



Association between short-term exposure to ultrafine particles and hospital admissions for stroke in Copenhagen, Denmark

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Aims

The relevance of ultrafine particles (UFPs, particles <0.1 µm diameter), the smallest fraction of ambient particulate matter, on stroke morbidity has not been documented. We studied the effects of short-term changes in exposure to these particles on stroke, separately for ischaemic and haemorrhagic strokes, mild and severe strokes, and ischaemic strokes with (likely embolic) and without (likely thrombotic) atrial fibrillation (AF).

Methods and results

We used a time-stratified case-crossover design to study the association between short-term exposure to UFPs, particulate matter <10 µm in diameter (PM₁₀), nitrogen oxides (NO_x) and carbon monoxide (CO) (measured at single background station) and hospital admissions for stroke in Copenhagen (2003–2006). Of 7485 stroke admissions, 6798 were ischaemic and 687 haemorrhagic, 3485 mild, and 2248 severe. Of the ischaemic stroke cases, 1204 had AF and 5273 did not. We found significant positive association with exposure to UFPs, NO_x and CO, and ischaemic strokes, and UFPs and NO_x and mild strokes, 4 days before admission. The strongest associations were with UFPs. Exposure to UFPs lead to a 21% increase in hospital admissions (per interquartile range of 5-day averages; 95% confidence interval 4–41%) for mild ischaemic stroke of without AF (likely thrombotic origin).

Conclusion

Our results indicate possible effects of traffic-related air pollution, mainly UFPs, on hospital admissions for ischaemic stroke, especially for mild ischaemic stroke of likely thrombotic origin (without AF). These are novel findings regarding the relevance of UFPs and the heterogeneous effect of air pollution on the severity and origin of stroke, and need confirmation by other data.

Keywords

Stroke • Air pollution • Ultrafine particles • Cerebrovascular disease • Epidemiology

Introduction

Stroke is one of the leading causes of death, with cancer and cardiovascular disease, and a major cause of serious, long-lasting disability worldwide.¹ Whereas the adverse effects of air pollution on cardiovascular disease in general are well-established,^{2–4} air pollution was recognized as a risk factor for stroke only recently.^{5–6} Early data on air pollution and stroke morbidity showed no or weak associations.^{7,8} When the effect of air pollution on different types of stroke, namely ischaemic and haemorrhagic stroke,^{9–13} begun to be studied, the associations with air pollution became clearer, especially for ischaemic strokes.^{10–13}

Increasing air pollution from traffic occurs in parallel with industrialization and urbanization, and presents a significant public health burden. Among the pollutants generated by traffic, ultrafine particles (UFPs, <0.1 µm diameter) are suspected of being particularly harmful, owing to their extensive pulmonary deposition and ability to induce inflammation and oxidative stress.¹⁴ Yet, data linking stroke to this important fraction of traffic emissions is sparse: a single study found a weak association with fatal stroke¹⁵ and none has linked UFPs to stroke morbidity. The fact that UFPs are key constituents of tobacco smoke, a well-established risk factor for stroke,⁴ makes studies of UFPs effect on stroke even more pressing.

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In this study, we examined the effects of short-term changes in exposure to UFPs on hospital admissions for stroke. Whereas myocardial infarct, which has been linked to air pollution,^{3,4} is associated with arterial thrombosis, the aetiology of stroke is much more variable.⁵ We addressed the associations of air pollution with various stroke subtypes, as our dataset allowed us to stratify the cases into ischaemic and haemorrhagic stroke and into subtypes according to severity and origin. If air pollutants affect stroke morbidity, this effect seems to be subtype-specific, affecting ischaemic and haemorrhagic stroke differently.^{10–13} We also hypothesized that air pollution might differently affect strokes due to large and small vessel occlusions (defined as severe and mild strokes) and strokes of cardiac (more likely embolic) and non-cardiac (more likely thrombotic) origin.

