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Methodological Considerations for Epidemiological Studies of Air Pollution and the SARS and COVID-19 Coronavirus Outbreaks

Paul J. Villeneuve[1,2] and Mark S. Goldberg[2,3,4,5]

[1]School of Mathematics and Statistics, Carleton University, Ottawa, Canada
[2]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Canada
[3]Department of Medicine, McGill University, Montreal, Canada
[4]Gerald Bronfman Department of Oncology, McGill University, Montreal, Canada
[5]Centre for Outcomes Research and Evaluation, Research Institute of the McGill University Hospital Centre, Montreal, Canada

Background: Studies have reported that ambient air pollution is associated with an increased risk of developing or dying from coronavirus-2 (COVID-19). Methodological approaches to investigate the health impacts of air pollution on epidemics should differ from those used for chronic diseases, but the methods used in these studies have not been appraised critically.

Objectives: Our study aimed to identify and critique the methodological approaches of studies of air pollution on infections and mortality due to COVID-19 and to identify and critique the methodological approaches of similar studies concerning severe acute respiratory syndrome (SARS).

Methods: Published and unpublished papers of associations between air pollution and developing or dying from COVID-19 or SARS that were reported as of 10 May 2020 were identified through electronic databases, internet searches, and other sources.

Results: All six COVID-19 studies and two of three SARS studies reported positive associations. Two were time series studies that estimated associations between daily changes in air pollution, one was a cohort that assessed associations between air pollution and the secondary spread of SARS, and six were ecological studies that used area-wide exposures and outcomes. Common shortcomings included possible cross-level bias in ecological studies, underreporting of health outcomes, using grouped data, the lack of highly spatially resolved air pollution measures, inadequate control for confounding and evaluation of effect modification, not accounting for regional variations in the timing of outbreaks' temporal changes in at-risk populations, and not accounting for nonindependence of outcomes.

Discussion: Studies of air pollution and novel coronaviruses have relied mainly on ecological measures of exposures and outcomes and are susceptible to important sources of bias. Although longitudinal studies with individual-level data may be imperfect, they are needed to adequately address this topic. The complexities involved in these types of studies underscore the need for careful design and for peer review. https://doi.org/10.1289/EHP7411

Introduction

Recent reports in the media have suggested that exposure to ambient air pollution increases the risk of death among individuals infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2 or COVID-19) (Carrington 2020a, 2020b, 2020c; Friedman 2020). For COVID-19, there has been a rush to disseminate these findings, and many papers have not been peer-reviewed, yet they appear to be shaping the proposed environmental policies of several prominent politicians (Grandoni and Firozi 2020; Griffiths 2020; Laing 2020; O'Sullivan 2020).

It is recognized widely that exposure to air pollution has a substantial impact on human health. Ambient air pollution has been estimated to be responsible for 4.2 million deaths worldwide annually (Cohen et al. 2017). Past exposures to fine particulate matter with aerodynamic diameter $\leq$2.5 μm ($PM_{2.5}$) and other criteria air pollutants are recognized to increase the risk of cardiorespiratory disease (Brook et al. 2010; Hoek et al. 2013) and possibly diabetes (Yang et al. 2020). Air pollution is considered by the World Health Organization to be a human carcinogen (IARC 2016). Although both chronic and acute exposures to air pollution adversely affect human health, exposures that have occurred in the more distant past appear to have larger harmful impacts (Pope 2007).

Several biologically plausible pathways have been proposed to explain the apparent associations between incidence or mortality from COVID-19 with past or current exposure to air pollution (Conticini et al. 2020; Dutheil et al. 2020; Martelletti and Martelletti 2020). Chronic exposure to air pollution may increase the risk of severe sequelae by increasing the prevalence of diabetes, atherosclerosis, and other comorbid conditions associated with higher mortality in patients infected with COVID-19 (Yan et al. 2020; Zhou et al. 2020). Exposure to air pollution may also influence immune responses (Tsai et al. 2019) and alter host immunity to respiratory infections (Ciencewicki and Jaspers 2007). Findings from time series and case-crossover studies indicate that short-term fluctuations in air pollution may be relevant, and people with existing health conditions are more vulnerable. For example, individuals with underlying chronic health conditions such as diabetes and cardiorespiratory conditions were at greater risk of death or hospitalization for stroke with daily increases in air pollution (Goldberg et al. 2013; Villeneuve et al. 2012). It has also been suggested that increased concentrations of $PM_{2.5}$ increase the rate of COVID-19 transmission by facilitating virus survival and transport over larger distances (Martelletti and Martelletti 2020).

The possibility that air pollution may increase the severity of COVID-19 infections has substantial public health implications and has attracted considerable media and political attention. However, accurately estimating the effects of air pollution on COVID-19 while the pandemic is still underway poses a number of challenges. To highlight these challenges, we conducted a review of research related to ambient air pollution and incidence and mortality due to COVID-19 and the original SARS virus outbreak in 2003 (WHO 2020). Our primary goals were to identify the strengths and limitations of these studies

Address correspondence to Paul Villeneuve, School of Mathematics and Statistics Carleton University, Herzberg Building, Room 5413, Ottawa, ON, Canada K1S 5B6. Telephone: (613) 520-2600. Email: Paul.Villeneuve@carleton.ca

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and provide recommendations for the design and implementation of future epidemiological studies of the effects of air pollution on the severity of communicable respiratory diseases and resulting mortality.

Methods

We sought to identify research articles relevant to the hypothesis that exposure to ambient air pollution affects the risk of developing COVID-19 or SARS or the hypothesis that ambient pollution worsens the prognosis of individuals with these conditions. For peer-reviewed publications, we searched the OVID and PUBMED databases through 10 May 2020 using the search terms: {Coronavirus Infections/ep, et, mo, pa [Epidemiology, Etiology, Mortality, Pathology]; OR COVID-19.m_titl; OR SARS-CoV-2.m_titl} and {air pollution.mp. or Air Pollution/} and {SARS Virus/or Severe Acute Respiratory Syndrome/OR sars.m_titl} and {air pollution.mp. or Air Pollution/}. We also used Google Scholar to search for other papers using the search strategy "coronavirus and air pollution" or "COVID-19 and air pollution" and "SARS and air pollution." We also searched through the reference lists of the papers retrieved.

Because of the media attention given to some nonpeer reviewed papers and in the hope that these studies may provide insights on methods, but not necessarily on results, we included a selected number of nonpeer reviewed papers. We did not conduct a systematic search of the Internet for these papers, and we did not search preprint servers but relied on media reports and private communications with individuals.

As of 10 May 2020, our search of OVID, PubMed, and Google Scholar retrieved 53 peer-reviewed publications concerning SARS and COVID-19. Of these, we selected only those studies that presented some form of statistical analysis relevant to the hypothesis. We excluded published studies that discussed only the hypothesis (Conticini et al. 2020; Dutheil et al. 2020; Martelletti and Martelletti 2020) and papers that had no bearing on the research question, which included, for example, control strategies (Chen et al. 2006), travel (WHO 2005), and perspectives of physicians (Misra et al. 2020; Gori et al. 2020).

For SARS, we found three peer-reviewed papers (Cai et al. 2007; Cui et al. 2003; Kan et al. 2005) that were eligible for the present review of methods. The design of these studies was an ecological study of case–fatality rates (Cui et al. 2003), a time series study of mortality (Kan et al. 2005), and a cohort study of secondary attack rates of index cases (Cai et al. 2007).

For COVID-19, only one published study (ecological design) met the eligibility criteria for this analysis (Ogen 2020), but just after our initial submission of the present paper, on 11 May 2020, we found a published time series study (Zhu et al. 2020).

As of 29 April 2020, we identified four nonpeer reviewed ecological studies of air pollution and COVID-19 infections or mortality that, as of 10 May 2020, had not been published in peer-reviewed journals. Three were posted on the medRxiv preprint server: Wu et al. (2020) (United States, including the originally posted version from 7 April 2020, and an updated version posted 27 April 2020), Travaglio et al. (2020a) (Italy, version 2 posted 20 April 2020 used herein), and Yao et al. (2020) (China, posted 10 April 2020). The fourth nonpeer reviewed study (Andrée 2020) was a policy working paper published by the World Bank (data from the Netherlands, posted in April 2020).

We provide below a brief review of each study but focus on their strengths and limitations. We also abstracted from each study details on the study design, location, time period, methods used to characterize exposure and health outcomes, and covariables (Tables 1 and 2). A listing of the strengths and weaknesses of each of these studies is provided in Table 3.

Table 1. Summary of peer-reviewed studies estimating associations between exposures to ambient air pollution and incidence or mortality from SARS.

Study	Design	Location	Unit of observation	Health outcome and time period	Air pollution metric and time period	Method of analysis	Covariables	Notes
Cui et al. 2003	Ecological	Guangdong, Shanxi, Hebei, Beijing, and Tianjin City	City	Case-fatality ratio: April–May 2003	API[a]: April–May 2003, June 2000–October 2002	Linear regression and analysis of proportions	None	
Kan et al. 2005	Time series	Beijing	Day	Daily SARS mortality: 25 April–31 May 2003	5 d moving average PM_{10}, SO_2 and NO_2 from 12 fixed-site monitoring stations: 25 April–31 May 2003	Poisson time series model of counts using Generalized Additive Models	Daily mean temperature, relative humidity, dew point, time trends (smoothing splines), day-of-week	Short time-period; few deaths/d (avg. 3.8); possible concurvity and convergence issues; unclear how trends in SARS mortality over 37 d were accounted for in the model
Cai et al. 2007	Secondary attack rates[b]	22 provinces	Individuals	Incidence rates among those who had contact with 350 primary cases diagnosed 1 January–31 May 2003	Province-level maximum API.[a] Time period: not stated	Logistic regression	Daily average temperature, relative humidity, air pressure, wind velocity, daily hours of sunshine; area (Hebei Province or Inner Mongolia); time of onset	Limited information on exposure assessment methods

Note: API, Chinese air pollution index; avg, average.
[a]Derived from the concentrations of particulate matter, sulfur dioxide, nitrogen dioxide, carbon monoxide, and ground-level ozone.
[b]Secondary attack rates derived from the follow-up of close contacts of individuals diagnosed with probable SARS.

Table 2. Summary of peer-reviewed and unpublished studies estimating associations between exposures to ambient air pollution and incidence or mortality from COVID-19.

