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Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdowns in Early 2020

Kai Chen, Yiqun Ma, Anne Marb, Federica Nobile, Robert Dubrow, Massimo Stafoggia, Susanne Breitner, and Patrick L. Kinney

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with a Commentary by the HEI Review Committee

Research Report 224
Health Effects Institute
Boston, Massachusetts

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- identifies the highest-priority areas for health effects research
- competitively funds and oversees research projects
- provides an intensive independent review of HEI-supported studies and related research
- integrates HEI's research results with those of other institutions into broader evaluations
- communicates the results of HEI's research and analyses to public and private decision-makers.

HEI typically receives balanced funding from the US Environmental Protection Agency and the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. HEI has funded more than 390 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in more than 275 comprehensive reports published by HEI, as well as in more than 2,500 articles in the peer-reviewed literature.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research.

All project results and accompanying comments by the Review Committee are widely disseminated through HEI's website (*www.healtheffects.org*), reports, newsletters, annual conferences, and presentations to legislative bodies and public agencies.

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Research Report 224, *Effect of Air Pollution Reductions on Mortality During the COVID-19 Lockdowns in Early 2020*, K. Chen et al.

INTRODUCTION

The COVID-19 pandemic along with the associated closing of nonessential businesses and implementation of stay-at-home or "lockdown" policies created unprecedented conditions that lent themselves to conducting timely and policy-relevant research on air pollution. As described in the Preface to this report, HEI issued Request for Applications (RFA*) 20-1B: Air Pollution, COVID-19, and Human Health to solicit applications for research on new and important aspects of exposure to air pollution and the potential health outcomes. The first objective of RFA 20-1B was to conduct accountability research on how interventions taken to control the COVID-19 pandemic affected emissions, air pollution, and human health. The second objective was to assess whether populations exposed to high levels of air pollution were at greater risk of mortality from COVID-19 than were populations exposed to low levels of pollution and whether the potential associations between air pollution and COVID-19 outcomes differed by race, ethnicity, or socioeconomic background. The current study addressed the first objective of the RFA.

In response to the RFA, Dr. Kai Chen of Yale University submitted an application titled "Effect of air pollution reductions on mortality during the COVID-19 lockdown: A natural experiment study." Dr. Chen and colleagues proposed to assess the effect of reductions in daily exposure to nitrogen dioxide (NO_2) and particulate matter with aerodynamic diameter ≤2.5 µm ($PM_{2.5}$) on daily mortality during COVID-19 lockdowns in specific areas of four countries (China, Germany, Italy, and the United States). HEI's Research Committee recommended funding Dr. Chen's study because it included countries from different regions of the world where the study team had access to large, high-quality datasets on both air quality and health outcomes. The Committee also appreciated the proposed difference-in-differences analyses and other causal modeling approaches to study air quality and health changes during the lockdowns.

This Commentary provides the HEI Review Committee's independent evaluation of the study. It is intended to aid the sponsors of HEI and the public by highlighting both the strengths and limitations of the study and by placing the results presented in the Investigators' Report into a broader scientific and regulatory context.

Dr. Kai Chen's 2-year study, "Effect of Air Pollution Reductions on Mortality during the COVID-19 Lockdown: A Natural Experiment Study," began in June 2021. Total expenditures were $500,000. The draft Investigators' Report from Chen and colleagues was received for review in November 2023. A revised report, received in March 2024, was accepted for publication in April 2024. During the review process, the HEI Review Committee and the investigators had the opportunity to exchange comments and clarify issues in both the Investigators' Report and the Review Committee's Commentary. Review Committee member Ulrike Gehring was not involved in the review of this report due to a conflict of interest.

* A list of abbreviations and other terms appears at the end of this volume.

SCIENTIFIC BACKGROUND

HEALTH EFFECTS OF SHORT-TERM EXPOSURE TO AIR POLLUTION

Short-term exposure to NO_2 is considered to have a causal relationship with respiratory effects and a likely or suggestive causal relationship with total mortality (Health Canada 2016; Orellano et al. 2020; US EPA 2016; WHO 2021). Short-term exposure to NO_2 has also been associated with cardiovascular and respiratory mortality and with cardiovascular effects, although the evidence for a relationship of cause-specific mortality with NO_2 is weaker than the evidence for an association of total mortality with NO_2 (US EPA 2016; Wang et al. 2021; WHO 2021; Zheng 2021). Biological mechanisms by which short-term exposure to NO_2 can result in respiratory effects include pulmonary or allergic inflammation and airway responsiveness that can lead to asthma exacerbation (Hesterberg et al. 2009; US EPA 2016). The biological mechanisms by which NO_2 exposure can lead to extrapulmonary effects or mortality are less well understood, although inflammation and oxidative stress might play a role in cardiovascular effects (Huang et al. 2012; US EPA 2016). Many epidemiological studies on the relationships of health outcomes with NO_2 and other traffic-related air pollutants report only single-pollutant models; however, newer studies are increasingly reporting associations between adverse health outcomes and NO_2 that are robust to controlling for $PM_{2.5}$, thus providing support for an independent effect of NO_2 (HEI 2022; Meng et al. 2021; Mills et al. 2015, 2016). NO_2 is mainly generated through the burning of fuel in vehicles, power plants, and industrial facilities. Additionally, NO_2 contributes to the formation of other pollutants, including ozone and secondary $PM_{2.5}$ (Health Canada 2016; US EPA 2016). NO_2 is often used as an indicator of the broader traffic-related air pollution mixture (HEI 2022; Patton et al. 2024).

The evidence for an association of mortality with short-term exposure to $PM_{2.5}$ is stronger than that supporting such an association with NO_2. Epidemiological studies have demonstrated links between short-term exposure to $PM_{2.5}$ and all-cause and cause-specific mortality, cardiovascular disease, and respiratory effects (Cai et al. 2016; Le Tertre et al. 2002; Orellano et al. 2020). The US Environmental Protection Agency (EPA) concluded that there is a causal relationship between short-term exposure to ambient $PM_{2.5}$ and both cardiovascular effects and mortality as well as a likely to be causal relationship with respiratory effects (US EPA 2019). The evidence for health effects of short-term $PM_{2.5}$ exposure is supported by plausible biological pathways. For example, proposed biological pathways for the effect of $PM_{2.5}$ on cardiovascular disease include respiratory tract and systemic inflammation, alteration of the autonomic nervous system through activation of sensory nerves, and direct interaction between the particles and the cardiovascular system (Brook et al. 2010; Rückerl et al. 2011; US EPA 2019). There are many sources of $PM_{2.5}$, including windblown dust, wildfires, and emissions from energy production, transportation, and residences (US EPA 2019). Additionally, secondary $PM_{2.5}$ forms via chemical reactions in the atmosphere.

