American Journal of Epidemiology

Vol. 188, No. 1
DOI: 10.1093/aje/kwy194
Advance Access publication:
August 28, 2018

Original Contribution

Associations of Long-Term Exposure to Ultrafine Particles and Nitrogen Dioxide With Increased Incidence of Congestive Heart Failure and Acute Myocardial Infarction

Li Bai, Scott Weichenthal, Jeffrey C. Kwong, Richard T. Burnett, Marianne Hatzopoulou, Michael Jerrett, Aaron van Donkelaar, Randall V. Martin, Keith Van Ryswyk, Hong Lu, Alexander Kopp, and Hong Chen*

* Correspondence to Dr. Hong Chen, Public Health Ontario, 480 University Avenue, Suite 300, Toronto, ON M5G 1V2, Canada (e-mail: hong.chen@oahpp.ca).

Initially submitted December 4, 2017; accepted for publication August 21, 2018.

Although long-term exposure to traffic-related air pollutants such as nitrogen dioxide has been linked to cardiovascular disease (CVD) mortality, little is known about the association between ultrafine particles (UFPs), defined as particles less than or equal to 0.1 μm in diameter, and incidence of major CVD events. We conducted a population-based cohort study to assess the associations of chronic exposure to UFPs and nitrogen dioxide with incident congestive heart failure (CHF) and acute myocardial infarction. Our study population comprised all long-term Canadian residents aged 30–100 years who lived in Toronto, Ontario, Canada, during the years 1996–2012. We estimated annual concentrations of UFPs and nitrogen dioxide by means of land-use regression models and assigned these estimates to participants' postal-code addresses in each year during the follow-up period. We estimated hazard ratios for the associations of UFPs and nitrogen dioxide with incident CVD using random-effects Cox proportional hazards models. We controlled for smoking and obesity using an indirect adjustment method. Our cohorts comprised approximately 1.1 million individuals at baseline. In single-pollutant models, each interquartile-range increase in UFP exposure was associated with increased incidence of CHF (hazard ratio for an interquartile-range increase (HR_{IQR}) = 1.03, 95% confidence interval (CI): 1.02, 1.05) and acute myocardial infarction (HR_{IQR} = 1.05, 95% CI: 1.02, 1.07). Adjustment for fine particles and nitrogen dioxide did not materially change these estimated associations. Exposure to nitrogen dioxide was also independently associated with higher CHF incidence (HR_{IQR} = 1.04, 95% CI: 1.03, 1.06).

acute myocardial infarction; air pollution; congestive heart failure; incidence; nitrogen dioxide; particulate matter; ultrafine particles

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; CVD, cardiovascular disease; CI, confidence interval; HR, hazard ratio; LUR, land-use regression; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; UFPs, ultrafine particles.

Long-term exposure to traffic-related air pollutants (e.g., nitrogen dioxide and particulate matter) has been consistently linked to an increased rate of cardiovascular disease (CVD) mortality (1–4). There is also growing evidence linking nitrogen dioxide, a common marker of traffic-related air pollution (3), to the development of major CVDs, such as congestive heart failure (CHF) (5) and acute myocardial infarction (AMI) (6–9). Recently, there has been rising attention to the impacts of ultrafine particles (UFPs), defined as particles less than or equal to 0.1 μm in diameter, which are contributed substantially by diesel vehicles in proximity to major roads (10). It has been hypothesized that the health effects of UFPs might differ from those of particulate matter and nitrogen dioxide due to their small size and large surface area.

A handful of studies on short-term exposure have found positive associations between UFPs and daily mortality and

rates of hospitalization due to CVD (11–14). However, less is known about the impact of long-term exposure to UFPs because of the difficulties involved in characterizing spatial contrasts in population exposures to UFPs over a long period of time (10, 15, 16). To date, only 1 cohort study has been conducted to investigate the association of long-term exposure to UFPs with CVD events, and the researchers found a 10% (95% confidence interval (CI): 2, 18) increased rate of mortality from ischemic heart diseases related to chronic UFP exposure (17).

Given the considerable health burden of CHF and AMI worldwide (18, 19) and current uncertainties regarding the role of UFPs in the development of these 2 conditions, we conducted a population-based cohort study in Toronto, Ontario, Canada, to evaluate incidence of CHF and AMI in association with long-term exposure to UFPs. We also investigated the associations with nitrogen dioxide for comparison.

METHODS

Study population

This study used the Ontario Population Health and Environment Cohort, which comprised all Canadian-born adults who resided in Ontario and were registered with Ontario's provincial health insurance plan on April 1, 1996 (20). It was established through record linkage of population-based health administrative databases. In Ontario, hospital, laboratory, and physician services are funded by the provincial government through a single-payer universal health-care system that covers virtually all residents (20).

We included all residents of Toronto, who were followed until December 31, 2012, for determination of incident cases of CHF and AMI. We restricted our cohort to persons who, at baseline, were aged 30–100 years (21, 22), had been living in Toronto for at least 3 years prior to cohort entry, and had no history of physician-diagnosed CHF or AMI (i.e., prevalent cases).

The Research Ethics Board of the University of Toronto approved the study.