Study	Design	Location	Unit of observation	Health outcome and time period	Air pollution metric and time period	Method of analysis	Covariables	Notes
Peer-reviewed								
Ogen 2020	Ecological	Italy, Spain, France, Germany	Administrative region ($n=66$)	Reported COVID-19 deaths up to 19 March 2020	Tropospheric NO_2 concentration[a]: Jan–Feb 2020	Scatterplot of deaths by NO_2 concentration	None	High spatial resolution exposure
Zhu et al. 2020	Time series	People's Republic of China	City ($n=120$) (excluding Wuhan)	Confirmed COVID-19 cases: 23 Jan–29 Feb 2020	Daily average $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 concentrations	GAMs (gaussian distribution), log (case counts), moving avg. air pollution concentrations (lags of 0–7, 0–14, 0–21 d)	Daily mean temperature, relative humidity, air pressure, wind speed, time trends	Normal vs. Poisson models; short time-period; final model covariates unspecified
Unpublished								
Travaglio et al. 2020a (posted 16 April 2020)	Ecological	England	Region ($n=7$)	Reported COVID-19 cases (>2,000) and deaths (>200): through 8 April 2020	Avg. NO_2, NO, O_3 concentrations (2018–2019) and AQI from fixed-site monitoring stations	Correlation coefficients	None	
Yao et al. 2020 (posted 10 April 2020)	Ecological	People's Republic of China	City ($n=49$) including Wuhan	Case fatality rates through 22 March 2020	Daily mean concentration of $PM_{2.5}$ and PM_{10} from fixed-site monitoring stations	Slope and associated chi-square statistic derived by modeling death rate versus city wide mean exposure adjusted for meteorology, hospital beds and population size	Number of hospital beds and population size (at province level). Daily temperature and relative humidity	
Andrée 2020 (posted 3 May 2020)	Ecological	Netherlands	Municipalities ($n=355$)	Reported incidence up to 22 March 2020	Annual average $PM_{2.5}$ 2017 derived from spatial interpolation of fixed site monitors; Remote sensing estimates of $PM_{2.5}$ derived using data collected between 1998 and 2014	Multiple linear regression	Population density, gender, age groups, marital status, household composition, the share of migrants, as several other population health indicators	
Wu et al. 2020 (posted 7 April 2020)	Ecological	United States	Counties (of 3,080 counties 1,783 with covariable data were used in main analyses)	Reported deaths until 4 April 2020	Average concentrations of $PM_{2.5}$ at a county level 2000–2016 from prediction models	Zero-inflated Poisson models	Contextual variables: population density, percent of the population ≥65, percent living in poverty, median household income, percent black, percent Hispanic, percent of the adult population with less than a high school education, median house value, percent of owner-occupied housing, population mean BMI (an indicator of obesity), percent ever-smokers, number of hospital beds, and the average daily temperature and relative humidity for summer (June–September) and winter (December–February, number of individuals tested for COVID-19.	
Wu et al. 2020 (posted 27 April 2020)	Ecological	United States	Counties (3,079)	Reported deaths until 22 April 2020	Average concentrations of $PM_{2.5}$ at a county level 2000–2016 from prediction models	Negative binomial, mixed models	Same as above but added the timing of social distancing policies, date of first COVID-19 case, and population age distribution	

Note: Avg., average.
[a]Tropospheric NO_2 concentration (surface up to ~10 km) based on Sentinel-5 Precursor space-borne satellite data (spatial resolution 5.5 km^2).

Table 3. Summary of principal strengths and weaknesses of studies estimating associations between exposures to ambient air pollution and incidence or mortality from SARS or COVID-19.

	Strengths	Weaknesses
SARS studies		
Cui et al. 2003	Population-based Case-fatality rates	Ecological study design[a] Exposure index: API No adjustment for potential confounding factors
Kan et al. 2005	Average daily concentrations of pollutants from 12 fixed-site monitoring stations Generalized additive models Accounted for time trends and weather	Short-time period to assess trends Few deaths per day (average of 3.8) Possible concurvity and convergence issues with this version of the models
Cai et al. 2007	Individual data for index cases and contacts Incidence of SARS for contacts Adjusted for weather, area, and time of onset	Exposure index: API and not clear how computed
COVID-19 studies		
Ogen 2020	Population-based Adequate spatial resolution of air pollutants	Ecological study design[a] No statistical analyses
Travaglio et al. 2020a	National-level analyses of administrative data from Public Health England (incidence) and UK National Health System (mortality)	Ecological study design[a] Underestimates of incident infections and deaths attributed to COVID-19 No statistical analyses other than correlation coefficients
Yao et al. 2020	Mortality from COVID-19	Underestimates of incident infections and deaths attributed to COVID-19 Exposure period not stated No statistical analyses other than correlation coefficients
Andrée 2020	Spatially interpolated measures of $PM_{2.5}$ Adjustment for many area-wide variables	Ecological study design[a] Multiple linear regression of rates
Zhu et al. 2020	Generalized additive models Average daily concentrations of pollutants Accounted for time trends and weather	Normal instead of Poisson errors in the statistical models Short-time period to assess trends Unclear what the final models were (e.g., how the weather variables were included in the final models)
Wu et al. 2020 (posted 5 April 2020)	Large sample size Adjustment for a range of contextual variables	Ecological study design[a] Underascertainment of mortality Counties as the unit of observation Air pollution data only available through 2016 Regional differences related to timing on pandemic curve and protective measures not accounted for
Wu et al. 2020 (posted 27 April 2020)	National-level analyses with large sample size Adjustment for a range of contextual variables Consideration of contextual variables related to physical distancing	Same as above

Note: API, Chinese Air Pollution Index.
[a]All studies of COVID-19 are prone to biases related to the undercounting of COVID-19 incident cases, and deaths as well as the potential biases listed in the "Discussion" section.

Results

Air Pollution and SARS

Cui et al. (2003) conducted an ecological study to determine the association between air pollution and case–fatality rates from SARS (reported deaths/probable cases) in five regions in China with 100 or more cases. Deaths and incident cases were extracted from a publicly available source (Chinese Center for Disease Control and Prevention). The maximum Air Pollution Index (API; Chinese National Environmental Protection Agency), which combined concentrations of inhalable particles with aerodynamic diameter of $\leq$10 μm (PM_{10}), SO_2, NO_2, CO, and ozone for each of the five areas, was used. A summary measure of the API was derived for the two time periods April–May 2003 and June 2000–October 2002. The former period was considered representative of "short-term" exposures and corresponded to the time when the majority of cases were diagnosed. In contrast, the latter period was used to represent "longer-term," average exposure. A total of 349 deaths were reported among 5,327 probable SARS cases in the five study regions. Ordinary linear regression was used to estimate the slope of the linear relationship between the case–fatality percentages for SARS and the API across the five cities, with a slope of 0.001 (no measure of precision was provided) per unit increase in the API. Categorizing the API into three categories (>100, 75–100, <75) yielded for the two highest categories (relative to the lowest) a rate ratio of 2.18 [95% confidence interval (CI): 1.31, 3.65] and 1.84 (95% CI: 1.41, 2.40), respectively, for API during April–May 2003, whereas the corresponding ratios for average API during June 2000–October 2002 were 1.71 (95% CI: 1.34, 3.33) and 2.26 (95% CI: 1.53, 3.35). The authors acknowledged that they did not account for potential confounding factors such as age, sex, sociodemographic status, or regional differences in the quality of care.

Kan et al. (2005) employed a time series analysis, using generalized additive models (GAMs; Hastie and Tibshirani 1993), to determine whether daily fluctuations in ambient concentrations of PM_{10}, SO_2, and NO_2 in Beijing were associated with daily mortality from SARS from 25 April to 31 May 2003 (37 d). The authors indicated that they adjusted for trends for day of observation using splines as well as including a term for day-of-the-week. The authors reported an average of 3.8 SARS deaths per day over a span of 37 d (141 deaths, total). Daily mean ambient pollution concentrations (averaged over 12 fixed-site monitoring

stations) were: 149.1 $\mu g/m^3$ for PM_{10}; 60 $\mu g/m^3$ for NO_2; and 37 $\mu g/m^3$ for SO_2. The authors estimated associations with a variety of exposures lagged from 0 to 5 d using log-linear models adjusted for day of the week, daily temperature, dew point, and relative humidity. Relative increases of SARS mortality counts with a 10-$\mu g/m^3$ increase in the 5 d moving average of PM_{10}, SO_2, and NO_2 were 1.06 (95% CI: 1.00, 1.12), 0.74 (95% CI: 0.48, 1.13), and 1.22 (95% CI: 1.01, 1.48), respectively.

A novel cohort design was used to investigate secondary attack rates among individuals who were in contact with 350 probable index cases diagnosed in China between 1 January and 31 May 2003 (Cai et al. 2007). This study identified health outcomes by using individual-level data and relied on area-wide measures of weather and air pollution. The study first identified 365 probable SARS cases in mainland China. Close contacts were identified using individual-level survey databases of these cases and other contacts of these cases, SARS transmission chains in affected areas, and hospital records. Telephone interviews were used to confirm histories of the close contacts. This process resulted in the identification of 6,727 close contacts for the time periods when the corresponding probable case exhibited symptoms but had not yet been admitted to hospital. Of these close contacts, 135 (2%) were later diagnosed with probable SARS by 31 May 2003. For the primary cases, daily average values for weather and the API for the period between the onset of symptoms and hospital admission were modeled. Logistic regression was used to estimate the associations between the frequency of secondary attacks and these weather and air pollution measures. The API was based on individual maximal pollution index—this was typically particulate matter. The authors considered several daily average weather variables, including temperature, relative humidity, air pressure, wind velocity, and hours of sunshine. The models incorporated both the weather and air pollutant covariables and a binary variable to denote whether the onset date for the primary case was before or after 21 April 2003. This date corresponded to when major intervention measures to control the epidemic were enacted. The multivariable models included terms for the weather variables (described above) and the API. For a unit increase in the API (Mean $\pm$ SD $= 87.9 \pm 25.3$, range from 34.3 to 260.3), the unadjusted odds ratio (OR) was 0.99 (95% CI: 0.85, 1.17), and the adjusted OR was 0.88 (95% CI: 0.76, 1.02). Stronger associations were observed with weather variables including daily average temperature, air pressure and relative humidity.

Air Pollution and COVID-19

An ecological study was undertaken with the objective to determine whether average exposure to NO_2 was associated with mortality (Ogen 2020). The study included 4,443 deaths attributed to COVID-19 as of 19 March 2020 in 66 administrative regions in Europe (Italy, Spain, France, and Germany) in relation to tropospheric concentrations of NO_2 derived from the Sentinel-5 Precursor satellite (spatial resolution of 5.5 km). These concentrations were averaged over a 2-month period (January–February 2020) before the COVID-19 outbreak in Europe. Ogen showed scatterplots of counts of death against concentrations of NO_2 for these 66 data points, and these plots showed an increase in the number of deaths with increasing concentrations of NO_2, but no quantitative measure of association was provided.