EFFECTS OF COVID-19 INTERVENTIONS ON AIR QUALITY AND HEALTH

Unprecedented lockdowns during the COVID-19 pandemic were quickly identified as a unique opportunity for a natural experiment to study how reductions in human activity could potentially lead to reductions in air pollutant emissions, concentrations, and associated effects on human health. Initial evidence suggested that changes in economic activity and human mobility following government restrictions related to COVID-19 led to noticeable reductions in air pollutant emissions and concentrations in ambient air (particularly NO_2) in many cities worldwide during the spring of 2020 (Ogen 2020; Schiermeier 2020; Zhang et al. 2020). Changes in $PM_{2.5}$ emissions and concentrations were observed less consistently, likely due to the regional nature of $PM_{2.5}$ and the influence of long-range transport on regional concentrations (Dantas et al. 2020; Sharma et al. 2020). The early studies motivated calls for individual-level (cohort) analyses that were carefully controlled for relevant confounders and underlined the importance of rigorous research on air pollution and COVID-19 (for example, Villeneuve and Goldberg 2020). Hence, HEI launched new studies addressing some of the concerns from earlier published research (Boogaard et al. 2021). Some of these newer studies have been published, revealing positive associations between exposure to ambient air pollution and COVID-19 outcomes, particularly among individuals with pre-existing conditions or low socioeconomic status (Andersen et al. 2023; Tonne et al. 2024).

Unrelated to COVID-19, there is a substantial body of accountability (or intervention) research focused on evaluating the effects of air pollution policies or interventions intended to improve air quality and health (for example, Boogaard et al. 2017; Burns et al. 2020; HEI 2010; Rich 2017). Several previous studies have analyzed natural experiments such as an unplanned shutdown of a steel mill in Utah (Pope 1989), a nationwide copper smelter strike (Pope et al. 2007), the reunification of East and West Germany (Peters et al. 2009), and decreased traffic associated with the Summer Olympic Games in Atlanta (Peel et al. 2010). Evaluation of such accountability research indicates that well-designed and rigorous analyses are critical for characterizing the effects of such interventions on air pollutant emissions, on the associated changes in pollutant concentrations, and, ultimately, on measures of human health. Challenges in study design often include a lack of statistical power and the need to develop methods to account appropriately for background trends in air quality and health (Boogaard et al. 2017; Rich 2017).

Using a natural experiment or accountability research framework to conduct studies on health outcomes during a pandemic is especially challenging because of the inherent dynamics of the pandemic and resulting changes in health systems and their utilization. Differences in availability of and access to COVID-19 tests as well as varying diagnostic criteria for COVID-19 and respiratory outcomes across countries and over time added to the complexity of obtaining reliable data. At the time of HEI's RFA, it was not clear how well studies that were investigating changes in air pollution and mortality could account for these complexities.

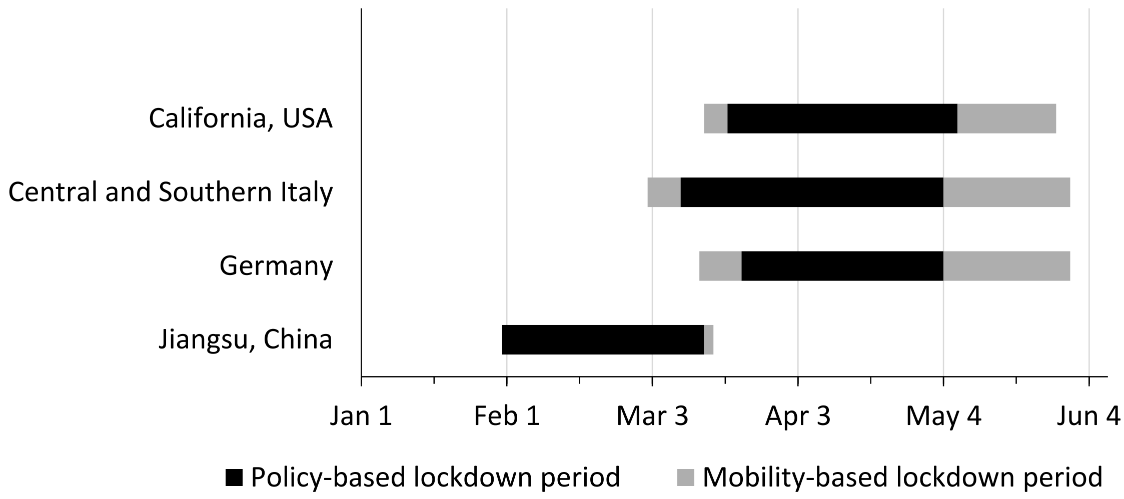
SUMMARY OF THE STUDY

STUDY OBJECTIVES

The overall purpose of this study was to examine the effect of COVID-19 lockdowns on changes in daily air pollutant concentrations and the associated mortality in California, United States; Central and Southern Italy; Germany; and the coastal Jiangsu region of eastern China. To accomplish this, Dr. Chen and colleagues pursued three aims:

1. To quantify changes in NO_2 and $PM_{2.5}$ concentrations that resulted from COVID-19 lockdowns in each region during early 2020
2. To estimate the prepandemic associations between daily changes in NO_2 and $PM_{2.5}$ concentrations and changes in daily all-cause, natural, and cardiovascular mortality rates using a causal modeling approach
3. To estimate the changes in mortality that could be attributed to lockdown-induced changes in air pollution

The four regions implemented lockdowns in early 2020, before their populations were substantially affected by COVID-19 mortality or pandemic-related disruptions of health systems. The investigators conducted separate analyses for each region and used lockdown periods that reflected the situations in the different regions (**Commentary Figure 1**).



Commentary Figure 1. Policy-based lockdown periods (used in main analyses) and mobility-based lockdown periods (used in sensitivity analyses) in the four study regions during early 2020 and during earlier years for comparison.

