ORIGINAL ARTICLE

Airborne Nanoparticle Concentrations Are Associated with Increased Mortality Risk in Canada's Two Largest Cities

Marshall Lloyd[1], Toyib Olaniyan[2], Arman Ganji[3], Junshi Xu[3], Alessya Venuta[1], Leora Simon[1], Mingqian Zhang[3], Milad Saeedi[3], Shoma Yamanouchi[3], An Wang[3], Alexandra Schmidt[1], Hong Chen[4], Paul Villeneuve[5], Joshua Apte[6], Eric Lavigne[7], Richard T. Burnett[4], Michael Tjepkema[2], Marianne Hatzopoulou[3], and Scott Weichenthal[1]

[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Québec, Canada; [2]Statistics Canada, Ottawa, Ontario, Canada; [3]Department of Civil and Mineral Engineering, University of Toronto, Toronto, Ontario, Canada; [4]Health Canada, Ottawa, Ontario, Canada; [5]Department of Neuroscience, Carleton University, Ottawa, Ontario, Canada; [6]Department of Civil and Environmental Engineering, University of California, Berkeley, Berkeley, California; and [7]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada

ORCID IDs: 0000-0001-7252-7344 (M.L.); 0000-0002-1222-3987 (T.O.); 0000-0001-9462-5324 (A.G.); 0000-0003-2834-2291 (J.X.); 0000-0002-2508-5130 (A.V.); 0000-0001-6360-4141 (L.S.); 0000-0002-2491-9981 (M.Z.); 0000-0002-5681-1342 (M.S.); 0000-0002-2019-2308 (S.Y.); 0000-0002-1874-2702 (A.W.); 0000-0002-6448-6367 (A.S.); 0000-0003-0353-3622 (H.C.); 0000-0001-7786-7997 (P.V.); 0000-0002-2796-3478 (J.A.); 0000-0001-6146-9839 (E.L.); 0000-0001-6772-4239 (R.T.B.); 0000-0002-7107-7086 (M.H.); 0000-0002-9634-5323 (S.W.).

Abstract

Rationale: Outdoor fine particulate air pollution (particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{2.5}$) contributes to millions of deaths around the world each year, but much less is known about the long-term health impacts of other particulate air pollutants, including ultrafine particles (a.k.a. nanoparticles), which are in the nanometer-size range (<100 nm), widespread in urban environments, and not currently regulated.

Objectives: We sought to estimate the associations between long-term exposure to outdoor ultrafine particles and mortality.

Methods: Outdoor air pollution levels were linked to the residential addresses of a large, population-based cohort from 2001 to 2016. Associations between long-term exposure to outdoor ultrafine particles and nonaccidental and cause-specific mortality were estimated using Cox proportional hazards models.

Measurements and Main Results: An increase in long-term exposure to outdoor ultrafine particles was associated with an increased risk of nonaccidental mortality (hazard ratio = 1.073; 95% confidence interval = 1.061–1.085) and cause-specific mortality, the strongest of which was respiratory mortality (hazard ratio = 1.174; 95% confidence interval = 1.130–1.220). We estimated the mortality burden for outdoor ultrafine particles in Montreal and Toronto, Canada, to be approximately 1,100 additional nonaccidental deaths every year. Furthermore, we observed possible confounding by particle size, which suggests that previous studies may have underestimated or missed important health risks associated with ultrafine particles.

Conclusions: As outdoor ultrafine particles are not currently regulated, there is great potential for future regulatory interventions to improve population health by targeting these common outdoor air pollutants.

Keywords: ambient air pollution; particle number concentrations; particulate matter; respiratory mortality; ultrafine particles

Outdoor fine particulate air pollution (particulate matter with an aerodynamic diameter ≤2.5 μm; $PM_{2.5}$) contributes to millions of deaths around the world each year (1, 2), but much less is known about the long-term health impacts of other particulate air pollutants, including ultrafine particles (UFPs; a.k.a. nanoparticles). UFPs are in the nanometer-size range (<100 nm). Outdoor UFPs contribute little to particle mass concentrations but are produced in large number concentrations (i.e., number of particles per cubic centimeter; pt/cm^3) in urban areas by various combustion (e.g., vehicle traffic) and noncombustion (e.g., brake and tire wear) processes (3–5). For example, in North American cities, outdoor UFPs often range from a few thousand to

(Received in original form November 2, 2023; accepted in final form June 26, 2024)

Supported by the Health Effects Institute (grant 4976-RFA19-1/20-10), an organization jointly funded by the U.S. Environmental Protection Agency (Assistance Award CR 83998101) and certain motor vehicle and engine manufacturers. The contents of this article do not necessarily reflect the views of the Health Effects Institute or its sponsors, nor do they necessarily reflect the views and policies of the Environmental Protection Agency or motor vehicle and engine manufacturers.

Am J Respir Crit Care Med Vol 210, Iss 11, pp 1338–1347, Dec 1, 2024

Originally Published in Press as DOI: 10.1164/rccm.202311-2013OC on June 26, 2024
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Outdoor fine particulate air pollution (particulate matter with an aerodynamic diameter $\leq$2.5 μm) contributes to millions of deaths around the world each year, but much less is known about the long-term health impacts of other particulate air pollutants, including ultrafine particles (UFPs; a.k.a. nanoparticles). UFPs deposit efficiently in the human lung, where they can translocate to the systemic circulation and deposit into various organs, leading to oxidative stress and inflammation.

What This Study Adds to the Field: We conducted a cohort study of long-term exposures to outdoor UFP number concentrations and observed consistent associations with nonaccidental and cause-specific mortality in Canada's two largest cities. Our analysis suggests that UFP size must be considered to obtain unbiased estimates of UFP number concentrations, and excluding information on UFP size can result in an underestimation of health risks related to UFP exposure.

hundreds of thousands of particles per cubic centimeter, with the highest concentrations typically observed near major roadways (4, 6). More important, UFPs deposit efficiently in the human lung and can translocate to the systemic circulation and deposit into various organs (5, 7–11). Once deposited, UFPs contribute to oxidative stress and trigger inflammation, leading to possible tissue damage, DNA modification, and disruption of cell growth (5, 7, 9, 10, 12–15). Although regulatory actions have dramatically reduced outdoor $PM_{2.5}$ mass concentrations in North America (16), outdoor UFPs are not currently regulated, and UFP concentrations are not necessarily reduced by existing regulations for $PM_{2.5}$ (4, 6, 17–19). For example, in New York State, UFP concentrations recently rose over several years of $PM_{2.5}$ decline (18), and during 20 years of continuous monitoring in Boston, UFP reductions were smaller than expected with respect to $PM_{2.5}$ reductions (19). The World Health Organization has proposed classifying UFP particle number concentrations above 10,000 pt/cm^3 as "high" (20); thus, large populations remain highly exposed to these pollutants both in North America and around the world (4, 21–29).

