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NEUROLOGICAL DISEASES

Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada

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Abstract. Inconsistent results have been obtained from studies that have examined the relationship between air pollution and hospital visits for stroke. We undertook a time-stratified case-crossover study to evaluate associations between outdoor air pollution and emergency department visits for stroke among the elderly according to stroke type, season, and sex. Analyses are based on a total of 12,422 stroke visits among those 65 years of age and older in Edmonton, Canada between April 1, 1992 and March 31, 2002. Daily air pollution levels for SO_2, NO_2, $PM_{2.5}$, PM_{10}, CO and O_3 were estimated using data from fixed-site monitoring stations. Particulate matter data were only available from 1998 onwards. Conditional logistic regression was used to estimate the odds ratios (ORs) and their 95% confidence intervals in relation to an increase in the interquartile range (IQR) of each pollutant. ORs were adjusted for the effects of temperature and relative humidity. We found no association between outdoor measures of air pollution and all stroke visits. In contrast, elevated risks were observed between levels of air pollution and acute ischemic stroke between April and September. During this season, the ORs associated with an increase in the IQR of the 3-day average for CO and NO_2 were 1.32 (95% CI = 1.09–1.60) and 1.26 (95% CI = 1.09–1.46), respectively. CO exposures in the same season, lagged 1 day, were associated with an increased risk of hemorrhagic stroke with ORs was 1.20 (95% CI = 1.00–1.43). Our results suggest it is possible that vehicular traffic, which produces increased levels of NO_2 and CO, contributes to an increased incidence of emergency department visits for stroke.

Key words: Air pollution, Case-crossover, Ischemic stroke, Risk, Stroke

Abbreviations: C.I. = Confidence interval; ED = Emergency Department; ICD-9 = International Classification of Diseases, 9th Revision; NAPS = National Air Pollution Surveillance; OR = Odds ratio; TIA = Transient ischemic attack; WHO = World Health Organization

Introduction

In Canada, the public health burden associated with stroke is considerable. It is the fourth leading cause of death, and an estimated 16,000 Canadians die from it each year [1]. It is also a common cause of hospitalization, and leading cause of long-term disability [2]. Approximately 80% of strokes result from clot (thrombus) formation and impairment of blood supply to brain tissue; these are referred to as *ischemic strokes*. Strokes resulting from leakage of blood from vascular beds in and around the brain are referred to as *hemorrhagic strokes* and account for the remaining 20%. In transient ischemic attacks (TIA), thrombus formation results in stroke symptoms that resolve (usually without treatment) prior to permanent damage; these events are considered harbingers of future strokes. Epidemiologic studies have played an important role in clarifying the role of a large number of risk factors in the etiology of stroke. These factors include diabetes, hypertension, diet, smoking, lipid disease, and exercise [1].

In the last decade, an increasing body of literature has provided compelling evidence to link outdoor air pollution to stroke mortality [3–6]. Published reports have also evaluated the relationship between ambient air pollution and hospitalization for stroke. Positive associations have been observed for PM_{10} [7–10], and nitrogen oxides [7, 10–12], however, associations were not found in five other studies [13–17]. For stroke, hospitalization data offer a distinct advantage over death data in that, for a given population, morbidity counts are higher than those from deaths, thereby providing increased statistical power to characterize associations with air pollution. Moreover, hospitalization data better permit an evaluation of the temporal sequence between exposure and clinical presentation of disease. Hospitalization data

represent an excellent means to capture stroke events since all but the most minimal strokes are admitted to hospital, and deaths due to stroke are sometimes misclassified. This can occur, in part, because death may occur long after the initial stroke, and the underlying cause of death are sometimes attributed to cardiovascular, respiratory, or infectious causes.

Clarifying the role that air pollution plays in the etiology of stroke is an important undertaking. Unlike most risk factors for stroke, air pollution represents a potentially modifiable risk factor that is not dependent on individual behavioral change. Several biological mechanistic arguments that link exposure to air pollution to an increased risk of stroke have been advanced. Some have suggested that exposure to ambient air pollution may provoke alveolar inflammation, which may in turn release harmful cytokines that may increase blood coagulation and promote thrombus formation [18]. Others have speculated that increased risks of stroke relate to the ability of air pollution to increase plasma viscosity [19], raise heart rate [20], and alter heart rate variability [21]. Elsewhere, studies have documented associations between plasma fibrinogen and particulate matter and NO_2, [22, 23] and recently, long-term exposure to ambient air pollution was found to promote atherosclerosis in animals [9]. As atherosclerosis is the most common cause of ischemic stroke [24], air pollution may be particularly relevant for this type of stroke. Further support for this hypothesis comes from a case-crossover study of hospital admissions among adults in nine US cities that found that air pollution increased the risk of ischemic, but not hemorrhagic stroke [10]. Spatial differences in exposure to particulate matter have also been associated with carotid intima-media thickness [25], and exposure to carbon monoxide (CO) has been shown to decrease the ability of blood to carry oxygen [26]. These effects may in turn increase the risk of stroke.

Here, we report findings from a case-crossover study of ambient air pollution and emergency department visits for hemorrhagic, and acute ischemic stokes and TIAs in Edmonton (Canada). Such analyses are valuable in light of the limited number of studies that have characterized air pollution risk by stroke subtype. Additionally, this study also examines variations in air pollution stroke risks between men and women. *A priori*, we hypothesized that women are more susceptible to the effects of air pollution given sex differences in air pollution lung deposition [27], and because a greater proportion of women have airway hyper-responsiveness than men [28].

Materials and methods

Study population

Data on emergency department (ED) visits were supplied by Capital Health (CH) for all five Edmonton area hospitals and covered the period between April 1, 1992 and March 31, 2002. The EDs are linked by a joint academic and teaching program at the University of Alberta. These hospitals have full service EDs with in-patient beds, operate 24-hour service EDs, and are staffed by full-time emergency physicians. The overall catchment size covered by the hospitals is estimated at approximately 1.5 million individuals.

