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COMMENTARY BY THE HEI IMPROVED EXPOSURE ASSESSMENT STUDIES REVIEW PANEL

Long-Term Exposure to Outdoor Ultrafine Particles and Black Carbon and Effects on Mortality in Montreal and Toronto, Canada

Weichenthal et al.

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Exposure to Outdoor Ultrafine Particles and Black Carbon and Effects on Mortality in Montreal and Toronto, Canada

Scott Weichenthal, Marshall Lloyd, Arman Ganji, Leora Simon, Junshi Xu, Alessya Venuta, Alexandra Schmidt, Joshua Apte, Hong Chen, Eric Lavigne, Paul Villeneuve, Toyib Olaniyan, Michael Tjepkema, Richard T. Burnett, and Marianne Hatzopoulou

with a Commentary by the HEI Improved Exposure Assessment Studies Review Panel

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

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

CONTRIBUTORS

RESEARCH COMMITTEE

Heather A. Holmes *Associate Professor, Department of Chemical Engineering, University of Utah, Salt Lake City, Utah, USA*

Marianthi-Anna Kioumourtzoglou* *Associate Professor of Environmental Health Sciences, Columbia University Mailman School of Public Health, New York, New York, USA*

Gregory Wellenius *Professor, Department of Environmental Health, Boston University School of Public Health and Director, BUSPH Center for Climate and Health, Boston, Massachusetts, USA*

IMPROVED EXPOSURE ASSESSMENT STUDIES REVIEW PANEL

Jana Milford, Chair and HEI Review Committee member *Professor Emerita, Department of Mechanical Engineering and Environmental Engineering Program, University of Colorado Boulder, Boulder, Colorado, USA*

Susanne Breitner-Busch *Senior Scientist, IBE Chair of Epidemiology, LMU Munich and Institute of Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany*

Jamie Hart *Associate Professor, Brigham & Women's Hospital, Harvard Medical School, and Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA*

Anna Oudin *Associate Professor, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden, and Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden*

Shu Yang *Associate Professor, Department of Statistics, North Carolina State University, Raleigh, North Carolina, USA*

Jeff Yanosky *Associate Professor, Department of Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania, USA*

HEI PROJECT STAFF

Allison Patton *Senior Staff Scientist (Study Oversight)*

Hanna Boogaard *Consulting Principal Scientist (Report Review)*

Kristin Eckles *Senior Editorial Manager*

Hope Green *Editorial Project Manager*

Progressive Publishing Services *Consulting Editor*

*Kioumourtzoglou was a consultant for this report. The complete and up-to-date *Research* and *Review* committee rosters are available on the HEI website.

COMMENTARY
HEI Improved Exposure Assessment Review Panel

HEI

Research Report 217, *Long-Term Exposure to Outdoor Ultrafine Particles and Black Carbon and Effects on Mortality in Montreal and Toronto, Canada*, S. Weichenthal et al.

INTRODUCTION

Outdoor air pollution is a major global public health risk factor. There is now broad expert consensus that exposure to ambient air pollution causes an array of adverse health effects based on evidence from a large body of scientific literature that has grown exponentially since the mid-1990s.[1–5]

Assessment of long-term exposure to ambient air pollution for epidemiological studies remains challenging. Early cohort studies characterized exposure to individual participants by assigning the average concentration measured at one or a few central sites within a city to each participant from this city.[6,7] Fixed-site networks — even those in North America and Western Europe — still have relatively limited spatial coverage in many areas, particularly in suburban and rural locations, and insufficient density to capture small-scale (within-city) variations of air pollution.

Recent developments in measurement technologies and approaches to modeling long-term exposure to air pollution have increasingly been used to provide air pollution estimates at fine spatial scales for epidemiological studies of large populations. Advances include novel air pollution sensors, mobile monitoring, satellite data, hybrid models, and machine learning approaches.[8] There remain important limitations and challenges, however, when predicting long-term air pollution exposure, particularly for pollutants that vary highly in space and time.

In 2019, HEI issued Request for Applications (RFA*) 19-1, *Applying Novel Approaches to Improve Long-Term Exposure Assessment of Outdoor Air Pollution for Health Studies* (see Preface). The goal of the RFA was to develop and apply scalable novel approaches to improve assessments of long-term exposures to outdoor air pollutants that vary highly in space and time — such as ultrafine particles (UFPs), nitrogen dioxide (NO_2), and ozone (O_3). Studies were intended to evaluate exposure measurement error quantitatively and to determine how exposure assessment approaches might ultimately affect the health effects estimates derived.

Dr. Weichenthal and colleagues proposed to estimate associations between long-term exposures to outdoor UFPs, black carbon (BC), and other pollutants and mortality in Toronto and Montreal, Canada, using several exposure modeling approaches. The HEI Research Committee recommended the study for funding because it would compare different exposure modeling approaches, including state-of-the-art machine learning models that use aerial image data. They also appreciated the focus on UFPs, the mobile monitoring campaign, and the leveraging of a large population-based cohort.

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

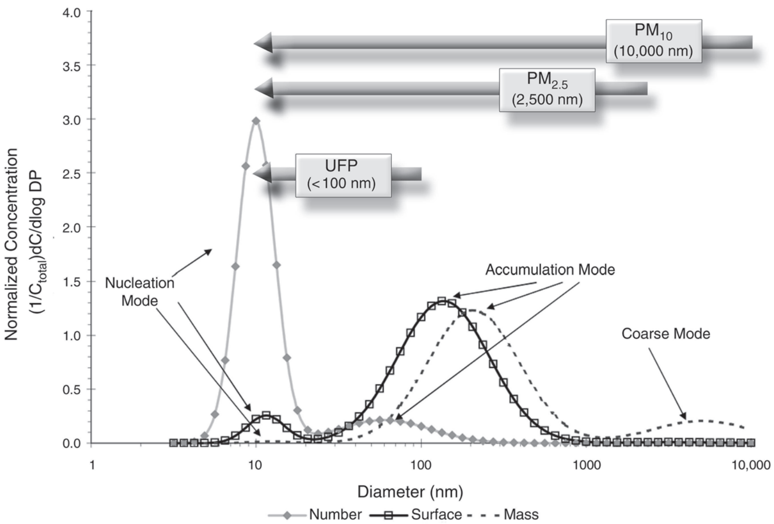
SCIENTIFIC AND REGULATORY BACKGROUND

Particulate matter (PM) is a mixture of solid particles and liquid droplets in the ambient air. It encompasses multiple size fractions, such as PM_{10} (PM with an aerodynamic diameter less than 10 µm), $PM_{2.5}$ (PM with an aerodynamic diameter less than 2.5 µm), and UFPs (PM with an aerodynamic diameter less than 100 nm), and comprises various components, such as metals and BC.