In a nonpeer reviewed paper, Travaglio et al. (2020a) estimated for seven regions of England the correlation between presumed mortality from COVID-19, until April 8, 2020. Their aim was to investigate associations between annual ambient concentrations of air pollution in 2018 and rates of infection and mortality from COVID-19. Data for the daily number of infections for each region were obtained from Public Health England. Similarly, the number of deaths were extracted from national health data and included the number of deaths of patients who died in hospitals who tested positive for COVID-19. The analyses excluded deaths that did not occur in hospitals. Exposure comprised annual average concentrations of NO_2, NO, and ozone, and the English AQI measured at 120 fixed-site monitoring stations during the period 2018–2019. The analysis comprised estimating Spearman's and Pearson's correlation coefficients between pollutants and mortality from COVID-19, and these statistics ranged from 0.32 to 0.67. Plots of average concentrations of air pollution against the total number of COVID-19 deaths across the regions were also presented.

A preprint by Yao et al. (2020) presented a cross-sectional analysis of ecological data to determine whether city-specific measures of $PM_{2.5}$ and PM_{10} were associated with death rates of COVID-19. They estimated spatial correlations in 49 Chinese cities between case–fatality rates of COVID-19 and concentrations of $PM_{2.5}$ and PM_{10} on the day of death (time period not specified). Sixteen of these cities were inside the province of Hubei, including Wuhan, the apparent origin of the pandemic, and the remaining 33 cities that were outside of Hubei. They also obtained per capita gross domestic product (GDP), number of hospital beds, and population size for each province, and it appears that values of these were assigned to each city. The results for $PM_{2.5}$ and PM_{10} were presented as scatterplots, and two ordinary linear regression lines were shown for cities inside and outside Hubei. For $PM_{2.5}$, the correlation coefficient with case-fatality rates of COVID-19, adjusted for temperature, relative humidity, GDP per capita, and hospital beds per capita; for cities outside Hubei was 0.56 and for cities inside of Hubei, excluding Wuhan, it was 0.33.

In another posted study by the World Bank Group, Andrée conducted an ecological analysis of incident COVID-19 cases against annual average concentrations of $PM_{2.5}$ across 355 municipalities in the Netherlands (Andrée 2020). The analyses comprised 4,004 confirmed cases of COVID-19 until 22 March 2020 for which residential addresses were available. For the main analyses, annual spatially interpolated measurements of $PM_{2.5}$ for 2017 at a 25-m grid were derived from fixed-site monitors. Andrée (2020) also modeled a remote sensing measure of $PM_{2.5}$ derived using data between 1998 and 2014 at a 10×10 km resolution. Adjustment was made for a number of area-wide variables (Table 1). Multiple linear regression using a gaussian error term was used to model COVID-19 cases (per 100,000) and, depending on the covariables included, an increase of 1 $\mu g/m^3$ of $PM_{2.5}$ increased the number of cases by between 3.5 and 10.2 cases per 100,000.

A published time series study by Zhu et al. (2020) made use of daily confirmed cases of COVID-19 in 120 cities in China after the lockdown started (observation period of 23 January to 29 February 2020). The objective of their study was to estimate associations between 1-, 2-, and 3-wk measurements of ambient pollution and confirmed incident cases of COVID-19. Using another GAM framework (Wood 2006), the authors regressed logarithmically transformed daily counts of cases (average of 12 deaths per day) against daily mean concentrations that were used to create $PM_{2.5}$, PM_{10}, SO_2, CO, NO_2, and O_3 metrics for 0–7, 0–14, and 0–21 d before death. They also adjusted for mean temperature, relative humidity, air pressure, and wind speed. Count data usually require Poisson or quasi-likelihood models, and often distributed lag nonlinear models are used (Gasparrini et al. 2012), but the authors used a gaussian error term instead. All of the covariables were modeled as thin plate splines [maximum of 3 degrees of freedom (df)]. Usually a filter is applied to remove any long-term trends in the outcome as well as including day-of-the-week effects (Goldberg et al. 2003), but in this study only a categorical variable was included for day of study and a first order autoregressive term. Their models also included a fixed-effect term to capture variability by city. The

pollutants were modeled as linear terms. The main results across the 120 cities were as follows: for a mean 10 $\mu g/m^3$ increase across lags of 0–14 d, the percent change in the number of counts were: $PM_{2.5}$, 2.24% (95% CI: 1.02, 3.46); PM_{10}, 1.76% (95% CI: 0.89, 2.63); NO_2, 6.94% (95% CI: 2.38, 11.51); O_3, 4.76% (95% CI: 1.99, 7.52); and SO_2, −7.79% (95% CI: −14.57 to −1.01).

The research that appears to have generated the most attention in the media during the COVID-19 pandemic is an unpublished ecological study that considered as the unit of observation data from a total of 3,080 counties in the United States (Wu et al. 2020). We found two versions of this manuscript online that used slightly different methods (Table 1), and in our view, it is important to provide details on both versions, given that the original analyses generated considerable media attention, and the latter version provided a lower risk estimate. The aim of the study was to investigate whether chronic exposure to ambient pollution, over 17 y, was associated with increased risk of COVID-19 mortality. Deaths from COVID-19 were obtained from the Johns Hopkins University Center for Systems Science and Engineering Coronavirus Resource (Xu and Kraemer 2020). The first report comprised mortality data up to 4 April 2020, and the second incorporated additional data until 22 April 2020. Reported counts of deaths from COVID-19 and total estimates of the population for each county were used. The summary county data provided only aggregated COVID-19 death data and therefore did not allow for these deaths to be tabulated by age group, sex, race, or other sociodemographic characteristics. In the first report, concentrations of $PM_{2.5}$ were derived for the period from 2000 to 2016 using an exposure prediction model that conjoins satellite, modeled, and monitored and has a resolution of about $0.01^\circ \times 0.01^\circ$ (van Donkelaar et al. 2019). These values were combined to represent county-level averages. County-specific rates of mortality attributed to COVID-19 were regressed against average county-specific concentrations of $PM_{2.5}$ using a zero-inflated Poisson model with a random effect for state. Adjustments included 16 county-level variables and the number of COVID-19 tests performed in each state (Table 1). In the first version of the paper, a number of counties were excluded because they lacked covariable data or had a small number of identified COVID-19 deaths. Specifically, the main analyses derived risk estimates using 1,783 counties, which represented 90% of all COVID-19 deaths identified in the United States as of 4 April 2020. The authors reported that for an increase of 1 $\mu g/m^3$ of $PM_{2.5}$, the rate ratio for COVID-19 mortality was 1.15 (95% CI: 1.05, 1.25).

An updated version of this paper was posted online on 27 April 2020. These analyses differed in several ways from the earlier version. First, the more recent preprint incorporated additional deaths that occurred up to 22 April 2020. A number of new county-level risk factors were included: days since the first COVID-19 case and days since the issuance of stay-at-home orders. Some minor changes to other county-level factors were made, which included capturing the percentage of the population between the ages of 45–64 and 15–44 and the percent who were obese [from mean body mass index (BMI) used in original analysis]. The authors used a negative binomial mixed model instead of a zero-inflated one. There were 3,087 counties from which data were drawn from. The updated rate ratio for COVID-19 mortality in relation to 1 $\mu g/m^3$ increase of $PM_{2.5}$ was 1.08 (95% CI: 1.02, 1.15). The authors also pursued a large number of sensitivity analyses and estimated the minimum magnitude of the association between an unmeasured confounding variable and the outcome and exposure that could entirely explain the observed association (*E*-value). The *E*-value was estimated to be 1.37, and the authors used this value to suggest that it was unlikely that the findings could be explained by unmeasured confounding.

Discussion

Our systematic review identified nine epidemiological studies, and all but one paper reported positive associations between ambient air pollution and the incidence or mortality from SARS or COVID-19. This series of papers included several unpublished studies. We acknowledge that these studies may change in important ways as they proceed through the review process, as already demonstrated by the more recent analyses of Travaglio et al. (2020b) and Wu et al. (2020), although there is no guarantee that they will all be published. That said, there are common design features of these studies that are important to consider. This section discusses the various sources of bias and their possible impacts on findings obtained from different study designs. We have structured our discussion to address critical features that should be considered in epidemiological research that investigates how air pollution is associated with COVID-19–related health outcomes, and then we will discuss specific types of epidemiological designs.

Specification of the Target Population

Most of the studies implicitly defined the target population to include the population of an entire region or country, but their methods may not adequately capture relevant data for all segments of the population who may be more vulnerable and who account for a large portion of COVID-19 deaths. For example, the target population for the Wu et al. (2020) paper was that of the entire continental United States, but many of the county-level adjustment factors were drawn from the Behavioral Risk Factor Survey that excluded institutionalized residents. For COVID-19, this is relevant because a large number of deaths are likely to occur in institutionalized settings, and the risk factor profile of these individuals would differ from those not in institutions.

Even though many of the studies were designed to have broad target populations, misclassification and underreporting may make them nonrepresentative. For example, it is likely that a large percentage of COVID-19 deaths in the United States, especially in nursing homes, may not have been counted (Perls 2020). The same concern likely applies to other countries; for example, in Canada, as of 6 May 2020, 82% of all deaths occurred in long-term care homes for the elderly (MacCharles 2020). Media reports have suggested that the corresponding estimates in the United States are ∼40% (Coletta 2020) and that 99,000 deaths occurred as result of individuals contracting the disease in American jails (Pilkington 2020). On 16 June 2020, it was reported that the five largest clusters of COVID-19 cases in the United States were in correctional institutions (Williams et al. 2020). Although it is valid to define a target population that excludes institutionalized individuals, this will not assist in understanding the true impact of a pandemic.