Methods

Definition of stroke

We used the nationwide registry of the Danish National Indicator Project founded in 1999 to measure the quality of care provided by Danish hospitals.¹⁶ All Danish hospitals have reported a predefined set of data on stroke patients, including age, gender, severity of stroke on admission as measured on the Scandinavian Stroke Scale (SSS)¹⁷ and a cardiovascular risk profile including alcohol consumption, smoking, diabetes, atrial fibrillation (AF), myocardial infarct, previous stroke, and intermittent claudication. The SSS is a validated neurological stroke scale widely used in Scandinavia, in which the level of consciousness, eye movement, power in the arm, hand and leg, orientation, aphasia, facial paresis, and gait are evaluated on a score 0 to 58.¹⁷ The SSS and the National Institute of Health Stroke Scale (NIHSS) can be interconverted by equation $SSS = 50 - 2 * NIHSS$.¹⁸ We defined mild strokes as >44 and severe strokes as ≤ 44 on the median SSS score. Ischaemic and haemorrhagic strokes (primary intracerebral hematomas) were differentiated by computed tomography (CT) or magnetic resonance (MR) scan. The presence of AF was determined by electrocardiography. Patients with transient ischaemic attacks or subarachnoid haemorrhage and patients for whom a CT or MR scan was not performed (1.1%) were excluded from the study. The NIP Registry coverage in this study period (2003–2009) was about 80% of all stroke admissions in Denmark. The very high proportion of stroke patients in the area represented in this study are admitted to hospital (90%), due to free hospital care in Denmark.¹⁹ Incident stroke, defined as first hospital admission for stroke between 1 January 2003 and 31 December 2006, in all nine Copenhagen hospitals located within a 15-km radius of the central background air pollution monitor, was used as the outcome in this study. The date of symptom onset was used for 75% of stroke cases, and the date of hospital admission for the rest, with missing symptom onset date.

Exposure monitoring and meteorology

We obtained daily means of air pollutants and meteorological data from the background monitor in the centre of Copenhagen (1 January 2003 to 31 December 2006). The UFPs levels were measured with a Differential Mobility Particle Sizer, as described elsewhere.²⁰ Additionally, we obtained concentrations of particulate matter $<10 \mu\text{m}$ in diameter (PM_{10}) (Beta attenuation by SM200 monitor, Opsis, Sweden), nitrogen oxides (NO_x) (M 200A monitor, API, San Diego, USA), and carbon monoxide (CO) (M 300 monitor, API, San Diego, USA) and temperature, relative humidity, and wind speed.

Study design and data analyses

The case-crossover design was developed as a variant of the case-control design to study the effects of transient exposures on acute events.²¹ This study design compares each person's exposure experience in a time period just prior to a case-defining event with that person's exposure at other times. Since there is perfect matching on all measured or unmeasured personal characteristics that do not vary over time, there can be no confounding by those characteristics. If in addition, the control days are chosen to be close to the event day, personal characteristics that vary slowly over time are also controlled by matching. We used the time-stratified case-crossover design²² to estimate the effect of air pollution on admissions for stroke, separately for each stroke subtype. By definition of time-stratified method for choosing control days, we compared the air pollution exposure on the day (lag 0) of the stroke admission to exposure on other days of the same month falling on the same weekday as stroke admission.²² We additionally considered pollution concentrations on the previous day (lag 1), and up to 4 days (lag 4) before stroke admission and the accumulated exposure over 5 days (lag 0–4, mean of lag 0–lag 4). We performed conditional logistic regression (R statistical package), stratifying on each day, to obtain estimates of odds ratios (OR) and 95% confidence intervals (CIs). We reported effects estimates as the change in the rate of hospitalization associated with an interquartile range increase in mean daily pollutant levels. We adjusted for meteorological conditions by fitting daily mean temperature, relative humidity, and wind speed by restricted cubic splines for the same lag as the pollutant in the model. Days with missing air pollution concentrations were excluded from analyses, whereas lag 0–4 was calculated with available data. To test the sensitivity of the findings against our definitions of mild and severe strokes above and below and equal to $SSS = 44$, we estimated the effect of UFPs at each severity score. The number of cases of stroke attributable to UFPs exposure, given the observed associations, was calculated by standard methods.²³