UFPs in ambient air make up the smallest size fraction in what is actually a continuum of particles with diameters ranging from a few nanometers to several micrometers (illustrated in **Commentary Figure 1** for a typical roadway aerosol). UFPs contribute little to the mass of particles but are the dominant contributors to particle number. Hence, total particle number concentration is commonly used as a proxy for UFPs. Commonly used instrumental methods for particle number concentration measurement do not provide information on particle size distribution or the fraction of the particles in the UFP-specific size range (<100 nm). In addition, both the lower and upper detection limits of different instruments vary; the lower limit typically ranges from 2 nm to 20 nm. The choice of the lower cut-off of measurement is usually critical because most UFPs are less than 20 nm, and even small differences in the lower cut point in the range below 20 nm can lead to substantial differences in particle number concentration.[9]

Dr. Scott Weichenthal's 3-year study, "Comparing the Estimated Health Impacts of Long-Term Exposure to Traffic-Related Air Pollution Using Fixed-Site, Mobile, and Deep Learning Models," began in May 2020. Total expenditures were $825,479. The draft Investigators' Report from Weichenthal and colleagues was received for review in August 2023. A revised report, received in November 2023, was accepted for publication in December 2023. During the review process, the HEI Improved Exposure Assessment Review Panel and the investigators had the opportunity to exchange comments and clarify issues in both the Investigators' Report and the Panel's Commentary.

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



Commentary Figure 1. Normalized particle size distributions of typical roadway aerosol.[9]

BC is a subset of $PM_{2.5}$ and a measure of airborne soot-like carbon that can be determined with several optical methods. It is closely related to the mass concentration of elemental carbon (i.e., carbon in various crystalline forms) that can be analyzed using chemical methods. BC is a potent agent that contributes to global warming through the absorption of light and release of heat. International or national standard methods to characterize UFPs and BC have not been established.[9,10]

In urban areas, road traffic and other forms of transportation, including aviation and shipping, are usually the main sources of UFPs.[11,12] UFPs are emitted directly by all combustion sources as primary particles. UFPs are also formed in the air as secondary particles through complex physiochemical new particle formation processes that involve inorganic and organic gaseous precursors.[12] BC is also typically formed through the incomplete combustion of fossil fuels, biofuel, and biomass and is emitted from both anthropogenic and natural sources.[5]

The current $PM_{2.5}$ annual average air quality standard is 9 µg/m^3 in both Canada and the United States.[13,14] The US Environmental Protection Agency recently lowered the National Ambient Air Quality Standards (NAAQS) for $PM_{2.5}$ from 12 µg/m^3 to 9 µg/m^3. This is the first change in the $PM_{2.5}$ NAAQS since 2012.[14] The World Health Organization (WHO) released new Air Quality Guidelines in 2021 and recommended that annual mean concentrations of $PM_{2.5}$ should not exceed 5 µg/m^3.[5] There are no specific ambient air quality standards or guidelines for UFPs and BC, and regulatory agencies do not commonly measure them. Although no air quality guidelines were developed for UFPs and BC, WHO provided "good practice statements" for these pollutants geared toward additional monitoring, mitigation, and epidemiological research.[5]

UFPs can be inhaled deeply into the lungs, enter the alveoli, and penetrate biological membranes, enabling them to pass into the systemic circulation, overcome the placental barrier, and finally diffuse into all organ systems, including the brain and nervous system.[9] Although studies investigating the health effects of short-term exposure are increasingly available, there are few long-term air pollution and health studies on UFPs, due partly to the difficulties of long-term exposure assessment.[5,9,15,16] Reliance on measurements at central-site monitors to represent broad population exposure — a central feature in many earlier epidemiological studies of long-term exposures to $PM_{2.5}$ and other pollutants — is likely to lead to errors in exposure estimates of UFPs or other pollutants that vary highly in space and time.

In recent years, researchers have increasingly used mobile monitoring by affixing monitoring devices to vehicles and making measurements while systematically and repeatedly traveling a road network. Mobile monitoring strategies can involve on-road mobile measurements made while driving predefined strategic routes or repeated short-term measurements made while in a parked vehicle and collected at many locations. Data collected through mobile monitoring have been used to develop land use regression (LUR) models and other air pollution maps.[17–19] Air pollution maps estimated from such monitoring are being increasingly applied in epidemiological studies.[20,21] As noted earlier, however, important limitations and challenges remain when predicting long-term air pollution exposure for pollutants that vary highly in space and time.

SUMMARY OF APPROACH AND METHODS

The study by Dr. Weichenthal and colleagues assessed associations of long-term exposures to outdoor UFPs and BC with mortality in Toronto and Montreal, Canada, using several exposure modeling approaches. They conducted mobile monitoring campaigns in both cities and used those data to develop various high-resolution exposure models of within-city spatial variability in annual outdoor UFPs and BC. They then applied those models to a large representative sample of Canadian adults (1.5 million) from the Canadian Census Health and Environment Cohort (CanCHEC). They used both single-pollutant and multipollutant Cox proportional hazard models to assess the association between air pollution exposure and nonaccidental and cause-specific mortality adjusted for important confounders, as described later in more detail.

During the course of the work, several unforeseen setbacks occurred, partly due to the COVID-19 pandemic. This led to incomplete monitoring for NO_2 and O_3, which precluded the development of new high-resolution exposure models and few data from a fixed-site monitoring campaign. Moreover, the limited fixed-site monitoring campaign suffered from instrument failure. Hence, the current report focuses on UFPs and BC obtained from the mobile monitoring campaigns.

EXPOSURE ESTIMATES

Mobile Monitoring Campaigns

In both cities, the investigators conducted year-long real-time mobile monitoring campaigns for UFPs and BC, using gasoline vehicles. The campaigns were conducted from September 2020 to August 2021, thus during the COVID-19 pandemic. Monitoring routes were designed to capture a variety of land use and road types. In total, 14 and 20 routes were selected in Montreal and Toronto, respectively. To obtain a representative annual average, the monitoring routes were measured repeatedly at randomly assigned times of the day (daytime and evening), on all days of the week (weekdays and weekends), and in all four seasons. Monitoring was conducted, on average, 5 days per week; for each measurement day, four routes were monitored for a total route length of 75 km and a duration of about 4 hours.