Incidence and Mortality of SARS and COVID-19

With a novel infectious disease, there will be challenges with its diagnosis (Arons et al. 2020; Li et al. 2020) and with the certification of underlying causes of death, both these challenges will lead to underascertainment of incidence and mortality. Especially for COVID-19, during the first month in which cases were identified, most countries lacked adequate testing and many jurisdictions were overwhelmed to treat COVID-19 patients; therefore, many cases and deaths that should have been attributed to COVID-19 were not identified (Arons et al. 2020; Li et al. 2020). There have also been concerns about the sensitivity and specificity of tests initially used to identify people with coronaviruses, and the performance of these tests with respect to detection methods and automation procedures has improved over time (Carter

et al. 2020). Furthermore, cases and deaths tended to cluster in individuals with other underlying health conditions, in the elderly or in noncommunity settings (e.g., long-term care homes, prisons, and meat-packing plants), where testing may not have been generally available. People with other preexisting health conditions would be more likely to have had their COVID-19 deaths misclassified. The extent of undercounting of COVID-19 deaths is not trivial; for example, in New York State underestimation of deaths could be as high as 22% (New York City Department of Health Mental Hygiene (DOHMH) COVID-19 Response Team 2020). Ascertainment of COVID-19 deaths in long-term care facilities is also incomplete in most jurisdictions, including the United States, where only 33 states reported nursing home–related deaths (Glenza 2020). A recent investigation by some U.S. senators found that in assisted care facilities there was a widespread lack of routine testing and reporting of COVID-19 cases and fatalities (Warren 2020).

It is our view that errors in case ascertainment and coding for causes of death from COVID-19 are significant. Misclassification of COVID-19 cases is likely related to levels of air pollution because the ability to accurately determine these health outcomes requires having sufficient resources to carry out testing and contact tracing and the poorest areas of countries usually have fewer resources. An inherent bias can occur in studies of air pollution and COVID-19 because those poorer areas also tend to experience higher pollution levels (Clark et al. 2014; Hajat et al. 2015). This tendency could attenuate a true positive association, but many uncertainties in case ascertainment occur, especially at small regional levels, and the resulting bias in the association between air pollution and COVID-19 deaths could either be toward or away from the null.

It is also important to account for the possibility that the degree of undercounting may change over time, as well as corrections to cause-of-death data (Rowe 2020). These delays in undercounting can extend for some time as suggested by recent reports that the coding of underlying cause of death data is several weeks or months behind in many regions of the United States (Katz et al. 2020). For all these reasons, at a national level, even in developed countries, it may take years before corrected data are available for analysis. Also, as noted by Cai et al. (2007), there may be difficulties in the accurate reporting of case information, and these difficulties could result in errors of assigning the correct date of death. For time series studies, those errors could be an important source of bias.

Timing on the Pandemic Curve

There are regional differences, particularly in larger countries, regarding where cities lie along the pandemic curve. In the United States, especially in early April 2020, counties were at different stages on the epidemic curves. Unfortunately, as of July 2020 the decisions by some U.S. states, such as Florida and Arizona, to abandon protective health measures in favor of reopening businesses have led to more recent surges in COVID-19 cases. Larger, more populous cities tend to have more people traveling to and from international locations, which results in increased opportunities for the spread of COVID-19, but such cities also tend to have higher concentrations of air pollution (U.S. EPA 2020). The practical implications are that there will be a greater number of identified incident cases and deaths in those cities that are further along the epidemic curve, and contrasting regions that have different time patterns in mortality rates will lead to bias that would be away from the null. Researchers must therefore control for where each city is on this curve or capture all COVID-19 deaths. It is unlikely that any of the studies on COVID-19 were able to accomplish this. To complicate matters further, the experience of the 1918 influenza epidemic suggests that the pandemic curve may be multimodal and involve several peaks and valleys (Ansart et al. 2009), thus suggesting analyses of air pollution and any novel coronavirus can be addressed only after the pandemic is over.

Physical Distancing and Other Public Health Interventions

A recent systematic review and meta-analysis provides evidence that the use of physical distancing, face masks, and eye protection greatly reduces the spread of COVID-19 in health care and community settings (Chu et al. 2020). The implementations of policies that encourage physical distancing, which vary by jurisdiction, have been shown to be successful in flattening the epidemic curve. As of 1 August 2020, New Zealand was at the forefront of countries in essentially eliminating infection (Baggaley 2020). In contrast, in March 2020 in the state of Georgia, areas that did not adopt physical distancing practices experienced higher incidence and mortality from COVID-19 when compared with other areas in the state that did (Bethea 2020). Cities in California that tend to have higher levels of fine particulate matter first adopted stay-in-place policies earlier (20 March 2020) than other regions (Karimi 2020). Because these policies differed by regional air pollution levels, including rural and urban areas, they can distort associations between air pollution and COVID-19 mortality, and these differences must be taken into account in the analyses. It is also important to note that the implementation of physical distancing practices and work restrictions may directly contribute to lower pollution levels through decreased reliance on vehicular and public transportation. A major difference between the two versions of the paper by Wu et al. (2020) was that the more recent version of the paper also adjusted for the time since each state issued a stay-at-home order and the time since the beginning of the outbreak. The consideration of these two ecological measures and additional deaths identified with just another 18 d of follow-up, and possibly use of the negative binomial instead of a zero-inflated Poisson model, may have resulted in a reduced estimate of excess mortality attributable to $PM_{2.5}$ from 15% to 8% (per increase of 1 $\mu g/m^3$).

Spatiotemporal Assignment of Air Pollution

Many of the studies relied on concentrations of air pollution that spanned large geographical areas, thus leading to misclassified estimates. For example, in the ecological study by Ogen (2020) averaged, highly resolved (5.5×5.5 km) estimates of NO_2 were used to derive a singular exposure measure for each of 66 large, heterogeneous administrative regions in four large European countries. Counties in the United States are also heterogeneous, being highly irregular in area, population, and other characteristics. In the paper by Wu et al. (2020), air pollution was assigned at a county level. To illustrate the heterogeneity in U.S. counties, Cook County, which includes the city of Chicago, is the second-most-populous county in the United States, with a population of approximately 5.1 million in 2019 and a land area of 1,635 square miles (U.S. Census Bureau 2020). In contrast, Mississippi, one of the poorest states, has 82 counties. One such county, Adams County, is only 462 square miles and had a population of 30,693 in 2019 (U.S. Census Bureau 2020), which is similar to other counties in that state. Because a single air pollution value was assigned to each county in the United States calculated over a 17-y period, potentially relevant differences in exposure across space and time were not captured, especially in larger, more populous counties; this exposure measurement error may be an important source of bias. Similarly, in the time series studies of mortality, misclassification of underlying causes of death and the date of death is a concern, and these may be magnified for COVID-19.

Specifying the relevant time period for assigning exposure is also essential. The studies undertaken to date used a variety of exposure definitions that cover varying time periods before diagnosis or death (Table 1). For epidemiological studies of chronic exposure to air pollution, ecological-level measures of pollution are employed to rank areas according to some estimate of "chronic" concentrations. The subsequent analyses often assume that the rank ordering remains constant in time. An understanding of the relevant etiological exposure period is important to reduce exposure measurement error. Methodological approaches such as the distributed lag models (Gasparrini et al. 2012) can offer insights.

Clustering of Cases and Deaths

Unlike studies of past exposure to air pollution and chronic disease where deaths can reasonably be assumed to be independent, COVID-19 cases and deaths occur in clusters (Cha 2020; Dyal et al. 2020; Hamner et al. 2020; McMichael et al. 2020; Park et al. 2020). Events occur together in high-risk groups, such as in retirement residences and certain occupational settings. For example, in South Dakota, half of the state's identified COVID-19 cases come from the Smithfield pork-processing plant (Wiener-Bronner 2020). Statistical approaches used to characterize the association between air pollution and infectious diseases must account for these strong correlations in the data.

Spatiotemporal Variations in the Strains of COVID-19

Disentangling possible associations between exposure to ambient air pollution and COVID-19 might be complicated by regional variations in the genetic variants or by mutations of the virus that occur over time that could change its virulence. Given that the pandemic only began in early 2020, the manner in which COVID-19 mutates is not yet well understood. Analyses of global tracking data have shown that the prevalence of the D614G genome mutation variant of COVID-19 has risen over time, and the increased viral load associated with this type may increase the transmissibility of the virus (Korber et al. 2020). To the extent that strains of COVID-19 vary geographically and by disease severity, these variations in strains could introduce bias in studies of air pollution and COVID-19 transmission and mortality.

Other Determinants of COVID-19 Mortality

In most ecological studies, adjustment for individual risk factors is not possible. In the study by Wu et al. (2020), for example, deaths were not classified by age, sex, or race. Gender-based differences in time-activity pattern contribute to different levels of exposure for men and women, and women may be more susceptible to the adverse health effects from air pollution (Bell et al. 2015; Colais et al. 2012). Although ecological studies can incorporate regional measures of some of these risk factors, such as using percent of the population older than 65 years of age, these types of adjustments often perform poorly (Greenland and Robins 1994; Morgenstern 1995; Wakefield 2008). Occupation is also a seemingly overlooked risk factor because those who provide medical care and other essential workers, including people who work in food processing, have increased risks of developing and, by extension, dying from COVID-19.

In the United States, it is also important to recognize that disadvantaged people (e.g., lacking health insurance, living undernourished, having underlying and not well-managed health conditions, such as cardiovascular conditions and/or diabetes) have a greater susceptibility for both contracting and dying from COVID-19. This aspect was pointed out by Yancy (2020), who indicated that myriad social and economic reasons led to high rates of infection and put individuals at higher risk from adverse health outcomes of COVID-19 (Yancy 2020). As well, Chowkwanyun and Reed (2020) indicated that disparities in COVID-19-related health effects need to be assessed after accounting for deprivation, especially race and socioeconomic conditions. We contend that all these factors (e.g., occupation, race, socioeconomic status, availability of health insurance) need to be carefully considered when estimating associations between air pollution and incidence and mortality of COVID-19. Misclassification of exposure and outcomes likely vary across these factors, and moreover, they may either confound or be effect modifiers of associations between air pollution and COVID-19 incidence, survival, or mortality.

The etiology of COVID-19 remains poorly understood, and other risk factors may be identified going forward. Such risk factors may also be related to pollution levels, and therefore, there is the potential for residual confounding in any studies published before that time. For example, recent work suggest that previous vaccinations may confer a reduced risk of becoming infected with COVID-19 (Sette and Crotty 2020).

It is possible that additional stratified analyses of ecological data could be conducted to shed light on some of these factors. For example, death certificates will have age, gender, and often race or ethnicity, so that even in an ecologic study, stratum-specific estimates of risk could be determined. However, it is likely that underascertainment of COVID-19 cases and mortality varies across race and socioeconomic conditions because testing is differentially available. Regardless, it is our view that it is not possible using these heterogeneous geographical units to overcome the influences arising from heterogeneity in terms of areas of deprivation and affluence within regions.