To date, relatively few epidemiological studies have examined the long-term health impacts of outdoor UFPs, and existing evidence supports possible associations with incident myocardial infarction, heart failure, hypertension, stroke, and brain tumors, with less consistent evidence observed for respiratory outcomes (6, 30–35). Studies of outdoor UFPs and nonaccidental or cause-specific mortality are particularly scarce, with one North American study reporting a positive association between UFPs and ischemic heart disease mortality (34) and one study in the Netherlands reporting positive associations between UFPs and nonaccidental mortality, respiratory mortality, and lung cancer mortality (36). A second study in the United States reported positive associations between long-term UFP exposures and mortality, but these estimates were sensitive to the inclusion of $PM_{2.5}$ in the models (37). Overall, epidemiological evidence regarding the potential relationship between outdoor UFPs and mortality is urgently needed, as mortality data play a critical role in driving cost–benefit calculations used in developing new regulatory interventions.

In this study, we examined the relationship between long-term exposures to outdoor UFPs and nonaccidental and cause-specific mortality in a population-representative cohort of approximately 1.5 million adults residing in Canada's two largest cities, Toronto and Montreal. Our high-resolution UFP exposure estimates were based on new, state-of-the-art models (22) that combine information from traditional geographic information systems as well as information captured in aerial images through machine-learning methods. Overall, our findings indicate that outdoor UFPs are associated with increased risks of both nonaccidental and cause-specific mortality independent of traditional outdoor air pollutants, including $PM_{2.5}$ and oxidant gases (i.e., NO_2, and O_3). Moreover, we estimate that outdoor UFPs contribute to approximately 1,100 nonaccidental deaths annually in Montreal and Toronto, suggesting that air quality regulations for outdoor UFPs could have important public health benefits.

Some of the results of this study have been previously reported in the form of an abstract (38).

Methods

Study Population and Mortality Outcomes

The Canadian Census Health and Environment Cohorts (CanCHECs) are a collection of probabilistically linked population-based datasets that merge data from respondents of the Canadian long-form census with administrative health data (i.e., mortality records) and annual residential postal code histories through the Statistics Canada

Author Contributions: M.L.: software, formal analysis, investigation, data curation, writing – original draft, and supervision. T.O.: primary software, primary formal analysis, investigation, and data curation. A.G.: software, formal analysis, investigation, and data curation. J.X.: software, formal analysis, investigation, and data curation. A.V.: investigation, data curation, and project administration. L.S.: investigation, data curation, and project administration. M.Z.: investigation and data curation. M.S.: software, formal analysis, investigation, and data curation. S.Y.: investigation and data curation. A.W.: investigation and data curation. A.S.: writing (review and editing). H.C.: writing (review and editing). P.V.: writing (review and editing). J.A.: writing (review and editing). E.L.: writing (review and editing). R.T.B.: methodology and writing (review and editing). M.T.: writing (review and editing) and supervision. M.H.: conceptualization, methodology, investigation, resources, writing (review and editing), and supervision. S.W.: conceptualization, methodology, investigation, resources, writing (review and editing), supervision, project administration, and funding acquisition.

Correspondence and requests for reprints should be addressed to Scott Weichenthal, Ph.D., Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, 2001 McGill College Avenue, Room 1277, Montreal, QC H3A 1G1, Canada. E-mail: scottandrew.weichenthal@mcgill.ca.

This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Social Linkage Data Environment (39). In this study, multiple CanCHEC datasets (Census Years 1991, 1996, 2001, and 2006) were used to create a study population that included noninstitutionalized respondents under the age of 90 who lived in Toronto or Montreal for at least 1 year between 1998 and the end of follow-up in 2016. To estimate time-varying exposures to outdoor air pollutants, we used residential postal code histories from mailing addresses reported on annual income tax filings to account for residential mobility both within and between the cities of Toronto and Montreal. Mortality outcomes included: nonaccidental (International Classification of Diseases, 10th revision [ICD-10]: A–R), cardiovascular (ICD-10: I10–I69), cardiometabolic (ICD-10: I10–I69 plus E10–E14), ischemic heart disease (ICD-10: I20–I25), cerebrovascular (ICD-10: I60–I69), nonmalignant respiratory (ICD-10: J00–J99), and lung cancer (ICD-10: C33–C34). The creation of the CanCHEC dataset was authorized by Statistics Canada senior management (reference number: 019-2019), as per the Directive on Microdata Linkage and this study was approved the McGill University Institutional Review Board, study number A12-M61-19A(19-12-04).

Outdoor Air Pollution Exposure Assessment

Estimates of annual average outdoor UFP number concentrations (pt/cm^3) and mean UFP size (in nanometers) were obtained from recently developed exposure models for Montreal and Toronto (black carbon data were also obtained through these models) (22). Briefly, these models were based on large-scale mobile monitoring campaigns conducted across each city over a 1-year period between 2020 and 2021, and final models explained the majority of spatial variations in these pollutants across each city (22). Historical values for traffic emissions (nitrogen oxides; NO_x) were used to project estimated UFP and black carbon concentrations into the past (1998–2016; i.e., back-cast) for use in epidemiological analyses. These model estimates were linked to cohort members using six-digit postal codes (about the size of a city block face). All exposures were assigned using a 3-year moving average with a 1-year lag to ensure that estimates of long-term exposures preceded the outcome, as postal codes in the CanCHECs are updated at the end of the year. For example, UFP exposures in 2001 were the average of the pollutant estimates in 1998, 1999, and 2000. The same approach was used to link estimates of outdoor $PM_{2.5}$ mass concentrations and oxidant gases (O_x; a combination of NO_x and O_3) to cohort members (40–42). Previous research suggests that combining NO_2 and O_3 into a single measure of exposure to O_x on the basis of their redox potentials (43) is more relevant to mortality than treating them as separate exposures (44–46).

(For additional details on air pollution exposure assessment, including the machine-learning model and the process of back-casting, *see* the online supplement.)

Statistical Analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) for mortality outcomes per 10,000 pt/cm^3 increase in annual average outdoor UFP number concentration. The assumed relationship between our main exposure of interest (i.e., outdoor UFP number concentrations) and mortality along with covariates identified and included as potential confounding variables is presented in an acyclical graph (*see* Figure E1 in the online supplement). Specifically, all models were stratified by age (5-year groups), immigrant status, sex, and census cycle and were additionally adjusted for education, occupational level, income, marital status, and visible minority status. To account for long-term exposure to other air pollutants that have been associated with mortality, the models also adjusted for residential outdoor mass concentrations of black carbon and $PM_{2.5}$, and for O_x (a combined metric of NO_2 and O_3) (47). In addition, models were adjusted for mean UFP size. This was done to adjust for possible confounding bias that could occur if UFP size is independently associated with mortality and UFP number concentrations (outdoor UFPs tend to be smaller at higher number concentrations, so this relationship is typically inverse). Penalized spline terms were used for UFP size to capture potential nonlinear associations between UFP size and mortality. This increased the degree of adjustment for confounding by mean UFP size (as opposed to adjusting using a linear term), but as a result, no HRs were estimated for mean UFP size in the main analysis. As sensitivity analyses, our main models for outdoor UFPs and black carbon (with and without back-casting) were also examined with an additional adjustment for neighborhood-level socioeconomic status (SES) using the Material Deprivation metric (five levels) (48), developed by Statistics Canada at the dissemination-area level (which include 400–700 people), which captures multiple aspects of neighborhood-level SES including the proportion of the population ages $\geqslant$20 years without a high school diploma, the proportion of families who are lone-parent families, the proportion of the population that receives government transfer payments, the proportion of the population ages $\geqslant$15 years who are unemployed, the proportion of the population that is considered low income, and the proportion of households living in dwellings that are in need of major repair. The time scale used was time on study, and follow-up time started on January 1, 2001 for the 1991 and 1996 cohorts and census day for the 2001 and 2006 CanCHECs. Subjects were censored if they moved out of the study area, were lost to follow-up, reached the end of follow-up at the end of 2016, or if they died from a cause other than the outcome of interest.

