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Supplemental Material

Ambient Air Pollution and the Risk of Atrial Fibrillation and Stroke: A Population-Based Cohort Study

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Table S1: Ascertainment of pre-existing comorbidities

Condition	Validated Database	Case definition	ICD-9 Codes	ICD-10 Codes
Congestive heart failure (Schultz et al. 2013)	CHF (Congestive Heart Failure)	At least one hospitalization, or one physician claim or emergency department visit within two years by either a second physician claim or emergency department visit or a hospitalization	428	I50
Coronary heart disease	-	At least one hospitalization	410-414	I20-I25
Diabetes (Hux et al. 2002)	ODD (Ontario Diabetes Dataset)	At least one hospitalization, or 2 or more physician claims within a two-year period	250	E10-E14
Hypertension (Tu et al. 2007)	HYPER (Ontario Hypertension Dataset)	At least one hospitalization, or a physician claim followed within two years by either a physician claim or a hospitalization	401-405	I10-I13, I15

Note: Congestive heart failure, diabetes, and hypertension cases were obtained from the Institute for Clinical Evaluative Sciences (ICES)-derived cohorts, which were created based on validated, linked disease algorithms.

Table S2: Mean annual concentrations of $PM_{2.5}$, NO_2, O_3, and O_x at baseline in 2001

	Air Pollutant			
	$PM_{2.5}$ ($\mu g/m^3$)	**NO_2 (ppb)**	**O_3 (ppb)**	**Ox (ppb)**
Mean annual concentration (SD)	9.8 (2.9)	15.3 (8.0)	45.8 (4.2)	35.7 (3.5)
Interquartile range	4.0	12.9	6.1	3.7
Percentiles				
Minimum	1.0	1.2	14.3	10.7
25^{th}	8.0	8.4	42.7	34.2
50^{th}	10.1	14.1	46.4	36.7
75^{th}	11.9	21.3	48.9	37.9
Maximum	20.0	67.0	63.3	50.7

Table S3: Hazard ratios (HR) and 95% confidence intervals (CIs) for the incidence of atrial fibrillation and stroke using multi-pollutant models in Ontario, Canada

	HR (95% CI)	
	Stroke	**Atrial Fibrillation**
Two-pollutant models		
1. $PM_{2.5}$	1.045 (1.032-1.059)	1.025 (1.017-1.034)
NO_2	1.008 (0.985-1.032)	0.997 (0.982-1.012)
2. $PM_{2.5}$	1.030 (1.018-1.043)	1.022 (1.014-1.030)
O_3	1.041 (1.028-1.054)	1.003 (0.995-1.011)
3. $PM_{2.5}$	1.019 (1.005-1.033)	1.022 (1.013-1.031)
O_x	1.039 (1.028-1.051)	1.002 (0.994-1.009)
4. NO_2	1.050 (1.028-1.073)	1.017 (1.003-1.030)
O_3	1.054 (1.041-1.066)	1.011 (1.003-1.018)
Three-pollutant models		
1. $PM_{2.5}$	1.021 (1.007-1.036)	1.023 (1.014-1.032)
NO_2	1.031 (1.007-1.057)	0.997 (0.982-1.013)
O_3	1.045 (1.032-1.059)	1.002 (0.994-1.011)

Note: We adjusted for all covariates in the main model, which was stratified by a dichotomous indicator for residing in the Greater Toronto Area (GTA) or outside the GTA; adjusted for four area-level variables at dissemination area level (income quintile, proportion of individuals with less than high school education, unemployment rate, and proportion of recent immigrants who obtained landed immigrant or permanent residency status within five years of Canadian census); and included two geographic indicators (i.e., northern/southern Ontario and urban/rural areas). The associations are reported per interquartile range of $PM_{2.5}$ (4.8 $\mu g/m^3$), NO_2 (12.5 ppb), O_3 (6.7 ppb), and O_x (3.7 ppb).

Table S4: Pearson correlation coefficients for air pollutants during the entire follow-up for cohorts by outcome

	$PM_{2.5}$	NO_2	O_3	O_x
Stroke				
$PM_{2.5}$	1.000	0.656	0.275	0.668
NO_2	-	1.000	-0.127	0.579
O_3	-	-	1.000	0.735
O_x	-	-	-	1.000
Atrial Fibrillation				
$PM_{2.5}$	1.000	0.655	0.276	0.668
NO_2	-	1.000	-0.127	0.579
O_3	-	-	1.000	0.735
O_x	-	-	-	-

Note: All correlation coefficients have $p<.0001$.