Each ED chart was coded by an experienced medical record nosologist using triage information, nursing notes, ED records and consultation notes. ED department visits were classified according to the International Classification for diseases 9th revision (ICD-9) and was based on the discharge diagnosis. The time and date of presentation were also extracted from ED records. We restricted our analyses to visits for stroke (ICD-9: 430–438). Stratified analyses were also performed for stroke subtypes including: ischemic stroke (ICD-9: 434–436); hemorrhagic stroke (ICD-9: 430, 432), and TIA (ICD-9: 435).

Air pollution and meteorological data

Air pollution data were obtained from automated fixed-site continuous monitoring stations maintained by Environment Canada as part of the National Air Pollution Surveillance Network [29]. In Edmonton, there were 3 such monitoring stations in operation during the study period. For each site, daily mean and maximum pollution levels were constructed from hourly mean values. Daily pollution measures for Edmonton were then calculated from the average of the values across the monitoring stations. The measures consisted of the daily maximum for ozone (O_3), and daily means for nitrogen dioxide (NO_2), sulfur dioxide (SO_2), carbon monoxide (CO), particulate matter (PM_{10}), and fine particulate matter ($PM_{2.5}$). Only limited data for particles were available, as they were not routinely monitored until 1998. Environment Canada also provided meteorological data from the monitoring station at the Edmonton airport. These daily data included the mean temperature and relative humidity; these factors were used as adjustment factors in our multivariable conditional logistic regression models.

Statistical methods

All statistical analyses were conducted using SAS software [30]. Associations between outdoor air pollution and stroke visits were formally investigated using statistical methods appropriate for the case-crossover study design. This design is an adaptation of the case–control study in which cases serve as their own controls [31]. For each ED visit, an individual's exposure at the ''index'' time was compared to their exposure at referent time intervals. Because within-

individual comparisons are being made, there is no confounding due to time-independent risk factors. By selecting referent intervals that are close in time to the case event, seasonal patterns in disease occurrence are controlled for. Similarly, the matching of control to case periods by day of week ostensibly controls for the influence of ''day of week'' effects on the frequency of ED visits. In our study, the case period refers to the day that the ED visit for stroke occurred.

While referent periods are individually matched to case periods, epidemiologic studies have used several different strategies to select them. The implications of these selection methods on risk estimates have recently been described in great detail [32]. Based on this work, we chose our referent periods by using a time-stratified design. Specifically, referents were selected from the same day of the week, month and year as the case interval. This approach to the selection of referent intervals is not subject to time trend biases, and ensures unbiased conditional logistic regression estimates [32]. Once these matched sets consisting of one case period and either 3 or 4 referent periods had been assembled, conditional logistic regression was used to produce the risk estimates. These were represented by the odds ratios (OR), and the accompanying 95% confidence intervals were used to assess statistical significance. The SAS procedure PHREG [30] was used to perform these analyses. Similar analyses were undertaken to examine whether associations between air pollution and stroke were similar between men and women, and by season (April–September, October–March). Further partitioning of the data by season was not pursued due to concerns about small sample sizes, and issues related to multiple testing. Two pollutant models were also fit in an attempt to better understand effects of the pollutant mix.

Three different time lags for pollution levels were used in our analyses: same day, 1-day lag, and 3-day average. The 3-day average was calculated as the mean of pollution levels on the same day, the day before, and two days before the ED visit (or control day). The use of the 3-day average allowed us to evaluate potential cumulative effects of higher pollution levels that persisted for several days. As is commonly done, for each pollutant, we expressed our ORs according to an increase in the interquartile range (IQR). The IQR was calculated based on the daily mean levels of each air pollutant over the entirety of the study period (April 1, 1992–March 31, 2002).

Results

A total of 12,422 ED stroke visits were identified during the study interval and formed the basis of the case-crossover analyses (Table 1). Of these, 6,001 (48.3%) visits occurred among males. TIAs and acute ischemic strokes each accounted for approximately 39% of all stroke ED visits. An approximately equal proportion of visits occurred between October and March as between April and September. Table 2 summarizes the daily mean air pollution levels for gases (SO_2, NO_2, CO, O_3) and weather variables (temperature, relative humidity) between 1992 and 2002. Similar data for particulate matter between 1998 and 2002 are also presented in the same table.

Table 1. Number of emergency department visits for stroke among patients 65 years of age and older, by age, sex, stroke type and season, in Edmonton from March 31, 1992 to April, 2002

Variable	Number of visits	%
Age-group (in years)		
65– < 75	5435	43.7
75– < 85	5129	41.3
85 +	1858	15.0
Sex		
Male	6001	48.3
Female	6421	51.7
Stroke type		
Acute ischemic (ICD-9: 434, 436)	4850	39.0
Hemorrhagic (ICD-9: 430, 432)	2329	18.7
Transient ischemic attacks (ICD-9:435)	4855	39.1
Other (ICD-9:433,437,438)	388	3.1
Season		
Spring/Summer: (April–September)	6213	50.0
Fall/Winter (October–March)	6209	50.0
Total visits	12422	100.0

In Table 3, we present seasonal Pearson correlations between the daily measures of air pollution and temperature and relative humidity. Given the number of daily measures, it is not surprising that all correlations were statistically significant ($p < 0.05$). Stronger correlations were evident amongst $PM_{2.5}$, CO and NO_2. As expected, the mean and daily maximum ozone values were also strongly correlated with each other. In contrast, relative humidity was inversely correlated with ozone.

