Estimation of Short-Term Effects of Air Pollution on Stroke Hospital Admissions in Southern Sweden

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Key Words

Epidemiology · Epidemiological methods · Air pollution · Stroke · Stroke risk factors

Abstract

Background: Short-term exposure to high levels of air pollution can increase stroke risk. In this study we investigated the short-term effects of air pollution on hospital admissions for stroke in a setting where pollutant levels are rather low. We also addressed methodological issues in evaluating the short-term effects of air pollution. **Methods:** Daily admissions of ischemic ($n = 11,267$) and hemorrhagic ($n = 1,681$) stroke were obtained from a Swedish quality register for stroke, Riks-Stroke. We used two types of exposure data: (1) daily measured background levels of ozone, temperature and particles with a diameter $<10 \mu\text{m}$ (PM_{10}) and (2) modeled levels of a mixture of NO and NO_2 (NO_x) at the residential address of each individual. **Results:** We estimated a 13% (95% confidence interval, 4–22%) increased risk for hospital admissions for ischemic stroke for levels of PM_{10} above $30 \mu\text{g}/\text{m}^3$ compared to $<15 \mu\text{g}/\text{m}^3$, whereas temperature above 16°C decreased the risk. No consistent associations were found for hemorrhagic stroke or for ischemic stroke and ozone or NO_x . **Conclusion:** Particulate air pollution and temperature seemed to be associated with ischemic stroke hospital admissions. Individual exposure mod-

eling facilitates a detailed exposure assessment but may also be more prone to misclassification errors. The time series and case crossover approaches yielded similar effect estimates.

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Introduction

Short-term exposure to air pollution has been linked to an increased risk of stroke in previous studies. Online supplementary table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000274807) provides an overview of the literature on short-term associations between stroke and air pollution that we refer to in this paper.

Results from both animal and human experimental studies as well as observational studies have suggested several plausible mechanistic pathways linking air pollution to cardiovascular disease [1], including systemic inflammatory responses, arrhythmias, enhanced coagulation/thrombosis, acute arterial vasoconstriction, oxidative stress, endothelial function, hemodynamic responses and the chronic promotion of atherosclerosis [2, 3].

Although relying on monitoring sites often far from the vicinity of the study subjects, a short-term (acute) ef-

fect of particles in ambient air on cerebrovascular disease/stroke mortality has been reported in a number of studies [4–8], while others did not observe such an association [9, 10]. The relation between hospital admissions for stroke and particulate air pollution is less clear; some researchers report an association [11–16] while others do not [17–20]. Associations have been observed between ozone, black smoke, CO, NO₂ and SO₂ for both stroke mortality and hospital admissions [6, 9, 21–23]. In one study an association was observed between hospital admissions for ischemic stroke and ozone (in men), but not for particles [24].

The evidence that air pollution is a risk factor is stronger for ischemic stroke than for hemorrhagic stroke [5, 12–14, 22–24], although the different types of cerebrovascular disease were not differentiated in all studies [4, 6, 8–11, 15, 17–19, 25]. The biological mechanism behind ischemic and hemorrhagic stroke may be different. Also, the effects of pollution on ischemic and hemorrhagic stroke may be different. Therefore the two outcomes should be analyzed separately in studies of this kind.

Many of the previous studies have been conducted in areas where levels of air pollution have been substantially higher than they are in our study area Scania, Southern Sweden [4–6, 8, 13, 14, 17, 19]. Relations between pollution and stroke have also been reported from areas with rather low-level air pollution, although less frequently [12] and especially in the warm season [7, 22, 23]. There is thus evidence of a short-term association between stroke (especially mortality) and air pollution where levels of air pollution are high, but the evidence is less clear where levels of air pollution are rather low. The association between air pollution and stroke is less clear for hemorrhagic stroke than for ischemic stroke.

Our objective in this study was to explore associations between air pollution and hospital admissions for stroke in a low-level pollution setting. We obtained data from the Swedish stroke register, Riks-Stroke, on hospital admissions for stroke in Scania between 2001 and 2005. We investigated the relation between daily admissions for ischemic and hemorrhagic strokes and (1) shared data on particles with a diameter <10 µm (PM₁₀), ozone and temperature and (2) an individually modeled mixture of NO and NO₂ (NO_x). Moreover, we discussed methodological issues in evaluating the short-term effects of air pollution in observational studies of stroke risk.

Subjects and Methods

Study Area: Scania

The study area, Scania, is the southernmost county of Sweden (fig. 1). It covers 11,350 km², 2% of the total area of Sweden. The number of inhabitants in Scania was about 1.2 million in the year 2005, 13% of the total Swedish population [26]. The pollutant levels in Scania are generally higher than in Sweden overall, although relatively low in an international perspective [27].

Cases

Data on strokes occurring between January 1, 2001, and December 31, 2005, were obtained from Riks-Stroke, in total 11,267 ischemic strokes and 1,681 hemorrhagic strokes in persons registered as residing in Scania. The estimated registration coverage of hospital-treated stroke cases is 85–90% [28, 29]. Riks-Stroke does not include stroke patients who die out of hospital before the stroke is registered. We did not incorporate information from the national cause-of-death register. The outcome in this study is therefore hospital admissions for stroke. The proportion of computer tomographic examinations was high (99%), indicating accurate diagnosis.

