BMJ Open Ozone air pollution and ischaemic stroke occurrence: a case-crossover study in Nice, France

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ABSTRACT

Objectives: Relationship between low-level air pollution and stroke is conflicting. This study was conducted to document the relationship between outdoor air pollution and ischaemic stroke occurrence.

Design: Time-stratified case-crossover analysis.

Setting: University Hospital of Nice, France.

Participants: All consecutive patients with ischaemic stroke living in Nice admitted in the University Hospital of Nice (France) between January 2007 and December 2011.

Main outcome measure: Association (adjusted OR) between daily levels of outdoor pollutants (ozone (O₃), nitrogen dioxide (NO₂), particulate matter (PM₁₀) and sulfur dioxide (SO₂)) and ischaemic stroke occurrence.

Results: 1729 patients with ischaemic stroke (mean age: 76.1±14.0 years; men: 46.7%) were enrolled. No significant association was found between stroke occurrence and short-term effects of all pollutants tested. In stratified analysis, we observed significant associations only between recurrent (n=280) and large artery ischaemic stroke (n=578) onset and short-term effect of O₃ exposure. For an increase of 10 µg/m³ of O₃ level, recurrent stroke risk (mean D-1, D-2 and D-3 lag) was increased by 12.1% (95% CI 1.5% to 23.9%) and large artery stroke risk (mean D-3 and D-4 lag) was increased by 8% (95% CI 2.0% to 16.6%). Linear dose-response relationship for both subgroups was found.

Conclusions: Our results confirm the relationship between low-level O₃ exposure and ischaemic stroke in high vascular risk subgroup with linear exposure-response relation, independently of other pollutants and meteorological parameters. The physiopathological processes underlying this association between ischaemic stroke and O₃ exposure remain to be investigated.

INTRODUCTION

Outdoor air pollution is considered as a major environmental health issue, responsible for an excess of death in the world. It is defined as any undesirable modification of air by substances either toxic or likely to have

Strengths and limitations of this study

- The relationship between low-level air pollution and stroke is conflicting. This article confirms the relationship between low-level ozone exposure and ischaemic stroke in high vascular risk subgroup with linear exposure-response relationship, independently of other pollutants and meteorological parameters. PM_{2.5} was not studied because it was not monitored in Nice.

adverse effects on health. Outdoor air pollutants are known to increase morbidity and mortality of respiratory diseases.¹ However, in the 1950s and 1960s, epidemiological studies of acute severe pollution episodes have also shown an increasing cardiovascular and cerebrovascular mortality risk.² A link between acute air pollution and stroke mortality has been reported for the first time in the London fog incident study in December 1952.² In the last decades, the consequences of low-level air pollution on cardiovascular mortality and morbidity have been clearly described.^{3–6} By analogy, a few studies have examined the role of short-term air pollution on ischaemic stroke but actually no conclusion could be generalised.^{3 5–24} The purpose of the present study was to document the relationship between the characteristics of outdoor air pollution and the occurrence of ischaemic stroke.

MATERIALS AND METHODS

Population studied

We performed a 5-year (2007–2011) case-crossover analysis in Nice, France. We retrospectively enrolled consecutive patients with stroke admitted at the University Hospital of Nice between January 2007 and December 2011. Querying French DRG-based database (PMSI: Programme de Médicalisation des Systèmes d'Information) with I60–I69 codes

from the International Classification of Diseases (10th revision), we screened all patients hospitalised for stroke. We filtered the sample to patients living in Nice (geographical area defined by zip codes: 06000, 06100, 06200 and 06300). The diagnosis of ischaemic stroke was reviewed and confirmed by a panel of neurologists using clinical and radiological data of medical records. Patients with another diagnosis than stroke were excluded. Demographic data, vascular risk factors (WHO definitions), clinical and radiological characteristics of stroke were also collected from medical records.

Outdoor air pollution and meteorological data

Nice is an urban city situated in the south-eastern part of France on the Mediterranean coast. According to the latest census, Nice has a population of 340 735 in 2009. Its climate is temperate and qualified as Mediterranean type. Surrounded by hills and mountains (south Alps), the city of Nice is sheltered from continuous violent winds. Outdoor air pollution comes mainly from traffic due to high density of roads and an international airport (first one in France after Paris airports).