We found no statistically significant associations between any of air pollutants and all strokes combined in either the winter or summer ($p > 0.05$; results not shown). Associations between ambient levels of air pollution and ED visits for acute ischemic stroke are presented in Table 4. Between April and September, an interquartile increase in the 3-day average concentration of NO_2 was associated with an increased risk of an ED visit for ischemic stroke (OR = 1.26, 95% CI = 1.09, 1.46). Similar associations were observed with NO_2 exposure on the same day, and the day preceding the ED visit. Positive associations were also observed with same day exposures to SO_2 and CO. There were no statistically significant associations between any of the air

Table 2. Daily summaries at gaseous and particulate air pollution in Edmonton, by season, April 1, 1992 to March 31, 2002

Variable	Days	Missing days	Mean	Standard deviation	Median	25th percentile	75th percentile	IQR
All year								
SO_2 (ppb)	3616	36	2.6	1.9	2.0	1.0	4.0	3.0
NO_2 (ppb)	3650	2	24.0	9.8	22.0	16.5	30.0	13.5
CO (ppm)	3650	2	0.8	0.5	0.7	0.5	1.0	0.5
O_3-daily mean (ppm)	3652	0	17.0	9.1	16.5	9.5	23.5	14.0
O_3-daily max (ppm)	3652	0	31.2	13.0	30.5	22.0	40.0	18.0
$PM_{2.5}$	1440	2212	8.5	6.2	7.0	4.7	11.0	6.3
PM_{10}	1480	2172	24.2	14.8	20.0	14.0	30.0	16.0
Mean temperature (°C)	3652	0	3.9	11.9	5.4	−4.0	14.0	17.9
Relative humidity (%)	3652	0	65.9	13.6	66.1	57.1	75.6	18.5
Summer (April–September)								
SO_2 (ppb)	1804	26	2.1	1.6	2.0	1.0	3.0	2.0
NO_2 (ppb)	1829	1	18.6	6.4	17.5	14.0	22.0	8.0
CO (ppm)	1829	1	0.6	0.3	0.6	0.5	0.7	0.3
O_3-daily mean (ppm)	1830	0	21.8	8.0	21.5	16.0	27.0	11.0
O_3-daily max (ppm)	1830	0	38.3	11.6	38.0	29.5	46.0	16.5
$PM_{2.5}$	711	1119	8.7	7.1	7.0	4.5	11.0	6.5
PM_{10}	716	1114	25.9	16.4	22.0	15.0	32.5	17.5
Mean temp. (°C)	1830	0	13.1	5.7	13.9	9.8	17.2	7.3
Relative hum. (%)	1830	0	62.8	14.3	63.0	53.0	72.8	19.8
Winter (October–March)								
SO_2 (ppb)	1812	10	3.1	2.0	3.0	2.0	4.0	2.0
NO_2 (ppb)	1821	1	29.4	9.6	28.5	22.5	35.5	13.0
CO (ppm)	1821	1	1.0	0.6	0.9	0.7	1.3	0.7
O_3-daily mean (ppm)	1822	0	12.2	7.4	10.5	6.5	17.0	10.5
O_3-daily max (ppm)	1822	0	24.2	10.2	24.5	16.5	31.5	15.0
$PM_{2.5}$	729	1093	8.3	5.2	7.3	5.0	11.0	6.0
PM_{10}	764	1058	22.6	12.9	19.0	13.0	29.0	16.0
Mean temp. (°C)	1822	0	−5.3	9.2	−3.7	−11.1	1.6	12.7
Relative hum. (%)	1822	0	69.0	12.1	68.7	60.9	78.0	17.0

IQR = Interquartile range.

pollutants and ED visits for ischemic stroke between October and March, nor over the course of the entire year.

The patterns of risk for hemorrhagic stroke were similar in magnitude to those for acute ischemic stroke however they were of borderline significance (Table 5). The ORs that corresponded to an interquartile increase the 3-day average of CO and NO_2 were 1.25 (95% CI = 0.98–160), and 1.18 (95% CI = 0.95–1.46), respectively. Given that there were fewer cases for hemorrhagic stroke, there was less statistical power to detect increased risks. Findings from our evaluation of the relationship between TIA and air pollution are presented in Table 6. A positive relationship between same day exposure to SO_2 was observed (OR = 1.11, 95% CI = 1.02–1.22) during the summer months. No other statistically significant findings were observed.

Gender differences in air pollution risks between April and September, and October–March are presented in Figures 1 and 2, respectively. Consistent with earlier results, between April and September, an increase in the IQR of 3-day mean NO_2 levels was associated with a higher risk of ischemic stroke risk in both men and women; while this risk was slightly higher among women, a test for heterogeneity in these ORs was not statistically significant ($p > 0.05$). Similarly, there were no sex differences in the ORs for CO. Between October and March, among women, there were no statistically significant associations with 3-day average pollution levels; among men, the only statistically significant association was observed with the 3-day mean PM_{10} levels, and ER visits for hemorrhagic stroke in man.

To provide additional insights on the positive associations observed for NO_2 and CO, we fit two pollutant models for ED visits between April and September (Figures 3, 4). For both CO and NO_2, the risk estimates increased with the addition of indices of particulate matter, however, results were limited to the calendar periods from 1998 onwards. The risk estimates for NO_2 were modestly attenuated when CO was added to the model. Neither CO nor NO_2 were positively associated with transient ischemic attacks in any of the two pollutant models.

Table 3. Correlations between daily pollution levels and temperature and relative humidity, by season, Edmonton, April 1, 1992–March 31, 2002