Statistical Methodology

The studies by Andrée (2020), Cui et al. (2003), Ogen (2020), Travaglio et al. (2020a), Yao et al. (2020), and Zhu et al. (2020) did not follow generally accepted methods of epidemiological analysis, and it is our view that their estimates of association are not valid. In particular, the studies by Andrée (2020), Cui et al. (2003), Travaglio et al. (2020a), Yao et al. (2020), and Zhu et al. (2020) used regression models with normally distributed errors that are typically inappropriate for count data. Although the normal distribution can be used to provide a reasonable approximation of count data when there is a large number of counts, many of these studies relied on small numbers of cases within the regional areas that were studied. Moreover, when modeling rates, overdispersion needs to be accounted for using for example quasi-likelihood Poisson models, negative binomial, or zero-inflation models, with population size included as an offset variable. Not using these methods may result in overstating precision. Nonlinearity and lags in response functions can also be assessed, such as using distributed lag nonlinear models (Gasparrini et al. 2012; Imai et al. 2015).

Study Designs

In addition to the generic issues related to these pandemics, we describe additional points for the specific types of studies below. These designs each have inherent possible biases that need to be considered when interpreting findings.

Ecological studies. Most studies that investigated chronic exposure to air pollution and COVID-19 used an ecological design (Andrée 2020; Cui et al. 2003; Ogen 2020; Travaglio et al. 2020a; Wu et al. 2020). Ecological studies have a long history in epidemiology, and started with John Snow's investigation of cholera in London in the mid-1800s (Snow 1856). Much has been written about potential biases that may arise from these

designs, especially the ecological fallacy, or cross-level bias (Greenland and Robins 1994; Morgenstern 1995; Piantadosi et al. 1988; Piantadosi 1994; Wakefield 2008). A classic example is an ecological assessment of the association between rates of lung cancer and exposure to radon gas in the United States (Cohen 1995), which found an inverse association in comparison with positive associations from occupational cohort studies and population-based case–control studies (NRC 2006); the spurious association was due to a number of biases related to the ecological design (Greenland and Robins 1994).

In addition, ecological studies of chronic exposure to air pollution and COVID-19 are unable to account for residential mobility. This aspect may introduce exposure measurement error because these studies may not be able to accurately characterize exposures over time periods that span several years. Some studies, such as Wu et al. (2020), assigned air pollution exposures based on concentrations between 2000 and 2016 to deaths from COVID-19 that occurred in 2020. Those who died in 2020 may well have been living somewhere else in 2016, and therefore, exposure may be misclassified.

A critical review of the ecological study design concluded that "The only way to overcome such bias, while avoiding uncheckable assumptions concerning the missing information, is to supplement the ecologic with individual-level information" (Wakefield 2008). Most epidemiologists recognize that ecological studies cannot provide the evidence needed to inform causal associations. Agencies such as the U.S. Environmental Protection Agency and the International Agency for Research on Cancer, when evaluating environmental harms to human health, give greater scrutiny to findings derived from case–control and cohort studies that incorporate individual-level data. The findings from these stronger observational epidemiological studies, the consideration of some of the guidelines put forward by Hill (1965), and the careful weighing of all of the evidence, including experimental studies, is generally how causality is assessed.

We also have concerns that the ecologic studies that have investigated air pollution and COVID-19 incidence or mortality are mixing two potential phenomena. The first phenomenon is the extent to which air pollution may increase an individual's susceptibility to becoming infected with COVID-19 because either the virus is being transmitted via particulate matter pollution, or past air pollution exposure may have altered immune function. The second phenomenon relates to the extent that air pollution may affect the survival of those who have already been infected with COVID-19. Although it is our impression that most of the ecological studies have focussed on the latter phenomena, with an ecological study design it is impossible to differentiate between the two. To be fair, longitudinal studies with individual-level data would also be challenged to differentiate between these two phenomena unless they had very granular data for incident COVID-19 cases.

Poisson models are appropriate for analyzing count data. For example, Wu et al. (2020) used a zero-inflated Poisson model with the observed number of deaths as a count variable and that can take account of the population size of each area, as well as overdispersion and zero counts. Unfortunately, during a pandemic, events are not independent and will cluster in time and space, and the standard methods of analysis may lead to biased estimates of association with understated precision. Spatial clustering may also be an issue; for example, Wu et al. (2020) included a random intercept for state in both their analyses , but it is unlikely that would capture similarities of counties that border on adjoining states.

Time series studies of the acute effects of air pollution on SARS and COVID-19. The time series analyses of Kan et al. (2005) and Zhu et al. (2020) were used to determine whether changes in daily concentrations of air pollutants were associated with daily counts of deaths from SARS or COVID-19. The underlying hypothesis of these studies is that "acute" exposures increase mortality. The time series study design is a widely accepted approach to estimate immediate health effects associated with acute exposures because it does not suffer from the ecological fallacy, and confounding can occur only if there are rapidly varying confounders.

Time series studies also typically span several years and comprise thousands of deaths so that seasonal trends and other longer-term signals can be reasonably taken into account and so that risk estimates with a reasonable degree of precision can be estimated. Controlling for meteorological and seasonal effects presents a methodological challenge for time series studies of air pollution applied to infectious disease epidemics over a relatively short period of time. Notably, the study of Kan et al. (2005) had only 141 deaths over a 1-month period, and one may question the stability and validity of the model. The short time frame also introduces other concerns given that it is not long enough to reasonably represent the time since infection and time of death. This highlights the general challenge for these studies, namely that the progression of the epidemic is not easily teased apart from other factors related to secular changes. Individuals with severe infections would have been isolated to prevent the spread to others, and their exposure to ambient air pollution would be minimal because they would be spending a large portion of their time indoors. Time series studies also need to try to account for other important time-related changes, and for COVID-19 there are a large number of considerations, such as changes in public health policy (e.g., testing, physical distancing, hand washing, wearing of facemasks, opening of businesses), availability of health care resources for detecting and treatment, and changes in spatial clustering of cases.

Although we acknowledge the possible biological mechanisms for which daily increases in pollution may increase the risk of death among people with coronavirus, we are skeptical about the etiological relevance of these acute exposures. The time from initial infection to death can be quite lengthy, and preliminary estimates suggest it could be on average about 18 d (Verity et al. 2020). However, this interval can be much longer, as demonstrated by a number of deaths from SARS and COVID-19 that occurred more than 2 months after initial diagnosis (Chan et al. 2003; Chu et al. 2004).

There are also issues related to whether individuals with COVID-19 were exposed to air pollution in the days that preceded their deaths. For example, many who died of COVID-19 in hospitals from March to April 2020 were on ventilators [e.g., in New York State, 20% of hospitalized people were put on ventilators, and 25% of them died (Richardson et al. 2020)]. Concentrations of ambient pollution near the time of their death would not represent a relevant exposure for people who required ventilators to assist with their breathing. Moreover, individuals with COVID-19 may have been in environments in hospitals or at home that were air conditioned, and air conditioning reduces exposures to many air pollutants. Individuals who died from coronavirus while at home, in prison or jail, or in a long-term care facility likely also experienced significant distress over the days immediately preceding death, and thus indoor exposures would be expected to be far more relevant than ambient exposures.

A critical aspect of any time series study—and this is also true with all other designs—is the exact methods of statistical analyses, and we have concerns about the two studies that used this design. A possible limitation in the study by Kan et al. (2005) was the use of one version of the GAMs (Hastie and Tibshirani 1993) that was found subsequently to be subject to bias from concurvity (Ramsay et al. 2003) and insufficiently stringent convergence criteria (Katsouyanni et al. 2002); in addition, it is not clear whether that study used updated software. Zhu et al. (2020) made use of another

GAM framework (Wood 2006). Instead of using quasi-Poisson regression, the authors used a gaussian error term.

We mentioned the lack of stability of the population during a pandemic above and noted that the key methodological aspects that need to be accounted for are the rapidly changing at-risk populations, strong serial autocorrelation from the transmission of disease, overdispersion that may require nonstandard Poisson models, and complex lag structures that may also vary in time (Imai et al. 2015). As made clear by Imai et al. (2015), standard time series methods are not suitable for these pandemics.

These limitations, in our view, do not allow for effects of day-of-week and other time-varying covariables including effects of weather to be taken into account adequately. As well, this design would not be capable of disentangle the shape of the epidemic curve from deaths that would arise from seasonal changes in air pollution.

Effects of air pollution on secondary attack rates. The study by Cai et al. (2007) was the only study in which secondary attack rates in a group of individuals in contact with 350 probable SARS cases were estimated, and they did not find associations with air pollution. The design is exceedingly interesting because it provides a method for investigating contributing factors and not just air pollution or weather. Secondary cases (6,727) were identified from 350 primary cases, and although an evaluation determined that the primary cases were independent from each other, the design ensures that the secondary cases are not independent from each other. Therefore, a matched analysis or other approach that accounted for the correlations would be advised. Another important design issue relates to the geographical proximity of participants so that one would expect small differences from relatively spatially homogenous exposures, such as fine particulates.

In that study, Cai et al. (2007) appeared to have used unconditional logistic regression with each secondary case classified dichotomously as having developed SARS or not. The authors acknowledged that they were unable to account for individual-level differences in social behaviors that would affect the number of people at risk for secondary attacks (i.e., clustering within cases). The analyses also sought to estimate associations with meteorological factors and the spread of SARS, and they reported stronger associations for these factors than they did for air pollution.

Over such a short time period (5 months), it is difficult to isolate the respective associations due to meteorology, air pollution, and season given that individuals, on learning of the dangers, take more precautions to reduce their risk, and these behaviors coincide with seasonal changes. Epidemiological studies that investigate how air pollution influences secondary spread of disease must account for individual-level behaviors of physical distancing, the use of face masks, hand washing, and other precautions that communities take to prevent spread. They also require spatial-temporally resolved measurements of specific pollutants. The paper provided scant details about the spatial resolution of the fixed-site air pollution monitors, and therefore, exposure misclassification error due to the use of large area API measures may be an important source of bias.

Summary of Methodological Limitations of Using Observational Studies during Pandemics

The hypothesis that air pollution is a factor in not only mortality from SARS and COVID-19 but also from other serious complications of infection is plausible, and a number of authors have discussed possible mechanisms (Conticini et al. 2020; Dutheil et al. 2020; Martelletti and Martelletti 2020).

In our analyses of these studies, we have touched on a number of key epidemiological issues that can lead to serious biases in epidemiological investigations during the time of a pandemic. Of particular importance is the lack of a steady state in study populations, and this is magnified as the pandemic unfolds and environmental and social conditions change dramatically. The upshot of this, especially when one makes use of administrative data to identify health states, is the underreporting of events that will vary spatially and temporally. Heterogeneity in the rates of infection and sequelae will vary by region and over time. Clustering of events is also an important problem that is difficult to account for, as well as considerable confounding by time and space. This problem is especially evident when analyses are conducted in the middle of an active pandemic. Pandemics lead to chaos in social, economic, political, and administrative realms and especially in the health care system. Thus, the use of administrative data for identifying health events during a pandemic is problematic.

