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Original Research Article

Exposure to Ambient Ultrafine Particles and Nitrogen Dioxide and Incident Hypertension and Diabetes

Li Bai,[a,b] Hong Chen,[a,b,c] Marianne Hatzopoulou,[d] Michael Jerrett,[e] Jeffrey C. Kwong,[a,b,c]
Richard T. Burnett,[f] Aaron van Donkelaar,[g] Ray Copes,[a,c]
Randall V. Martin,[g,i] Keith van Ryswyk,[h] Hong Lu,[b]
Alexander Kopp,[b] Scott Weichenthal [h,j]

[a] Public Health Ontario, Toronto, ON, Canada
[b] Institute for Clinical Evaluative Sciences, Toronto, ON, Canada
[c] Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
[d] Department of Civil Engineering, McGill University, Montreal, Quebec, Canada
[e] Department of Environmental Health Sciences, Fielding School of Public Health, University of California, Los Angeles, California, USA.
[f] Population Studies Division, Health Canada, Ottawa, ON, Canada
[g] Department of Physics and Atmospheric Science, Dalhousie University, Halifax, Nova Scotia, Canada
[h] Air Health Science Division, Health Canada, Ottawa, Canada
[i] Harvard-Smithsonian Centre for Astrophysics, Cambridge, Massachusetts, USA
[j] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Correspondence:
Hong Chen, PhD
Public Health Ontario
480 University Avenue, Suite 300
Toronto, Ontario M5G 1V2
Tel: 647-260-7109
Email: hong.chen@oahpp.ca

eAppendix 1

Exposure Assessment of Fine Particulate Matter

We derived annual estimates of ground-level fine particulate matter (≤2.5 micrometers; $PM_{2.5}$) from observations obtained from satellite instruments. The $PM_{2.5}$ estimates were available on a grid with a spatial resolution of approximately 1 km×1 km. Details about the model have been reported previously.[1] Briefly, optimal estimation (OE) was used to retrieve aerosol optical depth (AOD) from satellite observations over North America from 1998 to 2012.[1,2] The simulated AOD-to-$PM_{2.5}$ relationship from the GEOS-Chem chemical transport model was then applied to estimate near-surface $PM_{2.5}$ concentrations (OE $PM_{2.5}$). The predicted bias between OE and in situ $PM_{2.5}$ was calculated using geographically weighted regression (GWR).[3] The GWR-predicted bias was then applied to OE $PM_{2.5}$ to produce an adjusted optimal estimate of $PM_{2.5}$. Subgrid elevation difference, urban surfaces, and aerosol composition were considered as GWR predictors. This adjustment approach using GWR significantly improved the overall agreement compared with unadjusted OE $PM_{2.5}$. These adjusted $PM_{2.5}$ estimates were strongly correlated with ground-level monitoring data across North America (R^2=0.82).[1] These data have been used in recent Canadian studies assessing the health effects of long-term $PM_{2.5}$ exposure.[4,5]

Similar to ultrafine particles (UFPs) and nitrogen dioxide (NO_2), we assigned the 3-year moving average of estimates of concentrations to $PM_{2.5}$ to the centroid of each subject's annual residential postal code for each year of follow-up from 1996 to 2012.

Postal Code-level Noise

We obtained data on postal code-level noise in Toronto from Public Health Ontario. Details about the noise data have been reported previously.[6] In brief, two measurement campaigns were performed at 554 locations across Toronto from June 2012 to January 2013. At each site, the noise level was recorded for a period of 30 minutes during daytime. Traffic volume, length of arterial road, and industrial area explained the majority of the spatial variability of noise (R^2=0.68 to 0.74, depending on the cycles). A continuous noise surface with 5-meter spatial resolution was modelled using the geostatistical models, which allowed assignment of the level of noise to each postal code across Toronto.

Similar to ultrafine particles, the high costs of collecting noise data prohibited us from conducting a long-term intensive campaign. However, in a recent study conducted in Paris, Brocolini et al (2013) compared over 50,000 noise samples of short-term field measurements with different durations (ranging from 5 minutes to 1 hour).[7] They observed that 10-20 minutes measurements were sufficient to characterize the longer-term noise level throughout the day in urban areas. In addition, Zuo et al. (2014) have demonstrated that the variability in

noise across Toronto was predominantly spatial in nature rather than temporal.[6] Therefore, we expect that our noise model can estimate longer-term average noise levels.

