Airborne pollutants and lacunar stroke: a case cross-over analysis on stroke unit admissions

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Abstract

Particulate air pollution is known to be associated with cardiovascular disease. The relation of particulate air pollution with cerebrovascular disease (CVD) has not been extensively studied, particularly in relation to different subtypes of stroke. A time-series study was conducted to evaluate the association between daily air pollution and acute stroke unit hospitalizations in Mantua, Italy. We analyzed 781 CVD consecutive patients living in Mantua county admitted between 2006-08. Data on stroke types, demographic variables, risk factors were available from the Lombardia Stroke Registry. Daily mean value of particulate matter with a diameter <10 μm (PM_{10}), carbon monoxide, nitric oxide, nitrogen dioxide, sulphur dioxide, benzene and ozone were used in the analysis. The association between CVD, ischemic strokes subtypes and pollutants was investigated with a case-crossover design, using conditional logistic regression analysis, adjusting for temperature, humidity, barometric pressure and holidays. Among the 781 subjects admitted 75.7% had ischemic stroke, 11.7% haemorrhagic stroke 12.6% transient ischemic attack. In men admission for stroke was associated with PM_{10} [odds ratio (OR) 1.01, 95%; confidence interval (CI) 1.00-1.02; P<0.05]. According to the clinical classification, lacunar anterior circulation syndrome stroke type was related to PM_{10} level registered on the day of admission for both genders (OR: 1.01, 95%; CI: 1.00-1.02; P<0.05) while for total anterior circulation syndrome stroke only in men (OR: 1.04, 95%; CI 1.01-1.07; P<0.05).

In conclusion, our study confirms that air pollution peaks may contribute to increase the risk of hospitalization for stroke and particulate matter seems to be a significant risk factor, especially for lacunar stroke.

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Introduction

Many studies conducted in several parts of the world documented consistent effects of air pollution on public health.[1-4] Air pollution is mostly generated by human activities such as industrial sources, fires and crustal material, but it also originates from natural events, like, for instance, the volcanic ashes recently observed in Ecuador and Iceland.[5] Specifically, exposure to particulate air pollution has been linked with increased mortality and morbidity from cardiovascular and respiratory disease mediated by the induction of oxidative stress by these particles triggering coagulation and thrombosis.[6] These effects have been explained by release of soluble mediators by the lungs, inducing systemic events including inflammation, blood coagulation, and atherosclerosis, by the direct translocation of ultra fine particles into the systemic circulation, or by the alteration in autonomic cardiac control.[6-9]

More recently, particulate air pollution was also associated with cerebrovascular diseases (CVD).[7,10,11]

The negative effect of airborne pollution on the population needs to be further clarified in order to reach agreement on the more appropriate safety thresholds for the public health.

The association between CVD and air pollution has been already studied, but just few studies have analysed the influence of environmental pollutants and different types of stroke.[12] The objective of our study is to assess the influence of airborne pollutants on the hospitalization for acute CVD, by their types, according to Oxfordshire Community Stroke Project (OCSP) and Trial of Org Acute Stroke Trial (TOAST) classifications.[13,14]

Materials and Methods

Study population

Of the 1680 consecutive patients admitted to Mantua (Italy) Stroke Unit from January 1st, 2006, to December 31st, 2008, we analysed 781 (46.5%) cases living in the urban area within 10 km from one of the urban air pollution stations. The limit of 10 km is considered an appropriate distance from the recording site for quantifying the exposure of the population to outdoor pollution. Preliminary data of the study are presented elsewhere.[15]

We analyzed all consecutive patients hospitalized in Mantua Stroke Unit for a Transient Ischemic Attack (TIA) or stroke over three years (from January the 1st , 2006 to December 31st, 2008) and enrolled in the Lombardia Stroke Unit Network (SUN) registry. All patients, or relatives, gave written informed consent to the SUN epidemiological survey, that was previously approved by the local health care authorities (Regione Lombardia) as a permanent diseases registry.[16,17]

The hospital registry recorded all strokes and TIA among patients admitted in the Stroke Unit of Carlo Poma Hospital in Mantua, which is the only tertiary centre of the county for stroke admission. The arrival time from stroke onset in the Mantua Stroke Unit, according to the periodical monitoring, ranges between 2 to 25 hours. The majority of stroke patients

(70%) in study period was admitted within 16 hours from onset.