Results

We observed 7485 incident admissions for stroke, of which 6798 (90.8%) were ischaemic and 687 (9.2%) haemorrhagic, whereas 3485 (46.6%) were mild and 2248 (30.0%) severe strokes [missing severity for 1752 (23.4%) cases]. Of the 6798 ischaemic strokes cases, 1204 (17.7%) had AF and 5273 (77.6%) did not [missing information for 321 (4.7%) cases]. Of 7485 stroke patients, 3969 (53.0%) were male; 2532 (33.8%) were current smokers at admission, 1237 (16.5%) were former smokers and 2157 (28.8%) had never smoked [missing smoking information for 1559 (20.8%) cases]. The mean age at admission was 73.3 years and the mean SSS score was 30.0. Mean number of days between symptom onset and hospital admission for 75% of stroke cases was 1 day with standard deviation of 3 days. About 26.6% of the 7485 incident admission had previous hospital admissions prior to 2003. *Table 1* shows the pollution and meteorological conditions in Copenhagen. The distribution of differences in air pollution and meteorology levels on case and control days, used as an exposure term in the analyses, is presented as supplementary online data, whereas correlation between these exposure terms were: UFPs and PM_{10} 0.43 (Spearman correlation coefficient), UFPs and NO_x 0.53, UFPs and CO 0.28, PM_{10} and NO_x 0.45, PM_{10} and CO 0.45, and NO_x and CO 0.74; temperature and UFPs, PM_{10} , NO_x , and CO 0.42, 0.46, 0.09, and -0.15 , relative

Table 1 Air pollutant levels and meteorological conditions in Copenhagen, 2003–2006

	Total = 1461	Mean (SD)	Percentile		Interquartile range (75th–25th percentile)
			25th	75th	
Air pollutants (units)					
UFPs (per cm ³)	939	6365 (3292)	4033	7951	3918
PM ₁₀ (µg/m ³)	1394	27.1 (13.2)	18.6	32.1	13.5
NO _x (ppb)	1418	15.3 (8.3)	9.8	18.6	8.8
CO (ppm)	1375	0.27 (0.10)	0.20	0.32	0.12
Meteorological factors (units)					
Temperature (C)	1438	9.7 (7.0)	4.1	15.4	11.3
Relative humidity (%)	1438	72.8 (10.5)	65.9	81.0	15.1
Wind speed (m/s)	1412	4.1 (1.4)	3.0	4.9	1.9

humidity and UFPs, PM₁₀, NO_x, and CO –0.24, 0.18, 0.09, and 0.14, and wind speed and UFPs, PM₁₀, NO_x, and CO –0.36, –0.12, –0.62, and –0.46, respectively.

Ischaemic and haemorrhagic strokes

We observed a significant positive association between ischaemic stroke admissions and NO_x and CO at lag 4, with an association of borderline significance with UFPs at lag 4 (Table 2). Following the 5-day accumulated exposure (lag 0–4), increase in hospital admissions of 8% (95% CI –3 to 19%) was associated with UFPs, 7% (–1 to 15%) with NO_x, and 7% (–2 to 18%) with CO (Table 2). PM₁₀ showed a weak positive effect. No significant associations were detected for haemorrhagic strokes.

Mild and severe strokes

We found positive significant associations between admissions for mild strokes and UFPs at lag 3 and lag 4 and NO_x at lag 4 (Table 2). The highest OR was observed for UFPs for lag 0–4: 13% (–2 to 30%) increase in admissions, as compared with 8% (–3 to 21%) for NO_x. Weaker positive associations were detected for PM₁₀ and CO. No significant associations were observed with admissions for severe stroke.

Ischaemic strokes with and without atrial fibrillation

We found significant positive associations between ischaemic strokes without AF and exposure to UFPs, PM₁₀, NO_x, and CO, all at lag 4 (Table 2). For lag 0–4, CO and UFPs were associated with an 11% (0–23%) and a 10% (–2 to 24%) increase in admissions, respectively. No significant associations were observed for ischaemic strokes with AF.

Mild ischaemic strokes without atrial fibrillation

In the *post hoc* analyses, we combined the three subtypes of stroke where strongest associations were observed with air pollution, we identified 2822 (1698 with available UFPs levels) patients with mild ischaemic strokes who have not had AF. Here, we observed significant positive associations with UFPs at lag 3 and with UFPs, NO_x,

and CO at lag 4 (Table 2); with the highest estimates seen for UFPs, with a 21% (4–41%) increase in hospital admissions for lag 0–4. This effect remained robust in the two-pollutant models (Table 3). We estimated the effect of UFPs (lag 0–4) on ischaemic strokes without AF at each severity score (Figure 1, top), and found that the adverse effect of UFPs was relatively consistent at about 15% for strokes with a SSS score <44, and increasing after a score of 44. At the same time, the number of strokes increased with decreasing severity of stroke and increasing SSS score (Figure 1, bottom). Finally, we have conducted analyses with generalized additive model for Poisson data, with count of stroke admission per day as an outcome, and found similar results.