The variables obtained from Riks-Stroke were type of stroke (ischemic or hemorrhagic), gender, year of birth, the date of the stroke and smoking status. The register data allowed definition of the smoking variable as smoking at least 1 cigarette per day or having quit during the 3 months prior to stroke. The geocoded residential address on December 31 the year before the stroke occurred was linked to each person and added to the data file.

For a small proportion (n = 2,630; 23%) of the ischemic stroke cases (those patients who had responded to a questionnaire that was sent out to surviving patients in October–December 2008), we had data on whether they were at home or not when the stroke occurred.

Exposure Assessment

A large proportion of the particulate air pollution in Scania stems from sources outside the area [30], therefore a measuring station on background PM₁₀ can be expected to account reasonably for the exposure contrasts in time for all individuals. Measured background levels of NO_x have been shown to correlate (Pearson correlation r = 0.59) with ultrafine particles, and with the total number of particles, but not with PM₁₀ in the Copenhagen urban area, which is located close to our study area [31]. NO_x is an indicator of combustion-related (often traffic) air pollution, and there is thus considerable geographic variation [32]. Somewhat in contrast to previous studies where background levels of nitrogen oxides (NO₂, NO or NO_x) were used [4–7, 9, 13–17, 19–24], we believed that data on background NO_x would not be valid for all the study subjects in a study area of the size of Scania. We therefore used two types of exposure data in this study: (1) data from two monitoring sites (one urban and one rural) on background ozone, background particulate air pollution (PM₁₀) and temperature, and (2) data on NO_x, modeled at the residential address of each case.

The data obtained from the urban site (Malmö; fig. 1) were daily mean temperature, background hourly ozone and background daily levels of PM₁₀, and from the rural site background hourly ozone (Vavihill; fig. 1). The hourly ozone measurements at each site were aggregated to give daily means as the 24-hour average from midnight to midnight.

Fig. 1. The study area in the south of Sweden.

Data were missing on some days. In total, data were lacking on at least one of the air pollutants on 150 days. In these cases, the mean value of the data 5 days before and 5 days after from the appropriate monitoring site was used. The Spearman correlation between the urban and rural levels of ozone was high ($r_s = 0.78$). We used ozone data from the rural site since that station had fewer days with missing values.

We used a Geographical Information System to model the individual exposure to NO_x at the residential address of each case. It used an emission database that allows for a spatial resolution of 500×500 m and a resolution in time of 1 h [33, 34]. Each residential address was geocoded and linked with available exposure data attributed to that address. The hourly NO_x exposure was aggregated to provide a daily mean value (midnight to midnight) for the 30 days before and 30 days after the day the stroke occurred

in order to facilitate the time-stratified selection of control days in the case crossover design (see below).

Annual means of modeled NO_x have been validated against data collected from 23 measurement stations in Scania, yielding a correlation coefficient of $r = 0.69$ [35]. The standard deviation of the measured values was $7.7 \mu\text{g}/\text{m}^3$ and that of the modeled values $8.3 \mu\text{g}/\text{m}^3$. The correlation coefficient for the modeled concentrations and the exposure measurement error (difference between measured and modeled concentrations) was 0.55, whereas the correlation between the measured concentrations (here regarded as the 'true' levels) and the error was marginal ($r = -0.016$), suggesting a classical measurement error structure and a bias towards the null [36]. In a recent validation study, the correlation coefficient between modeled concentrations (aggregated on a weekly basis) and measurements at the residential address was

found to be 0.7. The modeled weekly NO_x concentrations tended to underestimate actual levels, but by less than $5 \mu\text{g}/\text{m}^3$ on average.

Data Analysis Approaches and Statistical Methods

We estimated the short-term effect of exposure with reference to the day the stroke occurred (lag 0) as well as 1 and 2 days before the stroke occurred (lag 1 and lag 2). Two different methods were used to analyze the data as they were of two kinds: (i) time series analysis for shared data series (which is arguably preferable to the case crossover approach for such data [37]) and (ii) case crossover for individually modeled data (i.e. not shared exposure contrast over time).

The Time Series Approach

For the shared monitored data, we modeled the daily number of strokes with respect to measurements of PM_{10} , ozone and temperature in a time series analysis using Poisson regression (PROC GENMOD in SAS v 9.1). For the hemorrhagic stroke models, we corrected for slight overdispersion with the option `scale = deviance`. We used both single-pollutant models and multi-pollutant Poisson regression models with adjustment for month, year and weekday in all models. In the multi-pollutant models, temperature, background PM_{10} and background ozone were included simultaneously.

We used single lag models, i.e. included only 1 exposure data feature from 1 day at a time. In an extra analysis we included lag 0 to lag 2 in the same model.

The Case Crossover Approach

For individually modeled NO_x , we applied a time-stratified case crossover design, which we analyzed with conditional logistic regression (PROC TPHREG in SAS v 9.1).