To gain some understanding of the possible scale of mortality that might plausibly be attributable to long-term exposure to outdoor UFPs in in Montreal and Toronto, we used the estimated HR for nonaccidental mortality to estimate the possible mortality burden attributable to outdoor UFPs in the Montreal and Toronto populations. This approach assumed a causal relationship between exposure and mortality, a linear association between exposure and the logarithm of the mortality HR, constant confounding of the relationship across all levels of exposure, and that other mortality risks remained unchanged under hypothetical intervention scenarios. In this approach, we set the minimum exposure level to the first percentile of exposure in the cohort. Population attributable fractions (PAFs) were calculated for each dissemination area (small, relatively stable geographical units with an average population of 400–700 people) using the following formula from Ferguson (2020) (49):

$$PAF = 1 - \frac{P(Y = 1 \mid UFP_{min}, C)}{P(Y = 1 \mid UFP_{\bar{x}}, C)}.$$

With our assumptions, this simplified to the following equation:

$$PAF = 1 - e^{(-\beta_{UFP} * (UFP_{\bar{x}} - UFP_{\min x}))},$$

where β_{UFP} is the coefficient for UFP

number concentration from the Cox model (scaled to 1 pt/cm^3), $UFP_{\bar{x}}$ is the median UFP number concentration within a given dissemination area, and UFP_{min} is the minimum UFP number concentration (5,755 pt/cm^3) exposure. The number of annual nonaccidental deaths attributable to outdoor UFP number concentrations was calculated by multiplying a dissemination area's PAF by the estimated total number of deaths within said dissemination area. The number of deaths were estimated using age- and sex-specific populations in Montreal and Toronto from the 2016 Census and Canadian age- and sex-specific nonaccidental mortality rates from 2016. We examined changes in the nonaccidental mortality burden under hypothetical scenarios of reduced population exposure to outdoor UFPs. These scenarios included *1*) reduction of all outdoor UFP number concentrations by 25%, *2*) limiting outdoor concentrations to a maximum of 15,000 pt/cm^3, and *3*) limiting outdoor concentrations to a maximum of 10,000 pt/cm^3.

Nonlinear concentration–response relationships for outdoor UFP number concentrations and UFP size were examined using penalized splines with generalized cross-validation used to select the optimal smoothness parameters (50–52). To explore the impact of back-casting UFP and black carbon exposures, we repeated the main epidemiological analysis without back-casting (BC) estimated exposures. As an additional sensitivity analysis, we examined two additional approaches to modeling UFP exposures and conducted epidemiological analyses separately using the land use regression model and the machine-learning model that were combined to make our main exposure model (22). The purpose of this analysis was to examine potential differences in the magnitudes of associations detected for each modeling approach. To explore magnitude and direction of confounding bias cause by UFP size, we examined models without adjusting for mean UFP size and with linear terms instead of spline terms. Finally, to investigate the impact of adjusting for $PM_{2.5}$, we repeated the main analysis without adjusting for $PM_{2.5}$.

Results

In total, our study population included over 1,544,000 adults who were followed for a total of 22,848,100 person-years, with 174,240 nonaccidental, 46,270 cardiovascular, 51,790 cardiometabolic, 26,570 ischemic heart disease, 9,310 cerebrovascular, 17,830 respiratory, and 16,970 lung cancer deaths occurring during the follow-up period. (For descriptive statistics for cohort members, *see* Table E1). Annual average residential outdoor UFP number concentrations ranged from 3,242 to 162,932 pt/cm^3 (SD = 6,299), and mean UFP size ranged from 17.8 to 49.4 nm (SD = 3.43) across Montreal and Toronto. Outdoor $PM_{2.5}$ mass concentrations ranged from 1.4 to 18.4 μg/m^3, but variation in $PM_{2.5}$ exposure within the cohort was relatively low (SD = 1.56). UFP number concentrations were inversely correlated with mean UFP size (Pearson $r = -0.54$), moderately correlated with black carbon (Pearson $r = 0.38$), and weakly correlated with $PM_{2.5}$ (Pearson $r = 0.10$) and O_x (Pearson $r = 0.17$). (For additional descriptive statistics, including correlations between all pollutants, *see* Table E2).

HRs that describe observed associations between outdoor UFP number concentrations and mortality are shown in Figure 1. Outdoor UFPs were positively associated with all mortality outcomes, with the strongest association observed for respiratory mortality (HR = 1.174; 95% CI = 1.130–1.220) and ischemic heart disease mortality (HR = 1.094; 95% CI = 1.062–1.126). Long-term exposure to O_x was also positively associated with all mortality outcomes except lung cancer, and outdoor black carbon concentrations were weakly associated with nonaccidental, cardiovascular, and cardiometabolic mortality (*see* Table E3). Figure 2 shows the HRs for outdoor UFP number concentrations with and without adjusting for mean UFP size using a linear term or spline term (for numeric values, *see* Table E4). For all mortality outcomes except lung cancer, HRs were considerably lower when UFP size was not included in the model. This was particularly true for cerebrovascular mortality, where confounding by UFP size (i.e., not adjusting for UFP size) resulted in a null association with outdoor UFP number concentrations. Omitting mean UFP size from the models had very little impact on the black carbon and O_x associations with mortality (*see* Tables E5 and E6).

We estimate that 5.3% (95% CI = 4.5–6.1) and 4.8% (95% CI = 4.0–5.6) of nonaccidental mortality was attributable to outdoor UFPs in Montreal and Toronto, respectively. For 2016, this represented an annual mortality burden of 501 (95% CI = 421–580) and 668 (95% CI = 562–773) nonaccidental deaths in Montreal and Toronto, respectively. Of the three scenarios of reduced outdoor UFPs examined, limiting number concentrations to 10,000 pt/cm^3 resulted in the greatest change in nonaccidental deaths, with an estimated 246 (95% CI = 204–285) and 328 (95% CI = 276–379) fewer deaths in Montreal and Toronto, respectively (results for all three scenarios are presented in Table 1).