Discussion

Our study presents potentially two novel findings. First, our results indicate effects of short-term exposure to UFPs on hospital admissions for ischaemic stroke but not for haemorrhagic stroke. Secondly, the association between exposure to UFPs and ischaemic stroke seemed to be subtype-specific, most relevant for mild strokes. Furthermore, the association seemed strongest for ischaemic stroke without AF, probably representing non-cardiac (thrombotic) strokes. Weak association was seen for ischaemic stroke with atrial fibrillation, probably representing cardiac (embolic) strokes. These results suffer from low statistical power in subgroup analyses (haemorrhagic and ischaemic strokes without AF) and need replication.

This is the first study to detect UFPs as a risk factor for hospital admissions for ischaemic stroke. The only previous study linking exposure to UFPs to stroke showed a weak effect on mortality.¹⁵ A study have suggested that exposure to motor traffic (NO₂ and CO) affected the incidence of stroke.¹¹ In our study, exposure to NO_x, CO, and UFPs generated by motor vehicles where all associated with stroke, confirming that traffic is the main factor involved. The weak associations with larger particulates, PM₁₀, which is a poor proxy of local traffic in Copenhagen, sustain this finding.²⁴

Owing to the correlation between and the common sources of UFPs, NO_x, and CO, it is difficult to separate their individual effects on stroke. Some of these pollutants may have no pathological

Table 2 The change in the rate of hospitalizations for stroke associated with an interquartile range increase in pollutant levels, adjusted for temperature, relative humidity, and wind speed