To address Aim 1, the investigators used the natural experiment of lockdown periods in early 2020 to evaluate changes in NO_2 and $PM_{2.5}$ concentrations. They first compared air quality during the 2020 lockdown periods to air quality observations for the same periods in 2015–2019, after performing meteorological normalization to separate the effects of lockdowns on air quality from effects of variability due to changing weather. Then, they used a difference-in-differences approach to compare air quality during the lockdown periods with air quality during the period before the lockdown in the same calendar year.

For Aim 2, the investigators conducted an epidemiological analysis of prepandemic associations of mortality with mean daily concentrations of NO_2 and $PM_{2.5}$ over the 5 years before the lockdowns (i.e., 2015–2019). They used an interactive fixed effects model for each region to estimate the causal relationship between daily air pollutant concentrations (measured in California and modeled in the other regions) and daily mortality.

For Aim 3, the investigators combined the changes in NO_2 and $PM_{2.5}$ during the lockdowns, as quantified in Aim 1, with the mortality concentration-response functions from Aim 2 to calculate the changes in mortality that could be attributed to lockdown-induced changes in air pollution. Aim 3 analyses used prepandemic mortality data and thus estimated the isolated effect of changes in air pollution separate from the direct effects of COVID-19 or other changes in human behaviors or health systems. An overview of the objectives and approach of the study is presented in **Commentary Table 1**.

METHODS AND STUDY DESIGN

Study Populations and Health Outcomes

The study populations were large, and the study regions covered an entire country (Germany, study population 55 million) or parts of a country (California, a state on the west coast of the United States, study population 37 million; Central and Southern Italy, study population 13 million; and the coastal eastern region of Jiangsu, China, study population 27 million). These areas were selected because high-quality data on air quality and health outcomes were available and because the areas implemented lockdowns during the early months of the COVID-19 pandemic before their populations were substantially affected by COVID-19 mortality and disruptions of health systems.

The health analyses used daily mortality data from death certificates obtained from the relevant government agencies at the municipality (Italy) or county (all other regions) level. Specific outcomes included in the analyses were all-cause mortality, natural mortality (International Classification of Diseases, Ninth Revision [ICD-9] codes 001–799 and International Classification of Diseases, Tenth Revision [ICD-10] codes A00–R99), and cardiovascular mortality (ICD-9 codes 390–459 and ICD-10 codes I00–I99). Cause-specific mortality analyses in Italy were restricted to the smaller Lazio region because of data availability. The only individual-level data available for the study populations were data on age and sex.

Air Quality

The investigators collected two types of air quality data for each region for the analysis periods specific to the three aims. For Aims 1 and 3, routine governmental air quality measurements for January through May of 2015–2020 were used to assess changes in NO_2 and $PM_{2.5}$ concentrations before and during the lockdown periods. Hourly air quality data were available for California, Germany, and Jiangsu; daily air quality data were available for Central and Southern Italy. To account for the effects of meteorology on air quality, the

Commentary Table 1. Study Overview[a]

Aim	Period	Analysis	Output
Aim 1. Natural experiment exploring air quality changes during lockdowns	January through May 2015–2020, before and during lockdown periods	Meteorological normalization	Daily NO_2 and $PM_{2.5}$ concentrations, with variation due to weather removed for each municipality or county within each region
		Difference-in-differences approach	Changes in NO_2 and $PM_{2.5}$ concentrations between lockdown periods and periods before lockdowns, for each municipality or county within each region
Aim 2. Epidemiological study of relationship of mortality with daily concentrations of air pollution	2015–2019 (full 5 years preceding the pandemic)	Interactive fixed effects model to estimate concentration-response functions	Associations of all-cause and cause-specific (natural and cardiovascular) mortality with day-to-day changes in NO_2 and $PM_{2.5}$ concentrations for each region
Aim 3. Health impact assessment	During region-specific lockdown periods in early 2020	Apply concentration-response functions from Aim 2 to air pollutant concentration changes from Aim 1	Mortality that could be attributed to the lockdown-induced changes in NO_2 and $PM_{2.5}$ concentrations[b]

[a] Adapted from Investigators' Report Table 1.

[b] This study applied prepandemic concentration-response functions to estimate how reductions in human activity affected mortality related to air pollution and did not evaluate actual deaths that occurred during the pandemic.

investigators used hourly data on surface temperature, wind speed and direction, and other meteorological parameters from a global dataset (the fifth-generation European Centre for Medium-Range Weather Forecasts atmospheric reanalysis of the global climate [ERA5]) at 0.1° × 0.1° (about 10 km × 10 km) spatial resolution.

For Aim 2, the investigators used 1 km × 1 km spatiotemporal models (Germany, Central and Southern Italy, and Jiangsu) or routine air quality measurements (California) of NO_2 and $PM_{2.5}$ to estimate concentration-response functions between daily air pollution levels and mortality prior to the pandemic (2015–2019). These spatiotemporal models were sophisticated statistical models that applied advanced machine learning algorithms to estimate daily air pollutant concentrations based on data from satellite observations, chemical transport model simulations, land use or land cover characteristics, and meteorological data. The investigators did not find a comparable, publicly available spatiotemporal statistical model of daily air quality for California; therefore, they instead used county-level, measured daily mean concentrations of NO_2 and $PM_{2.5}$ for the 32 (out of 58) California counties that had US EPA monitoring sites for both pollutants.

For both datasets, the investigators aggregated all air quality and meteorological data to daily means for each municipality or county before linking those data to the daily mortality data.

Main and Sensitivity Analyses

Changes in Air Quality During Lockdowns (Aim 1)

To assess whether lockdowns had affected air quality, the investigators compared air quality during and before the lockdowns by accounting for meteorology and time trends (e.g., seasonality) in the daily concentrations of NO_2 and $PM_{2.5}$ aggregated to municipality or county. They first used a machine learning–based meteorological normalization technique to produce air quality time series in which the effects of changes in day-to-day meteorology had been removed. Then, they applied a difference-in-differences approach to the meteorologically normalized air quality data to remove time trends.

