% among 20 cities in North America, with a median of 21.6%.
(Huang et al., 2020)	Jan/March	Ground level measurement data and CTM	Yangtze River Delta Region	PM2.5	PM2.5 during lockdown period reduced by 22.9% to 54.0% compared to pre-lockdown level.
(Xiang et al., 2020)	Feb/May	Ground level measurement data	Seattle	UFP, BC, PM2.5, NO, NO_2, NOx, CO	COVID-19 responses were associated with significant decreases in median levels of traffic-related pollutants: UFPs (−7% [95% CI: −5%, −8%]), BC (−6% [95% CI: −5%, −7%]), PM2.5 (−2% [95% CI: −1%, −3%]), NO, NO_2, NO_x (ranging from −3% [95% CI: −2%, −4%] to −10% [95% CI: −18%, −12%]), and CO (−4% [95% CI, −3%, −5%]).
(Wang et al., 2021)	Feb/March	Ground level measurement data and TROPOMI satellite data	China	NO_2	The results indicate that due to the COVID-19 lockdown, the surface NO_2 concentrations decreased by 42% ± 8% and 26% ± 9% over China in February and March 2020, respectively.

Source: author's own elaboration.

Figure 12: Changes in mobility patterns in 2020



Note: Changes in mobility patterns (driving, walking, and public transport) from January to November 2020 as compared to previous years in selected European countries.

Source: APPLE, 2020.

6. POLICY ISSUES

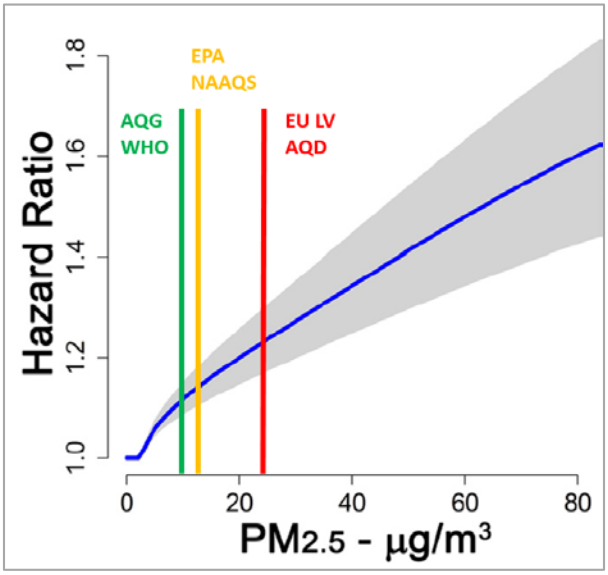
Clean air policy in the EU is implemented through a number of directives. Two EU Ambient Air Quality (AAQ) Directives (Directives 2008/50/EC and 2004/107/EC) (EU, 2004, 2008) are particularly relevant. The first directive on ambient air quality and cleaner air for Europe (Directive 2008/50/EC) sets limit values and targets for PM2.5, PM10, NO_2, SO_2, O_3, lead, benzene and CO. The second directive (2004/107/EC) on arsenic, cadmium, mercury, nickel and polycyclic aromatic hydrocarbons (PAHs) in ambient air covers metals and PAHs in ambient air. Another important act is the National Emissions Ceiling directive (EU) 2016/2284 (EU, 2016) of 14 December 2016 on the reduction of national anthropogenic atmospheric emissions of sulphur dioxide (SO_2), nitrogen oxides (NOx), non-methane volatile organic compounds (NMVOC), ammonia (NH_3) and fine particulate matter (PM2.5).

The directive on metals and PAHs (EU, 2004) is not of direct relevance to the association between air pollution and COVID-19 so we will not discuss it further. Directive 2008/50/EC has been critiqued from the beginning as not being sufficiently health protective when it comes to the long-term, annual limit value of 25 µg/m^3 (Brunekreef et al., 2008). In all fairness, the directive itself recognises this by including exposure reduction targets. So far, these have never been made part of legally enforceable instruments, however.

In March 2019, the European Parliament adopted a resolution calling for, inter alia, bringing the air quality limit values in the 2008/50/EC directive in line with the latest WHO Air Quality Guidelines (EP, 2019). This position is supported by the scientific evidence summarised in the current report. We note that the WHO Air Quality Guidelines are currently being revised, with an expected publication in the spring of 2021.

Figure 13 shows a joint concentration response curve based on an analysis of dozens of cohort studies from all parts of the world (Burnett et al., 2018). The figure also shows where the WHO Air Quality Guideline, the US EPA National Ambient Air Quality Standard and the EU Limit Value for PM2.5 are located relative to this function. It is clear that even the WHO AQG does not offer complete protection.

Figure 13: Global concentration-response function for PM2.5 and all-cause mortality



Note: Hazard Ratio = relative risk of death compared to the risk at the lowest observed concentrations. AQG WHO = World Health Organisation Air Quality Guideline. EPA NAAQS = Environmental Protection Agency National Ambient Air Quality Standard. EU LV AQD = European Union Limit Value from Air Quality Directive.

Source: Burnett et al., 2018.

The National Emission Ceiling (NEC) directive was updated in 2016 (EU, 2016). This directive spells out national emission ceilings for 2020 and 2030 for all member states. The imposed reductions will no doubt improve air quality across Europe, but the level of ambition is not as high as it could have been, especially for agricultural emissions of ammonia, NH_3 (Brunekreef et al., 2015).