Calculation of Moving Averages of Air Pollution Exposure

To account for variability in exposures associated with annual residential mobility patterns, we calculated moving averages of estimates of concentrations of each pollutant.[8,9] Given that the year 1996 is the earliest year of exposure data available to us, we were unable to estimate for a subject's exposure for 1996 using a moving window of past concentrations. We calculated a 2-year moving average for a subject's exposure for 1997, (i.e. the mean of the exposures assigned to that subject's postal code over the 2 years 1996-1997). For each year of follow-up between 1998 and 2012, we estimated for each subject a 3-year moving averages of estimates of concentrations. For example, a subject's moving window of exposure for 1998 would be estimated as the mean of the exposures assigned to that subject's postal code over the 3 years 1996-1998.

Competing Risk Analysis

By considering death as a competing risk, we conducted a sensitivity analysis to assess the associations of UFPs with incident hypertension and diabetes using subdistribution hazards (SHs) models, known as Fine-Gray models.[10] This model allows for covariate effects on the hazard of the target event to be evaluated in the presence of competing risk events. Because our study cohorts were too large to be handled when running competing risk analysis in R, we had to use a random sample of 5% of each cohort and consider time-fixed UFPs exposure at baseline. To further work around the computation constraints, we adjusted the models for age and sex only. As a comparison, we also repeated the analysis using standard Cox proportional hazard models in which death was treated as a censoring event. As shown in Supplementary Table 10, virtually similar effect estimates were observed between using SHs models and using traditional Cox models. This suggests that death would not likely bias substantially our observed associations. Given these findings, we have decided not to include death as a competing risk in our main analysis.

Effect Modification on Additive Scales

Given the estimates of effect modification may differ when analyses are performed on an additive or on a multiplicative scale, we conducted a new analysis by further estimating additive interactions between UFPs and age. To do this, we estimated the relative excess risks due to interaction (RERI).[11,12] As shown in Supplementary Table 7, we found statistically significant interactions between UFPs and age for the risk of incident hypertension and diabetes on the additive scale. This confirmed that age is an effect modifier for the relationships between UFPs and hypertension and diabetes incidence on both multiplicative and additive scales in our cohort.

Correlations among Pollutant Concentrations

Exposure to UFPs and NO_2 were weakly correlated in our study. This may be because in Canada, diesel vehicles are a major source of UFPs and are highest near roadways with large

numbers of diesel vehicles, while NO_2 is produced by all vehicles. It is thus possible to have areas with high NO_2 but low or moderate UFPs (like downtown Toronto) and thus a low correlation between these two pollutants. We have also observed weak correlations between pollutants in studies of personal air pollution exposures in Canada and this phenomenon is not limited to studies relying on LUR models (see Supplemental Table 3).[13]

We also observed that UFPs were not correlated with $PM_{2.5}$ in Toronto. Previous studies show that UFPs and $PM_{2.5}$ may be governed by different processes,[14-16] and the health effects of UFPs might be independent of those observed for other particle sizes.[17]

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eTable 1. International Classification of Diseases 9th (ICD-9) and 10th (ICD-10) revision diagnosis codes for study outcomes and selected comorbidities.

	ICD-9 codes	**ICD-10 codes**
Diabetes	250	E10-E14
Hypertension	401-405	I10-13, I15
Congestive Heart Failure	428	I50
Acute myocardial infarction	410	I21
Chronic obstructive pulmonary disease	491,492, 496	J40-J44
Asthma	493	J45
Cancer	140-208	C00-D49

eTable 2. Single-predictor linear regression models for ultrafine particles.

