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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 adverse effects on health. Outdoor air pollutants are known to increase morbidity and mortality of respiratory diseases. However, in the 1950s and 1960s, epidemiological studies on acute air pollution and stroke mortality has been reported for the first time in the London fog incident study in December 1952. In the last decades, the consequences of low-level air pollution on cardiovascular mortality and morbidity have been clearly described. By analogy, a few studies have examined the role of short-term air pollution on ischaemic stroke but actually no conclusion could be generalised. 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 (µg/m³) 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 observatinal monitoring station located at Nice Airport. We computed for each pollutant during 24 h measurements during the study period were carried out in 2 of 13 permanent monitoring stations in the study area. Measures (µg/m³) 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 observatinal 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-Côte-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. 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 µg/m³ 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 10172 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 µg/m³ 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.
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. 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. Few published studies investigated especially the association between occurrence of ischaemic stroke and O₃ exposure using the case-

| Table 1 Baseline characteristics of patients with ischaemic stroke (incident and recurrent) hospitalised in Nice University Hospital from 2007 to 2011 |
|---------------------------------|
| Demographic data                |
| 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 (8.18)  | 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 |
| Cardiovascular risk factors     |
| 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 |
| Classification of stroke aetiological subtypes (TOAST) |
| 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 |
| Hospitalisation in stroke unit  |
|                                 | 620 (35.86) | 546 (37.68) | 74 (26.43)  | 0.0003 |

TOAST, Trial of ORG 10 172 in acute stroke treatment.
|                      | 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 (1.0099 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   | 0.9934 (0.9347 to 1.0529) | 0.349   |
| 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) | 0.349   |
| 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   |
| NO2                  |                               |                          |                           |         |                           |         |
| 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   |
| SO2                  |                               |                          |                           |         |                           |         |
| D-1                  | 1.0069 (0.5986 to 1.6893)     | 0.979                    | 0.653 (0.164 to 2.5822)   | 0.544   | 1.0789 (1.0457 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.
Crossover design or the time series analysis method. Consistent with our results, the majority of these studies do not observe the relationship between O₃ exposure and occurrence of ischaemic stroke. Whenever a relationship was revealed, the association was borderline significant or was not confirmed by a second study on the same area of investigation. 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. 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. Associations in other ischaemic stroke subgroups are not systematically confirmed (age, gender, vascular risk factors and season). Our study confirms the short-term effects of O₃ exposure on patients with stroke with high vascular risk.

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. O₃ urban pollution effects on healthy participants are associated with systemic inflammatory responses, oxidative stress and blood coagulation. 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. As suggested by Henrotin et al, 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

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Figure 1  Dose relationship between ozone and ischaemic stroke events (A), recurrent ischaemic stroke subgroup and (B), large artery ischaemic stroke subgroup.
Consistent with previous reports, we show a linear exposure–response relationship between O3 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 O3 (median 53.3 (32.6–69.2) µg/m³). Moreover, in the stroke population studied, elderly patients are mostly retired and have daily activity in the study area. Since O3 concentration is correlated with meteorological parameters, temperature and humidity were incorporated into our models. Association between O3 pollution and stroke can be confounded by other pollutants studied, especially particles. Effects of O3 alone are not modified using adjusted models for each of the other pollutants (NO2, SO2 and PM10). PM2.5 was not studied because it was not monitored in Nice.

**SUMMARY**

The consequences of O3 pollution on the respiratory system and mortality are well documented.1 Our results confirm the relationship between low-level O3 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 O3 exposure. Even if the individual’s risk is low, to identify an association between O3 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 O3 exposure remain to be investigated.

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