Air pollution data were obtained from the regional agency for air quality monitoring (AirPACA). Exposure measurements during the study period were carried out in 2 of 13 permanent monitoring stations in the study area. Measures ($\mu\text{g}/\text{m}^3$) were performed in an urban station (Cagnes Ladoumègue) for following atmospheric pollutants: particulate matter (PM₁₀; tapered element oscillating microbalance), nitrogen dioxide (NO₂) (chemiluminescence), sulfur dioxide (SO₂; ultraviolet photometry) and ozone (O₃; ultraviolet photometry). Missing values were replaced by measures performed by the observational monitoring station located at Nice Airport. We computed for each pollutant during 24 h average and specifically for O₃ during 8 h daytime periods.

Daily meteorological data were obtained from the National Meteorological Office of Nice, including temperature (°C) and humidity (%). Moreover, data on influenza epidemics (weekly count) in the region of Provence-Alpes-Cote-d'Azur were obtained from the Sentiweb network.

Statistical analysis

Continuous variables were expressed as mean (SD) or median (IQR), and categorical variables as percentages. Spearman correlation coefficients (r) between air pollutants and atmospheric parameters were calculated. The time-stratified case-crossover design was used to examine the relationship between short-term effects of outdoor air pollutants and stroke. In this design, each participant enrolled was his own control. Case days were defined as the day of stroke. Control days were defined as the same day of the same stratum as the case day. Study time was stratified by months. Therefore, explicative variable levels at the case day were compared with levels of the same variables at control days. This method has the

main advantage to control individual factors, the day of the week, season and time trend.²⁴ Conditional logistic regression was performed to estimate the association between short-term effects of each air pollutant measured and stroke onset. OR and 95% CI for a 10 $\mu\text{g}/\text{m}^3$ increase of pollutant level were adjusted for temperature and humidity with a 1-day lag, influenza epidemics and holidays without day lag. The pollutant exposure was tested in models for 1-day, 2-day or 3-day lag. Stratified analyses by subgroups were performed according to age, gender, risk vascular factors (tobacco use, diabetes mellitus, hypercholesterolaemia and hypertension) and stroke aetiological subtypes according to the Trial of ORG 10 172 in acute stroke treatment (TOAST). We evaluated dose-response relationships across four exposure levels of pollutants studied, and the first quartile was used as the reference group. A p value less than 0.05 was considered as significant. The data were analysed using Stata V.10.0 SE software.

RESULTS

During the study period (January 2007 to December 2011), there were 2067 patients living in Nice and were admitted to the University Hospital Center for ischaemic stroke based on the DRG database. After neurologists review of medical records, 1729 patients with ischaemic stroke were enrolled for final analysis. Six hundred and twenty (35.9%) of these patients were hospitalised in the stroke unit. According to the last population census of 2009, annual ischaemic stroke incidence rates (by 100 000) in the studied area were, respectively, from 2007 to 2011: 100, 100, 98, 96 and 112. The mean age was 76.1±14.0 years, and 46.7% were men (table 1).

The distribution of air pollutants and meteorological variables is shown in table 2. Spearman correlation coefficients (r) were ranged from 0.01 to 0.25 between each studied pollutants, except between O₃ and NO₂ (r=−0.54). Correlation coefficient between minimal temperature and O₃ was r=0.67 (see online supplementary table 1).

No significant association was found between stroke occurrence and short-term effects of all pollutants tested. In addition, we performed stratified subgroup analysis according to gender, age by decade, incident/recurrent stroke status, vascular risk factors, presence of atrial fibrillation and stroke aetiological subgroups. We measured only significant associations between stroke and short-term effect of O₃ in following both groups: recurrent (n=280) and large artery stroke (n=578) (table 3). In recurrent stroke subgroup, for an increase of 10 $\mu\text{g}/\text{m}^3$ of O₃ level (mean D-1, D-2 and D-3 lag), stroke risk was significantly increased by 12.1% (95% CI 1.5% to 23.9%). Adjusted OR between O₃ exposure (mean D-3 and D-4) and large artery stroke subgroup was 1.080 (95% CI 1.002 to 1.166). No significant association was observed with other pollutants than O₃. Adjusted in two-pollutant models, OR was not affected.