Outcome assessment

We ascertained incident physician-diagnosed cases of CHF and AMI during the study period (1996–2012) using the Ontario Congestive Heart Failure Database and the Ontario Myocardial Infarction Database, respectively. The CHF database was created using hospital discharge abstracts from the Canadian Institute for Health Information's Discharge Abstract Database, physician service claims from the Ontario Health Insurance Plan database, and the National Ambulatory Care Reporting System (23). Any person who had either 1 hospital admission with a CHF diagnosis or a physician claim with a CHF diagnosis followed within 1 year by a second record with a CHF diagnosis from any source was considered an incident case of CHF. The AMI database was created using hospital discharge abstracts from the Canadian Institute for Health Information database (24). Incident AMI was defined as having at least 1 hospital admission for AMI and having had no hospital admissions for AMI in the previous year (*International Classification of Diseases, Ninth Revision*, and *International Classification of Diseases, Tenth Revision* diagnosis codes are listed in Web Table 1 (available at https://academic.oup.com/aje)).

To ensure that only first-ever cases of CHF and AMI were captured, we excluded patients who had a previous history of AMI or CHF prior to baseline in 1996. The estimated annual incidence rates of CHF and AMI were approximately 4 per 1,000 participants and 3 per 1,000 participants, respectively (20, 25), which are similar to those in the United States and Europe (26, 27).

The algorithm for the CHF definition has been previously validated through chart review and has been found to have a sensitivity of 85% and a specificity of 97% (23). Similarly, a previous study has shown high accuracy of coding of AMI, with a sensitivity of 89% and a specificity of 93% (24). Once people have been included in these 2 databases, they remain in them until death or termination of Ontario health insurance.

Furthermore, we a priori ascertained comorbid conditions which have been previously related to individual-level lifestyle (6, 28–30) on the basis of hospitalization and physician claims data (see Web Appendix 1). These conditions included hypertension, diabetes, chronic obstructive pulmonary disease, asthma, and cancer. All data sets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences.

Air pollution exposure estimates

Residential exposures to UFPs were derived using a land-use regression (LUR) model that was developed using mobile monitoring data collected in Toronto for 2 weeks in the summer (September 2010) and 1 week in the winter (March 2011) (31, 32). Briefly, real-time ambient UFPs at 1-second resolution were monitored using 3 separate vehicles equipped with rooftop monitoring devices (TSI model 3007; TSI Inc., Shoreview, Minnesota) (31). In total, data on 405 road segments were included in model development. The LUR model included terms for the logarithm of distances to highways, major roads, the central business district, Toronto Pearson International Airport, and bus routes, as well as variables for the numbers of on-street trees, parks, and open spaces and the length of bus routes within a 100-m buffer (Web Table 2). The final model explained 67% of the spatial variation in mean UFPs.

We also estimated residential exposures to nitrogen dioxide using a LUR model derived from an intense campaign of measurement of ground-level nitrogen dioxide concentrations conducted in the City of Toronto (33). Nitrogen dioxide samples were collected over a 2-week period using duplicate 2-sided Ogawa passive diffusion samplers (Ogawa & Company, Pompano Beach, Florida) at 95 locations across Toronto. The sampling campaign was conducted over the course of 2 seasons, one in the fall (September 2002) and the other in the spring (May 2004). The R^2 value for the final regression model was 70%.

We assigned estimates of concentrations of UFPs and nitrogen dioxide to the centroid of each subject's annual 6-character residential postal code for each year during follow-up between 1996 and 2012 (20), accounting for residential mobility. We calculated 3-year moving averages of estimated concentrations of UFPs and nitrogen dioxide, beginning from 1996. For example, a subject's moving window of exposure for 1998 was

estimated as the mean of the exposures assigned to that subject's postal codes over the 3 years from 1996 to 1998 (see Web Appendix 2).

Covariates

We extracted data on age, sex, and the 5 selected comorbid conditions at baseline. Indicators for neighborhood-level socioeconomic status, including the proportion of recent immigrants, the proportion of the population aged ≥15 years who had not completed high school, the unemployment rate, and mean annual household income, were also derived using 1996, 2001, and 2006 Canadian census tract data.

To investigate whether exposure to fine particles, defined as particulate matter with an aerodynamic diameter less than or equal to 2.5 μm ($PM_{2.5}$), might account for any observed associations of UFPs/nitrogen dioxide with AMI/CHF, we derived estimates of ground-level $PM_{2.5}$ concentration from satellite observations (34). The estimates of $PM_{2.5}$ exposure were available on a grid with a spatial resolution of approximately 1 km × 1 km (see Web Appendix 3).

Given that residential exposure to traffic-related noise has been associated with changes in blood pressure and adverse CVD outcomes (35, 36), we obtained data on traffic-related noise at the postal code level in Toronto (37) (see Web Appendix 4).

Statistical analyses

We used random-effects Cox proportional hazards models (38) to estimate associations between UFPs and nitrogen dioxide exposure and incident CHF and AMI. Random effects were represented by neighborhoods ($n = 140$). The neighborhoods were defined on the basis of Statistics Canada census tract boundaries. Each neighborhood is comprised of 2–5 census tracts, with a minimum population of 7,000–10,000. Previous studies suggested that lack of statistical control for spatial covariates may bias estimates of air pollution–health associations and underestimate standard errors (39).

All models stratified by 1-year age group and sex. The 3-year moving averages of exposure were fitted in models as time-dependent variables. Subjects were censored at the time of the adverse health outcome or if they reached the end of follow-up (December 31, 2012), became ineligible for provincial health insurance, or died. We first estimated hazard ratios in single-pollutant models that adjusted for the neighborhood-level factors, followed by additional adjustment for comorbidity. To differentiate the roles of multiple air pollutants (UFPs, nitrogen dioxide, and $PM_{2.5}$), we also developed 2- and 3-pollutant models that adjusted for all available covariates. Hazard ratios and 95% confidence intervals were calculated for an interquartile-range increase in the ambient concentration of UFPs or nitrogen dioxide. We tested for effect modification by age, sex, and comorbidity.