The key feature in a case crossover design is that each case is matched with itself, by letting one, or several, nearby time period(s) serve as control periods. The time-stratified approach for the selection of control periods has been suggested to eliminate control selection bias in the case crossover design [38, 39]. We chose the control days as the same weekday in the same month as the index day occurred. For example, if a case occurred on Sunday, March 9, 2003, the lag 0 control days were chosen as March 2, 16, 23 and 30 of that same year. The lag 1 control days were correspondingly chosen as March 1, 15, 22 and 29.

Künzli and Schindler [40] stress that the power of case crossover studies is dependent on the contrasts in exposure distribution between index days and control days. We therefore describe the exposure contrasts between index and control days. We produced both single-pollutant models and multi-pollutant models. In the multi-pollutant models, individual NO_x measurements were included together with shared monitoring site data on temperature, background PM_{10} and background ozone.

Evaluation of Effect Modification

We investigated possible effect modification by sex, age at diagnosis (below or above the median age of 78 years), warm/cold season, smoking status, and whether or not the individual was residing in a city in both the time series and case crossover approaches. The stratified effect estimates were presented if the p value for (lack of) effect modification in a multiplicative model was below 0.05. A city was defined as a town with more than

80,000 inhabitants (Helsingborg and Malmö; fig. 1). We defined the cold season as October to April and the warm season as May to September.

Presentation of Effect Estimates

We present the main results based on trichotomized exposure variables: NO_x , $3 < 10$, $10 < 30$ and $\geq 30 \mu\text{g}/\text{m}^3$; ozone, < 50 , $50 < 90$ and $\geq 90 \mu\text{g}/\text{m}^3$, and PM_{10} , < 15 , $15 < 30$ and $\geq 30 \mu\text{g}/\text{m}^3$. The effect of daily mean temperature was divided into 5 categories based on quintiles: -10 to < 2.5 , $2.5 < 6.5$, $6.5 < 12$, $12 < 16$ and $\geq 16^\circ\text{C}$. For the case crossover analysis, we also present the odds ratios (ORs; if the p value was below 0.05) for a 10-unit increase in the (continuous) exposure variable.

Results

Time Series Approach

During the study period 2001–2005, 11,267 ischemic strokes and 1,681 hemorrhagic persons with stroke that were registered as Scanian citizens were registered in Riks-Stroke (table 1; see also online suppl. fig. 1a, b). The median number of cases per day was 6 (80% central range, i.e. 10th–90th percentiles: 3–10) and 1 (80% central range: 0–2) for ischemic and hemorrhagic strokes, respectively.

The median (of the daily means) levels of PM_{10} , ozone and NO_x were $16 \mu\text{g}/\text{m}^3$ (80% central range: 10–29), $61 \mu\text{g}/\text{m}^3$ (80% central range: 36–89) and $11 \mu\text{g}/\text{m}^3$ (80% central range: 5–27), respectively. The median daily mean temperature was 9°C (80% central range: 0–19). Daily levels of ozone, PM_{10} and temperature are plotted in online supplementary figure 1c–e.

The correlations between the measured background levels of PM_{10} , ozone, temperature and modeled NO_x values were modest, with Spearman's correlation coefficient for all pairwise correlations $r_s \leq 0.28$ (table 2).

With an exposure time lag of 1 day, we estimated a 13% (95% confidence interval, CI: 4–22%) increase in risk of ischemic stroke for levels of PM_{10} above $30 \mu\text{g}/\text{m}^3$ compared with the reference category of $< 15 \mu\text{g}/\text{m}^3$ (table 3a). We did not observe any clear effect of PM_{10} in the intermediate exposure categories 10 – $30 \mu\text{g}/\text{m}^3$ (table 3a), not even when we analyzed the data with 5 exposure categories instead of 3 (data not shown).

The effect estimate of the highest daily mean temperature category ($\geq 16^\circ\text{C}$) compared with the lowest category ($< 2.5^\circ\text{C}$) was statistically significant for lag 1, with a relative risk of 0.88 (95% CI: 0.77–1.00; table 3a).

For hemorrhagic stroke, we found elevated effect estimates of PM_{10} and a decreased effect in the highest of the temperature categories, but the results were imprecise and not statistically significant (table 3a). For ozone,

Table 1. Characteristics of ischemic and hemorrhagic stroke cases with respect to age, sex, smoking habits, residence in an urban/rural area, and year and season of stroke