UFPs and BC were measured at a 1-second resolution with either the Naneos Partector 2 or Testo DiSCmini for UFPs and with a microAeth MA350 for BC. Both UFP monitors concurrently measured UFP number concentrations (particles/cm^3) and mean UFP size (nm), and data from the two devices were used interchangeably. Both UFP devices capture particles with a size range from 10 nm to 300 nm, and the reported uncertainty in the measurements can be up to 30%. The monitor calculated the mean UFP size using factory-calibrated formulas and assumptions about the particle size distribution as opposed to a more sophisticated method that provides measurements across the entire particle size distribution. Detailed quality assurance checks were performed throughout the campaign. Values above and below the manufacturer's reported limits of detection were replaced with the upper and half of the lower limit of detection, respectively. This occurred only in 0.5% of the samples.

The median of the 1-second data was calculated for each 100-m road segment (equivalent to about 6 seconds of observation per visit) and averaged over all sampling days; this value was log-transformed for UFP number concentrations and BC (not for UFP size) and used for subsequent exposure modeling. Road segments monitored on fewer than 6 separate days throughout the campaign were excluded from the analysis. In total, mobile monitoring data were aggregated to 5,819 and 7,051 road segments in Toronto and Montreal, respectively. On average, road segments were visited on 10 different days.

Land Use Regression and Machine Learning Exposure Models

The mobile monitoring data were randomly split into subsets to train (70%), validate (15%), and test (15%) the high-resolution exposure models of UFP number concentrations, UFP size, and BC.

The investigators developed three new exposure models for each city separately: (a) LUR models based on the mobile monitoring data combined with detailed land use and traffic information; (b) machine learning, specifically convolutional neural network (CNN) models using mobile monitoring data and aerial images from Google Maps; and (c) a combination of these two models.

Estimates from each model were developed using the training dataset and compared to observed values in the validation and test datasets. Moreover, the new UFP number concentration estimates were compared to earlier LUR models that were developed using mobile monitor data collected in the two cities in 2010–2012.[22,23]

Accounting for weather-related temporal variations in air pollution during the monitoring campaign was necessary despite the random order of the monitoring campaign. Hence, meteorological data were forced into the LUR models as predictors and adjusted for in the CNN models separately after training the model. In total, 32 different predictor variables were available for LUR model development, many of which were examined at three different buffer sizes (100 m, 200 m, and 300 m). Variables that were statistically significantly associated with the air pollutant without being driven by outliers became candidate variables. Pairs of correlated candidate variables were identified (Spearman's $r > 0.7$), and the variables with the lowest mean square error were selected in the final LUR to avoid overfitting. Latitude and longitude were added to the LUR to capture spatial dependencies not covered by other variables. LUR models were developed using generalized additive models that allowed for nonlinear relationships.

For the CNN models, two aerial color images from Google Maps were used to capture both local (140 m × 140 m) and contextual (280 m × 280 m) information per road segment. In short, the CNN algorithm performs mathematical transformations on the numeric values on the pixel data of the images. Through an iterative process, the CNN learns key features in the digital images that are predictive of the air pollution levels measured at the road segment. The detailed specifications of the CNN models can be found in the Investigators' Report.

Backcasting and Accounting for Mobility

The investigators examined the 2020–2021 exposure models with and without backcasting based on historical trends in traffic information and nitrogen oxides (NO_x) emissions back to 2006. Various modeling techniques were developed to interpolate traffic counts and NO_x emissions spatially and temporally across all roads in Toronto and Montreal; details are documented in Ganji and colleagues.[24,25]

In addition to the backcasting models, the investigators examined the exposure models with and without accounting for neighborhood-level (i.e., dissemination area, which represents a geographic unit with a population of about 400–700) daily mobility patterns by using data from travel demand surveys that are routinely collected in both cities every 5 years. The backcasting procedure and adjustment for neighborhood-level mobility were not thoroughly evaluated, due partly to the absence of historical data, but were applied in the health analyses as described below.

Additional Co-pollutant Data

$PM_{2.5}$ mass concentrations and oxidant gases (O_x, a combination of NO_2 and O_3) were obtained from previous models[26] in the absence of newly developed models. The $PM_{2.5}$ estimates were from satellite-based aerosol optical depth measurements that were subsequently adjusted using ground-based monitoring and land use data. The NO_2 estimates were from a national LUR model, and the O_3 estimates were from a chemical transport model, all with different spatial resolutions ranging from 1 km × 1 km ($PM_{2.5}$) to 21 km × 21 km (O_3). O_x was calculated as a weighted average of O_3 and NO_2 following a formula used by Weichenthal and colleagues.[27] Co-pollutant data were used in the epidemiological analysis as possible confounders of the UFP and BC association, as described next.

HEALTH ESTIMATES

Study Population and Mortality Outcomes

The investigators applied the new exposure models to a large representative sample of Canadian adults (1.5 million) from the CanCHEC cohort residing in Toronto or Montreal. The study population included adults who were 25 years and older from multiple Census years (1991, 1996, 2001, and 2006), with mortality follow-up from 2001 to 2016. There were 174,200 nonaccidental deaths observed during the follow-up period.

Exposure was assigned to the participants using six-digit residential postal codes (about the size of a city block) while accounting for address changes over time. Three-year moving average exposures were used with a 1-year lag to ensure that estimates of long-term exposures preceded the outcome.

In terms of mortality outcomes, both nonaccidental mortality and cause-specific mortality were investigated. Causes of death that were evaluated included the broad categories of cardiometabolic (cardiovascular + diabetes), cardiovascular, and nonmalignant respiratory disease, and the more specific causes of ischemic heart disease, cerebrovascular disease, and lung cancer.

Health Analyses

The investigators conducted Cox proportional hazards models to estimate associations between long-term exposures to UFP number concentrations and BC from the various models and nonaccidental and cause-specific mortality. The analyses were adjusted for age, sex, Census cycle, various sociodemographic factors (education, occupation, income, marital status, and minority and immigrant status), co-pollutants, and UFP size. Specifically, the UFP number concentrations analyses were adjusted for $PM_{2.5}$, O_x, UFP size, and BC; the BC analyses were adjusted for $PM_{2.5}$, O_x, UFP size, and UFP number concentrations. UFP size was added using a penalized spline to capture potential nonlinearities with mortality; a linear adjustment for UFP size was explored in an additional analysis. Single-pollutant models of UFP number concentrations and BC were also conducted.