We performed several sensitivity analyses by: 1) considering mean annual exposures to each pollutant during other time windows, including 1, 2, and 5 years before an incident event; 2) restricting the analysis to participants who had lived at their baseline address for more than 5 years prior to cohort entry; 3) adjusting for a linear term for time to account for potential changes in the diagnosis and incidence of AMI and CHF over time; and 4) adjusting for residential traffic-related noise exposure. Lastly, we indirectly adjusted for potential confounding by smoking habits and obesity, 2 major CVD risk factors (40, 41), using a recently developed method (42). This method requires spatial associations between the unobserved and observed variables from an auxiliary data set (see Web Appendix 5).

Statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina) and the coxme library in R 3.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 1,135,817 participants with complete information for all variables, we excluded 23,757 (2.1%) and 8,608 (0.8%) persons who had CHF and AMI at baseline, respectively. This left a total of 1,112,060 eligible participants in the CHF cohort and 1,127,209 in the AMI cohort (Table 1). The mean ages of the 2 cohorts at baseline were approximately 51 years. We identified 106,644 incident cases of CHF and 43,745 incident cases of AMI from 1996 to 2012. Compared with the entire cohort, patients diagnosed with the 2 conditions were older and had a higher prevalence of selected comorbid conditions.

The mean annual concentration of UFPs at the baseline residence was approximately 28,450 particles/cm^3 (Table 2). The mean annual concentrations of nitrogen dioxide and $PM_{2.5}$ were 21.4 parts per billion (ppb) and 10.7 μg/m^3, respectively. Exposures to UFPs and nitrogen dioxide were weakly correlated (Pearson correlation coefficient: $r = 0.24$). Exposure to $PM_{2.5}$ was also weakly correlated with exposure to UFPs ($r = -0.08$) and nitrogen dioxide ($r = 0.18$).

Table 3 shows adjusted hazard ratios and 95% confidence intervals for interquartile-range increases in UFP exposure and nitrogen dioxide. Individually, both UFPs and nitrogen dioxide were positively associated with incidence of CHF and AMI in the models that stratified by age and sex. Further adjustment for neighborhood-level covariates and comorbid conditions (fully adjusted models) led to slightly attenuated associations. In these models, the estimated hazard ratios for incident CHF and AMI corresponding to an interquartile-range increase in UFP exposure were 1.03 (95% CI: 1.02, 1.05) and 1.05 (95% CI: 1.02, 1.07), respectively. For nitrogen dioxide, the estimated hazard ratios for CHF and AMI were 1.04 (95% CI: 1.03, 1.06) and 1.01 (95% CI: 0.99, 1.03), respectively. We found no associations between $PM_{2.5}$ and incident CHF or AMI, which may be related to limited spatial variation in ambient $PM_{2.5}$ in Toronto (Web Table 3).

In the multipollutant models adjusting for $PM_{2.5}$ and nitrogen dioxide, exposure to UFPs remained positively associated with AMI (hazard ratio (HR) = 1.05, 95% CI: 1.02, 1.07) and CHF (HR = 1.02, 95% CI: 1.00, 1.03) (Table 3). Similarly, adjustment for UFPs and $PM_{2.5}$ did not materially change the estimated associations of nitrogen dioxide with incident CHF and AMI.

In the stratified analyses, we found significant effect modification by age for the associations of CHF incidence with UFPs and nitrogen dioxide (Web Tables 4 and 5). There was a stronger association with UFPs among subjects younger than age 60 years (HR = 1.06, 95% CI: 1.03, 1.09) as compared with those aged 60–74 years (HR = 1.01, 95% CI: 1.00, 1.03) and those aged 75 years or more (HR = 1.02, 95% CI: 1.01,

Table 1. Baseline Characteristics (%) of Participants in a Study of Exposure to Ultrafine Particles and Cardiovascular Disease Incidence, by Outcome, Toronto, Ontario, Canada, 1996

Baseline Characteristic	CHF Cohort[a]		AMI Cohort[a]	
	Total Cohort (n = 1,112,060)	CHF Cases (n = 106,644)	Total Cohort (n = 1,127,209)	AMI Cases (n = 43,745)
Individual risk factors				
Age, years[b]	51.4 (15.1)	67.9 (12.3)	51.8 (15.4)	63.5 (13.8)
Male sex	47.2	48.8	47.1	60.3
Comorbid conditions				
Hypertension	20.5	47.8	21.1	42.5
Diabetes	6.6	19.2	6.9	20.3
CHF	—		1.9	5.3
AMI	0.5	2.1	—	
COPD	2.3	7.1	2.6	5.6
Asthma	6.7	9.8	6.9	8.5
Cancer	3.7	8.1	3.9	6.1
Area-level risk factors				
% of population aged ≥15 years with less than a high school education	32.0	34.0	32.1	33.9
% of population aged ≥15 years without employment	10.3	10.3	10.3	10.5
% of recent immigrants	11.1	10.1	11.0	10.6
Average annual household income (all ages), Can$1,000[b]	61.9 (37.4)	60.0 (35.9)	61.9 (37.4)	59.0 (33.9)

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.

[a] For each cohort, prevalent cases were excluded.

[b] Values are expressed as mean (standard deviation).