	Ischemic stroke (n = 11,267)		Hemorrhagic stroke (n = 1,681)	
	male (n = 5,698)	female (n = 5,569)	male (n = 852)	female (n = 829)
Age				
<70 years	1,104 (19)	2,033 (37)	145 (17)	228 (27)
70–77 years	1,396 (24)	1,429 (26)	159 (19)	232 (28)
78–83 years	1,486 (26)	1,156 (21)	220 (26)	175 (21)
>84 years	1,712 (30)	951 (17)	328 (38)	194 (23)
Smokers				
No	3,893 (68)	4,164 (75)	597 (70)	573 (69)
Yes	1,052 (18)	649 (12)	94 (11)	69 (8)
Missing	753 (13)	756 (14)	161 (19)	187 (23)
Residing in city				
No	4,082 (72)	3,600 (65)	600 (70)	547 (66)
Yes	1,616 (28)	1,969 (35)	252 (30)	282 (34)
Year				
2001	1,039 (18)	899 (16)	145 (17)	154 (19)
2002	1,072 (19)	1,067 (19)	137 (16)	134 (16)
2003	1,061 (19)	1,140 (20)	176 (21)	156 (19)
2004	1,193 (21)	1,171 (21)	173 (20)	175 (21)
2005	1,333 (23)	1,292 (23)	221 (26)	210 (25)
Season				
Warm	2,326 (41)	2,280 (41)	361 (42)	326 (39)
Cold	3,372 (59)	3,289 (59)	491 (58)	503 (61)

Figures in parentheses are percentages.

the effect estimates were below unity but nonsignificant for both ischemic and hemorrhagic stroke. The results when including lag 0 to lag 2 simultaneously in the model were generally rather similar to those when including them separately.

Case Crossover Approach

A modeled value of NO_x was available on the index day and at least 1 control day was available for 11,014 ischemic stroke cases and for 1,625 hemorrhagic stroke cases. The median NO_x levels were similar on index days and control days ($11.1 \mu\text{g}/\text{m}^3$). Figure 2a and b illustrates in 3-dimensional plots that for both ischemic and hemorrhagic strokes, a large proportion of the index days are in the same NO_x category as the control days.

The ORs in the case crossover part of the study indicated that residential NO_x had no effect on either ischemic or hemorrhagic stroke risk (table 4a). The ischemic stroke point estimates (adjusted for PM_{10} , ozone and

Table 2. Spearman's correlation coefficients across days (n = 1,826) between the measuring station data on PM_{10} , ozone and temperature

	PM_{10}	Ozone	Temperature
PM_{10}	1	0.26	0.19
Ozone	0.26	1	0.28
Temperature	0.19	0.28	1
NO_x (modeled)	0.025	−0.11	−0.08

For the modeled levels of NO_x , the corresponding Spearman coefficients were assessed across cases (n = 12,948).

temperature) for a $10 \mu\text{g}/\text{m}^3$ increase in NO_x were: OR = 1.00 (95% CI: 0.97–1.02) for lag 0, OR = 1.00 (95% CI: 0.97–1.02) for lag 1 and OR = 0.99 (95% CI: 0.97–1.02) for lag 2.

The case crossover analysis of the shared exposure data on PM_{10} , ozone and temperature gave similar risk estimates to the time series analysis (tables 3a, 4a), although the CIs were generally slightly wider in the case crossover analysis.

Effect Modification

We observed no clear effect modifications on the association between any of the pollutants for either ischemic or hemorrhagic stroke with regard to the variables age, sex, smoking, residing in major city or warm/cold season ($p \geq 0.05$ for all variables).

Single-Pollutant Models

The results obtained using the single-pollutant models (tables 3b, 4b) generally suggest somewhat weaker effects than the corresponding multi-pollutant models in tables 3a and 4a.

Discussion

Key Results

We found evidence of a short-term association between recent PM_{10} and risk of ischemic stroke for PM_{10} levels above $30 \mu\text{g}/\text{m}^3$ and evidence of a reduced risk of ischemic stroke on warmer days. The corresponding effect estimates for hemorrhagic stroke were similar but with wider CIs and thus not conclusive.

The time series approach and the time-stratified case crossover approach yielded rather similar effect estimates

Table 3a. Relative risks of ischemic stroke and hemorrhagic stroke associated with measured background levels of PM₁₀, ozone and temperature, on the day of the stroke (lag 0) and 1 and 2 days before the stroke (lag 1, lag 2)

Category	Me- dian	Ischemic stroke						Hemorrhagic stroke					
		lag 0		lag 1		lag 2		lag 0		lag 1		lag 2	
		RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<i>PM₁₀</i>													
<15 µg/m ³	12	1		1		1		1		1		1	
15–<30 µg/m ³	19	1.01	0.97–1.05	1.04	0.99–1.08	1.03	0.98–1.07	1.00	0.89–1.13	1.03	0.92–1.17	1.13	1.00–1.28
≥30 µg/m ³	37	1.06	0.98–1.14	1.13	1.04–1.22	1.03	0.95–1.12	1.14	0.92–1.42	1.14	0.92–1.42	1.17	0.94–1.46
<i>Ozone</i>													
<50 µg/m ³	40	1		1		1		1		1		1	
50–<90 µg/m ³	67	1.00	0.96–1.06	0.98	0.93–1.03	0.98	0.93–1.03	1.11	0.96–1.29	1.05	0.91–1.21	1.01	0.87–1.17
≥90 µg/m ³	100	0.97	0.89–1.06	0.92	0.84–1.01	0.96	0.87–1.05	0.96	0.74–1.25	0.87	0.67–1.14	0.99	0.77–1.28
<i>Temperature</i>													
–10 to <2.5°C	0	1		1		1		1		1		1	
2.5–<6.5°C	5	1.03	0.96–1.09	0.98	0.92–1.04	0.999	0.94–1.06	1.03	0.87–1.23	1.06	0.89–1.26	1.08	0.91–1.28
6.5–<12°C	9	1.01	0.93–1.10	0.98	0.90–1.06	1.01	0.93–1.10	0.99	0.78–1.24	0.93	0.74–1.18	0.87	0.69–1.10
12–<16°C	14	1.02	0.92–1.14	0.99	0.89–1.10	1.03	0.93–1.15	0.87	0.64–1.19	0.92	0.67–1.25	0.78	0.56–1.06
16–<25°C	18	1.02	0.90–1.16	0.88	0.77–1.00	0.93	0.82–1.06	0.84	0.59–1.22	0.78	0.54–1.13	0.68	0.47–0.99