Concentration–response relationships between outdoor UFP number concentrations, UFP size, and nonaccidental, cardiovascular, respiratory, and lung cancer mortality are shown in Figure 3, along with the joint distribution of UFP size and UFP number concentrations (for other outcomes, *see* Figure E2). For nonaccidental mortality, the concentration–response curve for UFP number concentrations (Figure 3A) flattens at elevated UFP levels (above approximately 22,500 pt/cm^3), whereas the concentration–response curve for UFP size increases continuously as UFP size increases (Figure 3B). Figure 3B shows that the distribution of UFP size is heterogeneous across the range of UFP number concentrations, with a lower proportion of the most harmful particle sizes (i.e., those in the larger size range of UFPs based on Figure 3B) present at higher UFP number concentrations, thus explaining the observed decrease in the concentration response curve observed at higher concentrations in Figure 3A. A similar pattern was observed for other mortality outcomes, with the possible exception of lung cancer whereby the curve for UFP size flattens around approximately 31 nm and stays flat instead of peaking at the largest particle sizes. The concentration–response curve for UFP number concentration and lung cancer also decreases more dramatically at elevated UFP number concentrations.

Results of sensitivity analyses examining land use regression and machine-learning exposure models separately are presented (*see* Tables E7 and E8). These results were consistent with the main analyses, and in general, HRs estimated using UFP exposures based on machine-learning models and aerial images resulted in associations that were stronger than those based on traditional land use regression models. Results from repeating the main epidemiological analysis without back-casting exposures are also

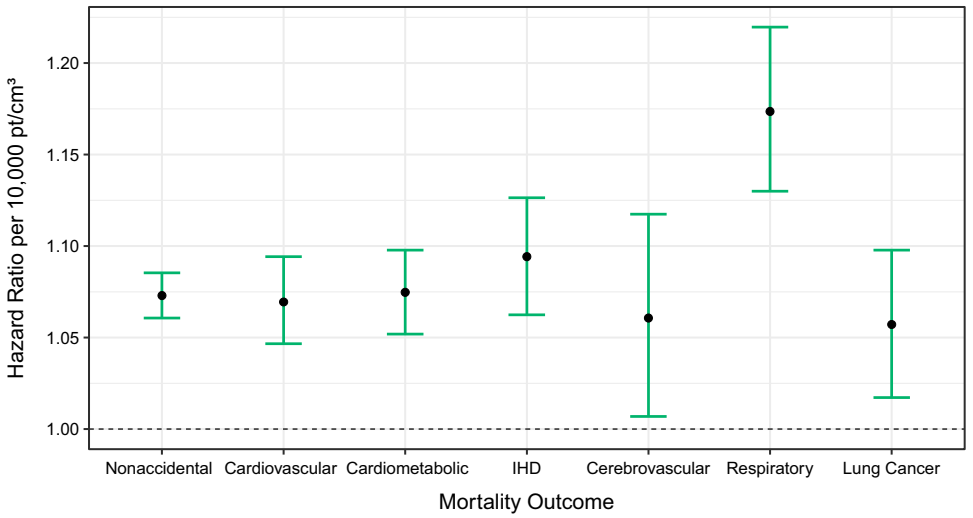

Figure 1. Hazard ratios (95% confidence interval) for an increase of 10,000 particles per cubic centimeter (pt/cm^3) in long-term average outdoor ultrafine particle number concentration and mortality. All models are adjusted for sociodemographic variables, mass concentrations of particulate matter with an aerodynamic diameter ⩽2.5 μm, and black carbon, oxidant gases, and mean ultrafine particle size.

presented (*see* Tables E9 and E10) and are similar to the results from the main analysis. $PM_{2.5}$ exposure was not associated with mortality, and the UFP and BC HRs remained virtually unchanged, regardless of $PM_{2.5}$ adjustment (*see* Tables E11, E12, and E13). Finally, repeating our main analyses for outdoor UFPs and black carbon with additional adjustment for neighborhood-level SES had little impact on observed associations or our overall conclusions (*see* Table E14). Specifically, the magnitude of association between outdoor UFPs and cerebrovascular mortality decreased slightly, but all other associations did not meaningfully change.

Discussion

In this population-based cohort study, we followed a large population of adults in Canada's two largest cities and found consistent positive associations between long-term exposure to outdoor UFP number concentrations and both nonaccidental and cause-specific mortality. These associations were independent of other outdoor air pollutants, including $PM_{2.5}$ and O_x (i.e., O_3 and NO_2). The associations that we observed persisted when different exposure models were used. It is important to note that our analysis considered possible confounding by UFP size, which has not been done in previous studies and could result in an underestimation of health risks when excluded from the analyses. This was an observational study, but if the associations we observed between long-term UFP

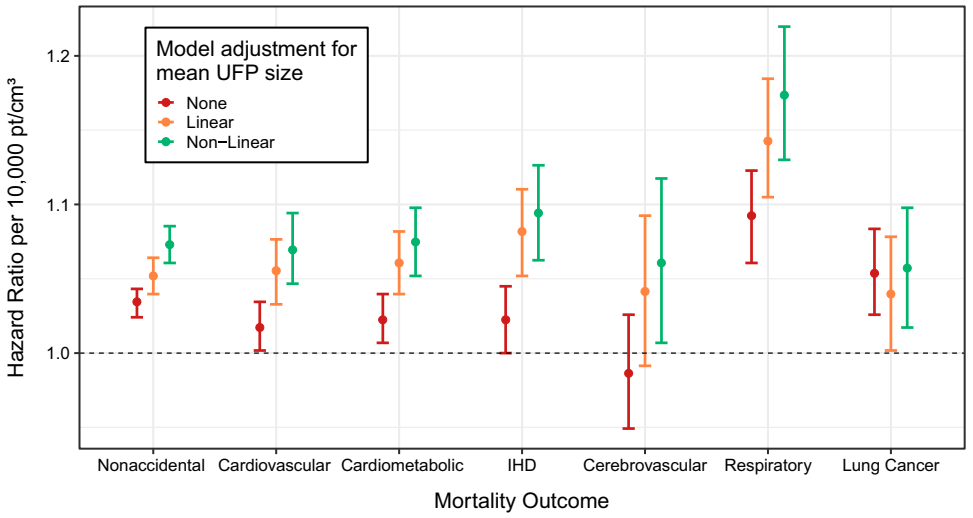

Figure 2. Hazard ratios (95% confidence interval) for an increase of 10,000 particles per cubic centimeter (pt/cm^3) in long-term average outdoor ultrafine particle number concentration and mortality with and without adjustment for mean ultrafine particle size. All models are adjusted for sociodemographic variables, mass concentrations of particulate matter with an aerodynamic diameter ⩽2.5 μm, and black carbon, and oxidant gases. IHD = ischemic heart disease.