1.04) ($P = 0.023$). Similarly, we found a heightened association of CHF with nitrogen dioxide among people younger than age 60 years (HR = 1.09, 95% CI: 1.07, 1.11) as compared with those aged 60–74 years (HR = 1.05, 95% CI: 1.03, 1.06) and essentially no impact among persons aged 75 years or more (HR = 1.00, 95% CI: 0.98, 1.02) ($P < 0.0001$). Additionally, we observed that nondiabetic subjects had a higher risk of incident CHF in association with UFPs than persons with diabetes ($P = 0.01$).

In the sensitivity analyses, consideration of 3 other time windows of exposure to UFPs and nitrogen dioxide did not materially alter the results (Web Table 6). Additionally, the results remained virtually unchanged after restricting the data to subjects who had lived at their baseline addresses at least 5 years prior to cohort entry or adjusting for a linear term for time. Adjustment for traffic-related noise also had little influence on the magnitude of the estimated hazard ratios. We did not observe any associations between traffic-related noise and incident AMI or CHF (see Web Table 7). Lastly, indirect adjustment for smoking and obesity had little impact on the hazard ratios (the associations of smoking and body mass index with exposure to UFPs and nitrogen dioxide are presented in Web Table 8).

DISCUSSION

In this large cohort study in Toronto, the most populous city in Canada, long-term exposure to UFPs was found to be associated with increased incidence of both CHF and AMI. Adjustment for $PM_{2.5}$ and nitrogen dioxide had no influence on the association of UFPs with AMI, but it slightly attenuated the association of UFPs with CHF. This is probably due to the weak correlations of UFPs with nitrogen dioxide and $PM_{2.5}$ (see Web Appendix 6). Additionally, we observed a positive association between nitrogen dioxide and incident CHF, independent of UFPs and $PM_{2.5}$. No strong evidence was found between nitrogen dioxide and incident AMI.

Epidemiologic evidence of the potential health impacts of chronic exposure to UFPs is sparse (10, 15, 16). To date, only a single cohort study (the California Teachers Study) has investigated the association between CVD events and chronic exposure to UFPs, using UFP data developed through a chemical transport model (17). In that study, the increased rate of mortality from ischemic heart disease was associated with long-term exposure to the mass concentration of UFPs and several components of UFPs. Several previous studies investigating associations with short-term exposure to UFPs also linked day-to-day variation in exposure to UFPs to CVD morbidity and mortality rates (11–14, 43). For example, in a study conducted in Rome, Italy, between 2001 and 2005, daily exposure to UFPs was related to a 2.4% increase in hospital admissions for CHF (95% CI: 0.2, 4.7) using a 5-day lag in exposure (12).

There is emerging evidence that UFPs may rapidly reach the smallest airways and alveoli and further penetrate the alveolar-capillary membrane, and may eventually enter the systemic circulation (44–46). The possible mechanisms through which

Table 2. Distributions of Annual Levels of Ambient Ultrafine Particles[a], Fine Particles[a], and Nitrogen Dioxide for 2 Study Cohorts (Acute Myocardial Infarction and Congestive Heart Failure) at Baseline, Toronto, Ontario, Canada, 1996

Descriptive Statistic	Estimated Exposure			
	UFPs, no. of particles/cm^3		Nitrogen Dioxide[b], ppb	$PM_{2.5}$[b], μg/m^3
	CHF Cohort	AMI Cohort		
Mean	28,441.7	28,453.5	21.4	10.7
Standard deviation	9,119.6	9,116.0	3.5	1.6
Median	25,943.3	25,961.4	21.1	10.8
Maximum	110,531.0	110,531.0	50.1	21.7
Minimum	6,697.0	6,697.0	9.9	3.0
Interquartile range	10,004.8	10,029.4	4.0	2.2

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; UFPs, ultrafine particles.

[a] Fine particles were defined as $PM_{2.5}$; ultrafine particles were defined as particles less than or equal to 0.1 μm in diameter.

[b] Distributions of annual concentrations of $PM_{2.5}$ and nitrogen dioxide for both the CHF and AMI cohorts at baseline were almost identical, because the absolute values of the concentrations of $PM_{2.5}$ and nitrogen dioxide were magnitudes smaller than the number of particles per cm^3 for UFPs.

exposure to UFPs can heighten the risk of adverse CVD events may be related to its roles in decreasing the antiinflammatory capacity of plasma high-density lipoprotein and increasing systemic oxidative stress, which can affect the development of atherosclerosis (47). Additionally, exposure to UFPs is associated with increased levels of plasma endothelin-2, which may lead to constriction of arteries and increases in blood pressure (48, 49). Furthermore, carbon UFP exposure may trigger thrombogenesis (50).

While a large body of evidence has associated short-term exposure to nitrogen dioxide with CHF-related mortality and hospitalization rates (51), few studies have evaluated the association between chronic exposure to nitrogen dioxide and CHF. In this study, we found an association between long-term

Table 3. Hazard Ratios for Incident Congestive Heart Failure and Acute Myocardial Infarction According to Long-Term Exposure to Ultrafine Particles and Nitrogen Dioxide, Toronto, Ontario, Canada, 1996–2012