RR = Relative risk. Designed as a time series study, analyzed for each lag separately with Poisson regression in multi-pollutant models with all 3 exposure variables included simultaneously together with month, weekday and year. For example, the PM₁₀ estimates are adjusted for ozone and temperature.

Table 3b. Single-pollutant models: relative risks for ischemic stroke and hemorrhagic stroke in association with measured background levels of PM₁₀, ozone and temperature, on the day of the stroke (lag 0) and 1 and 2 days before the stroke (lag 1, lag 2)

Category	Ischemic stroke						Hemorrhagic stroke					
	lag 0		lag 1		lag 2		lag 0		lag 1		lag 2	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
<i>PM₁₀</i>												
<15 µg/m ³	1		1		1		1		1		1	
15–<30 µg/m ³	1.01	0.97–1.05	1.02	0.98–1.06	1.02	0.98–1.06	0.98	0.87–1.10	1.00	0.90–1.12	1.09	0.97–1.22
≥30 µg/m ³	1.04	0.97–1.12	1.09	1.01–1.17	1.01	0.94–1.09	1.07	0.85–1.27	1.04	0.85–1.27	1.09	0.89–1.34
<i>Ozone</i>												
<50 µg/m ³	1		1		1		1		1		1	
50–<90 µg/m ³	1.01	0.96–1.06	0.97	0.92–1.02	0.91	0.92–1.02	1.11	0.96–1.28	1.03	0.90–1.19	1.00	0.87–1.15
≥90 µg/m ³	0.99	0.91–1.08	0.95	0.86–1.01	0.94	0.86–1.02	0.98	0.76–1.25	0.86	0.67–1.11	0.97	0.76–1.24
<i>Temperature</i>												
–10 to <2.5°C	1		1		1		1		1		1	
2.5–<6.5°C	1.02	0.96–1.09	0.98	0.92–1.04	1.00	0.94–1.07	1.03	0.86–1.22	1.06	0.90–1.26	1.09	0.92–1.29
6.5–<12°C	1.02	0.94–1.10	0.99	0.91–1.07	1.02	0.94–1.11	0.98	0.78–1.23	0.93	0.74–1.17	0.90	0.72–1.13
12–<16°C	1.03	0.92–1.14	1.01	0.91–1.13	1.05	0.95–1.17	0.87	0.64–1.17	0.92	0.68–1.25	0.84	0.62–1.15
16–<25°C	1.03	0.91–1.16	0.91	0.80–1.02	0.95	0.84–1.07	0.85	0.60–1.19	0.79	0.56–1.11	0.78	0.55–1.10

RR = Relative risk. Designed as a time series study, analyzed with Poisson regression. Adjusted for month, weekday and year.

Fig. 2. a A 3-dimensional plot of NO_x categories for index days and control days, for the day of ischemic stroke. The numbers of index day/control day pairs are shown on the y-axis and the NO_x categories for index days and control days are shown on the x- and z-axes, respectively. **b** A 3-dimensional plot of NO_x categories for index days and control days, for the day of hemorrhagic stroke. The numbers of index day/control day pairs are shown on the y-axis and the NO_x categories for index days and control days are shown on the x- and z-axes, respectively.

in our setting, but the precision was somewhat higher with the time series approach.

Strengths and Limitations of the Study – Methodological Reflections

A major strength of the study is the high-quality data obtained from the national stroke register Riks-Stroke, with a high coverage of all hospitalized stroke cases and a high accuracy of diagnosis [29].

In epidemiological studies where individual exposure is inferred from exposure proxies, misclassification of exposure (often denoted exposure measurement error in air pollution epidemiology) may be a problem. The overall measurement error is generally a combination of classical type errors, leading to a bias towards the null, and Berkson-type errors, which cause no bias but reduce the precision [36, 41–43]. Zeger et al. [43] divided measurement error in epidemiological studies on short-term exposure to air pollution into 3 components: (1) the error due to aggregation of exposure, (2) the difference between average personal exposure and true ambient level, and (3) the difference between the true and measured ambient level.

In a time series study employing shared data on air pollution, the first and third component can be expected

to cause Berkson-type errors (i.e. errors independent of the measured level), yielding no or little bias but decreased statistical power, whereas the second component is likely to cause a classical measurement error (i.e. error independent of the true level), yielding bias towards the null [41–43]. However, it is difficult to estimate the size of the bias due to the many different factors influencing that component of error.