The recent Fitness check (EU, 2020) assessed to what extent clean air policies in the EU are achieving what they are supposed to achieve. The outcome was rather positive but at the same time a number of shortcomings were identified, and improvements were suggested. One of these is to more closely align the EU Air Quality Limit Values with the WHO Air Quality Guidelines as they are currently being revised. A recent modelling exercise suggested that the current WHO AQG for PM2.5 is actually within reach in the next decade or so (Amann et al., 2020).

In its latest Air Quality in Europe report, the European Environment Agency estimated that PM2.5, NO_2 and ozone are responsible for 374,000, 68,000 and 14,000 premature deaths each year in the EU-28 (EEA, 2020). It is too early to tell what the 2020 death counts due to COVID-19 are going to be in Europe. As of November 17, more than 330,000 COVID-19 deaths have been reported for Europe in 2020 (ECDC, 2020). As was mentioned in section 3.6, it is very uncertain which fraction of these deaths could have been avoided in the absence of air pollution. It is clear, however, that the numbers of deaths due to other causes, attributed to air pollution is rather larger. Nevertheless, aggressive policies to further reduce air pollution in Europe will likely have a beneficial effect on COVID-19 death rates as well.

Finally, a word of caution about long-term ill after-effects in survivors of COVID-19. It is now suggested that patients who went through a COVID-19 infection might be at higher risk for developing chronic diseases of the respiratory, cardiovascular system and brain (Carfì et al., 2020). It is not yet clear whether any such damage is irreversible and/or if lifestyle and environmental factors play a role in chronic disease progression after a COVID-19 episode. Several patient cohorts are currently being initiated for long-term follow-up. Including air pollution in such long-term follow-up studies would be important.

RECOMMENDATIONS

1. The overall impact of air pollution on heart and chronic lung disease is more than large enough to motivate aggressive reduction policies. Current EU Limit Values for PM2.5 and NO_2 do not protect public health sufficiently and need to be lowered. Policies that protect the population from the effects of air pollution are likely to protect as well against COVID-19 deaths possibly attributable to air pollution.
2. In comparison to outdoor air pollution, the role of indoor air pollution continues to be undervalued. Regulation of indoor pollution has specific challenges, but no-regret policies such as aggressively discouraging smoking in the home, phase out of woodstoves and improved exhaust of cooking emissions will likely reduce the burden of respiratory and cardiovascular disease in Europe.
3. Measures aimed at reducing greenhouse gas emissions often lower emissions of hazardous air pollutants as well. In view of the EU ambitions to significantly lower greenhouse gas emissions, it is of vital importance to seek and strengthen co-benefits from measures taken in each of these two domains.
4. Air pollution causes chronic diseases such as asthma, COPD, lung cancer, heart disease and diabetes. Many of these conditions predispose to COVID-19 hospitalizations, ICU admissions and deaths. For this reason alone, there is serious concern about negative impacts of air pollution on the COVID-19 pandemic. Further studies are needed to quantify the magnitude of this indirect effect of air pollution on COVID-19.
5. Air pollution has been shown to reduce resistance against respiratory bacterial and viral infections other than SARS-CoV-2. Very limited evidence is available for the new SARS-CoV-2. Evidence is emerging that people living in high pollution areas might be more often infected by SARS-CoV-2, and more often develop COVID-19 once outbreaks of the disease occur. Almost all studies so far, however, have been conducted at the aggregate level of municipalities, counties, health regions etc. Outbreaks as well as air pollution are related to population density and other spatial variables. Studies at the individual level are urgently needed in which the development of COVID-19 is investigated in large, well characterised cohorts in Europe. There is a long tradition of EU funded research collaborations that have already created the necessary infrastructure and expertise to conduct such studies.
6. To make such studies valuable, it is of utmost importance to precisely define and standardise metrics for studying COVID-19 infection incidence and prevalence in the population.
7. Because of the reservations expressed in this report about the available ecological studies on COVID-19 and air pollution, we think the current evidence base does not allow estimates of the percentage of worldwide COVID-19 deaths attributed to PM2.5 to be made with any precision. Further work is needed, following methods elaborated by WHO and the Global Burden of Disease collaboration, to quantify the burden of COVID-19 attributable to air pollution.
8. A significant fraction of COVID-19 survivors has been burdened by adverse long-term conditions affecting the heart, the lungs and other organ systems. This is of great concern as these conditions can be worsened by long-term air pollution exposure and because short-term exposure to air pollution has been shown to increase hospital admissions for respiratory and heart conditions. Studies specifically focused on effects of air pollution among COVID-19 survivors are urgently needed as well.

9. Air pollution and COVID-19 likely affect disadvantaged populations more adversely due to higher exposures and/or increased vulnerability. Therefore, actions to mitigate the adverse effects of both air pollution and COVID-19 should be targeted at disadvantaged groups in particular, where the need is greatest.

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This study is about the effects of air pollution on health, notably COVID-19. The COVID-19 pandemic continues to wreak havoc in many areas of the world. The infection spreads through person-to-person contact. Transmission and prognosis, once infected, are potentially influenced by many factors, including air pollution. Studies have suggested that air pollution increases the incidence and the severity of the disease. However, the current data are too limited to be certain. Especially the quantitative contribution of air pollution to the disease is still very uncertain.

This document was provided by the Policy Department for Economic, Scientific and Quality of Life Policies at the request of the committee on the Environment, Public Health and Food Safety (ENVI).

PE 658.216

IP/A/ ENVI-2020-16

Print ISBN 978-92-846-7670-5 | doi: 10.2861/77364 | QA-06-20-225-EN-C
PDF ISBN 978-92-846-7669-9 | doi: 10.2861/46029 | QA-06-20-225-EN-N