Concentration-response relationships for UFPs and BC were characterized for nonaccidental and cause-specific mortality using penalized splines. Relationships between UFP size and mortality outcomes were also explored. For this analysis, only the estimates from the combined exposure model (LUR + CNN) with backcasting were used.

All analyses were conducted for both cities combined, and city-specific analyses were not conducted.

SUMMARY OF RESULTS

EXPOSURE ASSESSMENT

The LUR models performed better than the CNN models, although the predictions of both models were highly correlated. The exposure model that combined LUR and CNN model predictions performed slightly better as compared to LUR models alone and was considered the main exposure model in the health analyses. The combined model explained approximately half or more of the observed spatial variation in UFPs and BC in the test sets; the R^2 ranged between 0.49 and 0.73 (**Commentary Table 1**).

The final LUR models included various land use and traffic variables, ranging from 18 to 27 predictor variables. The predictor variables differed across UFP number concentrations, UFP size, and BC. Only two predictor variables were identical for UFP number, UFP size and BC in both cities (residential land use area within 100 m and distance to nearest chimney or point source reported to the National Pollutant Release Inventory for PM). Note that such information cannot be extracted from the CNN models, but various visualizations provided clues about what features in the images would be important for generating a prediction.

For both cities together, the annual average UFP number was 14,000 particles/cm^3, UFP size was 33 nm, and BC concentration was 1,109 ng/m^3 at cohort baseline, using the combined model (**Commentary Figure 2**). In the cohort, UFP number concentrations were inversely correlated with UFP size (r = −0.54) and were weakly correlated with the other air pollutants (r = 0.10–0.38). BC was weakly correlated with UFP size (r = 0.09) and moderately correlated with both O_x (r = 0.57) and $PM_{2.5}$ (r = 0.42).

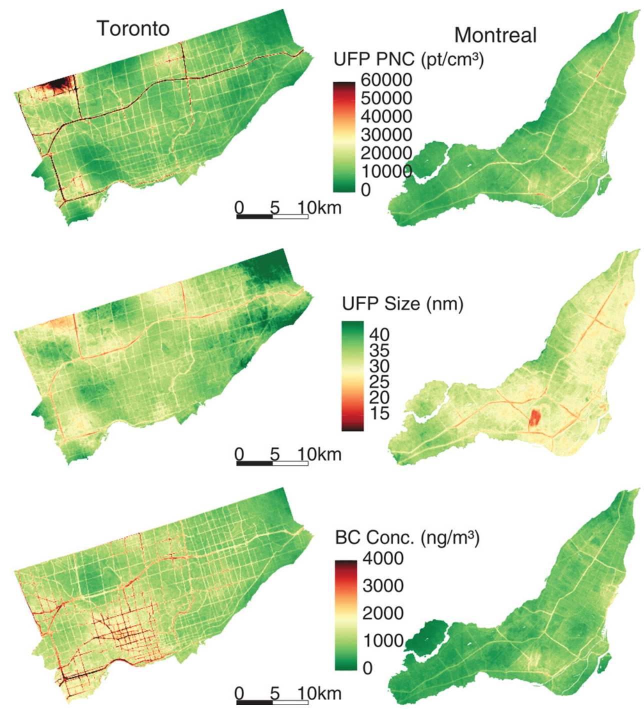
HEALTH ANALYSES

The concentration-response functions for UFP number concentrations, UFP size, and BC differed from each other. In most cases, the shape of the functions was roughly consistent across mortality outcomes. For UFP number concentrations, the functions typically flattened and decreased at elevated

Commentary Table 1. Performance of the Various Models (R^2)

City	Pollutant	LUR Model	CNN Model	Combined Model
Toronto	UFP number concentrations	0.71	0.66	0.73
	UFP size	0.56	0.43	0.55
	BC	0.60	0.53	0.61
Montreal	UFP number concentrations	0.59	0.49	0.60
	UFP size	0.48	0.41	0.49
	BC	0.58	0.50	0.60

BC = black carbon; CNN = convolutional neural network; LUR = land use regression; UFP = ultrafine particles.



Commentary Figure 2. Annual average concentrations in Toronto and Montreal from the combined exposure model with backcasting for UFP number concentrations, UFP size, and BC.

UFP levels. For UFP size, the functions increased continuously except for lung cancer, and the function for BC increased after a threshold but then decreased at higher concentrations. The authors used the shape of the concentration-response functions and the observation that particles tend to be smaller at higher number concentrations to justify the need to correct the main analyses for UFP size.