Table 1. Potential Changes in Annual Nonaccidental Mortality Burden in Scenarios of Reduced Outdoor UFP Number Concentrations in 2016

Scenario of Reduced Outdoor UFP Number Concentrations	Median Dissemination Area PAF (95% CI)		Estimated Reduction in Number of Annual Nonaccidental Deaths	
	Montreal*	Toronto†	Montreal*	Toronto†
25% Reduction	2.3 (2.0–2.7)	2.2 (1.8–2.5)	223 (187–259)	298 (249–346)
Limit of 15,000 pt/cm^3	0.6 (0.5–0.7)	0.7 (0.6–0.8)	54 (46–63)	107 (90–123)
Limit of 10,000 pt/cm^3	2.7 (2.2–3.1)	2.2 (1.9–2.6)	246 (207–285)	328 (276–379)

Definition of abbreviations: CI = confidence interval; PAF = population attributable fraction; pt/cm^3 = particles per cubic centimeter; UFP = ultrafine particle.
Results presented are based on assumptions including that the relationship between long-term UFP exposure and mortality observed in this study is causal and that other mortality risks would remain unchanged in the hypothetical scenarios.
*Total Montreal 2016 population of 1,378,650 adults (ages 25–90 yr).
†Total Toronto 2016 population of 1,967,820 adults (ages 25–90 yr).

exposure and mortality were assumed to be causal, we estimated that approximately 1,100 nonaccidental deaths each year are attributable to outdoor UFPs in Canada's two largest cities.

As noted earlier, few cohort studies have examined the relationship between long-term exposure to outdoor UFP number concentrations and mortality. A study in California reported a positive association between outdoor UFPs and ischemic heart disease mortality, and no association with respiratory mortality (20), but exposures were estimated at a spatial resolution of approximately 4 km, which is too coarse to capture fine-scale spatial variations that may impact health. Similarly, Pond and colleagues (42) reported positive associations between UFPs and nonaccidental and cause-specific mortality, but the associations disappeared with the inclusion of $PM_{2.5}$ in models. However, that study aggregated UFPs exposures to the census tract level, which likely contributed substantially to exposure measurement error for UFPs (more so than for $PM_{2.5}$), thus making it difficult to directly compare the results to those from studies using high-resolution exposure information. More recently, a cohort study in the Netherlands reported positive associations between outdoor UFP number concentrations and mortality using high-resolution estimates of spatial variations in long-term average outdoor UFP concentrations (22). The study did not adjust for UFP size, but the observed associations with nonaccidental, cardiovascular, and respiratory mortality were very similar in magnitude to those observed in the present study (when expressed on the same scale) when we excluded UFP size from our models. This consistency between recent studies may be, in part, due to the application of exposure models with high spatial resolution (e.g., 100 m × 100 m), whereas the aforementioned studies that observed no associations with mortality applied exposure models with much lower spatial resolution (e.g., 4 km × 4 km) and were likely subject to greater magnitudes of exposure measurement error. Other studies of long-term exposures to UFPs and mortality were not identified, but studies in Denmark have applied UFP exposure models with high spatial resolution to compare the health risks of total outdoor UFP number concentrations as well as traffic-related UFP number concentrations (23, 25). Specifically, in these studies, traffic-related UFPs were more strongly associated with Type 2 diabetes incidence (53), with weaker associations observed for incident myocardial infarctions (35). More generally, these observations and our results for UFP size highlight the importance of using UFP exposure models with high spatial resolution and the fact that we should not treat all UFP (i.e., nanoparticle) number concentrations as though they reflect a single type of exposure.

To our knowledge, this is the first study to address possible confounding by UFP size in studies of the long-term exposure to UFP number concentrations. Indeed, our results suggest that UFP size is independently associated with mortality and varies across the range of outdoor UFP number concentrations present in typical urban environments. As such, UFP size needs to be considered in epidemiological analyses to obtain an unbiased estimate of the health risks of UFP number concentrations. This is consistent with a recent review by Kittelson and colleagues (2022) that recommended using UFP number, mass, and surface area (i.e., size) to properly characterize UFP exposure (54). In our analyses, HRs were approximately four times smaller for cardiovascular mortality and disappeared altogether for cerebrovascular mortality when UFP size was excluded from the models. This suggests that previous studies that only examine UFP number concentrations may have underestimated (or entirely missed) important health risks of long-term exposures to UFPs and could also explain some of the heterogeneity in the current epidemiological literature for UFPs (i.e., magnitude of estimated associations varying across studies) (6, 55, 56).

One intriguing finding from our analysis is that larger particles in the UFP size range were more strongly associated with mortality than smaller particles. Mean UFP size ranged from approximately 18 to 50 nm in our study, and the probability of lung deposition is similar across this range (57, 58). Freshly emitted UFPs can rapidly grow in size as gaseous vapors condense into liquids and as particles aggregate together (i.e., nucleation and accumulation modes) (4, 5, 7), which is consistent with the inverse correlation that we observed between cohort exposure to UFP number concentration and particle size (i.e., very elevated UFP number concentrations tend to consist of smaller particles). As particles in UFP emissions aggregate into larger particles over time, they also interact with the outdoor environment, and this atmospheric aging can enhance the toxicity of the particles (59). Although we cannot conclusively state the reason for the observed concentration–response curve for UFP size in this study, the pattern may be explained by