Model[a]	Incident CHF		Incident AMI	
	HR	95% CI	HR	95% CI
UFPs				
Stratified by age and sex	1.06	1.04, 1.07	1.06	1.04, 1.08
Adjusted for neighborhood-level covariates[b]	1.04	1.02, 1.05	1.05	1.03, 1.07
Adjusted for comorbidity[c]	1.03	1.02, 1.05	1.05	1.02, 1.07
Adjusted for $PM_{2.5}$	1.03	1.02, 1.05	1.04	1.02, 1.06
Adjusted for nitrogen dioxide	1.02	1.00, 1.03	1.05	1.03, 1.07
Adjusted for $PM_{2.5}$ and nitrogen dioxide	1.02	1.00, 1.03	1.05	1.02, 1.07
Nitrogen dioxide				
Stratified by age and sex	1.08	1.06, 1.09	1.04	1.03, 1.06
Adjusted for neighborhood-level covariates[b]	1.05	1.04, 1.06	1.02	1.00, 1.04
Adjusted for comorbidity[c]	1.04	1.03, 1.06	1.01	0.99, 1.03
Adjusted for UFPs	1.04	1.03, 1.05	0.99	0.97, 1.01
Adjusted for $PM_{2.5}$	1.05	1.04, 1.06	1.01	0.99, 1.03
Adjusted for UFPs and $PM_{2.5}$	1.04	1.03, 1.05	0.99	0.97, 1.01

Abbreviations: AMI, acute myocardial infarction; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; $PM_{2.5}$, particulate matter with an aerodynamic diameter less than or equal to 2.5 μm; UFPs, ultrafine particles.

[a] Random-effects Cox proportional hazards models.

[b] Adjusted for census tract-level percentage of recent immigrants, percentage of the population aged ≥15 years without employment, percentage of the population aged ≥15 years with less than a high school education, and annual household income.

[c] For CHF, we further adjusted for comorbid hypertension, diabetes, AMI, chronic obstructive pulmonary disease, asthma, and cancer. For AMI, we adjusted for comorbid hypertension, diabetes, CHF, chronic obstructive pulmonary disease, asthma, and cancer.

exposure to nitrogen dioxide and incident CHF after adjusting for UFPs and $PM_{2.5}$ (per interquartile-range increase (4 ppb), HR = 1.04). Our finding is in line with that of an English national cohort study (5), which is the only study to date (to our knowledge) to have assessed the relationship between chronic nitrogen dioxide exposure and incident CHF. Those investigators reported that a 10.7-ppb increase in nitrogen dioxide exposure was related to increased CHF incidence (HR = 1.06, 95% CI: 1.01, 1.11) (5).

We also observed that the associations of CHF with UFPs and nitrogen dioxide were greater among persons under age 60 years than in those aged 60 years or more. A similar pattern has been reported in a handful of previous cohort studies, which showed increasing rates of CVD mortality in relation to long-term exposure to nitrogen dioxide or $PM_{2.5}$ as age decreased (22, 52, 53). However, these findings are inconsistent with those of some studies that found a stronger association among the elderly (54, 55) and those that showed no apparent effect modification by age (29, 56). Our finding might be explained by the reduced responsiveness to autonomic nervous system stimuli among older persons. It might be also be attributable to different time-activity patterns (e.g., time spent outdoors and means of transportation) between younger and older people (57, 58). Furthermore, our finding may indicate that relatively young age might be etiologically more relevant for the impact of UFP and nitrogen dioxide exposure on increasing the risk of developing CHF.

A number of previous studies suggested that there were stronger associations of CVD mortality and incidence with $PM_{2.5}$ and nitrogen dioxide in patients with comorbid conditions such as diabetes or chronic obstructive pulmonary disease (28, 59–61), but we found no evidence of effect modification of the associations of UFPs and nitrogen dioxide with incident CHF and AMI by preexisting diabetes or chronic obstructive pulmonary disease. Given the high prevalence of these conditions, further studies to investigate the potential interaction between these conditions and UFPs/nitrogen dioxide in the risk of developing CHF and AMI are needed.

Long-term exposure to nitrogen dioxide was not found to be associated with AMI incidence in our study, as reported in several large cohort studies from Europe and the United States (5, 29, 54, 62, 63). For example, investigators in the California Teachers Study (62) and the European Study of Cohorts for Air Pollution Effects (ESCAPE) (11 European cohorts) (54) reported weak positive but nonsignificant associations of nitrogen dioxide and oxides of nitrogen with AMI incidence. The finding that AMI incidence only increased in association with exposure to UFPs, not with exposure to nitrogen dioxide and $PM_{2.5}$, in our study could be due to chance; however, it may also indicate that UFPs might have a greater impact (due to their small size and large surface areas) on the onset of AMI than nitrogen dioxide and $PM_{2.5}$. Future experimental and epidemiologic studies are needed to confirm this observation.

To our knowledge, this is the first study to date that has examined associations between long-term exposure to ambient UFPs and the development of CHF and AMI. We derived UFP data using a LUR model which explains 67% of the spatial variation in ambient UFPs in Toronto. Another strength of our study was our ability to identify incident cases using provincewide registries and validated algorithms with high sensitivity and specificity. Additionally, we obtained a detailed residential history for each subject and assigned exposures to their residential postal codes for each year during follow-up. This accounted for residential mobility and reduced exposure misclassification. Furthermore, our study benefited from the use of Cox models containing random effects for neighborhoods. This method can help researchers to avoid underestimation of the standard errors of the fixed coefficients. Lastly, we adjusted for postal code-level traffic-related noise in a sensitivity analysis and found little change in the estimated associations. Few prior studies of the air pollution–health relationship have adjusted for residential traffic-related noise levels.

Several limitations of this analysis should be noted. First, our UFP and nitrogen dioxide exposure estimates from 1996–2012 were assigned using LUR models based on data collected from short-term intensive mobile monitoring campaigns. We were unable to evaluate patterns in UFP and nitrogen dioxide levels over longer periods because of technological challenges and high costs. However, previous studies have shown that traffic-related air pollution within large cities tends to remain constant over a long time period (approximately 10 years) (64, 65). Therefore, we expect that the LUR models would reflect long-term spatial differences in exposure.