Table 1 Baseline characteristics of patients with ischaemic stroke (incident and recurrent) hospitalised in Nice University Hospital from 2007 to 2011

	All patients (n=1729)	Incident n=1449 (83.81%)	Recurrent n=280 (16.19%)	p Value
<i>Demographic data</i>				
Men	808 (46.73)	683 (47.14)	125 (44.64)	0.0044
Age (years)	76.06±14.04	75.48±14.29	79.01±12.33	<0.0001
<55	141 (8.16)	132 (9.11)	9 (3.21)	0.0011
55–64	186 (10.76)	155 (10.70)	31 (11.07)	0.8532
65–74	324 (18.74)	279 (19.25)	45 (16.07)	0.2114
75–84	524 (30.31)	438 (30.23)	86 (30.71)	0.8712
≥85	554 (32.04)	445 (30.71)	109 (38.93)	0.0071
<i>Cardiovascular risk factors</i>				
Diabetes mellitus	311 (17.99)	249 (17.18)	62 (22.14)	0.0481
Hypertension	998 (57.72)	803 (55.42)	195 (69.64)	<0.0001
Dyslipidaemia	441 (25.51)	348 (24.02)	93 (33.21)	0.0012
Current smoker	410 (23.71)	357 (24.64)	53 (18.93)	0.0398
Overweight	226 (13.07)	204 (14.08)	22 (7.86)	0.0047
Coronary artery disease	263 (15.21)	209 (14.42)	54 (19.29)	0.0381
Atrial fibrillation	527 (30.48)	433 (29.88)	94 (33.57)	0.2198
<i>Classification of stroke aetiological subtypes (TOAST)</i>				
Large artery	578 (33.43)	479 (33.06)	99 (35.36)	0.4552
Cardioembolic	563 (32.56)	469 (32.37)	94 (33.57)	0.6938
Lacunar stroke	153 (8.85)	129 (8.90)	24 (8.57)	0.8582
Other determined aetiology	43 (2.49)	40 (2.76)	3 (1.07)	0.0966
Undetermined aetiology	392 (22.67)	332 (22.91)	60 (21.43)	0.5872
<i>Hospitalisation in stroke unit</i>	620 (35.86)	546 (37.68)	74 (26.43)	0.0003

TOAST, Trial of ORG 10 172 in acute stroke treatment.

Using O₃ quartiles (1st quartile as the reference group), linear dose–response relationship for both subgroups was observed (figure 1). Baseline characteristics in recurrent stroke and large artery stroke subgroups are shown in figure 2.

DISCUSSION

Our study assessed the short-term effect of O₃ exposure on a selected population of ischaemic stroke in a city especially polluted by O₃. An elevation of 10 µg/m³ of O₃ concentration increases stroke risk with few days lag in recurrent (≈12%) and large artery stroke (≈8%) subgroups only. Linear dose–response relationship was observed systematically in both groups. In these groups,

the common feature of the patients was that they cumulate vascular risk factors. No significant association was found between all ischaemic stroke groups and atmospheric pollutants studied (O₃, NO₂, SO₂ and PM₁₀).

Several studies have investigated the association between outdoor air pollution and stroke.^{3 5–24} Results of these studies are conflicting and hamper generalisation of conclusions. Heterogeneous methodological considerations are the main explanation of this conflict. Methodological differences are observed in patient selection, study design, outcomes choice (incidence, hospital admission, mortality) and assessment of individual exposure to selected pollutants.²⁰ Few published studies investigated especially the association between occurrence of ischaemic stroke and O₃ exposure using the case-

Table 2 Distribution of air pollution concentrations and meteorological parameters in Nice (France) between 2007 and 2012

	Mean	SD	Minimum	Quartile 1	Median	Quartile 3	Maximum
Ozone daily 8 h average (µg/m ³)	80.74	31.78	4.63	54.75	84.38	105.38	157.27
Ozone daily 1 h maximum (µg/m ³)	92.37	31.32	7.00	69.00	94.00	115.00	197.00
Ozone 24 h average (µg/m ³)	52.20	22.89	4.00	32.58	53.29	69.02	111.13
PM ₁₀ (µg/m ³)	28.48	9.81	1.00	22.00	28.00	34.00	74.00
NO ₂ (µg/m ³)	26.22	8.69	3.00	20.00	25.00	32.00	59.00
SO ₂ (µg/m ³)	1.23	1.18	0.00	0.00	1.00	2.00	10.00
Minimum temperature (°C)	13.02	5.98	−1.60	7.80	12.90	18.20	25.90
Maximum humidity (%)	81.40	9.07	40.00	76.00	83.00	88.00	97.00

NO₂, nitrogen dioxide; PM₁₀, particulate matter; SO₂, sulfur dioxide.