	SO_2	NO_2	CO	O_3-mean	O_3-max	PM_{25}	PM_{10}	Temperature	Humidity
All year									
SO_2	1	0.42	0.41	−0.25	−0.16	0.22	0.19	−0.18	−0.10
NO_2		1	0.74	−0.51	−0.33	0.41	0.34	0.48	0.04
CO			1	−0.54	−0.42	0.43	0.30	−0.36	0.13
O_3-mean				1	0.89	−0.07	0.07	0.45	−0.52
O_3-max					1	0.07	0.22	0.54	−0.54
PM_{25}						1	0.79	0.11	−0.10
PM_{10}							1	0.25	−0.38
Temperature								1	−0.28
Humidity									1
Summer (April – September)									
SO_2	1	0.22	0.21	−0.06	0.08	0.20	0.18	0.17	−0.20
NO_2		1	0.59	−0.09	0.26	0.52	0.57	−0.04	0.27
CO			1	−0.22	0.02	0.42	0.38	−0.09	−0.06
O_3-mean				1	0.83	0.11	0.20	0.12	−0.57
O_3-max					1	0.34	0.40	0.28	−0.56
PM_{25}						1	0.85	0.36	−0.25
PM_{10}							1	0.32	−0.43
Temperature								1	−0.17
Humidity									1
Winter (October – March)									
SO_2	1	0.41	0.40	−0.21	−0.11	0.28	0.27	−0.04	−0.15
NO_2		1	0.70	−0.49	−0.28	0.57	0.48	−0.13	0.01
CO			1	−0.54	−0.41	0.71	0.53	−0.01	0.09
O_3-mean				1	0.87	−0.45	−0.26	0.06	−0.36
O_3-max					1	−0.35	−0.09	0.21	−0.44
PM_{25}						1	0.70	−0.03	0.14
PM_{10}							1	0.24	−0.28
Temperature								1	−0.19
Humidity									1

Discussion

Our study summarizes the relationship between air pollution and ED visits for stroke in Edmonton over a 10-year interval. To date, this is the first Canadian study that has investigated the relationship between air pollution and stroke with an emphasis on examining variations in risk according to stroke type, and gender. These analyses suggest that exposure to outdoor air pollution is associated with hospitalization for stroke, and that these increased risks occur during non-winter months. Additionally, the results from our multi-pollutant modeling implicate NO_2 and CO as the pollutants of primary concern. We found little variation in risks between men and women.

The risk estimates presented here have been adjusted for meteorological effects of temperature and relative humidity. In addition, the case-crossover design is effective in controlling for the confounding of individual-level risk factors as many of these are unlikely to vary over short time intervals. For stroke, such factors are numerous and include: age, sex, presence of other comorbid conditions (e.g., hypertension, diabetes), and cigarette smoking. It is unlikely that the effects from indoor sources of air pollution would greatly confound our results, as particles generated indoors are different from ambient particles. Namely, outdoor particles consist of coarse dust and finer fractions of sulfates and carbon particles generated from internal combustion engines, whereas indoor air particles are generated from cigarette smoking, radon, indoor combustion of fuels, molds, fungi, and indoor activities [33, 34]. The time-stratified case-crossover approach has also been demonstrated as a suitable method to control for time trends in both air pollution exposures and outcomes [32]. As a result, the case-crossover design can offer a distinct advantage over the time-series design that has been shown to be quite sensitive to the choice of method used to control for seasonality [35]. This, in part, has contributed to an increasing popularity of the case-crossover method in recent years.

Findings from a 9-city US study of air pollution and hospitalization for stroke were recently reported [10]. They found that an increase in the IQR value of CO, NO_2, PM_{10} and SO_2 was associated with 2.83, 2.94, 2.33, and 1.35% increases, respectively, in hospital admissions for ischemic stroke; no associations

Table 4. Adjusted ORs* for emergency department visits for acute ischemic stroke among adults 65 years of age and older corresponding to an increase in the IQR of selected air pollutants by season, in Edmonton from 1992 to 2002

Pollutant	Mean	IQR	All seasons		Season			
			OR	95% CI	October–March		April–September	
					OR	95% CI	OR	95% CI
SO_2	Same day	3.0	1.05	0.99–1.11	1.00	0.93–1.09	1.11	1.01–1.22
	1-day lag		1.04	0.98–1.10	1.07	0.99–1.15	1.00	0.91–1.09
	3-day		1.06	0.97–1.16	1.08	0.96–1.21	1.02	0.88–1.18
NO_2	Same day	13.5	1.03	0.97–1.10	0.98	0.91–1.06	1.17	1.05–1.31
	1-day lag		1.05	0.98–1.11	1.00	0.93–1.08	1.18	1.05–1.32
	3-day		1.05	0.97–1.14	0.98	0.89–1.08	1.26	1.09–1.46
CO	Same day	0.5	0.99	0.94–1.05	0.97	0.92–1.03	1.16	1.00–1.33
	1-day lag		1.00	0.95–1.06	0.98	0.92–1.03	1.17	1.01–1.36
	3-day		1.01	0.94–1.08	0.97	0.90–1.04	1.32	1.09–1.60
O_3	Same day	18.0	0.99	0.91–1.07	0.98	0.87–1.11	1.03	0.92–1.15
	1-day lag		0.97	0.90–1.04	0.94	0.84–1.06	1.00	0.91–1.10
	3-day		1.00	0.89–1.12	0.98	0.82–1.16	1.08	0.92–1.28
$PM_{2.5}$	Same day	6.3	1.00	0.96–1.04	0.96	0.90–1.03	1.04	0.99–1.10
	1-day lag		1.00	0.96–1.05	1.01	0.94–1.07	1.01	0.96–1.07
	3-day		1.01	0.96–1.06	0.98	0.89–1.07	1.05	0.98–1.13
PM_{10}	Same day	16.0	0.98	0.94–1.03	0.93	0.87–1.00	1.04	0.97–1.11
	1-day lag		1.00	0.96–1.05	1.01	0.94–1.08	1.00	0.94–1.06
	3-day		0.99	0.93–1.05	0.96	0.88–1.04	1.05	0.95–1.15

IQR = Interquartile range; OR = Odds ratio.
*ORs were adjusted for relative humidity and temperature.