In the difference-in-differences approach, the investigators defined a reference period as spanning from January 1, 2020, to 7 days before the start of the first lockdown for each study region (Commentary Figure 1). They then calculated changes in air quality between the reference period and the first lockdown period in 2020, with further adjustment for changes in air quality during the same months in 2015–2019. This approach enabled the comparison of air quality during different periods, as if the meteorological factors had been constant and there were no seasonal or long-term trends in air quality. Only the first lockdown period was included in the comparisons with prepandemic observations, as the investigators expected that both increased baseline mortality rates from COVID-19 deaths and other pandemic-related changes during later lockdown periods would violate the underlying assumptions of the models used in the analyses.

Association of Mortality with Air Pollution Before the Pandemic (Aim 2) Chen and colleagues applied interactive fixed effects models to assess associations of mortality with daily NO_2 and $PM_{2.5}$ concentrations during the prepandemic years of 2015–2019. Interactive fixed effects models, an extension of two-way fixed effects models, control for unmeasured time-varying confounders. The process of variable selection for the models in this study was informed by directed acyclic graphs. The investigators calculated day-to-day changes in mortality rates, with adjustment for temperature trends and time-variant unmeasured spatial unit effects, and constructed concentration-response curves for each of the four regions.

They developed single-pollutant models and two-pollutant models for NO_2 and $PM_{2.5}$. Models were developed using multiple single-day and cumulative lags (i.e., the number of days between air pollution exposure and the date of death). They considered lags of up to 2 days for all-cause mortality and up to 7 days for natural and cardiovascular mortality. The main model for each pollutant in each region was defined as the model with the lag that had the largest effect in the single-pollutant model. The interactive fixed effects models were developed based on data from 2015 to 2019 (and not 2020), as it would have been difficult to account for time-varying confounders during the pandemic (e.g., ensuring that observed changes in mortality during the lockdowns were not affected by increasing COVID-19 deaths or by other changes in health systems and human behaviors that occurred during the same period). The interactive fixed effects models were not adjusted for age or sex because day-to-day changes in those demographic characteristics were not expected; however, the investigators conducted stratified sensitivity analyses by age and sex to check for differences between groups.

Health Impact Assessment of Changes in Air Pollution-Related Mortality During Lockdowns (Aim 3) Finally, by applying the region-specific, prepandemic concentration-response functions to the observed changes in NO_2 and $PM_{2.5}$ concentrations during the lockdown periods, Dr. Chen and colleagues calculated the changes in mortality rates that could be attributed to changes in air pollution during the lockdowns in early 2020. The total change in air pollution–related mortality during the lockdown periods was then calculated as the average modeled daily change in deaths multiplied by the duration of the lockdown period. Empirical confidence intervals (eCIs) for this health impact assessment were quantified using Monte Carlo simulations that incorporated the effects of variations in meteorology and the uncertainty in the concentration-response functions, but not uncertainty associated with the interactive fixed effects models, on estimated changes in air pollutant concentrations.

Sensitivity Analyses The investigators conducted various sensitivity analyses to test the robustness of their results. For example, they tested whether different definitions of lockdown periods affected the results of the air quality and health impact analyses (Aims 1 and 3). For the epidemiological interactive fixed effects models (Aim 2), the investigators conducted sensitivity analyses in which they examined only spatial correlations, included different covariate adjustments, or compared the novel interactive fixed effects approach to a more traditional two-stage Poisson time-series approach. Finally, for the health impact assessment (Aim 3), they conducted additional analyses using concentration-response functions from two-pollutant models and from time-series models.