Independent Variable	Buffer Size (m)	β (95% CI)	Adjusted R^2	RMSE
ln(Distance to Highway)		-4061 (-4527, -3596)	0.46	20,074
Distance to Highway		-8.93 (-10.51, -7.34)	0.29	22,940
ln(Distance to Major Road)		428.9 (-1067, 1924)	0.09	25,987
Distance to Major Road		-49.05 (-76.69, -21.41)	0.12	25,640
Distance to CBD		1.04 (0.645, 1.44)	0.15	25,234
ln(Distance to CBD)		6574 (4068, 9082)	0.15	25,236
Distance to Pearson Airport		-1.37 (-1.69, -1.04)	0.22	24,186
ln(Distance to Pearson Airport)		-12,683 (-15,290, -10,077)	0.26	23,440
Distance to Bus Route		52.68 (32.53, 72.83)	0.15	25,284
ln(Distance to Bus Route)		4209 (3183, 5234)	0.21	24,278
Total Road Length	100	12.75 (-1.59, 27.10)	0.10	25,906
	200	-0.374 (-4.75, 4.00)	0.09	25,996
	300	-0.597 (-2.78, 1.59)	0.09	25,988
Total Intersections	100	-12,909 (-17,293, -8525)	0.19	24,513
	200	-6250 (-8203, -4297)	0.20	24,343
	300	-3550 (-4649, -2452)	0.20	24,321
Land Use				
Residential	100	-18,850 (-26,475, -11,224)	0.14	25,317
	200	-13,704 (-21,970, -5439)	0.12	25,684
	300	-11,328 (-20,115, -2542)	0.11	25,807
Commercial	100	-20,803 (-31,814, -9793)	0.12	25,593
	200	-18,238 (-31,481, -4995)	0.11	25,780
	300	-16,815 (-31,875, -1754)	0.10	25,854
Industrial	100	-6296 (-14,442, 1849)	0.09	25,928
	200	-3015 (-11,738, 5709)	0.09	25,983
	300	-2340 (-11,780, 7099)	0.09	25,990
Parks	100	-16,157 (-31,059, -1256)	0.10	25,862
	200	-15,165 (-31,778, 1447)	0.10	25,901
	300	-17,743 (-35,967, 480)	0.10	25,888
Open Space	100	53,374 (45,724, 61,024)	0.37	21,715
	200	61,617 (50,565, 72, 670)	0.29	23,008
	300	68,619 (55,050, 82,188)	0.26	23,463
Total Restaurants and Bars	50	-1869 (-2731, -1007)	0.13	25,469
	100	-1052 (-1429, -675)	0.15	25,140
	200	-351 (-481, -221)	0.15	25, 194
	300	-173 (-241, -105)	0.14	25, 274

Total On Street Trees	100	-404 (-528, -280)	0.20	24,299
	200	-88.2 (-122, -54.1)	0.18	24,732
	300	-35.1 (-50.6, -19.6)	0.16	24,902
Total Bus Stops	100	-3783 (-4873, -2692)	0.18	24,746
	200	-2124 (-2659, -1590)	0.21	24,379
	300	-379 (-845, 87.1)	0.10	25,982
Total Length of Bus Routes	100	-1.93 (-2.78, -1.08)	0.13	25,463
	200	-0.564 (-0.940, -0.189)	0.11	25,787
	300	-0.195 (-0.491, 0.101)	0.10	26,009
Meteorology[a]				
Temperature		2515 (1512, 3518)	0.10	25,967
$Temperature^2$		-165 (-215, -116)		

[a] Model includes both temperature variables. All models for candidate predictors include linear and quadratic terms for ambient temperature and all distances are in meters.
CBD: central business district

eTable 3. Spearman correlations between personal air pollution exposures

	UFPs	Black Carbon	$PM_{2.5}$	NO_2
UFPs	1			
Black Carbon	0.26	1		
$PM_{2.5}$	0.08	0.13	1	
NO_2	0.17	0.21	0.04	1
O_3	0.24	0.16	0.05	0.33

Source: Weichenthal S, Hatzopoulou M, Goldberg MS. Exposure to traffic-related air pollution during physical activity and acute changes in blood pressure, autonomic and micro-vascular function in women: a cross-over study. Particle and Fibre Toxicology. 2014;11:70.

eTable 4. Descriptive statistics for residential noise level and Pearson correlations with ultrafine particles (UFPs), fine particles ($PM_{2.5}$), and nitrogen dioxide (NO_2).