Table 5. Adjusted ORs* for emergency department visits for hemorrhagic stroke among adults 65 years of age and older corresponding to an increase in the IQR of selected air pollutant, by season, in Edmonton from 1992 to 2002

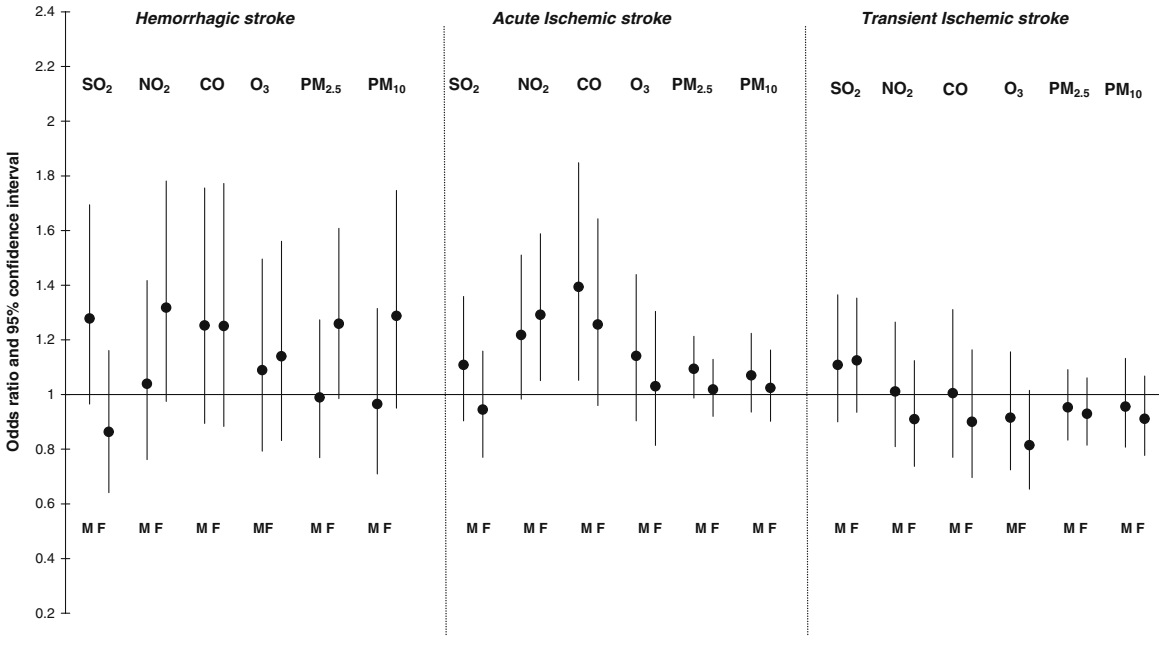
Pollutant	Mean	IQR	All seasons		Season			
			OR	95% CI	October–March		April–September	
					OR	95% CI	OR	95% CI
SO_2	Same day	3.0	0.98	0.90–1.06	0.94	0.84–1.05	1.03	0.90–1.17
	1-day lag		1.00	0.92–1.09	1.05	0.94–1.17	0.93	0.81–1.06
	3-day		1.04	0.92–1.17	1.02	0.88–1.18	1.06	0.87–1.30
NO_2	Same day	13.5	1.05	0.97–1.14	1.02	0.92–1.12	1.16	0.99–1.37
	1-day lag		1.04	0.96–1.13	1.01	0.92–1.11	1.14	0.97–1.35
	3-day		1.05	0.95–1.17	1.01	0.90–1.14	1.18	0.95–1.46
CO	Same day	0.5	1.00	0.94–1.06	0.97	0.91–1.04	1.16	0.98–1.38
	1-day lag		0.98	0.92–1.04	0.95	0.89–1.02	1.20	1.00–1.43
	3-day		0.97	0.90–1.05	0.94	0.86–1.02	1.25	0.98–1.60
O_3	Same day	18.0	1.00	0.89–1.11	0.92	0.78–1.08	1.11	0.95–1.30
	1-day lag		0.94	0.85–1.04	0.91	0.78–1.06	0.99	0.86–1.15
	3-day		1.02	0.88–1.18	0.97	0.78–1.20	1.11	0.89–1.38
$PM_{2.5}$[a]	Same day	6.3	0.99	0.90–1.08	0.99	0.86–1.15	1.04	0.92–1.18
	1-day lag		1.07	0.98–1.16	1.12	0.97–1.30	1.08	0.97–1.20
	3-day		1.05	0.93–1.19	1.08	0.88–1.31	1.11	0.94–1.31
PM_{10}[b]	Same day	16.0	1.01	0.90–1.12	1.02	0.88–1.20	1.05	0.90–1.22
	1-day lag		1.03	0.93–1.15	1.07	0.91–1.26	1.04	0.91–1.19
	3-day		1.13	0.98–1.30	1.20	0.98–1.46	1.11	0.90–1.37

IQR = Interquartile range; OR = Odds ratio.
*ORs were adjusted for relative humidity and temperature.
[a]Exposure data were only available between April 18, 1998 and December 31, 2002.
[b]Exposure data were only available between January 1, 1998 and December 31, 2002.

Table 6. Adjusted ORs* for emergency department visits for transient cerebral ischemic among individuals 65 years of age and older corresponding to an increase in the IQR of selected air pollutant, by season, in Edmonton, April 1, 1992 to March 31, 2002

Pollutant	Mean	IQR	All seasons		Season			
			OR	95% CI	October–March		April–September	
					OR	95% CI	OR	95% CI
SO_2	Same day	3.0	1.06	1.00–1.12	1.03	0.95–1.11	1.11	1.02–1.22
	1-day lag		0.99	0.93–1.05	1.01	0.93–1.08	0.96	0.88–1.05
	3-day		1.05	0.97–1.15	1.02	0.92–1.14	1.12	0.97–1.28
NO_2	Same day	13.5	0.99	0.93–1.05	0.99	0.92–1.06	0.99	0.88–1.11
	1-day lag		0.94	0.89–1.00	0.95	0.88–1.02	0.93	0.83–1.05
	3-day		0.95	0.88–1.03	0.95	0.87–1.04	0.96	0.82–1.11
CO	Same day	0.5	1.00	0.95–1.04	0.99	0.95–1.04	1.04	0.91–1.18
	1-day lag		0.98	0.93–1.02	0.98	0.93–1.02	0.98	0.86–1.13
	3-day		0.96	0.91–1.02	0.97	0.91–1.03	0.95	0.79–1.14
O_3	Same day	18.0	0.98	0.91–1.06	1.05	0.93–1.17	0.92	0.82–1.03
	1-day lag		0.96	0.89–1.02	1.01	0.91–1.13	0.91	0.83–1.00
	3-day		0.98	0.88–1.09	1.10	0.94–1.28	0.86	0.73–1.01
$PM_{2.5}$[a]	Same day	6.3	0.98	0.93–1.03	1.00	0.92–1.08	0.97	0.90–1.05
	1-day lag		0.99	0.95–1.04	1.03	0.95–1.12	0.97	0.91–1.04
	3-day		0.96	0.90–1.03	0.98	0.88–1.09	0.94	0.86–1.03
PM_{10}[b]	Same day	16.0	0.96	0.90–1.02	0.97	0.89–1.06	0.95	0.87–1.04
	1-day lag		0.99	0.94–1.05	0.99	0.91–1.08	0.99	0.92–1.07
	3-day		0.94	0.87–1.01	0.94	0.84–1.04	0.93	0.83–1.05