Air Pollutant	Lag	Stroke type		Stroke severity ^a		Ischaemic stroke subtype		Mild ischaemic stroke without AF [OR (95% CI)], n = 1698
		Ischaemic [OR (95% CI)], n = 4092	Haemorrhagic [OR (95% CI)], n = 419	Mild [OR (95% CI)], n = 2084	Severe [OR (95% CI)], n = 1335	Without AF* [OR (95% CI)], n = 4727	With AF [OR (95% CI)], n = 772	
UFPs	0	1.06 (0.99–1.13)	0.96 (0.78–1.18)	1.05 (0.96–1.15)	1.08 (0.96–1.21)	1.08 (1.00–1.17)	0.99 (0.85–1.16)	1.11 (1.01–1.23)
	1	0.99 (0.93–1.06)	1.00 (0.81–1.23)	1.01 (0.92–1.11)	0.95 (0.85–1.07)	0.99 (0.92–1.07)	0.98 (0.84–1.14)	1.03 (0.93–1.14)
	2	1.00 (0.93–1.07)	0.93 (0.75–1.16)	0.99 (0.90–1.08)	1.02 (0.90–1.15)	1.00 (0.93–1.08)	1.04 (0.88–1.22)	0.99 (0.89–1.10)
	3	1.06 (0.99–1.13)	0.86 (0.70–1.07)	1.11 (1.01–1.22) ^b	0.99 (0.88–1.11)	1.06 (0.99–1.15)	1.06 (0.91–1.23)	1.13 (1.02–1.25)*
	4	1.06 (0.99–1.13)	0.83 (0.67–1.03)	1.14 (1.04–1.25)*	0.91 (0.81–1.02)	1.09 (1.01–1.17) ^b	1.04 (0.89–1.21)	1.16 (1.05–1.28) ^b
	0–4	1.08 (0.97–1.19)	0.86 (0.62–1.18)	1.13 (0.98–1.30)	0.96 (0.81–1.15)	1.10 (0.98–1.24)	1.05 (0.83–1.33)	1.21 (1.04–1.41) ^b
		n = 5784	n = 585	n = 3001	n = 1889	n = 6878	n = 1085	n = 2440
PM ₁₀	0	0.99 (0.96–1.03)	1.09 (0.96–1.24)	0.98 (0.93–1.03)	1.01 (0.95–1.08)	1.00 (0.96–1.04)	1.00 (0.92–1.08)	0.98 (0.93–1.04)
	1	1.02 (0.98–1.05)	1.03 (0.92–1.14)	1.04 (0.99–1.10)	0.98 (0.92–1.05)	1.01 (0.97–1.05)	1.03 (0.95–1.12)	1.04 (0.99–1.10)
	2	1.03 (0.99–1.06)	1.04 (0.94–1.17)	1.05 (0.99–1.10)	1.01 (0.95–1.08)	1.04 (1.00–1.08)	1.00 (0.92–1.09)	1.05 (0.99–1.11)
	3	1.01 (0.97–1.04)	0.91 (0.81–1.03)	1.02 (0.97–1.07)	0.95 (0.89–1.02)	1.03 (0.99–1.07)	0.94 (0.86–1.03)	1.03 (0.98–1.09)
	4	1.03 (0.99–1.06)	0.93 (0.83–1.05)	1.03 (0.99–1.08)	1.00 (0.94–1.07)	1.05 (1.01–1.09) ^b	0.96 (0.88–1.04)	1.04 (0.99–1.10)
	0–4	1.02 (0.97–1.08)	0.96 (0.81–1.14)	1.06 (0.99–1.14)	0.93 (0.85–1.02)	1.04 (0.98–1.11)	0.95 (0.84–1.08)	1.07 (0.99–1.16)
		n = 6355	n = 637	n = 3259	n = 2099	n = 7488	n = 1200	n = 2639
NO _x	0	1.04 (0.99–1.09)	0.99 (0.85–1.14)	1.00 (0.94–1.07)	1.08 (1.00–1.17)	1.05 (0.99–1.10)	0.98 (0.88–1.10)	1.01 (0.95–1.09)
	1	0.99 (0.95–1.04)	1.03 (0.89–1.19)	1.01 (0.95–1.08)	0.95 (0.88–1.03)	1.01 (0.95–1.06)	0.91 (0.82–1.02)	1.03 (0.96–1.10)
	2	1.01 (0.97–1.06)	1.11 (0.96–1.29)	1.01 (0.95–1.08)	1.03 (0.95–1.12)	1.02 (0.97–1.08)	0.98 (0.88–1.10)	1.01 (0.94–1.09)
	3	1.03 (0.99–1.08)	0.97 (0.83–1.12)	1.06 (0.99–1.13)	0.99 (0.92–1.08)	1.03 (0.98–1.09)	1.03 (0.92–1.14)	1.06 (0.99–1.14)
	4	1.06 (1.01–1.11) ^b	0.84 (0.72–0.97)	1.07 (1.01–1.14) ^b	1.01 (0.94–1.09)	1.06 (1.01–1.12) ^b	1.06 (0.95–1.17)	1.08 (1.01–1.15) ^b
	0–4	1.07 (0.99–1.15)	0.83 (0.64–1.07)	1.08 (0.97–1.21)	1.00 (0.87–1.15)	1.08 (0.99–1.13)	0.95 (0.79–1.15)	1.13 (1.00–1.27)
		n = 6220	n = 634	n = 3183	n = 2051	n = 7315	n = 1186	n = 2574
CO	0	1.03 (0.97–1.09)	0.86 (0.71–1.05)	0.97 (0.89–1.05)	1.10 (1.00–1.22)	1.05 (0.98–1.12)	0.95 (0.82–1.09)	1.00 (0.91–1.09)
	1	1.02 (0.96–1.08)	0.85 (0.70–1.03)	1.02 (0.94–1.11)	0.96 (0.86–1.06)	1.03 (0.96–1.10)	0.95 (0.82–1.10)	1.04 (0.94–1.14)
	2	1.03 (0.97–1.09)	1.12 (0.93–1.35)	1.04 (0.96–1.13)	1.02 (0.92–1.14)	1.06 (0.99–1.13)	0.91 (0.79–1.06)	1.05 (0.96–1.15)
	3	1.06 (1.00–1.13)	0.89 (0.73–1.08)	1.05 (0.97–1.14)	1.06 (0.96–1.18)	1.07 (1.00–1.15)	0.99 (0.87–1.14)	1.06 (0.97–1.17)
	4	1.07 (1.01–1.13) ^b	0.88 (0.72–1.07)	1.08 (0.99–1.17)	1.02 (0.93–1.13)	1.08 (1.01–1.15) ^b	1.02 (0.89–1.17)	1.09 (1.00–1.19)
	0–4	1.07 (0.98–1.18)	0.76 (0.57–1.01)	1.07 (0.95–1.21)	1.03 (0.88–1.20)	1.11 (1.00–1.23)	0.89 (0.72–1.00)	1.12 (0.98–1.29)

^aMild, Scandinavian stroke scale score >44; severe, Scandinavian Stroke Scale score ≤44.