The ischaemic or haemorrhagic subtype was identified by computed tomography (CT) scan or by magnetic resonance imaging (MRI) in more than 98% of the cases (87% CT scan, 13% DWI). We also collected data on risk factors for stroke such as gender, age, hypertension), ischaemic heart disease [history of angina pectoris or myocardial infarction or ischaemic features on electrocardiogram (ECG)], cardiac arrhythmia (history of atrial fibrillation, by electrocardiogram or diagnosed on ECG or Holter recording), diabetes mellitus (fasting plasma glucose level >7.8 mmol/L or patients who had been treated with insulin or oral hypoglycaemic drugs), dyslipidemia (total cholesterol level >6.0 mmol/L or treatment with lipid-lowering drugs) and smoking history (ex-smoker and current smoker). Two-dimensional echocardiography was performed to detect possible cardioembolic source. Carotid and vertebral ultrasonography were routinely performed. Diagnosis of the subtypes of stroke was always performed on clinical and cerebral imaging: ischaemic stroke from atheroma of large arteries; ischaemic stroke from small vessel disease, so called lacunar infarct; ischaemic stroke from cardiac embolism; primary cerebral haemorrhagic stroke; subarachnoid haemorrhagic stroke. All available data regarding the patients risk factors profile and hospital diagnostic procedures (*e.g.* vascular imaging, laboratory results etc.) were taken into account. When it was difficult to differentiate ischaemic stroke from atheroma of large arteries, lacunar infarct and cardiac embolism, consensus meetings were performed to classify the difficult cases in one of the three groups. A transient ischaemic attack was diagnosed when clinical symptoms disappeared within 24 hours without any infarct lesion on imaging.

Stroke subtypes were defined at discharge, according to the TOAST and OCSP criteria.[13,14,18,19]

Air pollution and meteorology data

The county of Mantua, which includes about 70 municipalities, is located in Lombardy, Northern Italy and has about 400,000 inhabitants with a population density of 172.6 people/Km^2. The city of Mantua has 47,649 inhabitants (December 2007) in an area of 63.9 km^2 and a population density of 745 people per Km^2.[20] The major air pollution sources in the area originate from combustion *(i.e.* automobile exhausts, heating systems) and other crustal erosion or mechanical processes (*i.e.* wind, fire, industrial activity).[21]

Mantua has a 4-seasons climate and an annual temperature range of 2.1°C to 33.2°C. Data on 24-hours average temperature and relative humidity were obtained from the National Meteorological Office.

Air pollution data were provided by the Regional Environmental Protection Agency - ARPA - of Lombardy.

For all air pollutants, we considered the daily average values. In particular the data collected for the following meteorological parameters and the following environmental pollutants concern: temperature, humidity, barometric pressure, particles of diameter <10 micron (PM_{10}), carbon monoxide (CO), nitrogen dioxide (NO_2), sulfur dioxide (SO_2), benzene, nitric oxide (NO) and ozone (O_3).

Exposure measurements during the study period were taken from 7 monitoring sites (1. Gramsci; 2. S. Agnese; 3. Tridolino; 4. Ariosto; 5. Lunetta; 6. Porto Mantovano; 7. Bosco Fontana), which provide hourly measurements of total suspended particles (TSP; by x-ray absorption) and gaseous pollutants: sulfur dioxide (SO_2; by ultraviolet fluorescence), nitrogen dioxide (NO_2; by chemiluminescence), ozone (O_3; by ultraviolet photometry), and carbon monoxide (CO; by non-dispersive infrared photometry).

We calculated the hourly mean value of each pollutant collected from the 7 monitoring stations and then computed their 24-hours average values. For ozone, a daytime 8-hours average interval instead of a 24-hours interval was used.

Data analyses

The case-crossover design was used to study the association between air pollution and hospital admission for CVD.[22] According to this design, a variant of the case-control design, each subject serves as his/her own control; controls were selected to focus on times (*e.g.* days) in which the event did not occur. Thus, all individual characteristics not varying during the given time are adjusted to fit the design. For this study, a bidirectional symmetric case-crossover design was used, selecting days 1, 3, 5, 7 before and after the event (admission for stroke) as control days.

To evaluate the effect of air pollution a multi-pollutant conditional logistic regression model was performed, considering the effect of all pollutants, controlling for barometric pressure, average temperature, weekdays, holidays, the day after a holiday and dividing the cases according to gender and stroke subtype.