Table 3 Adjusted ORs between ischaemic stroke and outdoor pollutants exposure for an increase of 10 µg/m³ in Nice (France) between 2007 and 2011

	All ischaemic stroke (n=1729)					Recurrent stroke (n=280)					Large artery stroke (n=578)				
	aOR	95% CI			p Value	aOR	95% CI			p Value	aOR	95% CI			p Value
Ozone															
D-1															
8 h average	0.9917	0.9584	to	1.0261	0.633	1.0899	1.0009	to	1.1867	0.047	0.9697	0.9119	to	1.0310	0.326
1 h maximum	0.9957	0.9644	to	1.0281	0.795	1.0641	0.9824	to	1.1527	0.127	0.9881	0.9334	to	1.0460	0.682
24 h average	1.0036	0.9578	to	1.0517	0.877	1.0793	0.9616	to	1.2115	0.195	0.9983	0.9190	to	1.0843	0.968
D-2															
8 h average	0.9976	0.9657	to	1.0306	0.888	1.0957	1.0086	to	1.1903	0.030	0.9903	0.9347	to	1.0491	0.741
1 h maximum	1.0040	0.9738	to	1.0351	0.795	1.0955	1.0144	to	1.1831	0.020	0.9979	0.9457	to	1.0529	0.940
24 h average	1.0015	0.9598	to	1.0451	0.942	1.0638	0.9587	to	1.1804	0.244	1.0097	0.9365	to	1.0885	0.801
D-3															
8 h average	0.9987	0.9670	to	1.0314	0.939	1.0601	0.9784	to	1.1487	0.154	1.0261	0.9703	to	1.0852	0.366
1 h maximum	0.9968	0.9671	to	1.0273	0.836	1.0380	0.9635	to	1.1184	0.326	1.0254	0.9728	to	1.0808	0.349
24 h average	1.0046	0.9644	to	1.0466	0.822	1.0838	0.9788	to	1.2000	0.122	1.0519	0.9802	to	1.1289	0.160
D-4															
8 h average	1.0067	0.9751	to	1.0393	0.681	1.0169	0.9395	to	1.1006	0.678	1.0359	0.9808	to	1.0941	0.205
1 h maximum	0.9978	0.9684	to	1.0280	0.887	1.0038	0.9321	to	1.0811	0.918	1.0290	0.9777	to	1.0829	0.272
24 h average	1.0114	0.9711	to	1.0534	0.583	1.0248	0.9260	to	1.1342	0.635	1.0787	1.0065	to	1.1561	0.032
PM10															
D-1	1.0143	0.9518	to	1.0806	0.659	1.0041	0.5586	to	1.7995	0.989	1.0347	0.9282	to	1.1527	0.536
D-2	0.9861	0.9238	to	1.0523	0.674	0.9518	0.8106	to	1.1167	0.545	0.9350	0.8349	to	1.0464	0.242
D-3	0.9788	0.9203	to	1.0405	0.493	1.0047	0.8532	to	1.182	0.955	0.9436	0.8475	to	1.0501	0.288
D-4	0.9780	0.9202	to	1.0391	0.473	0.9911	0.8520	to	1.152	0.908	0.9544	0.8572	to	1.0620	0.392
NO ₂															
D-1	1.0307	0.9367	to	1.1336	0.533	0.8960	0.7689	to	1.0434	0.158	1.0293	0.8699	to	1.2169	0.735
D-2	0.9931	0.9029	to	1.0918	0.887	0.9427	0.7403	to	1.1991	0.631	1.0494	0.8894	to	1.2372	0.565
D-3	0.9462	0.8607	to	1.0396	0.250	1.1262	0.8767	to	1.4449	0.349	0.9147	0.7743	to	1.0796	0.292
D-4	0.9462	0.8607	to	1.0396	0.250	0.8931	0.7047	to	1.1306	0.348	0.9147	0.7743	to	1.0796	0.292
SO ₂															
D-1	1.0069	0.5986	to	1.6893	0.979	0.653	0.164	to	2.5822	0.544	1.0789	0.4507	to	2.5712	0.864
D-2	0.8763	0.5138	to	1.4905	0.626	0.8916	0.2525	to	3.1284	0.858	1.1784	0.4790	to	2.8858	0.719
D-3	1.2539	0.7405	to	2.1174	0.397	0.7231	0.1983	to	2.6188	0.622	0.9351	0.3630	to	2.3973	0.889
D-4	1.4852	0.8956	to	2.4567	0.123	1.3587	0.3735	to	4.9101	0.640	1.6564	0.7140	to	3.8260	0.237

NO₂, nitrogen dioxide; PM10, particulate matter; SO₂, sulfur dioxide; aOR, adjusted odds ratio.