^bAF, atrial fibrillation.

*P < 0.05.

Table 3 The change in the rate of hospitalizations for mild ischaemic strokes without atrial fibrillation ($n = 1698$) associated with interquartile range increase in pollutant levels (lag0–4), adjusted for temperature, relative humidity, and wind speed

Air pollutant	One-pollutant model [OR (95% CI)]	Two-pollutant models		
		Model 1 [OR (95% CI)]	Model 2 [OR (95% CI)]	Model 3 [OR (95% CI)]
UFPs	1.21 (1.04–1.41)*	1.18 (0.98–1.42)	1.21 (1.02–1.44)*	1.20 (1.02–1.42)*
PM ₁₀	1.08 (0.98–1.19)	1.04 (0.93–1.15)	–	–
NO _x	1.11 (0.95–1.30)	–	1.02 (0.85–1.23)	–
CO	1.10 (0.92–1.32)	–	–	1.02 (0.84–1.23)

* $P < 0.05$.

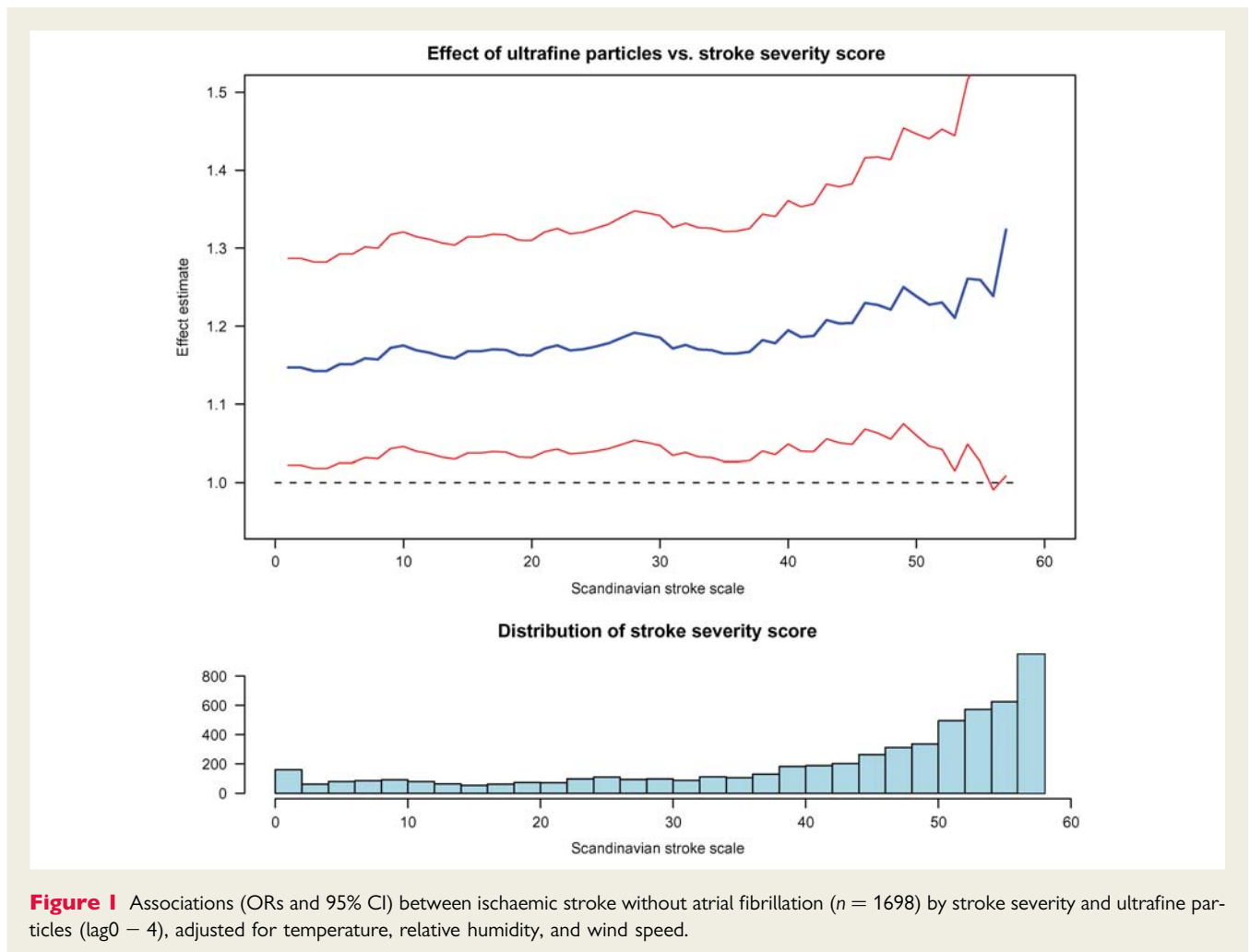


Figure 1 Associations (ORs and 95% CI) between ischaemic stroke without atrial fibrillation ($n = 1698$) by stroke severity and ultrafine particles (lag0–4), adjusted for temperature, relative humidity, and wind speed.

significance with regard to stroke, and just indicate the presence of a harmful pollutant. CO is probably such an indicator, as the outdoor CO concentrations are too low to be of biological significance. Although NO_x and UFPs may both be stroke-generating toxicants, UFPs are the most likely, as they resulted in the highest estimates, in both the single (Table 2) and the two-pollutant models (Table 3). Strokes occurred after 3–4 days of exposure to all three pollutants, indicating that they have a common stroke-

generating target rather than acting at different stages of the process leading to stroke.

Our finding of differential effect of air pollution by severity of stroke is novel. We found subtype-specific associations between ischaemic stroke and UFPs, NO_x, and CO. The strokes associated with these pollutants were at the milder end of the stroke spectrum and thus probably the result of small vessel occlusion. The finding that none of these pollutants is associated with the

occurrence of cardiac stroke (ischaemic stroke with AF) further supports this notion, as cardiac strokes are typically more severe than strokes of non-cardiac origin.²⁵ Although our results do not allow a definitive conclusion about the type of occlusion (thrombotic or embolic) associated with air pollution, our finding of an association between exposure to UFPs and small vessel strokes of non-cardiac origin point to thrombotic rather than embolic strokes. First, milder strokes are usually due to small, subcortical infarcts (such as lacunes), usually considered to be of thrombotic origin.