The statistical analyses were performed by the statistical software package SPSS Statistics 18.0 (IBM SPSS, Chicago, IL, USA).

Results

Demographic and baseline characteristics of the 781 cases are displayed on Table 1. The leading risk factor for stroke was hypertension followed by smoking history and diabetes. The more common index event was an ischemic stroke due to small artery occlusion.

The annual distribution of stroke unit admissions followed the typical seasonal variation, with a peak of ischemic event in fall-winter, and is described elsewhere.[23]

Stroke Unit admission

The estimated effects of air pollutants stratified by gender, adjusted for temperature, humidity holidays are displayed in Table 2. Higher level of PM_{10} were associated with increased risk of hospital admission for any cerebrovascular event [odds ratio (OR): 1.01, 95%; confidence interval (CI): 1.00-1.02; P<0.05]; men exposed to higher concentration of PM_{10} have a slight, not significant, higher risk of ischemic strokes (OR: 1.01, 95%; CI: 1.00-1.02; P=0.06), but not for haemorrhages and TIAs. In holidays, subjects were less prone to be hospitalized (OR 0.71; 95% CI: 0.56-0.91, P<0.05) for stroke, while they were more frequently admitted for ischemic stroke the day after an holiday (OR 1.30 , 95% CI: 1.04-1.63, P<0.05).

Table 1. Demographic, baseline, etiological and clinical characteristics of 781 cases.

N.	781
Age (mean ± SD)	71.2±10.5
Gender (male)	366 (46.8%)
Risk factors	
Atrial fibrillation	136 (17.4%)
Previous TIA/stroke	170 (21.8%)
Hypertension	587 (75.2%)
Ischemic heart disease	95 (12.2%)
Diabetes mellitus	176 (22.5%)
Hyperlipidemia	250 (32%)
Ever smoking	303 (38.8%)
Family history VD	196 (25.1%)
Obesity	52 (6.6%)
Alcohol abuse	12 (1.5%)
Type of stroke	
TIA	108 (13.8%)
Ischemic stroke	567 (72.6%)
Haemorrhagic stroke	106 (13.6%)
TOAST classification	
LVD	55 (9.7%)
CE	144 (25.4%)
SVD	218 (38.5%)
Unknown	126 (22.2%)
Other	24 (4.2%)
OCSP classification	
TACI	57 (10.1%)
PACI	199 (35.0%)
LACI	239 (42.2%)

TIA, transient ischemic attack; SVD, small vessel disease; LVD, large vessel disease; CE, cardioembolic disease; UNK, unknown cause; OTHER, other determined cause; PACI, partial anterior circulation syndrome; TACI, total anterior circulation syndrome; LACI, lacunar anterior circulation syndrome; POCI, posterior occipital circulation syndrome.

Ischemic stroke subtypes

The impact of air pollution on ischemic strokes subtypes according to the TOAST and OCPS classification is presented in Tables 3 and 4. In men, total anterior circulation syndrome (TACI) stroke subtype was associated to higher level of PM_{10} on the day of the hospital admission (OR 1.04, 95% CI: 1.01-1.07, P<0.05). Levels of PM_{10} was also associated in the general population to lacunar anterior circulation syndrome (LACI) stroke subtype (OR 1.01, 95% CI: 1.00-1.02, P<0.05). Subtypes of lacunar syndromes included pure motor stroke in 20% of patients, sensorimotor stroke in 33%, pure sensory stroke in 20% atypical lacunar syndrome in 15%, ataxic hemiparesis in 6% and dysarthria-clumsy hand in 6%.

According to the TOAST classification, PM_{10} influenced, though not significantly, small artery occlusions stroke subtype admission (OR 1.01, 95% CI: 0.99-1.01) and large artery disease stroke subtype admission (OR 1.02, 95% CI: 0.99-1.04).

Discussion

Environmental pollution and stroke subtypes

Our study suggests that environmental pollution by particulate matter could have a role as a risk factor in cerebrovascular diseases, even if our results deserve some caution in interpretation. To the best of our knowledge no earlier study has used both the TOAST and OCSP classification criteria to analyze the effect of airborne pollutants in stroke unit hospitalization.[12,24,25]

The largest studies conducted so far have been based on social security files (*e.g.* Medicare) without a detailed clinical assessment; furthermore, several of those based on more detailed clinical information available did not use any detailed brain imaging support.[12,24,25] The main benefits of our single centre design are that no patient was lost to follow-up in the consecutive series of subjects admitted in the stroke unit, standardized procedures were used for stroke ascertainment and classification, and all of the cases were selected for the study based on their usual living area.