Air pollution is neither uniform nor static, but differs between countries, regions and in time. In studies based on background measurements, it can be difficult to distinguish the effect of one pollutant from another if the pollutants are highly correlated. However, the correlations between the pollutants in our study were modest (table 2). Simultaneous measurement errors in several pollutants complicate the analysis and the interpretation of the results [43]. The single-pollutant effect of PM₁₀ lag 1 on ischemic stroke risk was smaller (9%; table 3b) than when adjusted for ozone and temperature (13%; table 3a). Generally, the effects in the single-pollutant models were somewhat weaker than those given by the multi-pollutant models, possibly due to the simultaneous measurement errors mentioned above.

Intuitively, the concentrations of ambient air pollution at the residential address should provide better indicators

Table 4a. ORs of ischemic stroke and hemorrhagic stroke in association with individually modeled levels of NO_x and measured background levels of PM₁₀, ozone and temperature, on the day of the stroke (lag 0) and 1 and 2 days before the stroke (lag 1, lag 2)

Category	Ischemic stroke						Hemorrhagic stroke					
	lag 0		lag 1		lag 2		lag 0		lag 1		lag 2	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
NO_x												
0–<10 µg/m ³	1		1		1		1		1		1	
10–<30 µg/m ³	1.01	0.95–1.08	1.00	0.94–1.07	0.98	0.92–1.05	0.94	0.79–1.10	0.94	0.86–1.10	0.93	0.79–1.09
≥30 µg/m ³	0.96	0.87–1.07	1.00	0.90–1.10	0.94	0.84–1.04	0.93	0.71–1.22	0.86	0.66–1.13	0.83	0.63–1.09
PM₁₀												
<15 µg/m ³	1		1		1		1		1		1	
15–<30 µg/m ³	0.98	0.94–1.03	1.08	1.02–1.13	1.04	0.99–1.09	0.95	0.83–1.08	1.00	0.88–1.14	1.16	1.01–1.32
≥30 µg/m ³	1.02	0.93–1.04	1.14	1.04–1.25	1.01	0.92–1.11	1.08	0.86–1.36	1.07	0.85–1.35	1.24	0.98–1.57
Ozone												
<50 µg/m ³	1		1		1		1		1		1	
50–<90 µg/m ³	0.98	0.92–1.05	0.95	0.89–1.01	0.94	0.89–1.00	1.09	0.92–1.28	1.04	0.88–1.21	1.03	0.88–1.22
≥90 µg/m ³	0.94	0.84–1.04	0.89	0.80–0.995	0.91	0.82–1.01	0.84	0.63–1.11	0.91	0.68–1.20	0.99	0.75–1.32
Temperature												
–10 to <2.5°C	1		1		1		1		1		1	
2.5–<6.5°C	1.02	0.94–1.11	0.93	0.86–1.01	0.97	0.89–1.05	1.08	0.88–1.32	1.11	0.91–1.35	1.19	0.98–1.45
6.5–<12°C	0.98	0.89–1.08	0.89	0.80–0.98	0.94	0.85–1.03	1.06	0.82–1.37	0.94	0.73–1.22	0.97	0.75–1.25
12–<16°C	1.04	0.91–1.18	0.91	0.80–1.03	0.96	0.85–1.10	0.86	0.61–1.20	0.88	0.63–1.23	0.82	0.58–1.15
16–<25°C	1.03	0.89–1.20	0.80	0.68–0.93	0.86	0.74–1.00	1.01	0.68–1.50	0.82	0.55–1.20	0.74	0.50–1.10

Designed as a case crossover study, analyzed for each lag separately with logistic regression in multi-pollutant models with all 4 exposure variables included simultaneously. For example, the PM₁₀ estimates are adjusted for ozone, temperature and NO_x at the same lag. The median NO_x level in the category <10 µg/m³ was 7 µg/m³, in the category 10–<30 µg/m³ it was 16 µg/m³ and in the category ≥30 µg/m³ it was 41 µg/m³. For ischemic stroke, a statistically significant OR for a 10-unit increase in the exposure variable (pollutants and temperature) was observed for ozone lag 0, OR = 0.98 (0.97–1.00), PM₁₀ lag 1, OR = 1.04 (1.01–1.07), temperature lag 1, OR = 0.89 (0.82–0.97), and temperature lag 2, OR = 0.90 (0.83–0.98).