SUMMARY OF KEY RESULTS

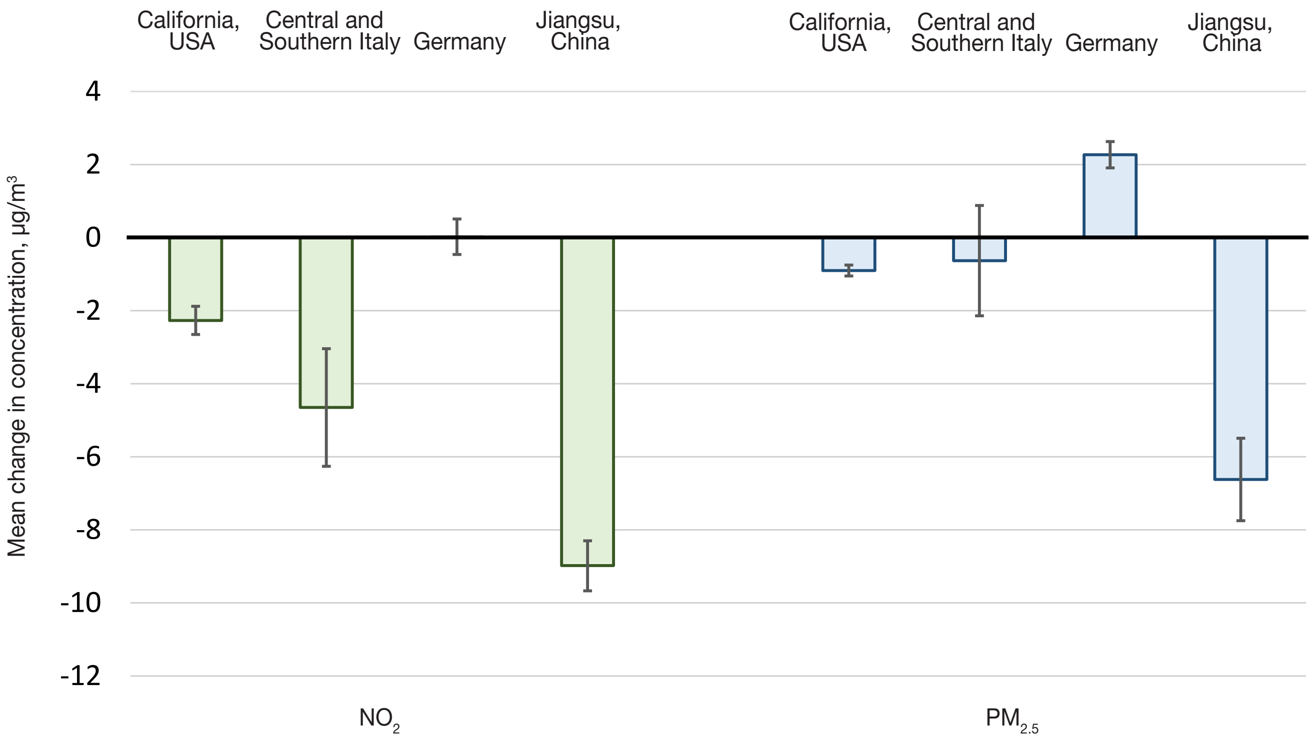
Air Quality Before and During Lockdowns

During the 5-year prepandemic reference period (2015–2019), the average measured NO_2 and $PM_{2.5}$ concentrations were highest in Jiangsu (NO_2: 32.2 μg/m^3; $PM_{2.5}$: 50.8 μg/m^3). The average measured prepandemic NO_2 concentration was lowest in Germany (12.2 μg/m^3), and the average measured $PM_{2.5}$ concentration was lowest in California (9.9 μg/m^3). Except for $PM_{2.5}$ in Germany, lower air pollutant concentrations were observed in January through May in 2020 (even before any lockdowns) than in the same months in 2015–2019, and air pollutant concentrations decreased in the period from January to May of each year. There was a moderate correlation between the measured NO_2 and $PM_{2.5}$ concentrations in Central and Southern Italy, Germany, and Jiangsu and a weak correlation between these pollutants in California.

In 2020, the average measured concentrations of NO_2 and $PM_{2.5}$ in California, Central and Southern Italy, and Jiangsu were lower during the lockdown periods compared to the pre-lockdown reference periods. After removal of meteorological variation and temporal trends, the reductions in regional-average air pollutant concentrations between the reference and lockdown periods ranged from 2.3–9.0 μg/m^3 for NO_2 and 0.6–6.6 μg/m^3 for $PM_{2.5}$, with decreases in concentrations of both air pollutants in most parts of these three regions (**Commentary Figure 2**). Reductions in NO_2 were consistently larger than reductions in $PM_{2.5}$. To put these changes into context, they were comparable to hourly and annual average improvements in NO_2 and $PM_{2.5}$ concentrations between 1990 and 2023 in the United States (US EPA 2024).

By contrast, in Germany there was no statistically significant change in NO_2 concentrations and $PM_{2.5}$ concentrations were 2.3 μg/m^3 higher during the lockdown period than during the prelockdown reference period, even after removing the effects of meteorology and temporal trends.

The estimated changes in air pollutant concentrations during lockdowns were robust to different definitions of the lockdown and reference periods. After weather normalization, the estimated changes in NO_2 and $PM_{2.5}$ concentrations remained, albeit with smaller magnitudes compared to the changes estimated using measured pollutant concentrations. Comparisons between urban and rural areas yielded mixed results (Investigators' Report [IR] Appendix Table A6).



Commentary Figure 2. Mean changes in concentrations of NO_2 and $PM_{2.5}$ during COVID-19 lockdowns in early 2020 compared to prelockdown reference periods in California, USA; Central and Southern Italy; Germany; and Jiangsu, China, after removing the influence of weather, seasonality, and year-to-year trends. Error bars show variation (95% empirical confidence intervals) among municipalities or counties.

Association of Mortality with Air Pollution Before the Pandemic

In the interactive fixed effects models of daily air pollution and mortality during the 5 years before the pandemic, daily all-cause mortality rates were positively associated with daily NO_2 and $PM_{2.5}$ concentrations in single-pollutant models for all four regions (**Commentary Figure 3**). The largest associations of daily all-cause mortality rates with daily NO_2 and $PM_{2.5}$ concentrations were observed for cumulative lags of 1 or 2 days. In sensitivity analyses, estimated associations from two-pollutant models including NO_2 and $PM_{2.5}$ were qualitatively similar to estimates from single-pollutant models, although the estimated coefficients were smaller in the two-pollutant models (IR Figure 7).

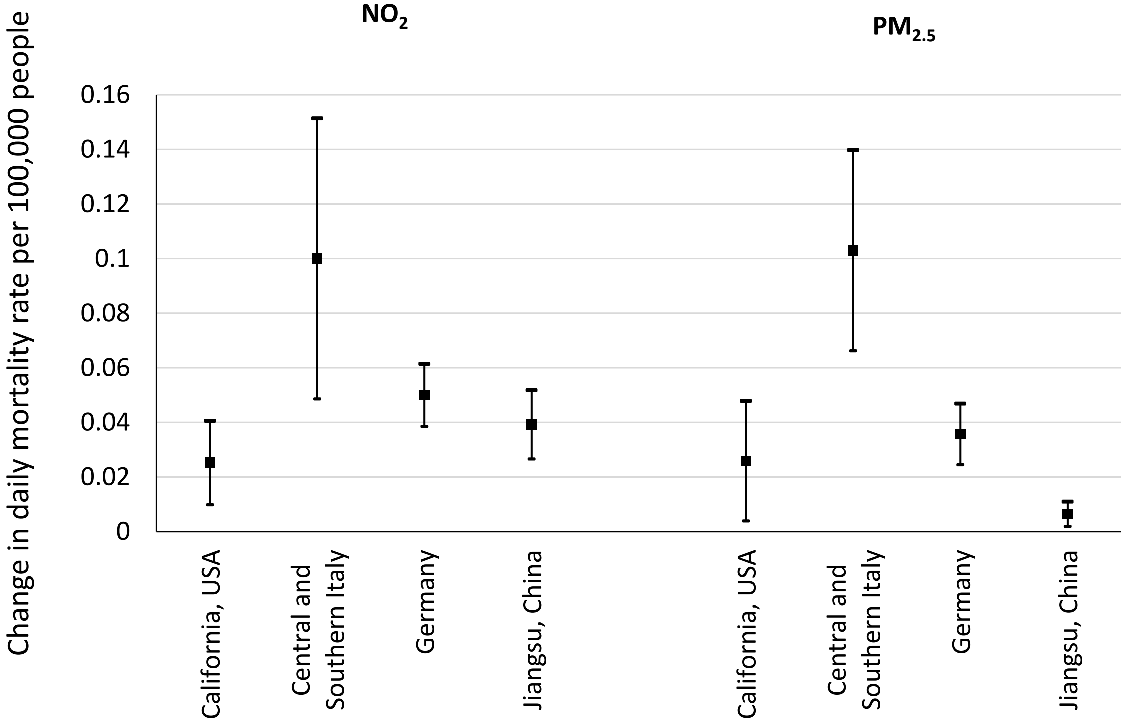
There were also significant positive associations of daily natural and cardiovascular mortality with daily concentrations of NO_2 and $PM_{2.5}$. Effects were largest for cumulative lags of 7 days. The associations were generally weaker for cardiovascular mortality than for natural or all-cause mortality. Significant heterogeneity across regions was observed in the estimated associations of mortality (all-cause, natural, and cardiovascular) with concentrations of NO_2 and $PM_{2.5}$.