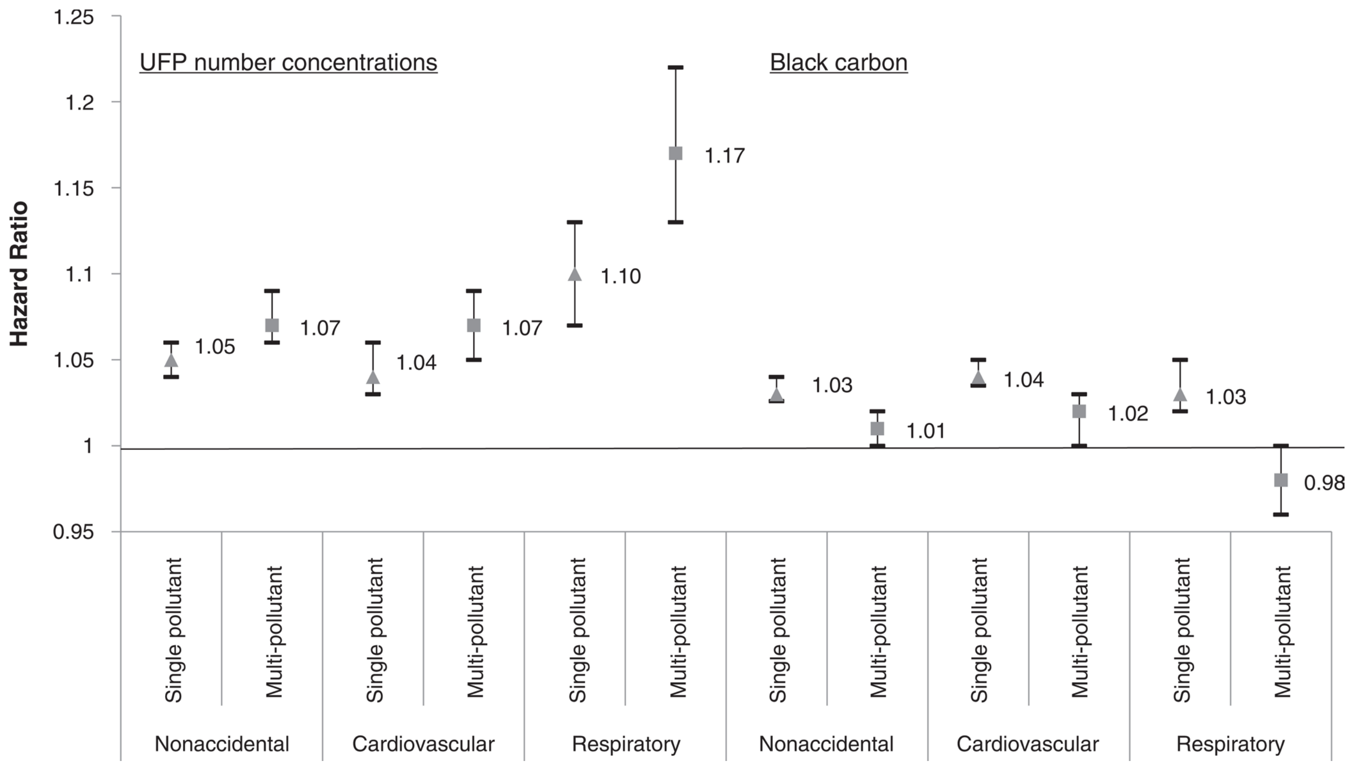
Using the combined exposure model with backcasting, the investigators found that long-term exposures to UFP number concentrations and BC were positively associated with nonaccidental, cardiovascular, and respiratory mortality in single-pollutant models, ranging from 1.03 to 1.10. The hazard ratios were sensitive to adjustment for co-pollutants and UFP size. After adjusting for UFP size, associations between UFP number concentrations and mortality increased, ranging from 1.06 to 1.17. Associations between BC and mortality became generally weaker or null, ranging from 0.98 to 1.02 after adjusting for UFP size (**Commentary Figure 3** and **Commentary Table 2**).

Health analyses were also conducted using the alternative exposure models without backcasting and accounting for mobility patterns. In short, similar findings were reported for BC across the different approaches, except for respiratory and lung cancer mortality, where a few slightly inverse associations were reported. For UFP number concentrations, the association's magnitude — but not the direction — differed substantially across the various approaches. Compared to the main exposure findings, associations were weaker when using the LUR model alone and when accounting for mobility. Associations between UFP number concentrations and nonaccidental and respiratory mortality became somewhat stronger using the CNN model. Backcasting did not change the associations from the main UFP exposure model (Commentary Table 2).

HEI IMPROVED EXPOSURE ASSESSMENT STUDIES REVIEW PANEL'S EVALUATION

In its independent review of the study, the Panel thought the research was well-motivated and addressed a clear research gap because there are few long-term air pollution and health studies on UFPs. This is partly due to the lack of comprehensive monitoring and the difficulties of long-term exposure assessment because UFPs vary highly in space and time. This research gap was also flagged in a recent systematic review from HEI on long-term exposure to traffic-related air pollution and health outcomes.[15]

In summary, the exposure models that combined LUR and CNN model predictions performed slightly better as compared to LUR models alone. The combined model explained half or more of the observed spatial variation in UFPs and BC and was considered the main exposure model in the health analyses. Long-term exposures to UFP number concentrations and BC were positively associated with mortality in single-pollutant models. The effect estimates were sensitive to adjustment for co-pollutants and UFP size. Associations



Commentary Figure 3. Adjusted hazard ratios for UFP number concentrations (per 10,000 particles/cm^3) and BC (per 500 ng/m^3) and selected mortality outcomes using the combined exposure model with backcasting.

between UFP number concentrations and mortality increased after adjusting for UFP size, whereas associations between BC and mortality became generally weaker or null. Generally, similar findings were reported for BC across various alternative exposure assessment approaches, including without backcasting and accounting for mobility patterns. For UFP number concentrations, the association's magnitude — but not the direction — differed substantially across the various alternative exposure approaches.

STRENGTHS OF THE STUDY

The Panel noted several strengths of the research. First, the extensive year-long mobile monitoring campaign in both cities was an impressive achievement. The investigators collected a rich dataset on UFPs and BC that covered various times of day between 7 a.m. and 11 p.m., weekdays, and weekends — thus including those times of day when people might be more likely to be at home — and all four seasons. Most other mobile monitoring campaigns have collected less data at each site, sampled during more restricted periods such as business hours only, or had short monitoring durations lasting only a few months.[28] This effort was even more impressive because the investigators had to navigate several unforeseen setbacks partly due to the COVID-19 pandemic.

Second, the rigorous development of new high-resolution models of within-city spatial variability in annual outdoor UFPs and BC was notable. Strengths of the LUR models were the large list of potential predictor variables, allowing for nonlinear relationships, and the strategy to avoid overfitting the data. The predictor variables in the LUR models differed across UFP number concentrations, UFP size, and BC, facilitating the estimation of "independent" effects in the epidemiological analyses because the correlation across pollutants was low to moderate. The innovative features of the state-of-the-art CNN models were considered another strength. The use of Google Maps images offers the potential for the CNN models to be scalable.

Third, evaluating the sensitivity of the epidemiological analyses to different exposure assessment approaches was considered another strength. The investigators leveraged a large representative sample of Canadian adults (1.5 million) from the CanCHEC cohort residing in Toronto or Montreal for this evaluation; this study design minimizes possible selection and participation bias. They conducted both single-pollutant and multipollutant models and included various sensitivity analyses.

Although the Panel broadly agreed with the investigators' conclusions, some limitations should be considered when interpreting the results, as explained next.