Other important issues include the lack of individual-level data, especially as it relates to potential vulnerabilities, including underlying health conditions, socioeconomic status, race, gender, social support networks, and the like. We underscore that appropriate statistical methods should be used in analyzing any data set.

Investigating the research question as to whether air pollution increases mortality from COVID-19 is not trivial; it is complex and challenging, and the potential for bias is high. Most of the studies to date have used an ecological design that likely suffers from severe biases, especially when arbitrarily defined administrative units, such as counties or census areas, are used. Not only can there be cross-level bias that no amount of adjustment can alleviate, but heterogeneity in populations, especially those who are at the greatest risk, and exposures cannot be accounted for when broad areas are used as the unit of observation. For this reason, it is our view that the application of an ecological study design at this time is fundamentally flawed and may well produce spurious results.

Moreover, for the reasons discussed, time series studies are also problematic given the trajectory between infection, treatment, and death and the relevance of exposure to ambient pollution during this period. It is important to note that the analysis of these data would require special methods that have not been well-developed (Imai et al. 2015).

Recommended Designs for Evaluating Impacts of Air Pollution on COVID-19

Our recommended epidemiological design to investigate whether air pollution increases the risk of COVID-19 mortality would be a longitudinal study with individual-level data, in which those diagnosed with COVID-19 would be followed through time. We suggest that these studies should be done after the pandemic has ended because of the challenges in detecting incidence and mortality. That said, some jurisdictions that lack the public health infrastructure may not be in a position to provide the high-quality health data needed to study this topic.

The design would be extremely challenging to undertake. Of course, defining the target population is very important. Selection bias would be an important concern when assembling the cohort if testing for COVID-19 was not done in a consistent way across areas with different levels of air pollution. Bias could be introduced if, for example, urban areas had more available testing that would capture both mild and severe COVID-19 patients, whereas in rural areas, with lower pollution levels, only the more severe cases would be identified. This potential bias could potentially be overcome with a carefully designed prospective cohort study, or alternatively, with a retrospective study where testing has identified all people irrespective of their access to health care. Knowing geographic coverage rates of testing could be used to

adjust for selection bias, although it is not clear to us that coverage is easily estimable.

The study would compare people who died or who had severe reactions from COVID-19 with those who did not. Mortality is not the only health outcome, because we now appreciate that many cases do not resolve easily or quickly (Tenforde et al. 2020). Furthermore, exposures to air pollutants should be estimated as closely as possible to the personal level, e.g., using satellite data at 0.5×0.5 km resolution or highly resolved land use models. With this design researchers can investigate acute and past effects of air pollution; for example, for the former objective, individual-based, case-crossover analyses can be conducted (Maclure and Mittleman 2008), and they can incorporate distributed lag nonlinear models (Guo et al. 2011). Moreover, this design, if it were extended to sample the cohort from the base population rather than just include those diagnosed with COVID-19, could be used to determine how air pollution is associated with the transmission of COVID.

Some key features of this design would entail use of personal information, including accurate ascertainment of health outcomes (e.g., having a specific definition of "severity" or minimizing misspecification of the underlying cause of death), a longitudinal component to follow individuals over time, a proper assessment of underlying health conditions, sociodemographic characteristics (e.g., age, sex, race, education, occupation, medical coverage, resident of a nursing home), date of infection, spatially and temporally resolved measures of air pollution, including near the time of the health event; information about quality of care (e.g., hospital's ability to deliver appropriate care), accounting for nonindependence of events (i.e., clustering in time and space), mode of infection (e.g., travel of community spread), accounting for time since beginning of the pandemic and possibly the time-incidence pattern, and local policies to minimize the spread of COVID-19, including, but not limited to, risk communication activities, physical distancing, use of face masks, and closures of businesses and restaurants. This design represents the only one that can avoid the many biases of the ecological or time series studies, but we caution that it would be highly complex, and it is entirely possible that one cannot define a study that can answer the question in an unbiased manner. Indeed, it may be case that incident cases of COVID-19, as well as death, may not be able to be adequately identified even retrospectively.

We would also like to draw attention to the fact that epidemiological studies of air pollution and chronic disease have benefitted from a number of studies that have assessed biases related to exposure measurement error due to time-activity behaviors (Ouidir et al. 2015), the role of indoor air quality (Ji and Zhao 2015; Ouidir et al. 2015), or methodology to indirectly control for possible confounding (Shin et al. 2014). There are similar opportunities and needs to conduct smaller exposure or methodological studies that could inform or complement larger studies. For COVID-19, this is particularly important given the profound impacts that the pandemic has had on human behaviors, reductions in ambient concentrations, and temporal complexities in characterizing exposure and disease risk due to seemingly ever-changing public health regulations. The use of time-activity patterns, perhaps from cellular-phone data during the pandemic represents an approach that could provide insights on how the pandemic has affected individuals' exposure to ambient pollution.

Conclusions

It is plausible that both daily increases and chronic, historical exposures to outdoor air pollution adversely impact prognoses among those with SARS or COVID-19. Our review of the design features of the studies that have disseminated their findings indicates that all studies had significant weaknesses that preclude them from providing insight about a causal association between historical or current levels of ambient air pollution and rates of mortality or secondary infections in either the SARS or COVID-19 pandemic.

Many of our concerns about the methodological limitations of these studies have been echoed in a recently published editorial (Heederik et al. 2020). We agree with the key message from that commentary that a more thoughtful and "go slow to go fast" approach is needed for researching the role of air pollution on mortality from COVID-19. Indeed, we feel strongly that there is no public benefit to conducting these analyses in the middle of an active pandemic. There is already overwhelming evidence that air pollution is a health hazard (Cohen et al. 2017; IARC 2016), and we cannot envision any additional value that these studies provide that further public health. In fact, we feel that the public is not served well by these studies, many of which have not undergone the scrutiny of peer review, especially because the press are on the lookout for sensational stories (Carrington 2020a, 2020b, 2020c; Friedman 2020), and candidates in the U.S. presidential election are prone to run with byline headlines. All observational studies are not created equal, and the rush to use a flawed design to investigate the association between air pollution and mortality from COVID-19 jeopardizes the clear and compelling evidence of chronic exposure to air pollution as a threat to human health and deflects from the increased rates of infection and health consequences caused by problems of social and income disparities, overcrowding, and other societal issues.

References

Andrée B. 2020. Incidence of COVID-19 and connections with air pollution exposure: evidence from the Netherlands. Policy Research Working Paper No. 9221. Paris, France: World Bank, https://doi.org/10.1596/1813-9450-9221.

Ansart S, Pelat C, Boelle PY, Carrat F, Flahault A, Valleron AJ. 2009. Mortality burden of the 1918–1919 influenza pandemic in Europe. Influenza Other Respir Viruses 3(3):99–106, PMID: 19453486, https://doi.org/10.1111/j.1750-2659.2009.00080.x.

Arons MM, Hatfield KM, Reddy SC, Kimball A, James A, Jacobs JR, et al. 2020. Presymptomatic SARS-CoV-2 infections and transmission in a skilled nursing facility. N Engl J Med 382(22):2081–2090, PMID: 32329971, https://doi.org/10.1056/NEJMoa2008457.

Baggaley K. 2020. What we can learn from New Zealand's successful fight against COVID-19. *Popular Science*. 10 June 2020. https://www.popsci.com/story/health/new-zealand-coronavirus-eliminated/ [accessed 17 June 2020].

Bell ML, Son JY, Peng RD, Wang Y, Dominici F. 2015. Ambient $PM_{2.5}$ and risk of hospital admissions: do risks differ for men and women? Epidemiology 26(4):575–579, PMID: 25906368, https://doi.org/10.1097/EDE.0000000000000310.

Bethea C. 2020. What the coronavirus is doing to rural Georgia. *New York Times*, 4 April 2020.

Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. 2010. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation 121(21):2331–2378, PMID: 20458016, https://doi.org/10.1161/CIR.0b013e3181dbece1.

Cai QC, Lu J, Xu QF, Guo Q, Xu DZ, Sun QW, et al. 2007. Influence of meteorological factors and air pollution on the outbreak of severe acute respiratory syndrome. Public Health 121(4):258–265, https://doi.org/10.1016/j.puhe.2006.09.023.

Carrington D. 2020a. Air pollution linked to far higher COVID-19 death rates, study finds. *The Guardian*, 7 April 2020, online edition. https://www.theguardian.com/environment/2020/apr/07/air-pollution-linked-to-far-higher-covid-19-death-rates-study-finds [accessed 28 April 2020].

Carrington D. 2020b. Air pollution may be 'key contributor' to COVID-19 deaths – study. *The Guardian*, 20 April 2020. https://www.theguardian.com/environment/2020/apr/20/air-pollution-may-be-key-contributor-to-covid-19-deaths-study [accessed 28 April 2020].

Carrington D. 2020c. Coronavirus detected on particles of air pollution. *The Guardian*, 24 April 2020. https://www.theguardian.com/environment/2020/apr/24/coronavirus-detected-particles-air-pollution [accessed 28 April 2020].

Carter LJ, Garner LV, Smoot JW, Li Y, Zhou Q, Saveson CJ, et al. 2020. Assay techniques and test development for COVID-19 diagnosis. ACS Cent Sci 6(5):591–605.

Cha AE. 2020. A funeral and a birthday party: CDC traces Chicago coronavirus outbreak to two family gatherings. *Washington Post*, 8 April 2020. https://www.washingtonpost.com/health/2020/04/08/funeral-birthday-party-hugs-covid-19/ [accessed 28 April 2020].

Chan KS, Zheng JP, Mok YW, Li YM, Liu YN, Chu CM, et al. 2003. SARS: prognosis, outcome and sequelae. Respirology 8(suppl 1):S36–S40, PMID: 15018132, https://doi.org/10.1046/j.1440-1843.2003.00522.x.

Chen SC, Chang CF, Liao CM. 2006. Predictive models of control strategies involved in containing. Indoor Air 16(6):469–481, PMID: 17100668, https://doi.org/10.1111/j.1600-0668.2006.00443.x.

Chowkwanyun M, Reed AL, Jr. 2020. Racial health disparities and COVID-19–caution and context. N Engl J Med 383(3):201–203, PMID: 32374952, https://doi.org/10.1056/NEJMp2012910.

Chu CM, Poon LL, Cheng VC, Chan KS, Hung IF, Wong MM, et al. 2004. Initial viral load and the outcomes of SARS. CMAJ 171(11):1349–1352, PMID: 15557587, https://doi.org/10.1503/cmaj.1040398.