Figure 1 Dose relationship between ozone and ischaemic stroke events ((A), recurrent ischaemic stroke subgroup and (B), large artery ischaemic stroke subgroup).

crossover design^{8 15 17 19 21} or the time series analysis method.^{3 12 16 22} Consistent with our results, the majority of these studies do not observe the relationship between O₃ exposure and occurrence of ischaemic stroke.^{3 8 17 19 21 22} Whenever a relationship was revealed, the association was borderline significant¹⁶ or was not confirmed by a second study on the same area of investigation.^{15 19} Despite the fact that the link between ischaemic stroke and O₃ exposure is not obvious, results in subgroup analyses seem to identify a population at risk for O₃ exposure. In a recurrent ischaemic stroke subgroup, a significant increase of 12.1% (95% CI 1.5% to 23.9%) in stroke risk was observed for each increase of 10 µg/m³ of O₃ concentration during previous days (mean D-1, D-2 and D-3 lag). Consistent with this result, a population-based study in Dijon (France) revealed the same association (OR 1.150; 95% CI 1.027 to 1.209) with 3 days lag.¹⁹ Similarly, a significant association was observed in a large artery stroke subgroup (mean D-3, D-4, OR 1.080; 95% CI 1.002 to 1.166). This link was observed in the previous study (Dijon) especially in this stroke aetiological subgroup.¹⁵ Associations in other ischaemic stroke subgroups are not systematically confirmed (age, gender, vascular risk factors and season).^{3 15 19 21 22} Our study confirms

the short-term effects of O₃ exposure on patients with stroke with high vascular risk.^{15 19}

Our findings suggest that exposure to O₃, the main photochemical pollutant, could increase the risk of ischaemic stroke in population subgroups (recurrent stroke, large arteries stroke) particularly exposed to vascular risk factors inducing atherosclerosis. Physiopathological pathways linking ischaemic stroke and O₃ exposure still remain largely unclear and probably complex. Some studies support a delayed effect (1–3 days lag) between acute exposure of O₃ pollution and stroke onset.^{15 19} O₃ urban pollution effects on healthy participants are associated with systemic inflammatory responses, oxidative stress and blood coagulation.^{25 26} These acute phenomena induced by even low levels of O₃ could be the trigger of ischaemic event consecutively to atherosclerotic plaque instability, alterations in endothelial function, and increased coagulation and thrombosis.²⁷ As suggested by Henrotin *et al*,¹⁹ we hypothesised that short-term effect of O₃ exposure could be involved especially among participants with high vascular risk.

In order to establish a causal relationship between O₃ exposure and stroke onset, we studied the exposure–response relationship, the main criteria identified by

Figure 2 Baseline characteristics according to recurrent stroke subgroup (A) and large artery stroke subgroup (B) (* $p < 0.05$).

Hill.²⁸ Consistent with previous reports, we show a linear exposure–response relationship between O_3 concentration and ischaemic stroke in subgroups identified in previous reports.^{15 19}

Our study has several limitations. The question of completeness of patients with stroke living in Nice in this hospital-based study was discussed. In Nice, patients with suspicion of stroke are admitted in priority in the University Hospital Center. Likewise, incidence of ischaemic stroke was consistent with epidemiological data in France. The question of individual exposure measurement is generally discussed. The main limitation is that we used air pollution levels from air monitoring station to represent individual exposure. However, we limited our investigations to a small geographical area (72 km²), not considered as a polluted town except for O_3 (median 53.3 (32.6–69.2) $\mu\text{g}/\text{m}^3$). Moreover, in the stroke population studied, elderly patients are mostly retired and have daily activity in the study area. Since O_3 concentration is correlated with meteorological parameters, temperature and humidity were incorporated into our models. Association between O_3 pollution and stroke can be confounded by other pollutants studied, especially particles. Effects of O_3 alone are not modified

using adjusted models for each of the other pollutants (NO_2 , SO_2 and PM_{10}). $\text{PM}_{2.5}$ was not studied because it was not monitored in Nice.

SUMMARY

The consequences of O_3 pollution on the respiratory system and mortality are well documented.¹ Our results confirm the relationship between low-level O_3 exposure and ischaemic stroke in high vascular risk subgroup with linear exposure–response relationship, independently of other pollutants and meteorological parameters. Reproducibility of previous results is one of the main Hill's criterion to induce causality of O_3 exposure. Even if the individual's risk is low, to identify an association between O_3 and ischaemic stroke incidence is important from a public health point of view, since a large population is concerned. The physiopathological processes underlying this association between ischaemic stroke and O_3 exposure remain to be investigated.

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