Commentary Table 2. Adjusted Hazard Ratios for UFP Number Concentrations and BC and Selected Mortality Outcomes Using Various Modeling Approaches

	Combined Model[a]			Combined Model[a] Accounting for Mobility	Combined Model without Backcasting	LUR Model[a]	CNN Model[b]
Mortality	Single-pollutant model	+$PM_{2.5}$, O_x, and either BC or UFP number	+UFP size				
UFP number concentrations (per 10,000 particles/cm^3)							
Nonaccidental	1.05 (1.04–1.06)	1.03 (1.02–1.04)	1.07 (1.06–1.09)	1.03 (1.02–1.05)	1.08 (1.06–1.09)	1.03 (1.02–1.04)	1.11 (1.10–1.13)
Cardiovascular	1.04 (1.03–1.06)	1.02 (1.00–1.03)	1.07 (1.05–1.09)	1.06 (1.03–1.09)	1.07 (1.04–1.10)	1.04 (1.02–1.05)	1.05 (1.02–1.08)
Respiratory[c]	1.10 (1.07–1.13)	1.09 (1.06–1.12)	1.17 (1.13–1.22)	1.12 (1.07–1.18)	1.20 (1.15–1.26)	1.07 (1.04–1.09)	1.27 (1.20–1.34)
Lung cancer	1.04 (1.02–1.07)	1.05 (1.03–1.08)	1.06 (1.02–1.10)	1.02 (0.98–1.07)	1.07 (1.03–1.12)	1.01 (0.99–1.04)	1.16 (1.10–1.22)
BC (per 500 ng/m^3)							
Nonaccidental	1.03 (1.03–1.04)	1.02 (1.01–1.02)	1.01 (1.00–1.02)	1.00 (0.99–1.01)	0.99 (0.99–1.00)	1.02 (1.01–1.02)	0.98 (0.97–0.99)
Cardiovascular	1.04 (1.04–1.05)	1.03 (1.02–1.04)	1.02 (1.00–1.03)	1.01 (0.99–1.02)	1.00 (0.98–1.02)	1.02 (1.01–1.03)	1.00 (0.98–1.02)
Respiratory[c]	1.03 (1.02–1.05)	1.00 (0.98–1.02)	0.98 (0.96–1.00)	0.97 (0.94–1.00)	0.95 (0.92–0.97)	1.00 (0.99–1.02)	0.94 (0.91–0.97)
Lung cancer	0.99 (0.97–1.00)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.95 (0.93–0.98)	0.98 (0.95–1.01)	1.00 (0.98–1.02)	0.99 (0.96–1.02)

BC = black carbon; CNN = convolutional neural network; LUR = land use regression; UFP = ultrafine particles.

Main analysis estimates are shaded.

[a]With backcasting.

[b]Without backcasting because estimates with backcasting were not reported.

[c]Lung cancer mortality excluded.

THE ADJUSTMENT FOR UFP SIZE

The adjustment for UFP size in health analyses of outdoor UFP number concentrations and BC was intriguing but requires further investigation. The authors provided justifications as to why the adjustment for UFP size was important in the current study and, more broadly, for future epidemiological analyses to obtain "unbiased" estimates of UFP number concentrations. They depend heavily on their recent discussion paper on estimating the causal effects of $PM_{2.5}$ using causal inference methods.[29] In that paper, they discuss a possible violation of one of the assumptions of causal inference methods, called the "causal consistency" assumption, which entails that the exposure or "treatment" is defined with enough specificity that different versions of the exposure do not have different effects on the outcome. They argue that $PM_{2.5}$ mass is a complex mixture — thus not a single treatment — with many features related to chemical composition, size, and other physical and biological properties of $PM_{2.5}$ that could be relevant for health.[30] Hence, variations in $PM_{2.5}$ components might translate into different versions of treatment, and the causal effect estimate of $PM_{2.5}$ mass could be biased if it does not account for those complexities.[29] Similar arguments were made for UFP number concentrations in the Investigators' Report, and the investigators therefore adjusted for UFP size in the current health analyses.

The Panel noted, however, that UFP size can represent many things. It might be that UFP size is a marker for some other characteristics of UFP (e.g., the age and composition of the particles). Alternatively, it might be an indicator for some other PM component, something completely different, or might even represent traffic noise. There are additional reasons to be cautious about the adjustment for UFP size. First, UFP size was the mean UFP size calculated by the Testo DiSCmini and Naneos Partector 2 instruments as opposed to a more sophisticated method that provides measurements across the entire particle size distribution. Second, the statistical approach of using the mean size to represent the complex, potentially nonlinear relationship between UFP size and health outcomes and all the other included pollutants might have been somewhat simplistic, as further discussed below. Third, no other epidemiological cohort study on UFP number concentrations has adjusted for UFP size.[16] Although intriguing, how to interpret UFP size remains unclear and warrants further research.

LIMITATIONS IN THE MONITORING DATA

Although the mobile monitoring was extensive and yearlong, 100-m road segments were, on average, visited on 10 different days, equivalent to about 6 seconds of observation per visit. That equates to a total sampling duration of about 60 seconds per year at each road segment. Longer monitoring times would provide more stable estimates of annual average UFP and BC levels. On the other hand, in a detailed comparison using Google Street View cars in Oakland, California, it was documented that only four to eight repeat visits per 30-m road segment produced robust long-term NO and BC exposure models.[19,31] Similar evaluation studies reported the need for at least 12 visits for stable UFP models.[17,32]

The absence of fixed-site monitor data prevented an evaluation of how well on-road measurements represent outdoor concentrations at nonroadway residential locations. Fixed-site monitor data could also be used for a temporal adjustment of the temporally imbalanced mobile measurements instead of or in addition to the current adjustment approach relying solely on meteorological data. In the absence of balanced data (e.g., lacking nighttime data), most other mobile monitoring studies have used fixed-site monitor data for the temporal adjustment, although questions remain about whether one or a few fixed-site monitors can sufficiently represent UFP and BC temporal patterns over space.[28] Typically, on-road measurements are higher than the air pollution values immediately outside residences, but the amount of overestimation varies. Partly due to COVID-19, the few fixed-site data that were collected in the study were plagued by instrument failure and eventually were not used in the study.

TEMPORAL MISMATCH AND BACKCASTING

In the application to the cohort, the UFP and BC models used were based on measurements that were conducted 5 years after the end of the mortality follow-up. This temporal mismatch between the period captured by the mobile measurements and the exposure window most relevant for epidemiological purposes is also apparent in some other cohort studies.[20,21,33–35] The investigators applied a backcasting procedure based on trends in traffic and NO_x emissions to overcome the lack of UFP and BC data in earlier years — back to 2006. This represents an advance over other studies. However, because data were lacking to evaluate the backcast surfaces, this procedure could introduce uncertainty that can affect the exposure and mortality estimates in unpredictable ways, depending on the quality of the data and modeling techniques used and how well NO_x and traffic counts correlate with UFPs and BC.