We found a high prevalence of lacunar syndromes in the study population and a predictive value for stroke unit admission of PM_{10} in this subtype of events. This finding can be related to the high prevalence of hypertension in the study population and an excess of lacunar strokes in hypertensive subjects is a well known issue in literature.[12,26-28] As a matter of fact, PM_{10} was recently associated to an increase of blood pressure in men.[29,30] The influence of PM_{10} levels was clear in some subtypes of ischemic events and mostly in the male gender, this phenomenon was previously demonstrated in other clinical studies and the possible mechanism taken into consideration is a larger involvement of microvessels angiopathy in these subjects, leading to higher risks of lacunar infarction as well as renal glomerular impairment.[31,32]

Validity issues

Our study, differently from other experiences, is not likely to be biased by the inclusion of events in patients not monitored by the air pollution stations taken into account.[1,24] The resident population in the province of Mantua is characterized by a marked permanence unlike residents in other provinces of Lombardy, which are often commuters to the urban area of Milan. Another

Table 2. Risk of admission for any cerebrovascular event or ischemic stroke and influence of air pollution, by gender.

	Any cerebrovascular event		Ischemic stroke	
	Men ORa (95% CI)	Women ORa (95% CI)	Men ORa (95% CI)	Women ORa (95% CI)
PM_{10}	1.01 (1.00-1.02)*	1.00 (0.99- 1.01)	1.01 (1.00-1.02)°	1.00 (0.99-1.01)
SO_2	0.99 (0.95-1.04)	0.99 (0.96-1.03)	0.99 (0.94-1.04)	0.97 (0.92-1.02)
NO_2	0.99 (0.97-1.01)	0.99 (0.97-1.02)	1.00 (0.97-1.02)	0.99 (0.97-1.02)
NO	1.00 (0.99-1.01)	1.00 (0.99-1.02)	1.00 (0.98-1.01)	1.01 (0.99-1.02)
O_3	0.99 (0.98-1.01)	1.01 (0.99 1.02)	0.99 (0.98-1.00)	1.00 (0.99-1.02)
CO	1.07 (0.54-2.13)	1.34 (0.66-2.74)	1.01 (0.45-2.26)	1.11 (0.47-2.63)
Benzene	0.95 (0.78-1.15)	1.13 (0.94-1.36)	0.94 (0.76-1.16)	1.16 (0.93-1.44)

Adjusted for temperature, humidity, barometric pressure, day of the week, holidays, day after holidays. PM_{10}, particles of diameter <10 micron; SO_2 sulfur dioxide; NO_2 nitrogen dioxide; NO nitric oxide; O_3 ozone; CO carbon monoxide. *(OR 1.008; 95% CI 1.000-1.016 with P<0.05). °(OR 1.008; 95% CI 1.000-1.017 with P=0.06).

Table 3. Risk of admission for stroke subtypes (TOAST classification) and influence of air pollution.

	LVD ORa (95% CI)	CE ORa (95% CI)	SVD ORa (95% CI)
PM_{10}	1.02 (1.00-1.04)	0.99 (0.98-1.01)	1.01 (1.00-1.02)
SO_2	1.00 (0.88-1.14)	0.97 (0.90-1.04)	0.97 (0.91-1.02)
NO_2	1.00 (0.94-1.06)	1.00 (0.97-1.04)	0.98 (0.95-1.01)
NO	1.01 (0.97-1.05)	1.01 (0.99-1.03)	1.00 (0.99-1.02)
O_3	1.02 (0.99-1.06)	0.99 (0.97-1.01)	1.00 (0.98-1.01)
CO	0.14 (0.01-1.78)	2.06 (0.65-6.52)	1.79 (0.71-4.54)
Benzene	1.51 (0.77-2.96)	0.98 (0.71-1.35)	0.92 (0.74-1.14)

Adjusted for temperature, humidity, barometric pressure, day of the week, holidays, day after holidays. PM_{10}, particles of diameter <10 micron; SO_2 sulfur dioxide; NO_2 nitrogen dioxide; NO nitric oxide; O_3 ozone; CO carbon monoxide. SVD, small vessel disease; LVD, large vessel disease; CE, cardioembolic disease.