Table S5: Hazard ratios (HRs) and 95% confidence intervals (CIs) per interquartile range increment for the analysis of effect modification by selected characteristics for atrial fibrillation

	HR (95% CI)			
	$PM_{2.5}$	**NO_2**	**O_3**	**O_x**
Sex				
Male	1.03 (1.01-1.04)	1.01 (1.00-1.03)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
Female	1.03 (1.01-1.04)	1.03 (1.01-1.05)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
P	1	0.115	1	1
Age				
35-44	1.03 (1.00-1.07)	1.04 (0.98-1.10)	1.05 (1.01-1.09)	1.05 (1.00-1.09)
45-54	1.01 (0.98-1.05)	1.01 (0.97-1.06)	1.03 (1.00-1.05)	1.02 (1.00-1.04)
55-64	1.04 (1.00-1.07)	1.02 (0.99-1.04)	1.01 (1.00-1.03)	1.01 (1.00-1.02)
65-74	1.04 (1.02-1.06)	1.03 (1.01-1.05)	1.01 (1.00-1.03)	1.01 (1.00-1.03)
75-85	1.02 (1.00-1.05)	1.04 (1.00-1.07)	0.99 (0.97-1.01)	1.00 (0.98-1.02)
P	0.736	0.862	0.027	0.292
Income Quintile				
Q1 (Lowest)	1.06 (1.04-1.08)	1.03 (1.00-1.06)	1.00 (0.99-1.02)	1.00 (0.99-1.02)
Q2	1.05 (1.03-1.07)	1.04 (1.02-1.07)	1.02 (1.00-1.03)	1.02 (1.01-1.03)
Q3	1.02 (1.00-1.04)	1.01 (0.99-1.04)	1.00 (0.97-1.03)	1.00 (0.98-1.02)
Q4	1.02 (1.01-1.04)	1.03 (1.01-1.06)	1.02 (0.99-1.04)	1.02 (1.00-1.04)
Q5 (Highest)	0.99 (0.97-1.02)	1.02 (0.97-1.07)	1.03 (1.00-1.06)	1.02 (1.00-1.05)
P	<0.001	0.488	0.453	0.129
Hypertension				
Yes	1.03 (1.02-1.04)	1.03 (1.01-1.05)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
No	1.02 (1.01-1.04)	1.02 (1.00-1.03)	1.04 (1.01-1.06)	1.02 (1.00-1.03)
P	0.276	0.433	0.028	0.278
Diabetes				
Yes	1.02 (1.01-1.04)	1.04 (1.01-1.06)	1.00 (0.98-1.02)	1.01 (0.99-1.02)
No	1.04 (1.01-1.06)	1.01 (1.00-1.03)	1.01 (1.00-1.03)	1.01 (1.01-1.02)
P	0.178	0.043	0.433	1
CHD				
Yes	1.05 (1.03-1.07)	1.05 (1.02-1.08)	0.99 (0.98-1.01)	1.01 (0.99-1.02)
No	1.02 (1.01-1.04)	1.02 (1.00-1.03)	1.01 (1.00-1.02)	1.01 (1.00-1.02)
P	0.018	0.077	0.030	1

Note: HR, hazard ratio; 95% CI, 95% confidence interval; CHD, coronary heart disease. We performed Cochran's Q to assess statistically significant heterogeneity between subgroups within the study. Associations are reported per interquartile range of $PM_{2.5}$ (4.8 μg/m^3), NO_2 (12.5 ppb), O_3 (6.7 ppb), and O_x (3.7 ppb).