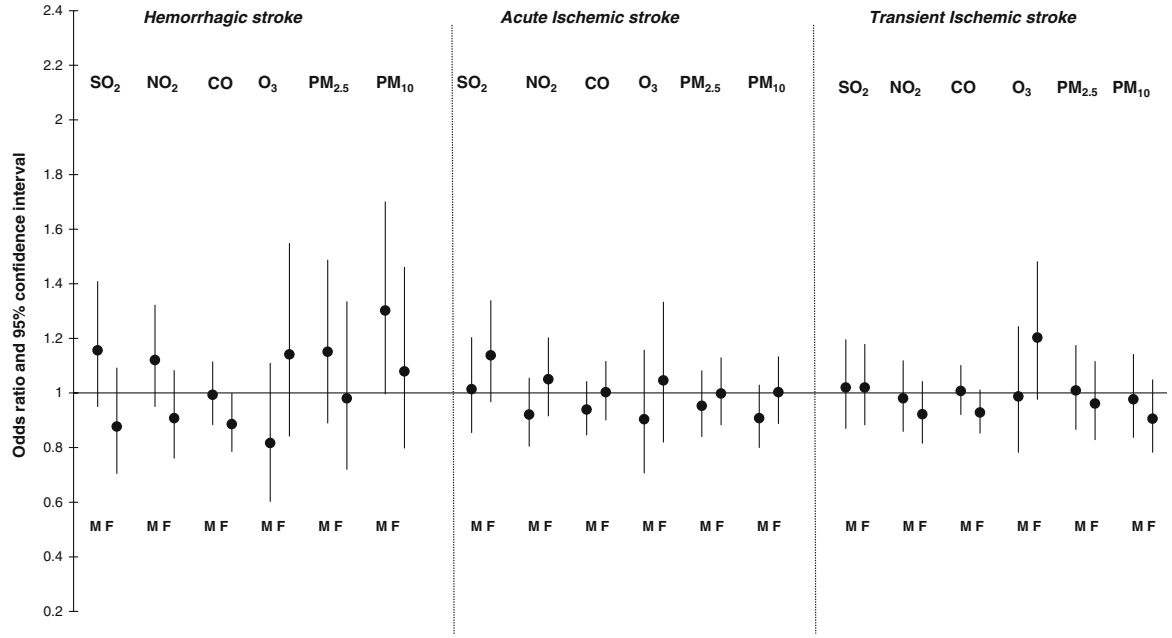
IQR = Interquartile range; OR = Odds ratio.
*ORs were adjusted for relative humidity and temperature.
[a]Exposure data were only available between April 18, 1998 and December 31, 2002.
[b]Exposure data were only available between January 1, 1998 and December 31, 2002.



* Adjusted for temperature and relative humidity.

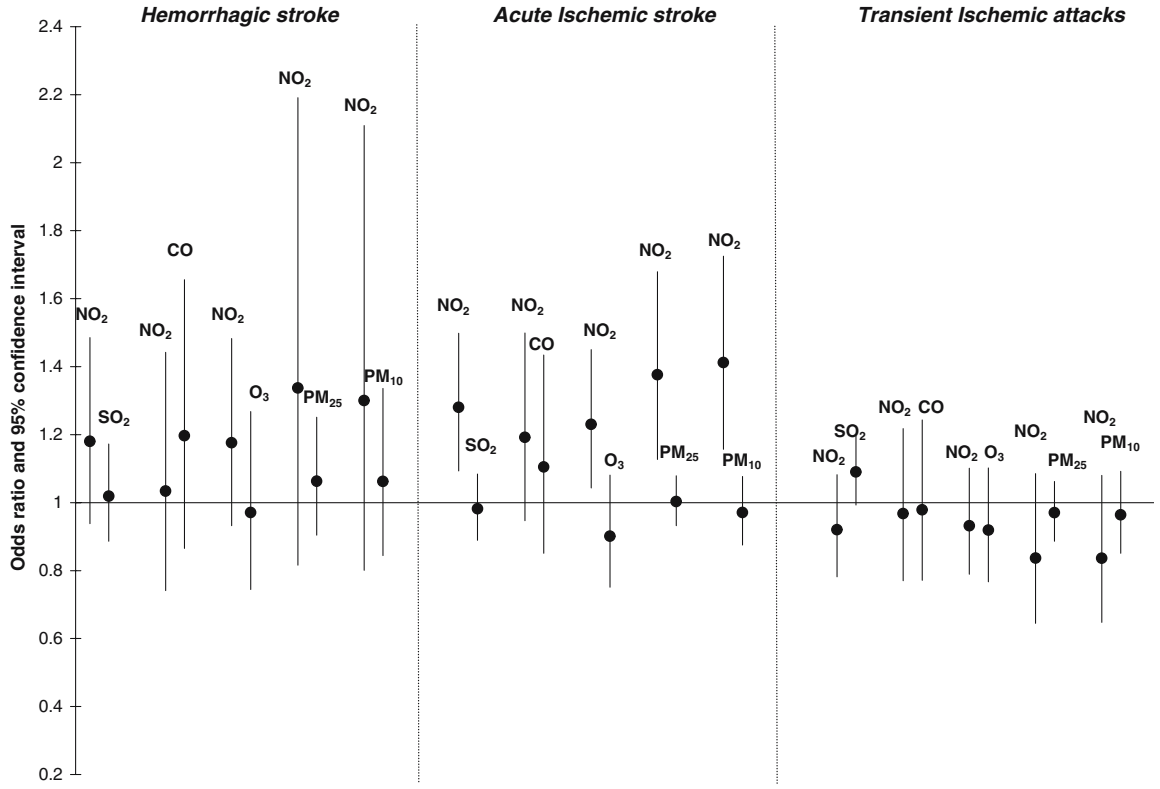
Figure 1. Adjusted ORs* for emergency department visits for individuals 65 years of age and older corresponding to an increase in the IQR of the 3-day mean of selected air pollutants, between April and September, by sex, in Edmonton from April 1, 1992 to March 31, 2002. *Adjusted for temperature and relative humidity.