In stratified models used for sensitivity analyses, associations of daily all-cause mortality with daily NO_2 and $PM_{2.5}$ concentrations were generally strongest among people aged 75 years or older, females, and people living in rural areas, although these differences were not fully consistent across pollutants, single- versus two-pollutant models, or the four study regions (IR Table 4 and IR Appendix Table A9).

In tests of robustness, results were similar across different specifications of the epidemiological model. Higher daily concentrations of NO_2 and $PM_{2.5}$ were associated with increased all-cause mortality in both the interactive fixed effects models and the time-series analyses, indicating that these associations were not artifacts of the model choice. Overall, the sensitivity analyses confirmed that daily mortality was positively associated with daily NO_2 and $PM_{2.5}$ concentrations in all four regions during the period 2015 to 2019, even as air quality improved over the 5-year period.

Estimated Mortality Changes Related to Lockdown-Induced Changes in Air Pollution

By combining their localized estimates of the relationship between air pollution and mortality during the 5 years before the pandemic with air quality measurements adjusted to remove the effects of meteorology and temporal trends, Chen and colleagues calculated the changes in mortality that would have been expected to result from changes in NO_2 and $PM_{2.5}$



Commentary Figure 3. Estimated change in daily all-cause mortality rate (per 100,000 people) associated with a 10-µg/m³ increase in NO_2 or $PM_{2.5}$ concentration during the prepandemic period (2015–2019). Data are presented with 95% confidence intervals and for main lags only (cumulative 0- to 1-day lag for associations with NO_2 in Germany and with $PM_{2.5}$ in both Germany and Jiangsu; cumulative 0- to 2-day lag for all other associations).

concentrations during the pandemic lockdowns. Their calculations indicated that reductions in all-cause mortality that could be attributed to decreased concentrations of NO_2 during the lockdowns ranged from 0.11 (95% eCI: –0.03, 0.25) deaths per 100,000 people (62 deaths over the lockdown period) in Germany to 4.66 (95% eCI: 2.03, 7.44) deaths per 100,000 people (601 deaths over the lockdown period) in Central and Southern Italy (**Commentary Table 2**). Reductions in all-cause mortality that could be attributed to decreased concentrations of $PM_{2.5}$ were smaller, with estimated reductions of 0.16 (95% eCI: 0.04, 0.29) deaths per 100,000 people (44 deaths over the lockdown period) in Jiangsu to 0.91 (95% eCI: 0.09, 1.78) deaths per 100,000 people (118 deaths over the lockdown period) in Central and Southern Italy. Estimated all-cause mortality attributed to changes in $PM_{2.5}$ concentrations in Germany increased during the lockdown, consistent with the observed increase in $PM_{2.5}$ concentrations.

Estimates of changes in natural mortality that could be attributed to changes in NO_2 and $PM_{2.5}$ concentrations during the lockdowns in most of the four regions were similar to the corresponding estimated changes in all-cause mortality, although with smaller magnitudes of effect on natural mortality — except in Italy, where the results were more variable.

In most regions, no statistically significant changes in cardiovascular mortality that could be attributed to lockdown-induced changes in NO_2 and $PM_{2.5}$ concentrations were found, possibly reflecting the weaker associations of cardiovascular mortality with NO_2 and $PM_{2.5}$ concentrations compared to the associations for natural or all-cause mortality. The one exception was in Jiangsu, where the decrease in cardiovascular mortality attributed to reduced NO_2 concentrations during the lockdown accounted for about one-third of the estimated reductions in all-cause and natural mortality attributed to NO_2 in that region.

In sensitivity analyses, the changes in all-cause mortality that could be attributed to lockdown-induced changes in air pollution generally remained robust across alternative definitions of the lockdown periods (i.e., defined by lockdown policies versus population mobility) and reference periods. The results also remained similar across concentration-response functions from two-pollutant versus single-pollutant models and for time-series analyses versus integrated fixed effects models.

Commentary Table 2. Estimated Changes in Mortality Attributed to Changes in Air Quality During Lockdowns, After Removing the Influence of Meteorology and Temporal Trends

Region	Total Population, 2015–2019	Total All-Cause Mortality, 2015–2019	Mean Daily All-Cause Mortality Rate per 100,000 People, 2015–2019	Air Pollutant	Changes in Daily Mortality Rates (95% eCI), per 100,000 People, That Were Attributed to Changes in Ambient NO_2 or $PM_{2.5}$ Concentrations During Lockdown Periods Defined by Policy		
					All-Cause	Natural	Cardiovascular
California, USA	37 million	1.2 million	1.8	NO_2	−0.44 (−0.71, −0.17)	−0.32 (−0.57, −0.08)	NS
				$PM_{2.5}$	−0.23 (−0.43, −0.03)	−0.10 (−0.28, 0.08)	NS
Central and Southern Italy	25 million	1.2 million	2.7	NO_2	−4.66 (−7.44, −2.03)	−5.84 (−15.63, 3.96)[a]	NS[a]
				$PM_{2.5}$	−0.91 (−1.78, −0.09)	−1.71 (−3.27, −0.28)[a]	NS[a]
Germany	83 million	3.9 million	2.6	NO_2	−0.11 (−0.25, 0.03)	−0.10 (−0.25, 0.04)	NS
				$PM_{2.5}$	0.35 (0.22, 0.48)	0.19 (0.06, 0.32)	NS
Jiangsu, China	78 million	2.6 million	1.9	NO_2	−1.41 (−1.88, −0.94)	−1.29 (−1.74, 0.85)	−0.41 (−0.58, −0.24)
				$PM_{2.5}$	−0.16 (−0.29, −0.04)	−0.14 (−0.29, 0.00)	NS

NS = not statistically significant.