of the exposure to air pollution than data from a fixed monitoring site (often not located in the immediate vicinity of the subject's home). However, outdoor concentrations at the residential address do not necessarily correlate well with the actual exposure. By modeling NO_x at the residential address, we introduced some additional sources of potential exposure misclassification compared with the use of shared exposure data. The aggregation of NO_x in the 500 × 500 m grid should produce a Berkson-type error corresponding to error component 1 above. We still expect error component 2 to produce a classical type of error, although the bias may be of a different magnitude from a series of shared exposure data [44, 45]. We reformulate error component 3 in the case crossover analysis as the difference between modeled and true NO_x concentrations. A recent validation study by our group indicated that this error is a classical type, thus producing a bias towards the null. However, the validation of our NO_x models has been done on yearly and weekly aver-

ages, whereas in this study we use mean daily levels. It is therefore possible that the validations do not appropriately reflect the size of error component 3. In addition, bias is introduced by modeling residential outdoor NO_x, because all the subjects were not at home when the stroke occurred. Out of the 2,630 cases with available data, 2,075 (79%) were at home when the stroke occurred. A sub-analysis restricted to include only that 79% still yielded an OR for ischemic stroke lag 1 of 1.00 associated with a 10 µg/m³ increase in NO_x but with a wider CI (95% CI: 0.94–1.06; not in results).

Errors caused by moving house must also be considered in the case crossover analysis. The modeled NO_x level for the fraction of patients who moved within Scania during the stroke year, before the date the stroke occurred (less than 5% according to available data), will be erroneous, causing a bias towards the null.

Although we consider our NO_x modeling to have high accuracy, exposure misclassification is hence possible. In

Table 4b. Single-pollutant models: ORs for ischemic stroke and hemorrhagic stroke in association with individually modeled levels of NO_x and measured background levels of PM₁₀, ozone and temperature, on the day of the stroke (lag 0) and 1 and 2 days before the stroke (lag 1, lag 2)

Category	Ischemic stroke						Hemorrhagic stroke					
	lag 0		lag 1		lag 2		lag 0		lag 1		lag 2	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
NO_x												
0–<10 µg/m ³	1		1		1		1		1		1	
10–<30 µg/m ³	1.01	0.95–1.08	1.01	0.95–1.07	0.99	0.93–1.05	0.92	0.79–1.08	0.95	0.82–1.11	0.91	0.78–1.07
≥30 µg/m ³	0.96	0.87–1.06	1.01	0.92–1.12	0.96	0.87–1.06	0.93	0.72–1.20	0.89	0.69–1.15	0.79	0.61–1.03
PM₁₀												
<15 µg/m ³	1		1		1		1		1		1	
15–<30 µg/m ³	0.98	0.94–1.03	1.04	0.99–1.08	1.01	0.97–1.06	0.94	0.84–1.06	0.99	0.88–1.12	1.11	0.99–1.25
≥30 µg/m ³	1.00	0.92–1.09	1.07	0.98–1.16	0.99	0.91–1.07	1.00	0.81–1.24	1.03	0.82–1.27	1.17	0.94–1.45
Ozone												
<50 µg/m ³	1	0.94–1.05	1		1		1		1		1	
50–<90 µg/m ³	0.99	0.85–1.03	0.95	0.90–1.01	0.95	0.90–1.01	1.10	0.95–1.28	1.05	0.91–1.22	1.02	0.88–1.19
≥90 µg/m ³	0.94		0.92	0.83–1.01	0.91	0.83–1.01	0.90	0.70–1.16	0.92	0.71–1.19	1.02	0.79–1.31
Temperature												
–10 to <2.5°C	1		1		1		1		1		1	
2.5–<6.5°C	1.03	0.95–1.10	0.94	0.87–1.01	0.98	0.91–1.06	1.05	0.87–1.28	1.12	0.93–1.35	1.19	0.98–1.43
6.5–<12°C	0.99	0.90–1.09	0.92	0.84–1.01	0.94	0.86–1.04	1.02	0.80–1.30	0.94	0.74–1.20	1.01	0.79–1.28
12–<16°C	1.04	0.92–1.17	0.96	0.85–1.08	0.98	0.87–1.10	0.81	0.59–1.11	0.88	0.65–1.21	0.90	0.65–1.24
16–<25°C	1.01	0.88–1.16	0.86	0.75–0.98	0.88	0.77–1.01	0.89	0.62–1.28	0.80	0.56–1.15	0.86	0.60–1.23

Designed as a case crossover study, analyzed with logistic regression. A statistically significant OR for a 10-unit increase in the exposure variables (pollutants and temperature) was found for: ischemic stroke, temperature lag 1, OR = 0.93 (0.86–1.00), and ozone lag 3, OR = 0.95 (0.91–1.00); hemorrhagic stroke, temperature lag 0, OR = 0.80 (0.66–0.97).

summary, it is likely that the effects we observed are biased towards the null. Moreover, it is possible that the bias caused by measurement error in modeled NO_x concentrations is greater than the bias caused by measurement errors in the shared monitoring site exposure data.

For Poisson models, the expected value and the variance are assumed to be similar. If the variance is larger than the expected value, overdispersion occurs, which we corrected for in the hemorrhagic stroke models. The standardized residuals should be independent and normally distributed around zero with constant variance. The residual analysis indicated that our modeling assumptions were reasonable (not shown).

The case crossover approach assumes that the background risk is constant. Our data indicated a slight increase in stroke cases during the last 2 or 3 years (table 1). We observed no tendency of effect modification by year (data not shown), and the exposure estimates obtained with the case crossover and the time series analyses are similar for the exposure variables that are available for both approaches.