Table S6: Hazard ratios (HRs) and 95% confidence intervals (CIs) per interquartile range increment for the analysis of effect modification by selected characteristics for stroke

	HR (95% CI)			
	$PM_{2.5}$	NO_2	O_3	O_x
Sex				
Male	1.04 (1.02-1.06)	1.03 (1.00-1.06)	1.04 (1.02-1.06)	1.04 (1.03-1.06)
Female	1.06 (1.04-1.08)	1.05 (1.02-1.07)	1.06 (1.04-1.07)	1.05 (1.04-1.07)
P	0.166	0.019	0.119	0.353
Age				
35-44	1.04 (1.00-1.09)	1.07 (1.00-1.14)	1.02 (0.98-1.07)	1.03 (1.00-1.07)
45-54	1.08 (1.03-1.13)	1.07 (0.99-1.16)	1.03 (0.99-1.08)	1.05 (1.01-1.10)
55-64	1.06 (1.02-1.11)	1.04 (0.99-1.09)	1.06 (1.02-1.10)	1.05 (1.03-1.08)
65-74	1.04 (1.01-1.07)	1.01 (0.97-1.04)	1.06 (1.03-1.08)	1.04 (1.02-1.06)
75-85	1.03 (1.00-1.05)	1.03 (1.00-1.06)	1.06 (1.03-1.09)	1.05 (1.02-1.08)
P	0.335	0.431	0.654	0.876
Income Quintile				
Q1 (Lowest)	1.08 (1.04-1.12)	1.08 (1.05-1.12)	1.02 (1.00-1.05)	1.04 (1.01-1.06)
Q2	1.08 (1.05-1.11)	1.05 (0.99-1.11)	1.07 (1.02-1.12)	1.07 (1.05-1.09)
Q3	1.04 (1.00-1.08)	1.05 (1.00-1.11)	1.05 (1.02-1.07)	1.05 (1.02-1.08)
Q4	1.01 (0.99-1.04)	0.98 (0.94-1.02)	1.03 (1.00-1.06)	1.02 (1.00-1.04)
Q5 (Highest)	1.01 (0.99-1.04)	1.01 (0.97-1.06)	1.08 (1.05-1.11)	1.06 (1.04-1.09)
P	0.001	0.001	0.038	0.010
Stroke Subtype				
Ischemic	1.06 (1.04-1.08)	1.04 (1.01-1.07)	1.06 (1.04-1.07)	1.05 (1.04-1.06)
Hemorrhagic	1.04 (1.01-1.07)	1.06 (1.01-1.10)	1.02 (0.99-1.05)	1.03 (1.00-1.05)
P	0.279	0.469	0.021	0.150
Hypertension				
Yes	1.05 (1.03-1.07)	1.04 (1.02-1.07)	1.06 (1.04-1.08)	1.05 (1.03-1.07)
No	1.05 (1.02-1.07)	1.04 (1.00-1.07)	1.04 (1.02-1.06)	1.04 (1.03-1.06)
P	1	1	0.166	0.432
Diabetes				
Yes	1.06 (1.03-1.09)	1.04 (1.01-1.08)	1.07 (1.04-1.10)	1.06 (1.04-1.09)
No	1.05 (1.03-1.07)	1.03 (1.00-1.06)	1.05 (1.03-1.06)	1.04 (1.03-1.06)
P	0.586	0.670	0.240	0.175
CHD				
Yes	1.05 (1.01-1.10)	1.02 (0.96-1.08)	1.06 (1.03-1.10)	1.05 (1.02-1.08)
No	1.05 (1.03-1.07)	1.04 (1.01-1.06)	1.05 (1.03-1.06)	1.05 (1.04-1.06)
P	1	0.550	0.605	1

Note: HR, hazard ratio; 95% CI, 95% confidence interval; CHD, coronary heart disease. We performed Cochran's Q to assess statistically significant heterogeneity between subgroups within the study. Associations are reported per interquartile range of $PM_{2.5}$ (4.8 μg/m^3), NO_2 (12.5 ppb), O_3 (6.7 ppb), and O_x (3.7 ppb).

Table S7: Ensemble HRs of all models examined in SCHIF for the associations of $PM_{2.5}$, NO_2, O_3 and O_x with the incidence of atrial fibrillation and stroke by quartile of exposures