Accounting for the inherent (spatially varying) uncertainty and biases in modeled estimates of air pollution remains largely an unresolved problem in air pollution epidemiology,[36,37] although recent advances have been made.[38–42] Hence, it is unsurprising that the investigators did not formally propagate uncertainty in the exposure estimates in the health analyses, but it remains an important future research topic.

THE NEED FOR MORE ADVANCED MULTIPOLLUTANT STATISTICAL APPROACHES

The investigators conducted single-pollutant and multipollutant models using Cox proportional hazards models. For the multipollutant analyses, they added up to four pollutants or pollutant characteristics as potential confounders to the health model, either as a spline (UFP size) or as a linear term (co-pollutants). These models help understand how pollutants affect the risk when additional adjustments for other pollutants are being made. However, the methods used to assess multipollutant models might not adequately capture the complex relationships among the different pollutants.[43,44] For instance, there might be interactions between pollutants, and complex mixtures of all pollutants might be associated with the risk only when combined. Of particular interest is the combined effect of various constituents of an air pollution mixture and whether the combined effect differs from the effects of those individual pollutants within the mixture: combined pollutants might elicit health effects that are synergistic, additive, or less than additive. More advanced multipollutant statistical approaches might be needed to capture those complexities, and the Panel noted this topic as an important avenue for further research. Most multipollutant statistical approaches to date, however, cannot accommodate very large datasets such as CanCHEC. The development of multipollutant statistical approaches remains an active area of research, and many advanced approaches have been developed, particularly for omics analyses and in studies of the exposome.[45–47]

Ideally, in multipollutant modeling, pollutants should be measured and modeled at the same spatial and temporal scale. That approach was not able to be implemented in the current study because there were several unforeseen setbacks partly due to the COVID-19 pandemic. Those setbacks led to incomplete mobile monitoring for NO_2 and O_3, which precluded the development of new high-resolution exposure models. Hence, those pollutants (and $PM_{2.5}$) were obtained from previous models and were available only at a much coarser resolution. The Panel would also recommend investigating NO_2 and O_3 as separate terms in the health model instead of O_x (a weighted combination of NO_2 and O_3) to facilitate comparison with other (non-CanCHEC) studies.

OMISSION OF LIFESTYLE FACTORS IN COHORT APPLICATION

One study limitation is the lack of information on potential individual lifestyle covariates, such as smoking, in the health analyses. The investigators briefly discussed why they think the omission of lifestyle factors is not an important issue in the current analyses. However, the Panel thought they could have deepened that discussion.

A risk factor for mortality (e.g., smoking) confounds associations of air pollution with mortality if there is a correlation with air pollution exposure and if air pollution is not a determinant of that risk factor. Correlations between air pollution and lifestyle factors can be mediated by socioeconomic status, and typically, the concern of residual confounding by lifestyle factors is reduced by the adjustment for multiple socioeconomic variables at the individual and neighborhood levels.[48] In the current study, the authors did adjust for various individual-level sociodemographic factors: education, occupation, income, marital status, and minority and immigrant status. Those adjustments alleviate the concern to some extent.

There is often an implicit assumption that lack of adjustment for individual-level confounders such as smoking would lead to an overestimation of air pollution risks, although this assumption has been refuted previously.[49] Also, in earlier CanCHEC studies[26] and the European ELAPSE project,[50] smaller effect estimates were reported in the administrative cohorts that lacked lifestyle variables compared to the smaller survey cohort and the ELAPSE pooled cohort that had individual lifestyle information available. In the US Medicare study, smoking was found to be correlated only weakly with air pollution exposure conditional on the other covariates included in the model.[51] In recent systematic reviews of the association between $PM_{2.5}$ and mortality, the meta-analytical effect estimates were not affected by excluding administrative cohorts that did not have individual lifestyle data available,[52,53] implying that lack of data on smoking might not be critical in air pollution studies.

GENERALIZABILITY OF FINDINGS

Although the application to a large representative cohort in Toronto and Montreal was considered a strength, the Panel had some concerns about the generalizability of the findings. Compared to other countries, Canada typically has some of the cleanest ambient air quality and can be cold in winter. Lower ambient temperatures favor the formation of greater numbers of the smallest particles (<50 nm) in the roadside environment. Relatively low temperature is associated with higher rates of new particle formation and slower atmospheric dispersion, indicating that UFP concentrations will generally be higher in the winter than in summer.[9,54]

Canada was an ideal setting for one of the three studies in HEI's comprehensive research initiative to investigate the health effects of long-term exposure to low levels of $PM_{2.5}$, which was recently completed.[55] CanCHEC was also used for that study, but that study included participants nationwide and was not restricted to the two largest Canadian cities. The $PM_{2.5}$ concentration was low (10.2 μg/m^3) in the current study, and due to the limited within-city spatial contrast, $PM_{2.5}$ was not investigated as a main effect — only as a confounder. The mean UFP number concentrations (14,000 particles/cm^3) were typical of urban background areas in North America and a little lower than typical near-roadway locations.[11] The mean BC concentrations (1.1 μg/m^3) were at the low end of what is seen in other epidemiological studies, with concentrations typically ranging from 0.65 μg/m^3 to 3.9 μg/m^3.[5]

Hence, the findings in the current study of two Canadian cities might not hold in other settings, also because the monitoring was conducted during the COVID-19 pandemic. Thus, caution is warranted in generalizing the findings.

OTHER LONG-TERM AIR POLLUTION AND HEALTH STUDIES ON UFPS AND BC

Current evidence on the long-term health effects of UFPs is limited, and existing studies have not revealed definitive evidence for independent health effects of UFPs from $PM_{2.5}$.[3,4,9,16] Although no single long-term study was identified in the HEI 2013 review, Ohlwein and colleagues[16] identified 10 epidemiological studies that considered long-term UFP exposures, with only one study on mortality.[56] Additional cohort studies on UFPs have been published since the Ohlwein review, including two recent studies on mortality.[34,57]

The few studies of long-term exposure to UFPs and cardiorespiratory disease or lung cancer have been limited mainly to populations within one or a few cities.[21,33,35] Nationwide studies have emerged more recently.[34,57–59] See **Commentary Table 3** for a summary of selected studies. The current study adds to the small evidence base, but a clear research gap remains, and additional long-term UFP health studies are needed. Routine, long-term monitoring of UFPs and BC would be valuable to support such studies.