with hemorrhagic stroke were evident. In our study, we too found positive associations with CO and NO_2 for ischemic stroke. However, unlike their study, the magnitude of our risk estimates was similar between acute ischemic and hemorrhagic stroke. These latter risk estimates were not statistically significant, which



* Adjusted for temperature and relative humidity.

Figure 2. Adjusted ORs* for emergency department visits for individuals 65 years of age and older corresponding to an increase in the IQR of the 3-day mean of selected air pollutants, between October and March, by sex, Edmonton, April 1, 1992 to March 31, 2002 *Adjusted for temperature and relative humidity.



* Adjusted for temperature and relative humidity.

Figure 3. Adjusted ORs* from two pollutant models (NO_2 + other) for emergency department visits for individuals 65 years of age and older corresponding to an increase in the IQR of the 3-day mean of selected air pollutants, between April and September, Edmonton, April 1, 1992 to March 31, 2002 *Adjusted for temperature and relative humidity.

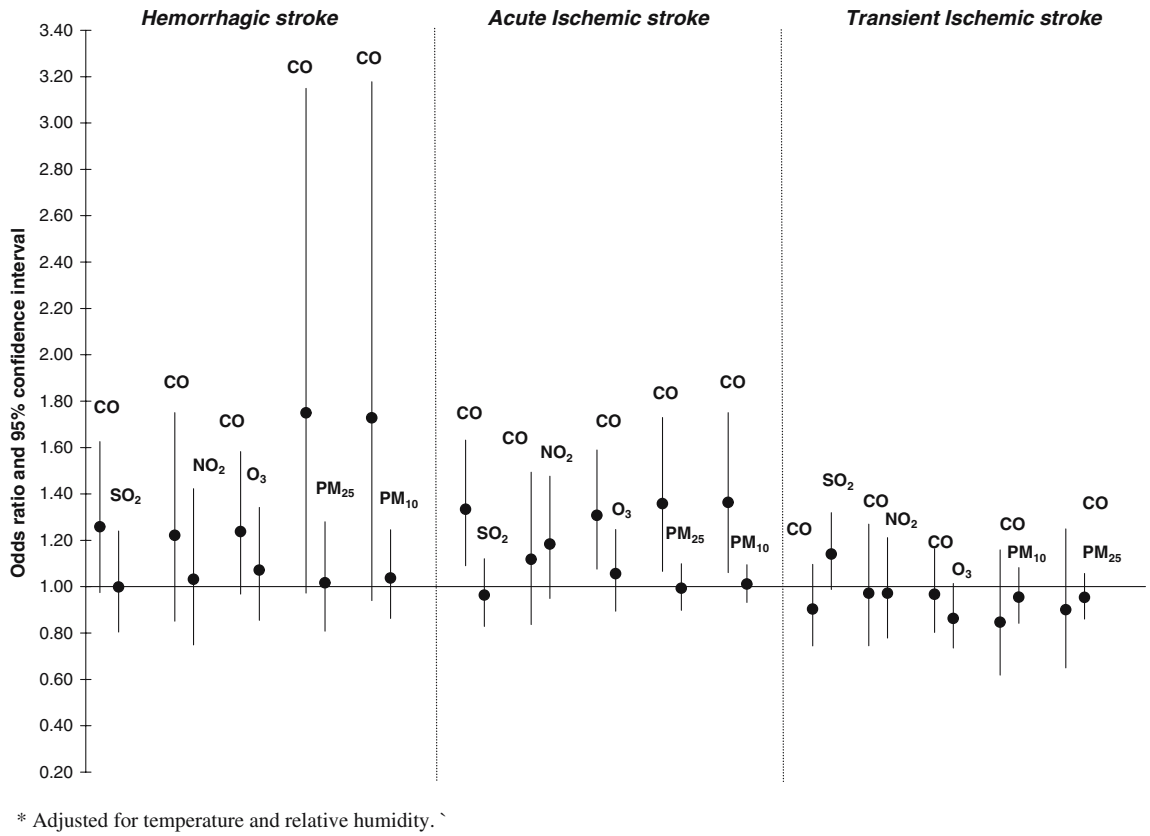


Figure 4. Adjusted ORs* from two pollutant models (CO + other) for ED visits for individuals 65 years of age and older corresponding to an increase in the IQR of the 3-day mean of selected air pollutants, between April and September, Edmonton, April 1, 1992 to March 31, 2002 *Adjusted for temperature and relative humidity.

may be partly due to reduced statistical power arising from a smaller number of hemorrhagic ED visits. While there is consistency in the nature of the pollutants involved, comparisons of risk estimates between our study and theirs are difficult given that their estimates are based on pooling estimates across 9 US cities. These cities differ from Edmonton with respect to the local mix of ambient pollutants and meteorology. Moreover, our estimates were found to differ by season, with excess risks found only between April and September. At these times, Edmonton residents are likely to spend a greater proportion of their time outdoors, and fixed-site data may be a better indicator of their exposure to ambient levels of pollution when compared to other times of the year. Unfortunately, the paper by Wellenius and colleagues did not report on seasonal variations in risk. Seasonal analyses would have been far more difficult in their study population given that data were collected from 9 different cities, and hence geographies.