	Q1	Q2	Q3	Q4
AF				
$PM_{2.5}$ range (μg/m^3)	6.5-3.4	8.7-6.5	10.6-8.7	14.6-10.6
HR (95% CI)	1.00 (0.98-1.02)	1.00 (0.97-1.03)	1.01 (0.97-1.05)	1.03 (0.98-1.08)
NO_2 range (ppb)	6.9-3.1	11.3-6.9	17.4-11.3	31.4-17.4
HR (95% CI)	1.02 (0.99-1.04)	1.02 (0.98-1.05)	1.02 (0.98-1.06)	1.03 (0.98-1.07)
O_3 range (ppb)	43.8-33.2	47.5-43.8	49.9-47.5	55.6-49.9
HR (95% CI)	1.01 (0.99-1.03)	1.01 (0.98-1.04)	1.00 (0.97-1.04)	1.01 (0.97-1.06)
O_x range (ppb)	33.9-24.0	36.2-33.9	37.9-36.2	41.6-37.9
HR (95% CI)	1.01 (0.98-1.04)	1.00 (0.96-1.05)	1.01 (0.96-1.05)	1.02 (0.97-1.07)
Stroke				
$PM_{2.5}$ range (μg/m^3)	6.5-3.4	8.7-6.5	10.6-8.7	14.6-10.6
HR (95% CI)	1.03 (1.00-1.07)	1.02 (0.98-1.07)	1.02 (0.98-1.07)	1.04 (0.98-1.10)
NO_2 range (ppb)	6.9-3.1	11.3-6.9	17.3-11.3	31.4-17.3
HR (95% CI)	1.03 (1.00-1.07)	1.02 (0.98-1.07)	1.02 (0.97-1.07)	1.03 (0.97-1.09)
O_3 range (ppb)	43.8-33.2	47.5-43.8	49.9-47.5	55.6-49.9
HR (95% CI)	1.07 (1.01-1.12)	1.01 (0.95-1.08)	1.01 (0.94-1.08)	1.01 (0.93-1.10)
O_x range (ppb)	33.9-24.0	36.2-33.9	37.9-36.2	41.6-37.9
HR (95% CI)	1.04 (0.97-1.11)	1.02 (0.91-1.13)	1.02 (0.90-1.15)	1.05 (0.91-1.20)

Note: HR, hazard ratio; CI, confidence interval; Q1, lowest quartile (25th vs. 1st percentiles); Q2, second quartile (50th vs. 25th percentiles); Q3, third quartile (75th vs. 50th percentiles); Q4, highest quartile (99th vs. 75th percentiles); and CI, confidence interval. Associations are reported based on the highest to lowest percentile in each quartile; for example, HR (95% CI) of 1.003 (0.985-1.022) is for $PM_{2.5}$ at 6.5 μg/m^3 with 3.4 μg/m^3 as the reference.

Table S8: Hazard ratios (HR) and 95% confidence intervals (CIs) for the incidence of atrial fibrillation and stroke across quintiles of ambient $PM_{2.5}$, NO_2, O_3 and O_x in Ontario, Canada

	HR (95% CI)			
	$PM_{2.5}$	**NO_2**	**O_3**	**O_x**
AF				
Q1 (Lowest)	-	-	-	-
Q2	1.01 (1.00-1.02)	1.02 (1.00-1.03)	0.99 (0.97-1.00)	1.02 (1.01-1.03)
Q3	1.02 (1.01-1.03)	1.03 (1.02-1.04)	1.00 (0.98-1.01)	1.01 (1.00-1.02)
Q4	1.02 (1.01-1.04)	1.05 (1.03-1.07)	1.01 (1.00-1.02)	1.02 (1.00-1.03)
Q5 (Highest)	1.05 (1.03-1.06)	1.04 (1.02-1.06)	1.02 (1.01-1.04)	1.04 (1.02-1.05)
P	<0.001	0.02	0.001	0.128
Stroke				
Q1 (Lowest)	-	-	-	-
Q2	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.03 (1.01-1.05)	1.04 (1.02-1.06)
Q3	1.05 (1.02-1.07)	1.02 (1.00-1.05)	1.10 (1.07-1.12)	1.05 (1.03-1.08)
Q4	1.05 (1.02-1.07)	1.06 (1.03-1.08)	1.10 (1.07-1.12)	1.06 (1.04-1.09)
Q5 (Highest)	1.08 (1.05-1.10)	1.06 (1.03-1.10)	1.10 (1.07-1.13)	1.12 (1.10-1.15)
P	0.025	0.137	<0.001	<0.001

Note: Q1 was the reference level. We performed Cochran's Q to assess statistically significant heterogeneity between subgroups within the study.