Chu DK, Akl EA, Duda S, Solo K, Yaacoub S, Schunemann HJ, et al. 2020. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. Lancet 395(10242):1973–1987, PMID: 32497510, https://doi.org/10.1016/S0140-6736(20)31142-9.

Ciencewicki J, Jaspers I. 2007. Air pollution and respiratory viral infection. Inhal Toxicol 19(14):1135–1146, PMID: 17987465, https://doi.org/10.1080/08958370701665434.

Clark LP, Millet DB, Marshall JD. 2014. National patterns in environmental injustice and inequality: outdoor NO_2 air pollution in the United States. PLoS One 9(4): e94431, PMID: 24736569, https://doi.org/10.1371/journal.pone.0094431.

Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, et al. 2017. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. Lancet 389(10082):1907–1918, PMID: 28408086, https://doi.org/10.1016/S0140-6736(17)30505-6.

Cohen BL. 1995. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys 68(2):157–174, PMID: 7814250, https://doi.org/10.1097/00004032-199502000-00002.

Colais P, Faustini A, Stafoggia M, Berti G, Bisanti L, Cadum E, et al. 2012. Particulate air pollution and hospital admissions for cardiac diseases in potentially sensitive subgroups. Epidemiology 23:473–481, PMID: 22441544, https://doi.org/10.1097/EDE.0b013e31824d5a85.

Coletta A. 2020. Canada's nursing home crisis: 81 percent of coronavirus deaths are in long-term care facilities. *Washington Post*, 18 May 2020. https://www.washingtonpost.com/world/the_americas/coronavirus-canada-long-term-care-nursing-homes/2020/05/18/01494ad4-947f-11ea-87a3-22d324235636_story.html [accessed 8 June 2020].

Conticini E, Frediani B, Caro D. 2020. Can atmospheric pollution be considered a co-factor in extremely high level of SARS-CoV-2 lethality in Northern Italy? Environ Pollut 261:114465, PMID: 32268945, https://doi.org/10.1016/j.envpol.2020.114465.

Cui Y, Zhang Z-F, Froines J, Zhao J, Wang H, Yu S-Z, et al. 2003. Air pollution and case fatality of SARS in the People's Republic of China: an ecologic study. Environ Health 2(1):1–5, PMID: 14629774, https://doi.org/10.1186/1476-069X-2-15.

Dutheil F, Baker JS, Navel V. 2020. COVID-19 as a factor influencing air pollution?. Environ Pollut 263(pt A):114466, PMID: 32283458, https://doi.org/10.1016/j.envpol.2020.114466.

Dyal JW, Grant MP, Broadwater K, Bjork A, Waltenburg MA, Gibbins JD, et al. 2020. COVID-19 among workers in meat and poultry processing facilities–19 states, April 2020. MMWR Morb Mortal Wkly Rep 69(18), PMID: 32379731, https://doi.org/10.15585/mmwr.mm6918e3.

Friedman L. 2020. New research links air pollution to higher coronavirus death rates. *New York Times*, 7 April 2020; Updated 17 April 2020. https://www.nytimes.com/2020/04/07/climate/air-pollution-coronavirus-covid.html [accessed 8 June 2020].

Gasparrini A, Armstrong B, Kenward MG. 2012. Multivariate meta-analysis for non-linear and other multi-parameter associations. Stat Med 31(29):3821–3839, PMID: 22807043, https://doi.org/10.1002/sim.5471.

Glenza J. 2020. COVID-19: nursing homes account for 'staggering' share of us deaths, data show. *The Guardian* (New York, USA edition). 11 May 2020. https://www.theguardian.com/us-news/2020/may/11/nursing-homes-us-data-coronavirus.

Goldberg MS, Burnett RT, Stieb D. 2003. A review of time-series studies used to evaluate the short-term effects of air pollution on human health. Rev Environ Health 18(4):269–303, PMID: 15025190, https://doi.org/10.1515/reveh.2003.18.4.269.

Goldberg MS, Burnett RT, Stieb DM, Brophy JM, Daskalopoulou SS, Valois MF, et al. 2013. Associations between ambient air pollution and daily mortality among elderly persons in Montreal, Quebec. Sci Total Environ 463-464:931–942, PMID: 23872247, https://doi.org/10.1016/j.scitotenv.2013.06.095.

Gori T, Lelieveld J, Munzel T. 2020. Perspective: cardiovascular disease and the Covid-19 pandemic. Basic Res Cardiol 115(3):32, PMID: 32277299, https://doi.org/10.1007/s00395-020-0792-4.

Grandoni D, Firozi P. 2020. The energy 202: Biden tweaks his environmental campaign message amid coronavirus pandemic. *Washington Post*, 30 April 2020. https://www.washingtonpost.com/news/powerpost/paloma/the-energy-202/2020/04/30/the-energy-202-biden-tweaks-his-environmental-campaign-message-amid-coronavirus-pandemic/5ea9b225602ff14578421a23/.

Greenland S, Robins J. 1994. Invited commentary: ecologic studies–biases, misconceptions, and counterexamples. Am J Epidemiol 139(8):747–760, PMID: 8178788, https://doi.org/10.1093/oxfordjournals.aje.a117069.

Griffiths BD. 2020. Power up: Trump should focus on air pollution in coronavirus response. *Washington Post*, 9 April 2020. https://www.washingtonpost.com/news/powerpost/paloma/powerup/2020/04/09/powerup-trump-should-focus-on-air-pollution-in-coronavirus-response-researchers-say/5e8e283d88e0fa101a75e456/ [accessed 7 June 2020].

Guo Y, Barnett AG, Pan X, Yu W, Tong S. 2011. The impact of temperature on mortality in Tianjin, China: a case-crossover design with a distributed lag nonlinear model. Environ Health Perspect 119(12):1719–1725, PMID: 21827978, https://doi.org/10.1289/ehp.1103598.

Hajat A, Hsia C, O'Neill MS. 2015. Socioeconomic disparities and air pollution exposure: a global review. Curr Environ Health Rep 2(4):440–450, PMID: 26381684, https://doi.org/10.1007/s40572-015-0069-5.

Hamner L, Dubbel P, Capron I, Ross A, Jordan A, Lee J, et al. 2020. High SARS-CoV-2 attack rate following exposure at a choir practice – Skagit County, Washington, March 2020. MMWR Morb Mortal Wkly Rep 69(19):606–610, PMID: 32407303, https://doi.org/10.15585/mmwr.mm6919e6.

Hastie TJ, Tibshirani RJ. 1993. *Generalized Additive Models*. New York: Chapman and Hall.

Heederik DJJ, Smit LAM, Vermeulen RCH. 2020. Go slow to go fast: a plea for sustained scientific rigour in air pollution research during the COVID-19 pandemic. Eur Respir J 56(1):2001361, PMID: 32586882, https://doi.org/10.1183/13993003.01361-2020.

Hill AB. 1965. The environment and disease: association or causation? Proc R Soc Med 58(5):295–300, PMID: 14283879, https://doi.org/10.1177/003591576505800503.

Hoek G, Krishnan RM, Beelen R, Peters A, Ostro B, Brunekreef B, et al. 2013. Long-term air pollution exposure and cardio-respiratory mortality: a review. Environ Health 12(1):43, PMID: 23714370, https://doi.org/10.1186/1476-069X-12-43.

Imai C, Armstrong B, Chalabi Z, Mangtani P, Hashizume M. 2015. Time series regression model for infectious disease and weather. Environ Res 142:319–327, PMID: 26188633, https://doi.org/10.1016/j.envres.2015.06.040.

IARC (International Agency for Research on Cancer). 2016. *Outdoor Air Pollution: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France: International Agency for Research on Cancer.

Ji W, Zhao B. 2015. Estimating mortality derived from indoor exposure to particles of outdoor origin. PLoS One 10(4):e0124238, PMID: 25860147, https://doi.org/10.1371/journal.pone.0124238.

Kan HD, Chen BH, Fu CW, Yu SZ, Mu LN. 2005. Relationship between ambient air pollution and daily mortality of SARS in Beijing. Biomed Environ Sci 18(1):1–4, PMID: 15861770.

Karimi F. 2020. California orders its nearly 40 million residents to stay home to prevent the spread of coronavirus, https://www.cnn.com/2020/03/19/us/california-coronavirus-stay-home-order/index.html [accessed 8 June 2020].

Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Monopolis Y, LeTertre A, et al. 2002. Different convergence parameters applied to the S-PLUS GAM function. Epidemiology 13(6):742–743, PMID: 12410021, https://doi.org/10.1097/00001648-200211000-00024.

Katz J, Lu D, Sanger-Katz M. 2020. What is the real coronavirus death toll in each state? *New York Times*, 5 May 2020. https://www.nytimes.com/interactive/2020/05/05/us/coronavirus-death-toll-us.html [accessed 8 May 2020].

Korber B, Fischer WM, Gnanakaran S, Yoon H, Theiler J, Abfalterer W, et al. 2020. Tracking changes in SARS-CoV-2 spike: evidence that D614G increases infectivity of the COVID-19 virus. Cell S0092-8674(20)30820–30825, PMID: 32697968, https://doi.org/10.1016/j.cell.2020.06.043.

Laing A. 2020. Winter pollution raises coronavirus threat for murky Chilean cities. *National Post*, 30 April 2020. https://nationalpost.com/pmn/environment-pmn/winter-pollution-raises-coronavirus-threat-for-murky-chilean-cities [accessed 8 May 2020].

Li R, Pei S, Chen B, Song Y, Zhang T, Yang W, et al. 2020. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science 368(6490):489–493, PMID: 32179701, https://doi.org/10.1126/science.abb3221.

MacCharles T. 2020. 82% of Canada's COVID-19 deaths have been in long-term care, new data reveals. *The Star* (Toronto, Ontario), 7 May 2020. https://www.thestar.com/politics/federal/2020/05/07/82-of-canadas-covid-19-deaths-have-been-in-long-term-care.html [accessed 8 June 2020].