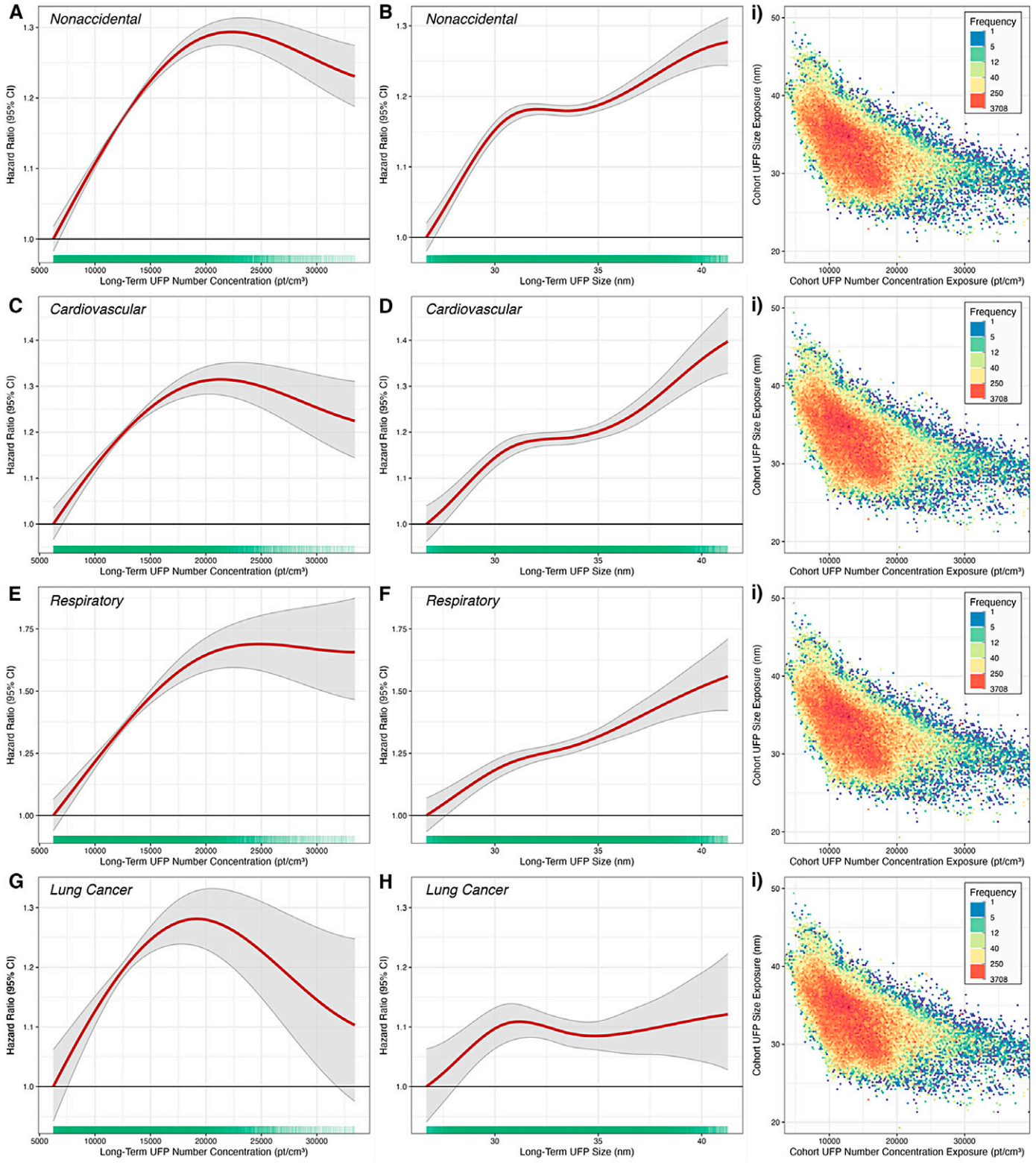

Figure 3. (*A* and *B*) Concentration–response curves of (*A*) ultrafine particle (UFP) number concentration and nonaccidental mortality and (*B*) mean UFP particle size and nonaccidental mortality. (*C* and *D*) Response curves for (*C*) UFP number concentration and (*D*) mean UFP particle size and cardiovascular mortality. (*E* and *F*) Response curves for (*E*) UFP number concentration and (*F*) mean UFP particle size and respiratory mortality, respectively. (*G* and *H*) Response curves for (*G*) UFP number concentration and (*H*) mean UFP particle size and lung cancer mortality. In the rightmost column, (*Bi*), (*Di*), (*Fi*), and (*Hi*) show a two-dimensional frequency plot of cohort joint exposures to UFP number concentration and mean UFP particle size.

differences in particle composition across the UFP size distribution or the propensity for particles of various sizes to reach the systemic circulation once deposited in the lung (5, 10). It may also help explain why the concentration–response curves for UFP number concentrations flattened and dipped at very elevated concentrations (i.e., elevated concentrations were typically fresh emissions of smaller particles that may be less harmful than the relatively larger particles of aged UFP emissions). Future studies should continue to explore the independent health effects of UFP size as well as composition to further elucidate this relationship.

Although this study had several notable strengths, including a large population-based cohort, adjustment for mean UFP size, and high-resolution exposure models that are based extensive year-long monitoring campaigns, it is important to note several limitations. First, the cohort also lacked individual-level data for mortality risk factors such as smoking or body mass index. However, such factors are unlikely to confound the relationship between outdoor UFP concentration and mortality, because they do not affect annual average outdoor pollution levels (*see* DAG in Figure E1). This is consistent with the fact that other studies of ambient air pollution have found that adjusting for such risk factors did not impact risk estimates (33, 36, 44, 60). In addition, the exposure models used in this study were developed using on-road measurements, and the absolute values of our estimated exposures may be more elevated than true long-term exposures.

Finally, as in all epidemiological studies, our study was impacted by exposure measurement error. In particular, one aspect of this error was likely attributable to the fact that the exposure models applied in the cohort analyses were based on data collected during 2020–2021 (with back-casting to 2001), whereas cohort follow-up occurred from 2001 to 2016. However, it is important to note that the aims of the exposure models applied in this study were to capture spatial contrasts in outdoor UFP and BC concentrations within cities. If spatial contrasts in outdoor pollutant concentrations are conserved over time (i.e., high-exposure areas tend to stay high, and low-exposure areas tend to stay low), then estimating past spatial contrasts with a current exposure model should not be a major concern. Indeed, this is likely the case for outdoor UFPs and black carbon, because major sources of these pollutants such as highways, airports, and rail do not move around within cities over the time period of interest. This assumption is supported by the fact that similar spatial patterns in outdoor UFP number concentrations were previously observed in both cities in models that were developed using data collected between 2010 and 2012 (61, 62). Although outdoor UFP concentrations observed in these past studies were higher than current concentrations, owing to systematic differences in study design (i.e., past exposure models focused only on rush hour periods on weekdays), similar spatial contrasts were apparent (higher levels on highways, near airports, etc.), thus supporting our assumption that major sources were stable over time. Therefore, although exposure measurement error likely reduced the precision of HRs estimated in our study, it is not a likely explanation for the observed associations between outdoor UFPs and mortality, given that major sources of UFPs do not move around within cities over the time period of interest, and existing data suggest that spatial patterns in outdoor UFP concentrations have been conserved over time.