To better understand which pollutants are the most important determinants of stroke risk, we also fit two-pollutant models. The risk estimates for both CO and NO_2 increased in magnitude when particulate matter metrics ($PM_{2.5}$, PM_{10}) were added to the model, however, these estimates are only based on the calendar period from 1998 onwards. The risk estimates for NO_2 and CO were attenuated with the addition of the other pollutant in the model. We did not extend the multi-pollutant models to include more than two pollutants at a time due to problems with collinearity. Previous research suggests a plausible biologic mechanism whereby NO_2 can increase the risk of stroke. NO_2 serves as a surrogate measure for vehicle exhaust and it is possible that some exhaust components are responsible for the observed effects. Vehicular traffic is a major contributor to outdoor air pollution and can produce high levels of fine particulate matter, carbon monoxide, and nitrogen oxides. NO_2 has been associated with plasma fibrinogen [22, 23], and also correlated with fine particulate matter, which can provoke alveolar inflammation, which can result in increased coagulability through the release of cytokines [18]. As described elsewhere [5], these mechanisms suggest that air pollution may produce hemodynamic disturbances that could increase the risk of cardiovascular, and by extension, cerebrovascular events. In this same study by Tsai and colleagues, CO was found to be associated with admissions for stroke on both warm and cold days.

For the most part, air pollution risk estimates did not differ substantially between men and women. This is in contrast to a study in Seoul, Korea that found elderly women more susceptible to the effects

of PM_{10}, for acute stroke mortality, when compared to their similarly aged male counterparts [3]. Elsewhere, a cohort study of 6,338 California Adventists found that associations between $PM_{2.5}$ and fatal coronary heart disease were stronger among women. It has been hypothesized that these differences might be attributed to a greater deposition of particulate matter in women [27], or alternatively that women have fewer red blood cells than men [36], rendering them more susceptible to environmental pollutants. More work is needed to clarify the variable associations between sex and air pollution as it relates to both cardiovascular disease and stroke.

Like most other time series and case-crossover studies, our risk estimates may be biased by assigning regional measures of air pollution from fixed site-monitoring stations to individuals. Individual-level exposure estimates are recognized to be superior for evaluating risk of environmental exposures. Measurement error from fixed-site monitoring stations can occur from the devices themselves, or from an inability to account for heterogeneous pollution levels that exist spatially within the region. The magnitude of these measurement errors vary between pollutants, for example, pollutants such as NO_2 and CO exhibit more spatial variability when compared to O_3. Assuming that these exposure measurement errors are non-differential between case and control intervals, the net effect would be risk estimates that are biased towards the null [37]. If so, the magnitude of our presented risk estimates are understated.

It is also possible that this exposure misclassification can vary by season. As Edmonton residents spend a greater proportion of their time outside during the spring and summer seasons, fixed site monitoring data may better reflect their exposures to ambient air pollution. Therefore, if the association between air pollution and stroke is real, there would be greater attenuation in risk estimates for winter time exposures. While reduced exposures misclassification could partly explain the increased risks between April and September under the above scenario, it is also possible weather modifies the effect. A case-crossover study in Kaohsing, Taiwan found that, for the most part air pollution was related to hospital admissions for stroke only on days where the temperature exceeded 20 °C [5]; in this study, CO was found to be associated with stroke visits for both cold and warm days. As outlined by these investigators, higher temperatures may increase plasma viscosity [38] and serum cholesterol levels [39], thereby contributing to an increased risk of stroke.

In addition to exposure misclassification, some misclassification of stroke outcomes is also likely based on previous work that has investigated the accuracy of using ICD-9. Specifically, previous studies suggest that the use of hospital discharge abstracts can overestimate the incidence of stroke [40, 41], and that agreement rates between coders were only ''fair'' [42]. While misclassification of exposure can produce biased risk estimates, misclassification of outcomes according to stroke type is unlikely to be related to air pollution exposure, a condition necessary to bias the results. Instead, misclassification of outcome as a result of diagnostic coding will reduce the precision of the risk estimates.

Our study provides limited information about the effects of particulate matter as these data were only available for a portion of the study period (1998–2002). As a result, we have limited statistical power to characterize the PM-related risks, particularly, within stroke-type, seasonal and gender strata. Previous work suggests that exposure to fine particulate matter could increase the risk of stroke by provoking alveolar inflammation which increases coagulability [14]. Other postulated mechanisms whereby particles increase the risk of stroke include their ability to induce progression of artherosclerosis in animals [9, 43], and the capability of inhaled ultrafine particles to enter the bloodstream [44]. For a subset of days where both PM and gaseous pollutant data were available, we found that NO_2 was strongly correlated to TEOM-based measures of fine particulate matter ($PM_{2.5}$) ($r = 0.41$, $p < 0.001$). Therefore, while our findings suggest that NO_2, which is primarily generated from vehicle exhaust, increases ED visits for stroke, the role of $PM_{2.5}$, which is also generated from traffic sources can not be entirely dismissed.

Conclusion

In summary, our analyses indicate that there are important associations between ED visits for stroke and outdoor air pollution in an urban area with relatively low levels of air pollution. These associations were evident between April and September each year; no associations were noted during the other months of the year. Findings from our two-pollutant models implicate CO and NO_2, but unfortunately, are unable to distinguish between their respective contributions. These associations persisted using a design that takes into account the effects of seasonality, day-of-week effects, and meteorological events. Further efforts to reduce pollutant emissions from traffic could represent an important initiative through which stroke morbidity could be reduced.

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