Compared to UFPs, there is more literature on the long-term health effects of BC, but similar questions remain as to the independent health effects of BC, particularly given the often-high correlation with UFPs, NO_2, and other combustion-related indicators.[15, 61–63]

SUMMARY AND CONCLUSION

Dr. Weichenthal and colleagues have assessed associations of long-term exposures to outdoor UFPs and BC with mortality in Toronto and Montreal, Canada, using several different exposure modeling approaches. The research was well-motivated and addressed a clear research gap. The extensive year-long mobile monitoring campaign and the rigorous development and innovative features of the new high-resolution models were considered to be strengths of the study. Another strength was the use of a large representative sample of Canadian adults to evaluate the sensitivity of the epidemiological analyses to different exposure assessment approaches.

The exposure models that combined LUR and CNN model predictions performed slightly better as compared to LUR models alone. The combined model explained half or more of the observed spatial variation in UFPs and BC and was considered the main exposure model in the health analyses. The study documented that long-term exposures to UFP number concentrations and BC were positively associated with mortality in single-pollutant models. The effect estimates were sensitive to adjustment for co-pollutants and UFP size. Associations between UFP number concentrations and mortality increased after adjusting for UFP size, whereas associations between BC and mortality became generally weaker or null. Generally, similar findings were reported for BC across various alternative exposure assessment approaches, including without backcasting and accounting for mobility patterns. For UFP number concentrations, the association's magnitude — but not the direction — differed substantially across the various alternative exposure approaches. Although the Panel broadly agreed with the investigators' conclusions, some limitations should be considered when interpreting the results.

Importantly, the adjustment for mean UFP size in health analyses of outdoor UFP number concentrations and BC was intriguing. However, it remains unclear how to interpret UFP size and this remains an area that warrants further research. More advanced multipollutant statistical approaches might be needed to capture the complex relationships among the different pollutants. Some uncertainties were noted in the monitoring and exposure assessment approaches, such as the lack of fixed-site monitoring and the temporal mismatch between the period captured by the mobile measurements and the exposure window most relevant for epidemiological purposes. The findings in the current study of two Canadian cities might not be generalizable to other settings, partly due to distinct characteristics of these cities. Data from mobile monitoring are useful for developing machine learning models and other exposure models but can have important limitations. Therefore, careful consideration is needed when using them in exposure assessment or epidemiological analyses.

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Commentary Table 3. Summary of Selected Studies on UFP Long-Term Exposure and Mortality Studies (in order of publication year)

Reference	Study Name	Location	Study Period	Sample Size	Exposure Assessment	Mean UFPs[a]	(Mortality) Outcome	Hazard Ratio	Increment
Ostro et al.,[56] 2015	California Teachers Study	California, United States	1995–2007	101,884	CTM	1,293	All–cause Cardiovascular Respiratory	1.01 (0.98–1.05) 1.02 (0.97–1.08) 1.01 (0.93–1.10)	969 ng/m^3
Weichenthal et al.,[35] 2017	ONPHEC	Toronto, Canada	2001–2014	1.06 million	LUR	24,473	Lung cancer (incidence)	1.00 (0.97–1.04)	10,097 particles/cm^3
Downward et al.,[21] 2018	EPIC-NL	Four cities in the Netherlands	1993–2015	33,831	LUR	11,110	Cardiovascular events (fatal + nonfatal)	1.18 (1.03–1.34)	10,000 particles/cm^3
Bai et al.,[33] 2019	ONPHEC	Toronto, Canada	1996–2012	1.2 million	LUR	28,453	Acute myocardial infarction (fatal + nonfatal)	1.05 (1.02–1.07)	10,029 particles/cm^3
Rodins et al.,[60] 2020	Heinz Nixdorf Recall Study	Ruhr areas, Germany	2000–2014	4,105	CTM	3,745	Cardiovascular events (fatal + nonfatal)	1.07 (0.93–1.23)	623 particles/cm^3
Pond et al.,[34] 2022	NHIS	United States	1986–2015	617,997	LUR	6,812	All–cause Cardiopulmonary	1.03 (1.02–1.04) 1.04 (1.02–1.06)	5,007 particles/cm^3
Bouma et al.,[57] 2023	DUELS	Netherlands	2013–2019	10.8 million	LUR	11,621	All–cause Cardiovascular Respiratory Lung cancer	1.012 (1.010–1.015) 1.005 (1.000–1.011) 1.022 (1.013–1.032) 1.038 (1.028–1.048)	2,723 particles/cm^3
Poulsen et al.,[58,59] 2023	Nationwide cohort	Denmark	2005–2017	2.0 million	Dispersion	11,106	Stroke (fatal + nonfatal) Acute myocardial infarction (fatal + nonfatal)	1.04 (1.03–1.05) 1.04 (1.03–1.06)	4,248 particles/cm^3

CTM = chemical transport model; LUR = land use regression; DUELS = Dutch Environmental Longitudinal Study; EPIC-NL = European Prospective Investigation into Cancer and Nutrition–Netherlands; NHIS = National Health Interview Survey; ONPHEC = Ontario Population Health and Environment Cohort.

[a] Units are in the increment column.

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ABBREVIATIONS AND OTHER ITEMS

BC	black carbon
CanCHEC	Canadian Census Health and Environment Cohort
CI	confidence interval
CNN	convolutional neural network
EC	elemental carbon
HR	hazard ratio
ICD-10	*International Classification of Diseases, Tenth Revision*
IQR	interquartile range
LUR	land use regression
MSE	mean square error
NAAQS	National Ambient Air Quality Standards
NO_2	nitrogen dioxide
NO_x	nitrogen oxides
O_3	ozone
O_x	oxidant gases (a combination of NO_2 and O_3)
PM	particulate matter
PM_{10}	particulate matter ≤10 µm in aerodynamic diameter
$PM_{2.5}$	particulate matter ≤2.5 µm in aerodynamic diameter
RFA	request for applications
RMSE	root mean square error
SD	standard deviation
UFP	ultrafine particles
US EPA	United States Environmental Protection Agency
WHO	World Health Organization

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HEI

Health Effects Institute

75 Federal Street

Suite 1400

Boston, Massachusetts 02110, USA

+1-617-488-2300

healtheffects.org