	Noise
Mean	58.48
Standard deviation	4.45
Maximum	94.45
Minimum	48.80
Correlations with air pollution	
UFPs	0.026
$PM_{2.5}$	0.010
NO_2	0.245

eTable 5. Comparisons between associations of incident hypertension and diabetes with each interquartile range (IQR) increases in ultrafine particles (UFPs) (count/cm^3), nitrogen dioxide (NO_2) (ppb), and fine particles ($PM_{2.5}$) ($\mu g/m^3$) using random-effects Cox models and using standard Cox models with and without adjustment for neighborhoods as a categorical variable.

		Hypertension				Diabetes			
Exposure [a]	**Model**	**IQR**	**HR**	**95% CI**		**IQR**	**HR**	**95% CI**	
UFPs	Random-effects Cox model	9,694.1	1.027	1.018	1.036	9,948.4	1.062	1.049	1.075
	Standard Cox model		1.024	1.020	1.028		1.024	1.018	1.029
	+ Further adjusting for neighborhoods as a categorical variable		1.020	1.011	1.030		1.067	1.053	1.081
NO_2	Random-effects Cox model	4.1	1.008	1.001	1.016	4.0	1.062	1.052	1.072
	Standard Cox model		0.957	0.953	0.961		0.996	0.990	1.002
	+ Further adjusting for neighborhoods as a categorical variable		1.015	1.010	1.019		1.062	1.052	1.072
$PM_{2.5}$	Random-effects Cox model	2.1	0.995	0.988	1.003	2.1	0.996	0.985	1.007
	Standard Cox model		0.975	0.969	0.980		0.965	0.957	0.974
	+ Further adjusting for neighborhoods as a categorical variable		0.994	0.985	1.000		0.996	0.985	1.007

[a] All models stratified by age and sex, and adjusted for selected comorbidities and neighborhood-level recent immigrants, unemployment rate, education, and household income.

eTable 6. Characteristics of subjects according to quintiles of ultrafine particles (UFPs) and nitrogen dioxide (NO_2).

	UFPs [a]					NO_2 [b]				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
Hypertension cohort										
Number of subjects	180,064	172,289	175,566	180,690	184,890	177,195	183,909	169,457	184,660	178,278
Number of incident cases	67,660	65,994	69,421	71,341	79,527	73,734	75,480	68,207	71,352	65,170
Percentage of incidence (%)	37.6	38.3	39.5	39.5	43.0	41.6	41.0	40.3	38.6	36.6
Mean concentration of exposure	19,104.6	22,802.5	25,770.4	30,262.6	43,183.1	17.1	19.5	21.1	22.7	26.8
Diabetes cohort										
Number of subjects	214,615	20,5381	207,261	213,916	214,839	208,554	206,854	200,158	226,811	213,635
Number of incident cases	34,856	33,763	35,745	37,989	40,937	37,024	35,676	34,937	39,125	36,528
Percentage of incidence (%)	16.2	16.4	17.3	17.8	19.1	17.8	17.3	17.5	17.3	17.1
Mean concentration of exposure	19,152.3	22,899.6	25,928.7	30,541.6	43,507.5	17.1	19.5	21.0	22.6	26.7

[a] For hypertension, quintiles of UFPs: Q1, ≤ 21,372; Q2, 21,372-24,157; Q3, 24,157-27,552; Q4, 27,552-34,193; Q5, > 34,193 count/cm^3. For diabetes, quintiles of UFPs: Q1, ≤ 21,436; Q2, 21,436-24,278; Q3, 24,278-27,736; Q4, 27,736-34,624; Q5, > 34,624 count/cm^3.
[b] For both hypertension and diabetes, quintiles of NO_2: Q1, ≤ 18.6; Q2, 18.6-20.4; Q3, 20.4-21.8; Q4, 21.8-23.9; Q5, > 23.9 ppb.

eTable 7. Addictive interactions between ultrafine particles (UFPs) and age on incident hypertension and diabetes.

	Hypertension			**Diabetes**		
	RERI	95% CI [a]		RERI	95% CI [a]	
UFPs	0.00267	0.00229	0.00367	0.00194	0.00164	0.00308

[a] The 95% confidential intervals were calculated using "MOVER", known as the method of variance estimates recovery.

