PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Ozone air pollution and ischemic stroke occurrence: a case-crossover study in Nice, France.
AUTHORS	SUISSA, Laurent; FORTIER, Mikael; LACHAUD, Sylvain; STACCINI, Pascal; MAHAGNE, Marie-Hélène

VERSION 1 - REVIEW

REVIEWER	Shigematsu, Kazuo National Hospital Organization, Minami Kyoto Hospital, Neurology
REVIEW RETURNED	13-Oct-2013

GENERAL COMMENTS	The reason I marked N/A on 15 is as follows: P 1 L 27 A number at the beginning of a sentence should be spelled out, isn't it? P 19 L 34 Coronary artery desease should be ~ disease. I am sorry that I am not sure for usage of articles and prepositions, since I have also difficulties on writing English. However, I think readers of the Journal understand well what they wanted to describe. The authors studied relationship between outdoor air pollution and ischemic stroke occurrence, which is interesting and important. Based on the large study cohort, they confirmed the relationship between low level ozone exposure and ischemic stroke in a certain subgroup. I think the study is worthwhile to be published in the Journal. However, I would like invite some comments from the authors. Firstly, definitions/criteria of risk factors they applied in the study would be helpful. Secondarily, what does flu (P1 L 24) stand for and how they defined it? Also, how and why the authors adjusted for flu? It may be associated with air pollution. Thirdly, were there any differences of air pollution between on holidays and on non-holidays? Holiday-non holiday may be a confounding factor, and therefore how

	to deal with the difference should affect the assessment of the effects of air pollution on stroke occurrence. Fourthly, were there any missing data? If so, how many were there in each parameter and how the authors dealt with them especially in the statistical analyses? Finally, how the authors dealt with the research ethics? I understand, however, the study reveals no private information identifiable and is beneficial for public as an epidemiological survey, and therefore, there should be no substantial problem. Minor points: P 1 L 27 A number at the beginning of a sentence should be spelled out, isn't it? P 19 L 34 Coronary artery desease should be ~ disease.

REVIEWER	Ali, Khalid Brighton and Sussex Medical School, Academic Department of Geriatrics
REVIEW RETURNED	21-Oct-2013

GENERAL COMMENTS	The paper did not address haemoraghic strokes, please explain. The Other illness such as lung cancer, myocardial infarcts, and their relationship to ozone air pollution in the studies population? Carotid stenosis was not mentioned in the risk factors addressed in the patient population, please explain.

REVIEWER	Arba, Francesco Neurological and Psychiatric Sciences
REVIEW RETURNED	21-Oct-2013

GENERAL COMMENTS	- Line 36: "Exposure measurements during the study p eriod were carried out in 2 of 13 permanent monitoring stations in study area." The majority of study area is not covered by direct data about pollution. Results and conclusions are strongly biased. - Main results of the study (line 44-49): in the adjusted analysis are not specified confounders and covariates (e.g. main predictors of stroke or recurrent stroke, presence of marge artery diesease). The results could be infer from chance.

VERSION 1 – AUTHOR RESPONSE

Response to Kazuo Shigematsu:

P 1 L 27: A number at the beginning of a sentence should be spelled out, isn't it? Corrected.

P 19 L 34 Coronary artery desease should be ~ disease. Corrected.

1/ Cardiovascular risk factors are defined by WHO standard definitions.

2/ In the literature, flu is considered as a risk factor of stroke. Epidemic flu is also sensitive to weather variables and air pollution. It is the reason why flu is classically considered as a confounding factor in studies measuring the relationship between air pollution and stroke incidence. Flu was clinically defined by Sentiweb* network as following: Above 39 ° C fever, sudden onset with myalgia and respiratory signs.

3/ As explained in statistical method, the holiday status was considered as confounding factor and all results were adjusted with this variable.
“Odds ratio (OR) and 95% confidence intervals (CI) for a 10 µg/m3 increase of pollutant level were adjusted for temperature and humidity with 1-day lag, influenza epidemics and holidays without day lag.”

4/ Only for the air outdoor pollution data, the problem of missing data was observed. As specified in method section, missing data was managed as following:
“Missing values were replaced by measures performed by the observational monitoring station located at Nice Airport.”

Response to Khalid Ali:

Patients with hemorrhagic stroke were not included in this study for followings reasons:
• First, physiopathology ischemic of stroke and hemorrhagic stroke are totally different.
• Secondly, it was less relevant to study hemorrhagic stroke because there is arguments in literature for the lack of relationship with pollution.
• Thirdly, atherosclerosis, a sub-etiology of ischemic stroke, seems to be the common point in vascular disease and air pollution in literature.

According TOAST classification, patients in group “Large artery stroke” require a carotid stenosis > 50%. Patients with carotid artery lesions were represented in this TOAST group.

For comprehension and according your comment the following text was changed:
“The question of completeness of stroke patients living Nice in this hospital-based study was discussed”.

Response to Francesco Arba:

1/ Exposure measurements during the study period were effectively carried out in 2 of 13 permanent monitoring stations in Nice. The 13 monitoring stations in Nice don’t serve to measure pollution in different parts of the city. In fact, each station is specialized in specifics measures (traffic stations, industrial stations, observational stations, peri-urban stations, urban stations, and rural stations). Urban station is representative of the average level of population exposure to basal air pollution in urban centers. According suggestions of air quality engineers in Nice, urban and observational stations were selected for our study.

2/ As specified in the method part, all results were adjusted with this variable.

“Odds ratio (OR) and 95% confidence intervals (CI) for a 10 µg/m3 increase of pollutant level were adjusted for temperature and humidity with 1-day lag, influenza epidemics and holidays without day lag.”

VERSION 2 – REVIEW

REVIEWER	Ali, Khalid Brighton and Sussex Medical School, Academic Department of Geriatrics
REVIEW RETURNED	09-Nov-2013

The reviewer completed the checklist but made no further comments.

REVIEWER	Arba, Francesco Neurological and Psychiatric Sciences
REVIEW RETURNED	13-Nov-2013

The reviewer completed the checklist but made no further comments.