²⁶ Secondly, the lack of association with AF-related strokes excludes an association with the most important embolic stroke subtype. Finally, the association between exposure to UFPs and ischaemic stroke without AF was amplified as the stroke score exceeded 44 (Figure 1). This finding further supports our interpretation that UFPs are closely associated with minor strokes originating from occlusive disease in the smaller cerebral arteries. This is novel finding, however, and needs replication before definite conclusions can be made.

Our findings of the adverse effects of air pollution are supported by the well-established causal association between active and passive smoking and heart disease and stroke.^{3,4} Like tobacco smoke, air pollution may accelerate coronary atherosclerosis and, in turn, thrombotic strokes.⁴ Plausible biological mechanisms, demonstrated in animal experiments, involve pulmonary oxidative stress, systemic inflammations, and activation of haemostatic pathways that impair vascular function and accelerate atherosclerosis.^{3,4} Such direct effects can be triggered by pollutants crossing the pulmonary epithelium into the circulation and disseminating systematically, such as gases and possibly UFPs.¹⁴ The UFPs may have enhanced biological toxicity, as they are deposited in large quantities in human alveoli and have a high surface-to-mass ratio.¹⁴ Thus, UFPs in busy Copenhagen streets have been shown to have a very high deposition fraction.²⁷ The observed delay in effects of 3–4 days in our study fits well with this biological mechanism, which can take several days, in contrast to the more acute mechanism linked to cardiac arrhythmia (activation of pulmonary neural reflexes by interaction of particulate matter with lung receptors and alteration of autonomic tone).⁴ Furthermore, we have observed an apparently bimodal distribution of effects of UFPs, with a strong same day signal, and a second peak after 3–4 days, in the groups of ischaemic, mild, strokes without AF, and mild ischaemic strokes without AF. Effect of exposure to UFPs leading to the same day hospitalization may reflect a more rapid mechanism at play in either more severe strokes, which need immediate hospital attention and/or in more susceptible patients, possibly elderly, with coexisting co-morbidities, where UFPs triggers stroke more immediately. On the other hand, a second wave of hospital admissions 3–4 days after UFPs exposure, may be either due to delayed effects of a exposure via postulated mechanism of 3–4 days, or due to the same rapid mechanism, but with milder strokes involved, where patients wait to seek medical attention. These hypotheses need to be confirmed with other data.