RERI: relative excess risks due to interaction

eTable 8. Sensitivity analyses for the associations of incident hypertension and diabetes with each interquartile range increases in ultrafine particles (UFPs) and nitrogen dioxide (NO_2).

Sensitivity analysis [a]	UFPs						NO_2					
	Hypertension			Diabetes			Hypertension			Diabetes		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Used different exposure estimates												
1-year moving average	1.029	1.020	1.039	1.069	1.056	1.083	1.011	1.003	1.018	1.063	1.053	1.074
2-year moving average	1.029	1.029	1.039	1.065	1.052	1.078	1.009	1.002	1.016	1.061	1.051	1.072
5-year moving average	1.026	1.017	1.035	1.059	1.046	1.072	1.008	1.001	1.015	1.062	1.053	1.072
Restricted to subjects who lived at their baseline addresses for ≥5 years prior to cohort entry	1.028	1.019	1.037	1.062	1.049	1.075	1.009	1.001	1.016	1.061	1.051	1.071
Adjusted for a linear term for time	1.027	1.018	1.036	1.062	1.049	1.075	1.008	1.001	1.016	1.062	1.052	1.072
Adjusted for postal code-level noise	1.028	1.018	1.037	1.063	1.050	1.076	1.009	1.001	1.016	1.061	1.051	1.071
Removed subjects living near Pearson Airport	1.026	1.016	1.036	1.057	1.042	1.071	1.008	1.000	1.016	1.058	1.048	1.069
Adjusted for population density at dissemination area-level[b]	1.029	1.019	1.038	1.062	1.045	1.075	1.009	1.001	1.016	1.061	1.050	1.071
Removed subjects who moved out of Toronto during the follow-up period	1.030	1.020	1.039	1.067	1.053	1.081	1.009	1.002	1.018	1.065	1.054	1.076

[a] All models stratified by age and sex, and adjusted for selected comorbidities and neighborhood-level recent immigrants, unemployment rate, education, and household income, and adjusted for random effects for neighborhoods.

[b] Dissemination area is the smallest census geographic area with population information that comprises one or more neighbouring dissemination blocks, with a population of 400 to 700 persons.

eTable 9. Sensitivity analyses for the associations of incident hypertension and diabetes with each interquartile range increases in ultrafine particles (UFPs) and nitrogen dioxide ($NO_{2)}$ using subcohorts excluding subjects with comorbid diabetes and hypertension at baseline.

Exposure	Hypertension			Diabetes		
	HR [a]	95%CI		HR [a]	95%CI	
Number of all cohort members	606,989			606,989		
UFPs						
Stratified by age and sex	1.039	1.027	1.051	1.103	1.083	1.122
Adjusted for medical comorbidities [b]	1.038	1.026	1.050	1.101	1.082	1.121
Adjusted for neighborhood-level covariates	1.028	1.017	1.040	1.070	1.052	1.089
NO_2						
Stratified by age and sex	1.016	1.007	1.026	1.105	1.090	1.120
Adjusted for medical comorbidities	1.015	1.006	1.024	1.104	1.089	1.118
Adjusted for neighborhood-level covariates	0.999	0.990	1.009	1.066	1.052	1.081

[a] Random-effects Cox model stratified by age and sex, and adjusted for selected comorbidities and neighborhood-level recent immigrants, unemployment rate, education, and household income

[b] For both hypertension and diabetes, we controlled for comorbid COPD, asthma, cancer, renal disease, and the Charlson comorbidity index.

eTable 10. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of incident hypertension and diabetes with exposure to ultrafine particles (UFPs) using subdistribution hazards models and Cox proportional hazard models with fixed exposures at baseline based on random samples of 5% of the two study cohorts.

UFPs	Hypertension		Diabetes	
	HR [a]	95%CI	HR [a]	95%CI
Standard Cox models[b]	1.039	1.023-1.056	1.028	1.006-1.051
Subdistribution hazards models	1.040	1.024-1.056	1.036	1.014-1.058

[a] All models were controlled for age and sex.

[b] Death was considered as a competing risk.