Table 4. Risk of admission for stroke subtypes (OCPS classification) and influence of air pollution.

	PACI ORa (95% CI)	TACI ORa (95% CI)	POCI ORa (95% CI)	LACI ORa (95% CI)
PM_{10}	1.00 (0.99-1.01)	1.00 (0.97-1.03)	1.00 (0.98-1.02)	1.01 (1.00-1.02)*
SO_2	0.98 (0.93-1.04)	0.87 (0.76-0.99)	1.00 (0.89-1.11)	1.01 (0.95-1.07)
NO_2	0.99 (0.96-1.02)	0.99 (0.94-1.06)	1.02 (0.97-1.07)	0.99 (0.96-1.02)
NO	1.00 (0.99-1.02)	1.02 (0.99-1.06)	1.00 (0.97-1.02)	1.00 (0.98-1.01)
O_3	0.99 (0.98-1.01)	1.01 (0.97-1.04)	0.99 (0.96-1.02)	1.00 (0.98-1.01)
CO	1.81 (0.63-5.20)	0.51 (0.04-6.62)	0.72 (0.15-3.36)	0.88 (0.38-2.02)
Benzene	1.19 (0.90-1.56)	1.03 (0.54-1.97)	0.99 (0.66-1.47)	0.95 (0.77-1.17)

Adjusted for temperature, humidity, barometric pressure, day of the week, holidays, day after holidays. PM_{10}, particles of diameter <10 micron; SO_2 sulfur dioxide; NO_2 nitrogen dioxide; NO nitric oxide; O_3 ozone; CO carbon monoxide. PACI, partial anterior circulation syndrome; TACI, total anterior circulation syndrome; POCI, posterior occipital circulation syndrome; LACI, lacunar anterior circulation syndrome. *(OR 1.012; 95%% CI 1.002-1.021), P<0.05.

strength of this research is the enrolment in the study of Mantua resident living within 10 km from the available urban air quality stations only.

This study took into account a large population that was analyzed by the technique of bidirectional case-crossover, minimizing common biases occurring in traditional case control studies and in unidirectional case-crossover designs. In fact, since each patient is his/her own control in the event-free days, confounding from time-invariant risk factors is avoided.[33,34]

To reduce the risk of bias due to overestimation of pollution levels many issues were carefully considered: i) the values of environmental pollutants were collected by excluding peak power units, which are those located close to major motorway networks, as they have excluded patients living within 10 km of major arterial roads. This was meant to limit overestimation of air pollution levels due to vehicular traffic near the monitors; ii) for the same reason, the analysis of collected data was adjusted for holidays and weekdays thereby taking into account changes in the vehicular traffic related to particular times and days of the year.

However, our study has several limitations. All patients with severe stroke who died before arriving to the hospital were not included in the study. Among these there may have been several cases of hemorrhagic stroke, which is often more severe and even fatal in a few hours. Similarly, we might have missed several TIAs and minor strokes that are a matter for the general practitioner without reaching the hospital.[35]

In this study we did not evaluate the effect of $PM_{2.5}$, the fraction of PM with a diameter less than 2.5 μm, which is known to better reflect the quantity of particles that are breathed deep into the lower airways and has been more consistently related with cardiovascular effects $PM_{2.5}$ data on local situation became available only in 2008.[30] Moreover the decreased risk of hospital admission associated to sulphur dioxide in patient with TACI is somewhat odd, contradicting previous results in animal studies and in humans;[36] anyway, the large OR confidence interval and the small number of TACI patients (57) suggest that this finding could be due to chance and need to be confirmed in another survey considering a larger number of TACI patients. Finally the magnitude of PM10 effects could be considered rather small and the statistical significance borderline, but similar issues are often evident in other similar studies[11] and common when a non-categorical variable is considered in a conditional regression model with other analogous variables with no strong effect expected.

Conclusions

In this study for the first time the effect of air pollution was assessed in several stroke subtypes according TOAST and OCSP classification, suggesting a possible effect of particulate matter on lacunar strokes. Even if with some limitations, our results highlight the importance to study environmental risk factors for stroke subtypes. As a matter of facts assessing pollution effects in stroke subtypes could help to provide biological plausible explanations of pollution influence in cerebrovascular diseases, reinforcing the need of adequate measures to reduce the impact of urban air pollution on health.

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