Second, we could not obtain information on time spent indoors and outdoors, indoor air pollution exposures, and occupation-related exposures, which is a limitation in large epidemiologic studies linking ambient air pollution data to health outcomes. However, previous studies have shown that indoor levels of traffic-related air pollution (e.g., nitrogen dioxide) exposure are strongly correlated with levels of outdoor exposure (66). Furthermore, in a previous survey, Matz et al. (67) found that urban Canadians spend 70% of their time indoors at home. Therefore, we expect that it is reasonable to use spatially derived residential outdoor exposure as a surrogate for personal exposure to air pollution. Given the inherent imprecision of these spatially derived exposures, our estimated hazard ratios were probably subject to nondifferential misclassification bias.

Third, we were unable to obtain individual data on CVD risk factors such as smoking and obesity. To address the concern of residual confounding, we further adjusted for these 2 factors using an indirect method (42); the indirect adjustment did not alter our hazard ratio estimates. Additionally, we further adjusted for selected comorbid conditions which are likely to be closely correlated with smoking habits, diet, or obesity (28–30), and found that the hazard ratios remained unchanged. However, despite the use of these methods, we were unable to completely rule out the possibility of residual confounding.

In conclusion, using data on a large cohort in Toronto, Ontario, Canada, we observed associations between long-term exposure to ambient UFPs and increased incidence of CHF and AMI. Long-term exposure to nitrogen dioxide was also linked to increased incidence of CHF but not of AMI.

ACKNOWLEDGMENTS

Author affiliations: Primary Care and Population Health Research Program, Institute for Clinical Evaluative

Sciences, Toronto, Ontario, Canada (Li Bai, Jeffrey C. Kwong, Hong Lu, Alexander Kopp, Hong Chen); Air Health Science Division, Health Canada, Ottawa, Ontario, Canada (Scott Weichenthal, Keith Van Ryswyk); Department of Epidemiology, Biostatistics and Occupational Health, Faculty of Medicine, McGill University, Montreal, Quebec, Canada (Scott Weichenthal); Department of Applied Immunization Research, Public Health Ontario, Toronto, Ontario, Canada (Jeffrey C. Kwong); Divisions of Clinical Public Health and Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Jeffrey C. Kwong); Division of Occupational and Environmental Health, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Hong Chen); Department of Family and Community Medicine, Faculty of Medicine, University of Toronto and University Health Network, Toronto, Ontario, Canada (Jeffrey C. Kwong); Population Studies Division, Health Canada, Ottawa, Ontario, Canada (Richard T. Burnett); Department of Civil Engineering and Applied Mechanics, Faculty of Engineering, McGill University, Montreal, Quebec, Canada (Marianne Hatzopoulou); Department of Environmental Health Sciences, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, California (Michael Jerrett); Department of Physics and Atmospheric Science, Faculty of Science, Dalhousie University, Halifax, Nova Scotia, Canada (Aaron van Donkelaar, Randall V. Martin); Smithsonian Astrophysical Observatory, Harvard-Smithsonian Centre for Astrophysics, Cambridge, Massachusetts (Randall V. Martin); and Department of Environmental and Occupational Health, Public Health Ontario, Toronto, Ontario, Canada (Hong Chen).

This work was supported by a contract from Health Canada (contract 4500332737). This study was also supported by the Institute for Clinical Evaluative Sciences, which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. Parts of this material were based on data and information compiled and provided by the Canadian Institute for Health Information.

This paper was presented as an abstract at the 50th Annual Meeting of the Society for Epidemiologic Research, Seattle, Washington, June 20–23, 2017 (68).

The opinions, results, and conclusions reported in this article do not necessarily represent the views of the Institute for Clinical Evaluative Sciences, the Ontario Ministry of Health and Long-Term Care, or the Canadian Institute for Health Information. No endorsement by the Institute for Clinical Evaluative Sciences or the Ontario Ministry of Health and Long-Term Care is intended or should be inferred.

Conflict of interest: none declared.