The limitations of our study include assessment of exposure from a single background monitor as a proxy for personal exposure, which might result in exposure misclassification. An inclusion criterion for stroke admissions in hospital within 15-km

radius from the central monitor was chosen to represent municipality limits of Copenhagen City with similar population and traffic density.²⁸ We have previously shown that UFPs levels measured at central background monitor (20 m height) correlated well with levels measured at a monitoring site at the kerbside (2 m height) of a busy street 3000 m away (Spearman correlation coefficient $R_s = 0.62$) and a rural monitoring site located in residential area 30 km southwest ($R_s = 0.80$).²⁸ This was despite the fact that UFPs levels were on average 4.6 times higher at the kerbside and 0.7 times lower at the rural site than at the background site.²⁶ This indicates that the daily oscillations in traffic-related air pollution on busy street due to variation in traffic density, weather conditions and other factors, are also reflected by urban background monitoring, and that radius of 15 km from central monitor is reasonable for the assessment of daily variation in population exposure. Nevertheless, exposure misclassification, if assumed random, usually causes bias towards the null, implying that the reported effects may be conservative.²⁹ However, if the majority of the stroke cases originate from people living along busy roads, where UFPs levels and oscillations are larger than those at the background monitor, the estimated ORs might be inflated. Thus, we conclude that direction of bias due to exposure misclassification in this study is rather uncertain. Frequent breakdowns and use of the UFPs measuring equipment for other purposes resulted in missing data for 36% of the period. However, missing days were found not systematically related to air pollution or weather conditions.³⁰ Data on PM_{2.5} were not included in this study, since the measurements were first available from late 2003. However, PM_{2.5} in Copenhagen is highly correlated with PM₁₀ ($R_s = 0.79$).²⁶ The potential for lag selection bias resulting from preferential selection of adverse effects with the lowest *P*-value is well recognized.²⁸ We, however, choose, a priori a lag window of 5 days, reported the results for each day lag and based our main conclusions on 5-day pollution averages. Finally, our study had limited statistical power to detect effects of air pollution exposure in the subgroups of hemorrhagic strokes (687) as well as strokes with AF (772). However, our conclusions on differential effects of exposure to air pollution in ischaemic and hemorrhagic strokes, as well as ischaemic strokes with and without AF, are based on the size of effect estimates, and are supported by plausible biological mechanisms from the existing literature.

The strengths of our study include the fact that data were derived from the National Indicator Project register, which allowed us to stratify the effect of air pollution by stroke type and severity. A further strength of our study was the availability of data on UFPs levels, which could be linked for the first time to stroke morbidity. Furthermore, we had available symptom onset data for 75% of the stroke cases. However, exposure misclassification due to assigning the exposure to air pollution based on date of hospital admission instead of time of symptom onset, which was the case for 25% of the strokes in this study, may give estimates biased toward zero.³¹ Finally, the time-stratified case-crossover design has been shown to be effective in controlling for confounding by time trends in both exposures and outcomes as well as for personal confounders, as cases serve as their own controls.²²

Summary

Our data argue for association between exposure to UFPs and morbidity due to stroke. Traffic-generated air pollution seems to be the source of this exposure. The association was subtype-specific, strongest for mild ischaemic strokes of non-cardiac origin. Although our study does not justify a conclusion of cause and effect, it reinforces the possibility that acute pathogenic processes in the cerebrovascular system are induced by air pollution. Furthermore, our findings give rise to the hypothesis that UFPs are a trigger of stroke, in particular stroke due to small vessel occlusion of thrombotic origin. The magnitude of the personal risk due to air pollution is lower than due to well-established risk factors for stroke. The population risk could, however, be substantial, as almost everyone is exposed. Assuming that the observed association with UFPs is causal and that population exposure to UFPs in Copenhagen corresponds to the levels measured at the central monitor, we can estimate that 147 (15.8%) new cases of mild ischaemic stroke of non-cardiac origin per year, corresponding to 5.9% of all new stroke admissions among 1 633 565 Copenhagen inhabitants, are attributable to UFPs. Thus, actions to reduce exposure might have an important impact on stroke morbidity. As traffic-generated air pollution appears to be associated with minor stroke and small vessel disease in particular, this kind of pollution might also be related to silent infarct and thus also to vascular dementia. As our findings are new, however, they must be replicated before further clinical implications can be made.

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