[a] In Italy, analyses of cause-specific mortality included the Lazio region only.

HEI REVIEW COMMITTEE EVALUATION

OVERVIEW

The Review Committee thought that the Investigators' Report describes a well-conducted study that leveraged a unique scenario to understand how a pause in human activity might affect both air pollution and its effects on health. The report clearly identifies potential limitations of the earlier literature that the investigators have addressed in the current study. Such improvements over prior studies included the approach to defining lockdown periods, accounting for changes in meteorology, accounting for unmeasured time-varying confounders, and using recent localized concentration-response functions in the health impact assessment.

The Committee members considered the major strengths of the study to be the focus on four regions across the globe that had large, high-quality local datasets, the use of a machine learning approach to remove meteorological influences from the air pollution observations, the removal of temporal trends via a difference-in-differences approach, and the use of extensive and appropriate sensitivity analyses. The Committee also appreciated that the analyses using the interactive fixed effects model added to the base of knowledge regarding epidemiological associations of mortality with daily concentrations of NO_2 and $PM_{2.5}$, thereby providing additional evidence for the health effects of those pollutants and the potential benefits of reducing their ambient concentrations.

The Committee also noted some limitations related to the challenges of conducting a study on mortality related to air quality during a global pandemic. Those limitations, as well as the contributions of the study, are discussed below.

NATURAL EXPERIMENT FOR STUDYING CHANGES IN AIR QUALITY DURING LOCKDOWNS

The Review Committee thought that using a natural experiment to explore changes in ambient air quality was a strong contribution to this study. The investigators went above and beyond usual practice by removing the influence of changing meteorology, seasonality, and year-to-year trends from the air quality data used in their main analyses and by comparing those results to findings from analyses in which these factors were not considered.

After using both a novel application of machine learning to correct for time trends and a difference-in-differences approach to remove effects of meteorology and temporal trends from air quality time series, the investigators showed that clear reductions in ambient NO_2 concentrations and smaller yet still clear decreases in $PM_{2.5}$ concentrations occurred during lockdowns in most areas of the study regions of California, Central and Southern Italy, and Jiangsu. Although the changes in air quality in Germany were less consistent, the investigators provided plausible interpretations of these results. Specifically, $PM_{2.5}$ concentrations in Germany were likely less affected by lockdowns than were NO_2 concentrations because long-range transport of air pollution from sources such as forest and land fires in Eastern Europe and Saharan dust from North Africa contributed substantially to the $PM_{2.5}$ concentrations during the lockdown. Overall, the Committee thought that the analyses and interpretation of results regarding changes in air quality during lockdowns were thorough and informative and could be referenced to account for temporal trends in other studies.

ASSOCIATIONS OF MORTALITY WITH DAILY AIR POLLUTANT CONCENTRATIONS

Contributions to the Literature on Short-Term Health Effects of Air Pollution

To produce region-specific concentration-response functions for associations of mortality with daily concentrations of air pollution, the investigators conducted epidemiological analyses using 5 years of data from four contrasting regions. Because these analyses were conducted with prepandemic data, the results were not confounded by pandemic-related changes in mortality, the health systems, or human behaviors. These analyses add to the general literature on epidemiological associations of mortality with daily exposures to ambient NO_2 and $PM_{2.5}$ — especially regarding NO_2 exposure and cause-specific mortality — and provide further support for an effect of NO_2 independent of $PM_{2.5}$ (for example, see reviews by US EPA 2016; Wang et al. 2021; WHO 2021; Zheng 2021).

Implications of Different Spatial Scales

As discussed in the report, heterogeneity in results across regions was to be expected, and the differing spatial scales used in the different regions likely introduced varying degrees of exposure measurement error. Specifically, the level of variability in the municipality-level results for Central and Southern Italy was higher than expected. For example, some epidemiological models appeared to suggest that NO_2 had a fluctuating or even protective relationship with mortality. The variability in the results for Central and Southern Italy might be at least partially explained by analysis units that were smaller than those in the other regions as well as the availability of cause-specific mortality data for only one small part of Central and Southern Italy (the Lazio region). Thus, the available dataset for the analysis was relatively small, with no recorded deaths on many days; this likely contributed to more variability in daily mortality and less stable results than in the other regions.

The Committee thought it could have been helpful to display the results for all three mortality outcomes side-by-side to assess the coherence of results across outcomes. Also, it might have been useful to test whether aggregating the data to larger areas in Central and Southern Italy would produce more stable results. However, the Committee understood the motivation behind conducting the multiregion study using local county or municipality definitions because that approach allowed for varying associations of all-cause, natural, and cardiovascular mortality with daily concentrations of NO_2 and $PM_{2.5}$ across different environments.

Implications of Model Structures and Assumptions

The Committee appreciated that the investigators explored the implications of the model structures and their inherent assumptions. The application of novel linear interactive fixed effects models in the main analysis in combination with sensitivity analyses that involved comparing the main findings with results from more traditional Poisson time-series models was a valuable approach, as these two types of models make different assumptions about how air pollution is associated with mortality. Although the different interpretations of the estimates from these models made direct comparisons inappropriate, results from both models suggested that short-term exposure to $PM_{2.5}$ or NO_2 was associated with increased all-cause mortality, which increased confidence in the results.

Regarding the various lags in the time-series analyses and health impact assessment, the Committee thought it would have been better to make an a priori lag selection that neither depended on effect sizes nor allowed for different lags for different locations. However, the Committee appreciated that the investigators presented results for all tested lags and then confirmed that selecting the lag in the main model for each pollutant on the basis of effect size did not substantially affect the overall conclusions. Although the investigators did not fully explore the assumptions and implications of the model structures, the Committee thought that the models were well justified, clearly explained, and provided useful epidemiological results.

USE OF PREPANDEMIC CONCENTRATION–RESPONSE FUNCTIONS IN THE HEALTH IMPACT ASSESSMENT OF CHANGES IN MORTALITY RELATED TO AIR POLLUTION DURING LOCKDOWNS

An important decision made by the investigators regarding the study design was to develop and apply relationships of mortality with air pollution (i.e., concentration-response functions) using data from the years before the pandemic and to then apply those relationships to observed changes in air quality during the pandemic lockdowns. As a result, the calculated changes in mortality related to changes in air quality during the lockdowns were characterized as a health impact assessment, whereas the analyses of changes in air quality based on direct observations before and during the lockdowns were considered a natural experiment. The Committee concurs with the investigators' choice to conduct a health impact assessment rather than a natural experiment for Aim 3 because it would have been difficult to tease out the effects of changes in air pollution against a backdrop of sweeping changes that may have simultaneously affected air pollution and health.