REFERENCES

1. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc*. 2006;56(6):709–742.
2. Chen H, Goldberg MS, Villeneuve PJ. A systematic review of the relation between long-term exposure to ambient air pollution and chronic diseases. *Rev Environ Health*. 2008; 23(4):243–297.
3. Health Effects Institute. Traffic-related air pollution: a critical review of the literature on emissions, exposure, and health effects. https://www.healtheffects.org/publication/traffic-related-air-pollution-critical-review-literature-emissions-exposure-and-health. Published January 17, 2010. Accessed August 14, 2017.
4. Hoek G, Krishnan RM, Beelen R, et al. Long-term air pollution exposure and cardio-respiratory mortality: a review. *Environ Health*. 2013;12:43.
5. Atkinson RW, Carey IM, Kent AJ, et al. Long-term exposure to outdoor air pollution and incidence of cardiovascular diseases. *Epidemiology*. 2013;24(1):44–53.
6. Miller KA, Siscovick DS, Sheppard L, et al. Long-term exposure to air pollution and incidence of cardiovascular events in women. *N Engl J Med*. 2007;356(5):447–458.
7. Tonne C, Melly S, Mittleman M, et al. A case-control analysis of exposure to traffic and acute myocardial infarction. *Environ Health Perspect*. 2007;115(1):53–57.
8. Rosenlund M, Picciotto S, Forastiere F, et al. Traffic-related air pollution in relation to incidence and prognosis of coronary heart disease. *Epidemiology*. 2008;19(1):121–128.
9. Madrigano J, Kloog I, Goldberg R, et al. Long-term exposure to $PM_{2.5}$ and incidence of acute myocardial infarction. *Environ Health Perspect*. 2013;121(2):192–196.
10. Health Effects Institute. Understanding the health effects of ambient ultrafine particles. https://www.healtheffects.org/publication/understanding-health-effects-ambient-ultrafine-particles. Published January 3, 2013. Accessed August 14, 2017.
11. Kettunen J, Lanki T, Tiittanen P, et al. Associations of fine and ultrafine particulate air pollution with stroke mortality in an area of low air pollution levels. *Stroke*. 2007;38(3):918–922.
12. Belleudi V, Faustini A, Stafoggia M, et al. Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases. *Epidemiology*. 2010;21(3): 414–423.
13. Lanzinger S, Schneider A, Breitner S, et al. Associations between ultrafine and fine particles and mortality in five central European cities—results from the UFIREG Study. *Environ Int*. 2016;88:44–52.
14. Andersen ZJ, Olsen TS, Andersen KK, et al. Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark. *Eur Heart J*. 2010;31(16):2034–2040.
15. Lane KJ, Levy JI, Scammell MK, et al. Association of modeled long-term personal exposure to ultrafine particles with inflammatory and coagulation biomarkers. *Environ Int*. 2016;92–93:173–182.
16. Li Y, Lane KJ, Corlin L, et al. Association of long-term near-highway exposure to ultrafine particles with cardiovascular diseases, diabetes and hypertension. *Int J Environ Res Public Health*. 2017;14(5):461–477.
17. Ostro B, Hu J, Goldberg D, 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(6):549–556.
18. Roger VL. Epidemiology of myocardial infarction. *Med Clin North Am*. 2007;91(4):537–552; ix.
19. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol*. 2011;8:30–41.
20. Chen H, Kwong JC, Copes R, et al. Cohort profile: the Ontario Population Health and Environment Cohort (ONPHEC). *Int J Epidemiol*. 2017;46(2):405–405j.

21. Krewski D, Jerrett M, Burnett RT, et al. *Extended Follow-Up and Spatial Analysis of the American Cancer Society Study Linking Particulate Air Pollution and Mortality: Special Report*. Cambridge, MA: Health Effects Institute; 2009.
22. Cesaroni G, Badaloni C, Gariazzo C, et al. Long-term exposure to urban air pollution and mortality in a cohort of more than a million adults in Rome. *Environ Health Perspect*. 2013;121(3): 324–331.
23. Schultz SE, Rothwell DM, Chen Z, et al. Identifying cases of congestive heart failure from administrative data: a validation study using primary care patient records. *Chronic Dis Inj Can*. 2013;33(3):160–166.
24. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002; 144(2):290–296.
25. Yeung DF, Boom NK, Guo H, et al. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ*. 2012;184(14):E765–E773.
26. Yeh RW, Sidney S, Chandra M, et al. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362(23):2155–2165.
27. Davies AR, Grundy E, Nitsch D, et al. Constituent country inequalities in myocardial infarction incidence and case fatality in men and women in the United Kingdom, 1996–2005. *J Public Health (Oxf)*. 2011;33(1):131–138.
28. Chen H, Burnett RT, Kwong JC, et al. Spatial association between ambient fine particulate matter and incident hypertension. *Circulation*. 2014;129(5):562–569.
29. Stockfelt L, Andersson EM, Molnár P, et al. Long term effects of residential NO_x exposure on total and cause-specific mortality and incidence of myocardial infarction in a Swedish cohort. *Environ Res*. 2015;142:197–206.
30. Zhang Z, Laden F, Forman JP, et al. Long-term exposure to particulate matter and self-reported hypertension: a prospective analysis in the Nurses' Health Study. *Environ Health Perspect*. 2016;124(9):1414–1420.
31. Weichenthal S, Van Ryswyk K, Goldstein A, et al. Characterizing the spatial distribution of ambient ultrafine particles in Toronto, Canada: a land use regression model. *Environ Pollut*. 2016;208(A):241–248.
32. Weichenthal S, Van Ryswyk K, Kulka R, et al. In-vehicle exposures to particulate air pollution in Canadian metropolitan areas: the Urban Transportation Exposure Study. *Environ Sci Technol*. 2015;49(1):597–605.
33. Jerrett M, Arain MA, Kanaroglou P, et al. Modeling the intraurban variability of ambient traffic pollution in Toronto, Canada. *J Toxicol Environ Health A*. 2007;70(3–4):200–212.
34. van Donkelaar A, Martin RV, Spurr RJ, et al. High-resolution satellite-derived $PM_{2.5}$ from optimal estimation and geographically weighted regression over North America. *Environ Sci Technol*. 2015;49(17):10482–10491.
35. Babisch W. Transportation noise and cardiovascular risk: updated review and synthesis of epidemiological studies indicate that the evidence has increased. *Noise Health*. 2006;8(30):1–29.
36. de Kluizenaar Y, Gansevoort RT, Miedema HM, et al. Hypertension and road traffic noise exposure. *J Occup Environ Med*. 2007;49(5):484–492.
37. Zuo F, Li Y, Johnson S, et al. Temporal and spatial variability of traffic-related noise in the City of Toronto, Canada. *Sci Total Environ*. 2014;472:1100–1107.
38. Pankratz VS, de Andrade M, Therneau TM. Random-effects Cox proportional hazards model: general variance components methods for time-to-event data. *Genet Epidemiol*. 2005;28(2): 97–109.
39. Ma R, Krewski D, Burnett RT. Random effects Cox models: a Poisson regression modelling approach. *Biometrika*. 2003; 90(1):157–169.
40. Pope CA 3rd, Burnett RT, Thurston GD, et al. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation*. 2004;109(1):71–77.
41. Poirier P, Giles TD, Bray GA, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. *Arterioscler Thromb Vasc Biol*. 2006;26(5):968–976.
42. Shin HH, Cakmak S, Brion O, et al. Indirect adjustment for multiple missing variables applicable to environmental epidemiology. *Environ Res*. 2014;134:482–487.
43. Weichenthal S. Selected physiological effects of ultrafine particles in acute cardiovascular morbidity. *Environ Res*. 2012; 115:26–36.
44. Nemmar A, Hoet P, Nemery B. Translocation of ultrafine particles. *Environ Health Perspect*. 2006;114(4):A211–A212.
45. Brook RD. Cardiovascular effects of air pollution. *Clin Sci (Lond)*. 2008;115(6):175–187.
46. Brook RD, Rajagopalan S, Pope CA 3rd, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation*. 2010;121(21):2331–2378.
47. Araujo JA, Barajas B, Kleinman M, et al. Ambient particulate pollutants in the ultrafine range promote early atherosclerosis and systemic oxidative stress. *Circ Res*. 2008;102(5):589–596.
48. Elder A, Couderc JP, Gelein R, et al. Effects of on-road highway aerosol exposures on autonomic responses in aged, spontaneously hypertensive rats. *Inhal Toxicol*. 2007;19(1): 1–12.
49. Elder A, Gelein R, Finkelstein J, et al. On-road exposure to highway aerosols. 2. Exposures of aged, compromised rats. *Inhal Toxicol*. 2004;16(suppl 1):41–53.
50. Khandoga A, Stoeger T, Khandoga AG, et al. Platelet adhesion and fibrinogen deposition in murine microvessels upon inhalation of nanosized carbon particles. *J Thromb Haemost*. 2010;8(7):1632–1640.
51. Shah AS, Langrish JP, Nair H, et al. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet*. 2013;382(9897):1039–1048.
52. Cohen AJ, Brauer M, Burnett R, et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet*. 2017;389(10082):1907–1918.
53. Naess Ø, Nafstad P, Aamodt G, et al. Relation between concentration of air pollution and cause-specific mortality: four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in Oslo, Norway. *Am J Epidemiol*. 2007;165(4):435–443.
54. Cesaroni G, Forastiere F, Stafoggia M, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. *BMJ*. 2014; 348:f7412.
55. Zhang Z, Guo C, Lau AKH, et al. Long-term exposure to fine particulate matter, blood pressure, and incident hypertension in Taiwanese adults. *Environ Health Perspect*. 2018;126(1): 017008.
56. Coogan PF, White LF, Jerrett M, et al. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. *Circulation*. 2012;125(6):767–772.
57. Esler MD, Thompson JM, Kaye DM, et al. Effects of aging on the responsiveness of the human cardiac sympathetic nerves to stressors. *Circulation*. 1995;91(2):351–358.