FIGURES

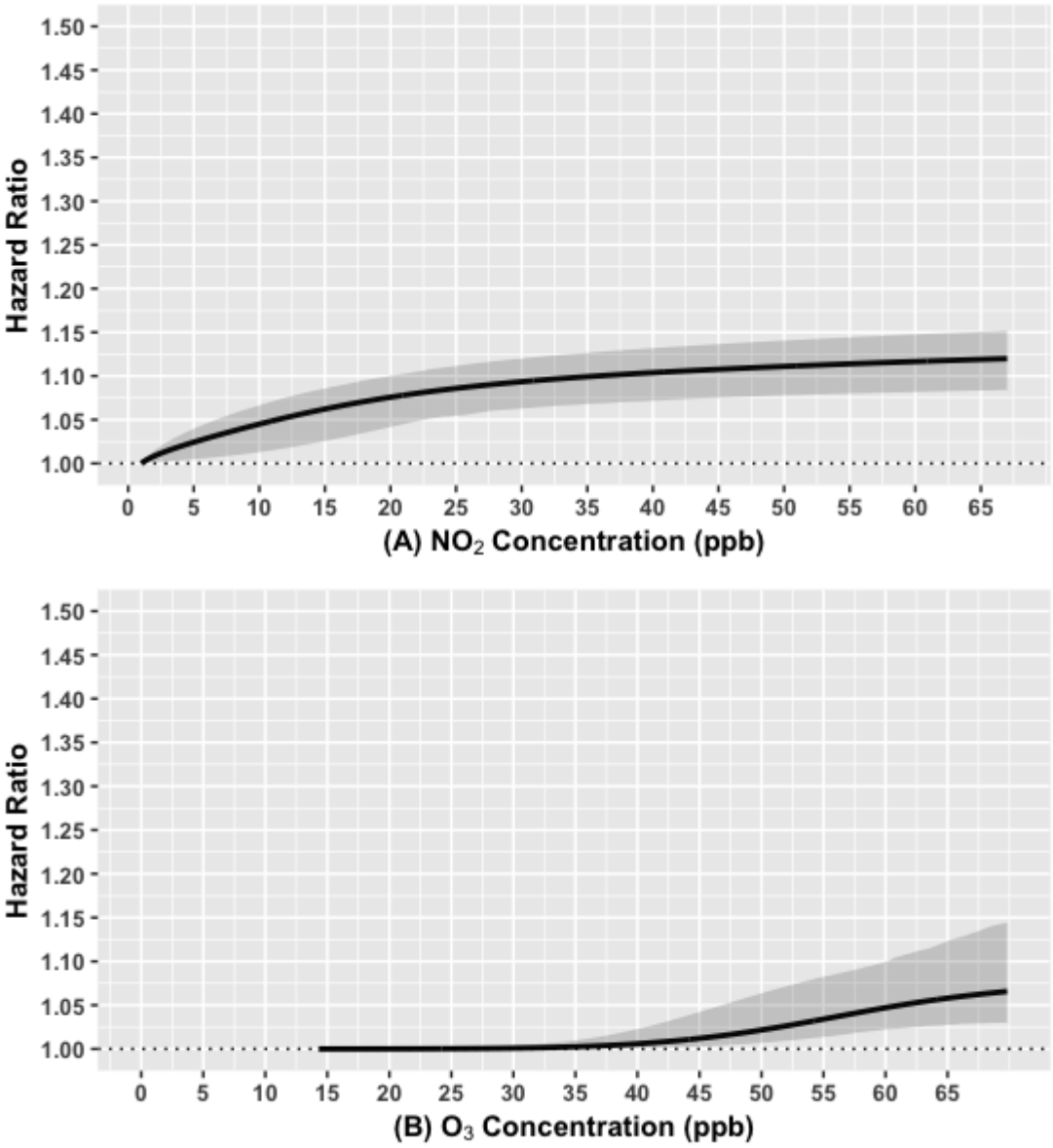

Figure S1: Pollutant-disease relationships for NO_2 and O_3 with atrial fibrillation

Grey area represents the 95% confidence interval. Fully adjusted model, stratified by an indicator for living in the Greater Toronto Area or not, and adjusted for age, sex, area-level socioeconomic status (education, recent immigrants, unemployment rate, and income quintile), urban/rural area, and northern/southern Ontario.