In conclusion, we conducted a cohort study of long-term exposures to outdoor UFP number concentrations and observed consistent associations with nonaccidental and cause-specific mortality in Canada's two largest cities. Our analysis suggests that UFP size must be considered to obtain unbiased estimates of UFP number concentrations and that excluding information on UFP size can result in an underestimation of health risks related to UFP exposure. Most important, our results suggest that outdoor UFPs have an important impact on population health that is independent of other outdoor air pollutants. As outdoor UFPs are not currently regulated, there is great potential for future regulatory interventions to improve population health by targeting these common outdoor air pollutants. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA III, *et al.* Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci USA* 2018;115: 9592–9597.
2. Alemayehu YA, Asfaw SL, Terfie TA. Exposure to urban particulate matter and its association with human health risks. *Environ Sci Pollut Res Int* 2020;27:27491–27506.
3. Fussell JC, Franklin M, Green DC, Gustafsson M, Harrison RM, Hicks W, *et al.* A review of road traffic-derived non-exhaust particles: emissions, physicochemical characteristics, health risks, and mitigation measures. *Environ Sci Technol* 2022;56:6813–6835.
4. Presto AA, Saha PK, Robinson AL. Past, present, and future of ultrafine particle exposures in North America. *Atmos Environ X* 2021;10: 100109.
5. Moreno-Ríos AL, Tejeda-Benítez LP, Bustillo-Lecompte CF. Sources, characteristics, toxicity, and control of ultrafine particles: an overview. *Geoscience Frontiers* 2022;13:101147.
6. HEI Panel on the Health Effects of Long-Term Exposure to Traffic-related Air Pollution. Systematic review and meta-analysis of selected health effects of long-term exposure to traffic-related air pollution [Special report 23]. Boston, MA: Health Effects Institute;2022.
7. Stone V, Miller MR, Clift MJD, Elder A, Mills NL, Møller P, *et al.* Nanomaterials versus ambient ultrafine particles: an opportunity to exchange toxicology knowledge. *Environ Health Perspect* 2017;125: 106002.
8. Kreyling WG, Semmler-Behnke M, Möller W. Ultrafine particle-lung interactions: does size matter? *J Aerosol Med* 2006;19:74–83.
9. Knol AB, de Hartog JJ, Boogaard H, Slottje P, van der Sluijs JP, Lebret E, *et al.* Expert elicitation on ultrafine particles: likelihood of health effects and causal pathways. *Part Fibre Toxicol* 2009;6:19.
10. Wang W, Lin Y, Yang H, Ling W, Liu L, Zhang W, *et al.* Internal exposure and distribution of airborne fine particles in the human body: methodology, current understandings, and research needs. *Environ Sci Technol* 2022;56:6857–6869.
11. Bongaerts E, Nawrot TS, Van Pee T, Ameloot M, Bové H. Translocation of (ultra) fine particles and nanoparticles across the placenta; a systematic review on the evidence of in vitro, ex vivo, and in vivo studies. *Part Fibre Toxicol* 2020;17:56.
12. Rao X, Zhong J, Brook RD, Rajagopalan S. Effect of particulate matter air pollution on cardiovascular oxidative stress pathways. *Antioxid Redox Signal* 2018;28:797–818.
13. Song Y, Li X, Du X. Exposure to nanoparticles is related to pleural effusion, pulmonary fibrosis and granuloma. *Eur Respir J* 2009;34: 559–567.