For example, numerous changes in population behaviors during the lockdowns could have affected associations between ambient air pollutant concentrations and exposure to air pollution. As the investigators noted, people living or working in densely populated urban areas may have transitioned to remote work and traveled less for work and recreation. Additionally, people in areas with lockdowns could have spent more time indoors at home, where their exposures to outdoor NO_2 and $PM_{2.5}$ concentrations might have changed and they might have had new exposures to indoor pollutant emissions (e.g., cooking, smoking, or fireplace use). The relationship between ambient air pollutant concentrations and actual exposures to air pollution might also have changed because of the widespread use of masks to reduce the spread of infection during the pandemic, further affecting the relationship between ambient air quality and health effects.

For all these reasons, the findings from the current health impact assessment study might differ quantitatively from the actual changes in mortality related to air pollution during the pandemic. Nonetheless, the general conclusions that air pollutant concentrations decreased in response to changes in human activity and that the improvements in air pollution would be expected to result in improved health are likely generalizable to other changes in human activities that affect ambient air pollutant emissions.

Finally, the Committee noted that the health impact assessment did not account for any differences by age, sex, and urbanicity, despite evidence of effect modification by these features. The investigators argued that there would be minimal day-to-day change in age structures before and during the lockdowns and that the study regions were specifically selected as places where COVID-19 did not substantially affect mortality rates. However, the Committee thought the need for this assumption could have been avoided by performing stratified analyses. In the end, this recommendation was largely theoretical, and the Committee agreed with the investigators that accounting for potential changes in population structure would likely not have changed the results.

BROADER IMPLICATIONS

Although the investigators have focused on a relatively narrow interpretation of their findings specific to changes in air quality and resulting effects on air pollution–related mortality during pandemic lockdowns, the Committee thought that the work has strong relevance beyond the pandemic setting. The observed changes in air quality were comparable to hourly and annual average improvements in NO_2 and $PM_{2.5}$ concentrations between 1990 and 2023 in the United States (US EPA 2024). Specifically, the results of this study are useful for considering the contributions of daily human activities to air pollutant emissions and the improvements in air quality and the health burden related to air pollution that might occur if certain human activities paused. The Committee thought the current study consisted of a well-conducted natural experiment, epidemiological analyses, and health impact assessment that demonstrated how changes in human activities, whether planned or unforeseen, can reduce air pollution, with potential benefits to health.

SUMMARY AND CONCLUSIONS

In summary, Chen and colleagues leveraged the unique scenario of lockdowns that occurred early in the COVID-19 pandemic to understand how a pause in human activity could affect air pollution and its effects on health. This clearly described and thoughtful study included estimates of potential changes in mortality related to air pollution levels, independent of the actual mortality due to COVID-19. The investigators conducted detailed analyses of observed changes in air quality and then calculated changes in mortality that could be attributed to those changes in air quality; they applied this same set of analyses in four study regions (California, USA; Central and Southern Italy; Germany; and Jiangsu, China) with large, high-quality, local datasets on daily meteorology, air quality, and mortality at the fine spatial resolutions of counties or municipalities.

The study demonstrated that in three of the regions (California, Central and Southern Italy, and Jiangsu), air pollutant concentrations — for NO_2 in particular — were lower during lockdowns than during prelockdown reference periods, both with and without adjusting for meteorology and temporal trends in air quality. The observed changes in air quality were comparable to hourly and annual average improvements in NO_2 and $PM_{2.5}$ concentrations between 1990 and 2023 in the United States (US EPA 2024). In the fourth region (Germany), NO_2 concentrations remained essentially unchanged, and concentrations of $PM_{2.5}$ increased during lockdowns.

Single-pollutant interactive fixed effects models for all four regions showed that, during the 5 years preceding the pandemic, increases in daily NO_2 and $PM_{2.5}$ concentrations were significantly associated with increases in daily all-cause, natural, and cardiovascular mortality rates. Application of the concentration-response functions from these models to the changes in observed air quality during the lockdowns resulted in estimated reductions in mortality related to daily NO_2 and $PM_{2.5}$ concentrations. The only exception was in Germany, where $PM_{2.5}$ concentrations and the estimated mortality from exposure to ambient $PM_{2.5}$ increased during the lockdown, although the reasons for the increases were most likely unrelated to the lockdown.

The results for mortality changes that could be attributed to changes in air quality during the lockdowns were robust to extensive sensitivity analyses. For example, the results were similar, regardless of whether lockdown periods were defined on the basis of policy or periods of decreased individual mobility. The results were much more variable in Central and Southern Italy than in the other areas.

Ultimately, this study has provided important evidence that reductions in air pollutant emissions related to daily human activity can lead to improved air quality that would likely result in reductions in mortality related to exposure to air pollution. These findings thus have relevance not only for the COVID-19 pandemic lockdowns but also for potential future changes in human activity that affect air pollutant emissions.

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ABBREVIATIONS AND OTHER TERMS

CI	confidence interval
DiD	difference-in-differences
eCI	empirical confidence interval
ERA5	fifth-generation European Centre for Medium-Range Weather Forecasts atmospheric reanalysis of the global climate
ERF	exposure-response function
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IFE	interactive fixed effects
IQR	interquartile range
lag0	0-day lag (current day)
lag1	single-day lag of 1 day after exposure
lag2	single-day lag of 2 days after exposure
lag01	cumulative lag of 0–1 day after exposure
lag02	cumulative lag of 0–2 days after exposure
lag37	cumulative lag of 3–7 days after exposure
lag07	cumulative lag of 0–7 days after exposure
Max	maximum
Min	minimum
NO_2	nitrogen dioxide
$PM_{2.5}$	particulate matter with aerodynamic diameter ≤2.5 μm
R^2	coefficient of determination
RF	random forest
RFA	request for applications
RMSE	root mean square error
SD	standard deviation
TWFE	two-way fixed effects
US EPA	US Environmental Protection Agency

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