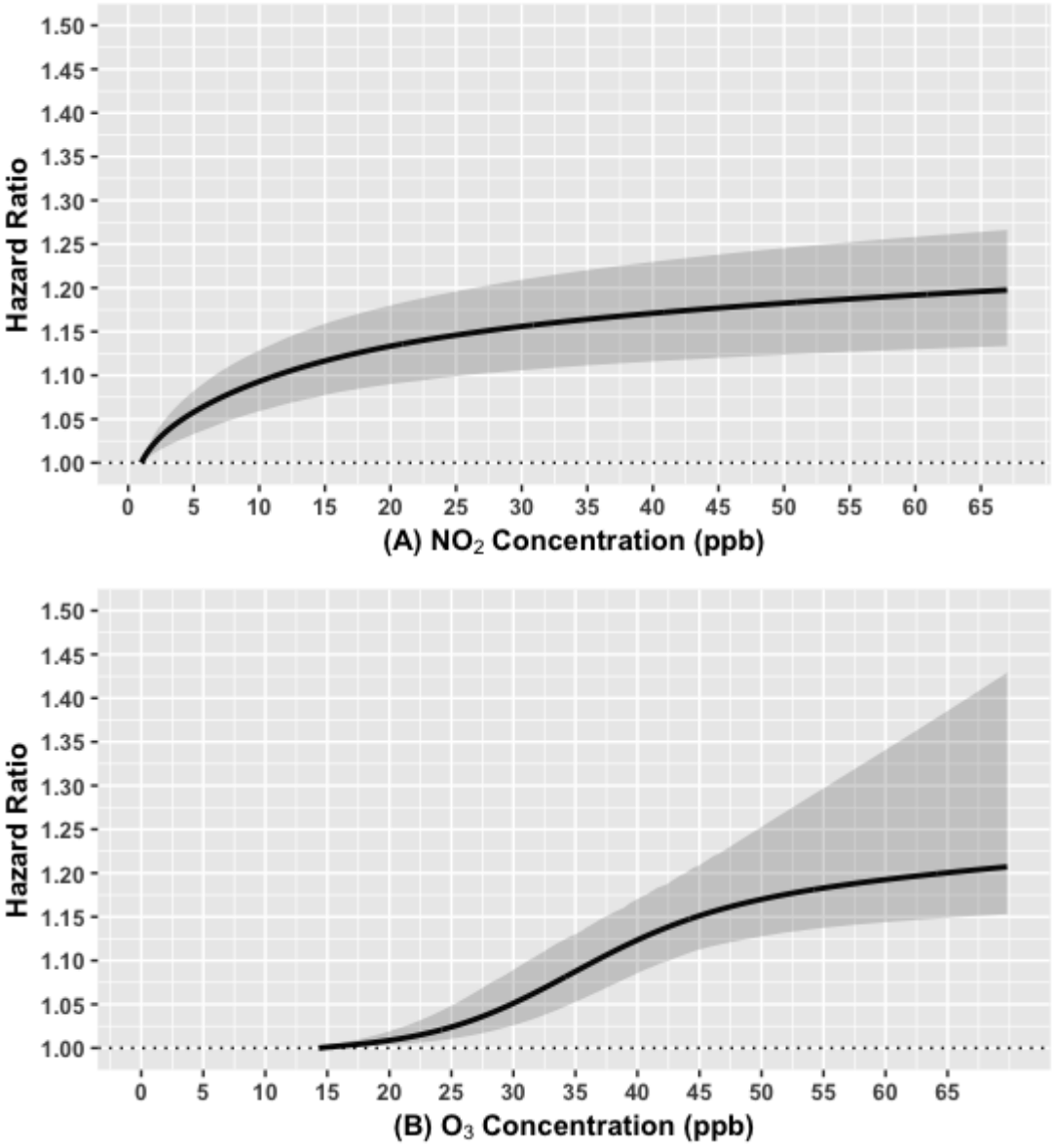

Figure S2: Pollutant-disease relationships for NO_2 and O_3 with stroke

Grey area represents the 95% confidence interval. Fully adjusted model, stratified by an indicator for living in the Greater Toronto Area or not, and adjusted for age, sex, area-level socioeconomic status (education, recent immigrants, unemployment rate, and income quintile), urban/rural area, and northern/southern Ontario.

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