The Results in Relation to Previous Studies and Issues for Future Research

Results from several previous studies support the observations made in this study, i.e. an association between recent particulate air pollution and hospital admissions for ischemic stroke [12–14]. More specifically, we observed an association with exposure on the day before stroke, whereas the time of exposure employed in the other studies differs from the previous day [12], the same day [14] and the cumulative exposure on the day of stroke and 2 days before [13]. Due to different types of data, the studies might not be directly comparable regarding timing of exposure; future studies are needed to more precisely determine the time window for exposure causing the risk elevations observed.

The PM₁₀ effect estimates for hemorrhagic stroke were elevated but not statistically significant in our study. A link between PM₁₀ and hemorrhagic stroke has previously been reported in only one study [13], whereas others report no clear association [5, 14, 24]. It would thus be desirable to further study hemorrhagic stroke and ambi-

ent air pollution in a larger study setting, where the power to detect associations would be high, perhaps in a meta-analysis.

In this rather low-level area, we observed a 13% (95% CI: 4–22%) increase in risk for an average increase in PM₁₀ level of 25 µg/m³ and a 4% increase (95% CI: –1 to 8%) for an average PM₁₀ increase of 7 µg/m³ (table 3a). Kettunen et al. [7] reported from a low-level area geographically close to ours an 11% (1–22%) increase in stroke mortality as a result of an interquartile range increase (approx. 10 µg/m³) in PM₁₀, only in the warm season. The studies differ with respect to outcome; Kettunen et al. [7] studied stroke mortality (stroke as underlying cause of death) while we studied ischemic stroke hospital admissions.

Moreover, Kettunen et al. [7] and several others [22, 23], in low-level areas, report associations mainly in the warm season. We observed a reduced risk on the warmest days ($\geq 16^{\circ}\text{C}$; lag 1) but cold/warm season was not a statistically significant modifier of the effect by any of the pollutants on the risk of ischemic stroke (or hemorrhagic stroke). Decreasing temperature has been observed to be associated with an increase in markers of inflammation and coagulation [46]. Decreasing temperature has also been observed to increase the risk of ischemic stroke [47, 48], somewhat in line with this study where we observed a reduced risk on the warmest days ($\geq 16^{\circ}\text{C}$). The risk on days below 16°C was rather homogenous. No statistically significant association was observed between cerebrovascular admissions and temperature in two European studies [49, 50]. Moreover, increased temperature is a rather established risk factor for cardiovascular disease in general [51, 52]. Thus, the literature is not consistent and the association between cerebrovascular disease/ischemic stroke admissions and temperature should be investigated further. Interestingly, in another study, the effect between temperature and cardiovascular mortality was modified by ozone, where higher levels of ozone increased the risk [53].

We observed that the time-stratified case crossover approach and the time series analysis yielded unbiased effect estimates, as previously suggested [38, 39]. However, the CIs were, not surprisingly due to the sampled control times, generally wider in the case crossover approach. Whitaker et al. [37] convincingly argued that bias can occur in certain situations in the case crossover approach and that time series analysis is more flexible to adjust for time trends and overdispersion. Given their arguments, and the difficulty for epidemiologists to know a priori whether the case crossover would yield bias or

not, and the better precision for the estimates in the time series approach, we conclude that the time series approach is likely preferable. However, in a situation with individual exposure measurement, the time-stratified case crossover approach can be attractive.

Fine particles have been observed to have effects in two studies. Lisabeth et al. [12] found a relation between PM_{2.5} and ischemic stroke/transient ischemic attack hospital admissions, and Kettunen et al. [7] observed associations between PM_{2.5}, ultrafine particles and stroke mortality. When Kettunen et al. [7] adjusted for fine and ultrafine particles, the PM₁₀ association they observed was attenuated. Unfortunately, we did not have access to data on PM_{2.5} or finer particles. Although the present study provided evidence of the association between stroke risk and particulate air pollution, we consider it important to further study the effect of finer particles.

We did not observe any association between stroke and NO_x in this study, where the levels were well below the WHO annual mean guideline of NO₂ of 40 µg/m³ [27]. The proportion of stroke cases with no NO_x contrast was high (ischemic: 59% and hemorrhagic: 55%), decreasing the power to detect an association. However, the ORs associated with a 10 µg/m³ increase in NO_x were close to unity, indicating a lack of association regardless of statistical power. Previous studies on background levels of nitrous oxides and stroke have produced both negative [7, 9, 17, 19–21, 24] and positive results [4–6, 13, 14, 16, 22, 23], and have all used shared monitoring station data, whereas we used individually modeled data. Background concentrations of NO_x have been shown to be an indicator for ultrafine particulate air pollution in an urban setting close to our study area [31].

In conclusion, since NO_x is an indicator for combustion-related air pollution, the negative results regarding NO_x in this study are somewhat in contrast to studies where associations with fine or ultrafine particles have been observed, results that call for implications towards reducing combustion-related particles. However, exposure misclassification might have caused the negative results in the present study, and we observed an association for PM₁₀, in which fine particles are included.

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