58. Cohen L, Curhan GC, Forman JP. Influence of age on the association between lifestyle factors and risk of hypertension. *J Am Soc Hypertens*. 2012;6(4):284–290.
59. Zanobetti A, Schwartz J. Cardiovascular damage by airborne particles: are diabetics more susceptible? *Epidemiology*. 2002; 13(5):588–592.
60. Goldberg MS, Burnett RT, Bailar JC 3rd, et al. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. *Environ Health Perspect*. 2001;109(suppl 4):487–494.
61. Hart JE, Puett RC, Rexrode KM, et al. Effect modification of long-term air pollution exposures and the risk of incident cardiovascular disease in US women. *J Am Heart Assoc*. 2015; 4(12):e002301.
62. Lipsett MJ, Ostro BD, Reynolds P, et al. Long-term exposure to air pollution and cardiorespiratory disease in the California Teachers Study cohort. *Am J Respir Crit Care Med*. 2011; 184(7):828–835.
63. Hart JE, Rimm EB, Rexrode KM, et al. Changes in traffic exposure and the risk of incident myocardial infarction and all-cause mortality. *Epidemiology*. 2013;24(5): 734–742.
64. Eeftens M, Beelen R, Fischer P, et al. Stability of measured and modelled spatial contrasts in NO_2 over time. *Occup Environ Med*. 2011;68(10):765–770.
65. Cesaroni G, Porta D, Badaloni C, et al. Nitrogen dioxide levels estimated from land use regression models several years apart and association with mortality in a large cohort study. *Environ Health*. 2012;11:48.
66. Blondeau P, Iordache V, Poupard O, et al. Relationship between outdoor and indoor air quality in eight French schools. *Indoor Air*. 2005;15(1):2–12.
67. Matz CJ, Stieb DM, Davis K, et al. Effects of age, season, gender and urban-rural status on time-activity: Canadian Human Activity Pattern Survey 2 (CHAPS 2). *Int J Environ Res Public Health*. 2014;11(2):2108–2124.
68. Bai L, Weichenthal S, Burnett RT, et al. Risk of incident acute myocardial infarction and congestive heart failure in relation to long-term exposure to traffic-related air pollution [abstract 1277]. In: *Society for Epidemiologic Research 50th Annual Meeting Abstract Book: Seattle, Washington—June 20–23, 2017*. Clearfield, UT: Society for Epidemiologic Research; 2017. https://epiresearch.org/annual-meeting/archives-2/50th-anniversary/. Accessed September 24, 2018.