14. Simón-Vázquez R, Lozano-Fernández T, Dávila-Grana A, González-Fernández A. Metal oxide nanoparticles interact with immune cells and activate different cellular responses. *Int J Nanomedicine* 2016;11: 4657–4668.
15. Münzel T, Gori T, Al-Kindi S, Deanfield J, Lelieveld J, Daiber A, *et al.* Effects of gaseous and solid constituents of air pollution on endothelial function. *Eur Heart J* 2018;39:3543–3550.
16. Hammer MS, van Donkelaar A, Li C, Lyapustin A, Sayer AM, Hsu NC, *et al.* Global estimates and long-term trends of fine particulate matter concentrations (1998–2018). *Environ Sci Technol* 2020;54:7879–7890.
17. de Jesus AL, Rahman MM, Mazaheri M, Thompson H, Knibbs LD, Jeong C, *et al.* Ultrafine particles and $PM_{2.5}$ in the air of cities around the world: are they representative of each other? *Environ Int* 2019;129: 118–135.
18. Nair AA, Lin S, Luo G, Ryan I, Qi Q, Deng X, *et al.* Environmental exposure disparities in ultrafine particles and $PM_{2.5}$ by urbanicity and socio-demographics in New York state, 2013–2020. *Environ Res* 2023; 239:117246.
19. Fiffer M, Kang C-M, Requia WJ, Koutrakis P. Long-term impact of $PM_{2.5}$ mass and sulfur reductions on ultrafine particle trends in Boston, MA from 1999 to 2018. *J Air Waste Manag Assoc* 2020;70:700–707.
20. World Health Organization. WHO global air quality guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. Geneva, Switzerland: World Health Organization; 2021. https://www.who.int/publications/i/item/9789240034228.
21. Lloyd M, Carter E, Diaz FG, Magara-Gomez KT, Hong KY, Baumgartner J, *et al.* Predicting within-city spatial variations in outdoor ultrafine particle and black carbon concentrations in Bucaramanga, Colombia: a hybrid approach using open-source geographic data and digital images. *Environ Sci Technol* 2021;55:12483–12492.
22. Lloyd M, Ganji A, Xu J, Venuta A, Simon L, Zhang M, *et al.* Predicting spatial variations in annual average outdoor ultrafine particle concentrations in Montreal and Toronto, Canada: integrating land use regression and deep learning models. *Environ Int* 2023;178:108106.
23. Frohn LM, Ketzel M, Christensen JH, Brandt J, Im U, Massling A, *et al.* Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979–2018 – part 1: regional and urban scale modelling and evaluation. *Atmos Environ* 2021;264:118631.
24. Abernethy RC, Allen RW, McKendry IG, Brauer M. A land use regression model for ultrafine particles in Vancouver, Canada. *Environ Sci Technol* 2013;47:5217–5225.
25. Ketzel M, Frohn LM, Christensen JH, Brandt J, Massling A, Andersen C, *et al.* Modelling ultrafine particle number concentrations at address resolution in Denmark from 1979 to 2018 – part 2: local and street scale modelling and evaluation. *Atmos Environ* 2021;264:118633.
26. van Nunen E, Vermeulen R, Tsai MY, Probst-Hensch N, Ineichen A, Davey M, *et al.* Land use regression models for ultrafine particles in six European areas. *Environ Sci Technol* 2017;51:3336–3345.
27. Ge Y, Fu Q, Yi M, Chao Y, Lei X, Xu X, *et al.* High spatial resolution land-use regression model for urban ultrafine particle exposure assessment in Shanghai, China. *Sci Total Environ* 2022;816:151633.
28. Kerckhoffs J, Khan J, Hoek G, Yuan Z, Hertel O, Ketzel M, *et al.* Hyperlocal variation of nitrogen dioxide, black carbon, and ultrafine particles measured with Google Street View cars in Amsterdam and Copenhagen. *Environ Int* 2022;170:107575.
29. Blanco MN, Gassett A, Gould T, Doubleday A, Slager DL, Austin E, *et al.* Characterization of annual average traffic-related air pollution concentrations in the greater Seattle area from a year-long mobile monitoring campaign. *Environ Sci Technol* 2022;56:11460–11472.
30. Bai L, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, *et al.* Associations of long-term exposure to ultrafine particles and nitrogen dioxide with increased incidence of congestive heart failure and acute myocardial infarction. *Am J Epidemiol* 2019;188:151–159.
31. Bai L, Chen H, Hatzopoulou M, Jerrett M, Kwong JC, Burnett RT, *et al.* Exposure to ambient ultrafine particles and nitrogen dioxide and incident hypertension and diabetes. *Epidemiology* 2018;29:323–332.
32. Weichenthal S, Bai L, Hatzopoulou M, Van Ryswyk K, Kwong JC, Jerrett M, *et al.* Long-term exposure to ambient ultrafine particles and respiratory disease incidence in in Toronto, Canada: a cohort study. *Environ Health* 2017;16:64.
33. Weichenthal S, Olaniyan T, Christidis T, Lavigne E, Hatzopoulou M, Van Ryswyk K, *et al.* Within-city spatial variations in ambient ultrafine particle concentrations and incident brain tumors in adults. *Epidemiology* 2020;31:177–183.
34. Ostro B, Hu J, Goldberg D, Reynolds P, Hertz A, Bernstein L, *et al.* Associations of mortality with long-term exposures to fine and ultrafine particles, species and sources: results from the California Teachers Study cohort. *Environ Health Perspect* 2015;123:549–556.
35. Poulsen, AH, Sørensen M, Hvidtfeldt VA, Brandt J, Frohn LM, Ketzel M, *et al.* 'Source-specific' air pollution and risk of stroke in Denmark. *Int J Epidemiol* 2023;52:727–737.
36. Bouma F, Janssen NA, Wesseling J, van Ratingen S, Strak M, Kerckhoffs J, *et al.* Long-term exposure to ultrafine particles and natural and cause-specific mortality. *Environ Int* 2023;175:107960.
37. Pond ZA, Saha PK, Coleman CJ, Presto AA, Robinson AL, Arden Pope C III. Mortality risk and long-term exposure to ultrafine particles and primary fine particle components in a national U.S. cohort. *Environ Int* 2022;167:107439.
38. Lloyd M, Toyib O, Ganji A, Xu J, Venuta A, Simon L, *et al.* Long-term exposure to outdoor ultrafine particles and nonaccidental mortality in a large population-based cohort: persistent associations across different approaches to exposure assessment. Health Effects Institute Conference. April 30–May 2, 2023, Boston, MA.
39. Tjepkema M, Christidis T, Bushnik T, Pinault L. Cohort profile: The Canadian Census Health and Environment Cohorts (CanCHECs). *Health Rep* 2019;30:18–26.
40. Hystad P, Setton E, Cervantes A, Poplawski K, Deschenes S, Brauer M, *et al.* Creating national air pollution models for population exposure assessment in Canada. *Environ Health Perspect* 2011;119:1123–1129.
41. Robichaud A, Ménard R. Multi-year objective analyses of warm season ground-level ozone and $PM_{2.5}$ over North America using real-time observations and Canadian operational air quality models. *Atmos Chem Phys* 2014;14:1769–1800.
42. van Donkelaar A, Martin RV, Spurr RJD, Burnett RT. High-resolution satellite-derived $PM_{2.5}$ from optimal estimation and geographically weighted regression over North America. *Environ Sci Technol* 2015;49: 10482–10491.
43. Bratsch S. Standard electrode potentials and temperature coefficients in water at 298.15 K. *J Phys Chem Ref Data* 1989;18:1–21.
44. Brauer M, Brook JR, Christidis T, Chu Y, Crouse DL, Erickson A, *et al.* Mortality-air pollution associations in low exposure environments (MAPLE): phase 2. *Res Rep Health Eff Inst* 2022;2022:1–91.
45. Weichenthal S, Pinault LL, Burnett RT. Impact of oxidant gases on the relationship between outdoor fine particulate air pollution and nonaccidental, cardiovascular, and respiratory mortality. *Sci Rep* 2017; 7:16401.
46. Crouse DL, Erickson AC, Christidis T, Pinault L, van Donkelaar A, Li C, *et al.* Evaluating the sensitivity of $PM_{2.5}$-mortality associations to the spatial and temporal scale of exposure assessment. *Epidemiology* 2020;31:168–176.
47. Kley D, Geiss H, Mohnen VA. Tropospheric ozone at elevated sites and precursor emissions in the United States and Europe. *Atmos Environ* 1994;28:149–158.
48. Matheson FI, Dunn JR, Smith KLW, Moineddin R, Glazier RH. Development of the Canadian Marginalization Index: a new tool for the study of inequality. *Can J Public Health* 2012;103(8 Suppl 2):S12–S16.
49. Ferguson J, Maturo F, Yusuf S, O'Donnell M. Population attributable fractions for continuously distributed exposures. *Epidemiol Methods* 2020;9:20190037.
50. Eilers PHC, Marx BD. Flexible smoothing with B-splines and penalties. *Stat Sci* 1996;11:89–121.
51. Golub GH, Heath M, Wahba G. Generalized cross-validation as a method for choosing a good ridge parameter. *Technometrics* 1979;21:215–223.
52. Therneau TM. A package for survival analysis in R, 2024. Available from: https://cran.r-project.org/web/packages/survival/index.html.
53. Sørensen M, Poulsen AH, Hvidtfeldt UA, Frohn LM, Ketzel M, Christensen JH, *et al.* Exposure to source-specific air pollution and risk for type 2 diabetes: a nationwide study covering Denmark. *Int J Epidemiol* 2022;51:1219–1229.
54. Kittelson D, Khalek I, McDonald J, Stevens J, Giannelli R. Particle emissions from mobile sources: Discussion of ultrafine particle emissions and definition. *J Aerosol Sci* 2022;159:1–31.
55. Ohlwein S, Kappeler R, Kutlar Joss M, Künzli N, Hoffmann B. Health effects of ultrafine particles: a systematic literature review update of epidemiological evidence. *Int J Public Health* 2019;64:547–559.

56. US EPA & Sacks. Integrated science assessment (ISA) for particulate matter (Final report, Dec 2019). Washington, DC: U.S. Environmental Protection Agency; 2019. Available from: https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=347534.
57. Geiser M, Kreyling WG. Deposition and biokinetics of inhaled nanoparticles. *Part Fibre Toxicol* 2010;7:2.
58. Shang Y, Chen R, Bai R, Tu J, Tian L. Quantification of long-term accumulation of inhaled ultrafine particles via human olfactory-brain pathway due to environmental emissions – a pilot study. *NanoImpact* 2021;22:100322.
59. Lei R, Wei Z, Chen M, Meng H, Wu Y, Ge X. Aging effects on the toxicity alteration of different types of organic aerosols: a review. *Curr Pollut Rep* 2023;9:590–601.
60. Sørensen M, Hvidtfeldt UA, Poulsen AH, Thygesen LC, Frohn LM, Ketzel M, *et al*. The effect of adjustment to register-based and questionnaire-based covariates on the association between air pollution and cardiometabolic disease. *Environ Res* 2022;203:111886.
61. Weichenthal S, Van Ryswyk K, Goldstein A, Shekarrizfard M, Hatzopoulou M. Characterizing the spatial distribution of ambient ultrafine particles in Toronto, Canada: a land use regression model. *Environ Pollut* 2016;208:241–248.
62. Weichenthal S, Van Ryswyk K, Goldstein A, Bagg S, Shekkarizfard M, Hatzopoulou M. A land use regression model for ambient ultrafine particles in Montreal, Canada: a comparison of linear regression and a machine learning approach. *Environ Res* 2016;146:65–72.