Maclure M, Mittleman MA. 2008. Case-crossover designs compared with dynamic follow-up designs. Epidemiology 19:176–178, PMID: 18277157, https://doi.org/10.1097/EDE.0b013e318162afb9.
Martelletti L, Martelletti P. 2020. Air pollution and the novel Covid-19 disease: a putative disease risk factor. SN Compr Clin Med 2:1–5, PMID: 32296757, https://doi.org/10.1007/s42399-020-00274-4.
McMichael TM, Clark S, Pogosjans S, Kay M, Lewis J, Baer A, et al. Public Health – Seattle & King County, EvergreenHealth, and CDC COVID-19 Investigation Team. 2020. COVID-19 in a long-term care facility – King County, Washington, February 27–March 9, 2020. MMWR Morb Mortal Wkly Rep 69(12):339–342, PMID: 32214083, https://doi.org/10.15585/mmwr.mm6912e1.
Misra DP, Agarwal V, Gasparyan AY, Zimba O. 2020. Rheumatologists' perspective on coronavirus disease 19 (COVID-19) and potential therapeutic targets. Clin Rheumatol 39(7):2055–2062, PMID: 32277367, https://doi.org/10.1007/s10067-020-05073-9.
Morgenstern H. 1995. Ecological studies in epidemiology: concepts, principles, and methods. Annu Rev Public Health 16:61–81, PMID: 7639884, https://doi.org/10.1146/annurev.pu.16.050195.000425.
NRC (National Research Council). 2006. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press.
New York City Department of Health Mental Hygiene (DOHMH) COVID-19 Response Team. 2020. Preliminary estimate of excess mortality during the COVID-19 outbreak – New York City, March 11–May 2, 2020. MMWR Morb Mortal Wkly Rep 69(19):603–605, PMID: 32407306, https://doi.org/10.15585/mmwr.mm6919e5.
Ogen Y. 2020. Assessing nitrogen dioxide (NO_2) levels as a contributing factor to coronavirus (COVID-19) fatality. Sci Total Environ 726:138605, PMID: 32302812, https://doi.org/10.1016/j.scitotenv.2020.138605.
O'Sullivan F. 2020. Paris has a plan to keep cars out after lockdown. Bloomberg CityLab. 29 April 2020. https://www.citylab.com/transportation/2020/04/paris-cars-air-pollution-health-public-transit-bike-lanes/610861/?utm_source=twb?utm_source=twb [accessed 8 June 2020].
Ouidir M, Giorgis-Allemand L, Lyon-Caen S, Morelli X, Cracowski C, Pontet S, et al. 2015. Estimation of exposure to atmospheric pollutants during pregnancy integrating space-time activity and indoor air levels: does it make a difference? Environ Int 84:161–173, PMID: 26300245, https://doi.org/10.1016/j.envint.2015.07.021.
Park SY, Kim YM, Yi S, Lee S, Na BJ, Kim CB, et al. 2020. Coronavirus disease outbreak in call center, South Korea. Emerg Infect Dis 26(8):1666–1670, PMID: 32324530, https://doi.org/10.3201/eid2608.201274.
Perls T. 2020. Failure to count COVID-19 nursing home deaths could dramatically skew us numbers. *The Conversation*, online edition. 13 June 2020. Online edition. https://theconversation.com/failure-to-count-covid-19-nursing-home-deaths-could-dramatically-skew-us-numbers-137212 [accessed 18 June 2020].
Piantadosi S, Byar DP, Green SB. 1988. The ecological fallacy. Am J Epidemiol 127(5):893–904, PMID: 3282433, https://doi.org/10.1093/oxfordjournals.aje.a114892.
Piantadosi S. 1994. Invited commentary: ecologic biases. Am J Epidemiol 139(8):761–764, PMID: 8178789, https://doi.org/10.1093/oxfordjournals.aje.a117070.
Pilkington E. 2020. Mass incarceration could add 100,000 deaths to us coronavirus toll, study finds. *The Guardian* (Manchester, UK), 22 April 2020. Online edition. https://www.theguardian.com/us-news/2020/apr/22/coronavirus-us-jails-incarceration-death-toll-study [accessed 8 June 2020].
Pope CA, 3rd., 2007. Mortality effects of longer term exposures to fine particulate air pollution: review of recent epidemiological evidence. Inhal Toxicol 19(suppl 1):33–38, PMID: 17886048, https://doi.org/10.1080/08958370701492961.
Ramsay TO, Burnett RT, Krewski D. 2003. The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. Epidemiology 14(1):18–23, PMID: 12500041, https://doi.org/10.1097/00001648-200301000-00009.
Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. 2020. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 323(20):2052, PMID: 32320003, https://doi.org/10.1001/jama.2020.6775.
Rowe DJ. 2020. Quebec records 37 new COVID-19 deaths, but adds 165 that weren't recorded. *CTV News Montreal Digital Reporter* (Montreal, Canada), 31 May 2020. https://montreal.ctvnews.ca/quebec-records-37-new-covid-19-deaths-but-adds-165-that-weren-t-recorded-1.4962370 [accessed 18 June 2020].
Sette A, Crotty S. 2020. Pre-existing immunity to SARS-CoV-2: the knowns and unknowns. Nat Rev Immunol 20(8):457–458, PMID: 32636479, https://doi.org/10.1038/s41577-020-0389-z.
Shin HH, Cakmak S, Brion O, Villeneuve P, Turner MC, Goldberg MS, et al. 2014. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. Environ Res 134:482–487, PMID: 24972508, https://doi.org/10.1016/j.envres.2014.05.016.
Snow J. 1856. On the mode of communication of cholera. Edinb Med J 1(7):668–670, PMID: 29647347.
Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, et al. 2020. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network – United States, March–June 2020. MMWR Morb Mortal Wkly Rep 69(30):993–998, PMID: 32730238, https://doi.org/10.15585/mmwr.mm6930e1.
Travaglio M, Popovic R, Yu Y, Leal NS, Martins LM. 2020a. Links between air pollution and COVID-19 in England. medRxiv. Preprint posted online April 17, 2020, https://doi.org/10.1101/2020.04.16.20067405.
Travaglio M, Yu Y, Popovic R, Selley L, Leal NS, Martins LM. 2020b. Links between air pollution and COVID-19 in England. medRxiv. Preprint posted online June 6, 2020, https://doi.org/10.1101/2020.04.16.20067405.
Tsai DH, Riediker M, Berchet A, Paccaud F, Waeber G, Vollenweider P, et al. 2019. Effects of short- and long-term exposures to particulate matter on inflammatory marker levels in the general population. Environ Sci Pollut Res Int 26(19):19697–19704, PMID: 31079306, https://doi.org/10.1007/s11356-019-05194-y.
U.S. EPA (U.S. Environmental Protection Agency). 2020. *Air Quality–Cities and Counties*. Washington, DC: U.S. Environmental Protection Agency.
U.S. Census Bureau. 2020. Quick facts. https://www.census.gov/quickfacts/cookcountyillinois [accessed 7 August 2020].
van Donkelaar A, Martin RV, Li C, Burnett RT. 2019. Regional estimates of chemical composition of fine particulate matter using a combined geoscience-statistical method with information from satellites, models, and monitors. Environ Sci Technol 53(5):2595–2611, PMID: 30698001, https://doi.org/10.1021/acs.est.8b06392.
Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, et al. 2020. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 20(6):669–677, PMID: 32240634, https://doi.org/10.1016/S1473-3099(20)30243-7.
Villeneuve PJ, Johnson JY, Pasichnyk D, Lowes J, Kirkland S, Rowe BH. 2012. Short-term effects of ambient air pollution on stroke: who is most vulnerable? Sci Total Environ 430:193–201, PMID: 22647242, https://doi.org/10.1016/j.scitotenv.2012.05.002.
Wakefield J. 2008. Ecologic studies revisited. Annu Rev Public Health 29:75–90, PMID: 17914933, https://doi.org/10.1146/annurev.publhealth.29.020907.090821.
Warren E. 2020. Warren, Maloney, Markey release findings from first comprehensive survey of COVID-19 in assisted living facilities & introduce assisted living facility coronavirus reporting act. [press release]. Washington, DC. 2 July 2020, https://www.warren.senate.gov/newsroom/press-releases/warren-maloney-markey-release-findings-from-first-comprehensive-survey-of-covid-19-in-assisted-living-facilities-and-introduce-assisted-living-facility-coronavirus-reporting-act.
Wiener-Bronner D. 2020. One of the largest pork processing facilities in the U.S. is closing until further notice. CNN Business. https://www.cnn.com/2020/04/12/business/meat-plant-closures-smithfield/index.html [accessed 25 August 2020].
Williams T, Seline L, Griesbach R. 2020. Coronavirus cases rise sharply in prisons even as they plateau nationwide. New York Times, 16 June 2020. https://www.nytimes.com/2020/06/16/us/coronavirus-inmates-prisons-jails.html [accessed 30 June 2020].
Wood S. 2006. *Generalized Additive Models: An Introduction with R*. Boca Raton, FL: Taylor and Francis CRC Press.
WHO (World Health Organization). 2005. Travel by air: health considerations. Wkly Epidemiol Rec 80(21):181–191. https://www.who.int/wer/2005/wer8021.pdf?ua=1 [accessed 4 August 2020].
WHO. 2020. SARS (severe acute respiratory syndrome). https://www.who.int/ith/diseases/sars/en/ [accessed 8 May 2020].
Wu X, Nethery R, Sabath M, Baun D, Dominici F. 2020. Exposure to air pollution and COVID-19 mortality in the United States. medRxiv. Preprint posted online 7 April 2020; updated 27 April 2020. https://doi.org/10.1101/2020.04.05.20054502.
Xu B, Kraemer M. 2020. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 20(5):532–533, PMID: 32087114, https://doi.org/10.1016/S1473-3099(20)30120-1.
Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. 2020. Clinical characteristics and outcomes of patients with severe COVID-19 with diabetes. BMJ Open Diabetes Res Care 8(1):e001343, PMID: 32345579, https://doi.org/10.1136/bmjdrc-2020-001343.
Yancy CW. 2020. COVID-19 and African Americans. JAMA 323(19):1891–1892, https://doi.org/10.1001/jama.2020.6548.
Yang B-Y, Fan S, Thiering E, Seissler J, Nowak D, Dong G-H, et al. 2020. Ambient air pollution and diabetes: a systematic review and meta-analysis. Environ Res 180:108817, https://doi.org/10.1016/j.envres.2019.108817.
Yao Y, Pan J, Wang W, Liu Z, Kan HD, Meng X, et al. 2020. Spatial correlation of particulate matter pollution and death rate of covid-19. medRxiv. Preprint posted April 10, 2020, https://doi.org/10.1101/2020.04.07.20052142.
Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395(10229):1054–1062, PMID: 32171076, https://doi.org/10.1016/S0140-6736(20)30566-3.
Zhu Y, Xie J, Huang F, Cao L. 2020. Association between short-term exposure to air pollution and COVID-19 infection: evidence from China. Sci Total Environ 727:138704, PMID: 32315904, https://doi.org/10.1016/j.scitotenv.2020.138704.