Author's response to reviews

Title: Incidence of first ever stroke during Hajj ceremony

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Author's response to reviews: see over
Dear Josefino

Subject: Manuscript revision, entitled “Incidence of first ever stroke during Hajj ceremony”
Authors: Azarpazhooh MR, Bavarsad Shahripour R, Kapral MK, Mokhber N, Shoeibi A, Farzafard MT, Rafati MR, Thrift AG, Sajedi SA, Azarpazhooh A

We are very pleased that the reviewers have found this article of importance in the field. We would like to thank them for the invaluable input and detailed and insightful feedback to our submitted manuscript. Please find below our responses to these concerns point by point. The changes are all highlighted in the revised documents.

**Responses to Reviewer 1: Giancarlo Logroscino**

1) *Are there any data suggesting the completeness of ascertainment in this pilgrim group?*
   **Authors’ response:** Described in the methodology: the ascertainment of the cases in the pilgrim group is complete as during the trip, there is a GP who is assigned to each caravan as the first point of contact for any medical concern. The GPs then referred cases with neurological findings to the study neurologist. The health data of the pilgrims, including their demographic characteristics, past medical history, medical events during and after the Hajj ceremony, decisions taken by GPs and subsequent referrals, cause of admission and outcome were registered in the central data bank of the Hajj and Pilgrimage Organization of Iran.

2) *Any data in the literature presenting the risk for stroke and MI in subjects attending religious or other type of events involving big crowds?*
   **Authors’ response:** We do not have enough information about the prevalence of MI in our study. A small-scale descriptive study examined the pattern of cardiac diseases among hospitalized patients during Hajj 2011. From one hundred and eleven patients admitted to the hospital, 34% had ischemic heart disease, 20% had elevated blood pressure and prevalence of stroke was 17%.(Almalaki, Pakistan Journal of Pharmacology, Vol. 29, No.2, July 2012, pp.29-34)

3) *The pilgrims come from all Iran while the comparison group is from the city of Mashhad. Is it reasonable to assume that the risk is similar in the whole Iran to the risk of the residents of Mashhad?*
   **Authors’ response:** We added the following to the discussion
Mashhad is the second populous metropolitan of Iran and a religious centre that attracts many migrants from all parts of the country. The MSIS has been so far the only comprehensive population-based study of stroke in Iran. Although the result of this study cannot readily be
generalized to the whole country, other unpublished local data suggest comparable cerebrovascular risk profile in other cities, similar to what we found in the MSIS. Therefore, with some degree of caution, we believe Mashhad can be regarded as an acceptable representative of the urban population of Iran and the MSIS results can provide a good proxy of the national incidence of urban population, but not the rural population.

4) In the discussion the authors suggest that a screening program similar to the screening program implemented for the Haji ceremony could be tested. The goal of the screening program is to select the more fit for the pilgrimage, a special event. How does this program could be comparable with screening programs in the general population in normal setting?

Authors’ response: As the reviewer correctly mentioned, the screening program for Hajj aims to select the more fit for the pilgrimage. However, the basis of screening is simple, comprising the evaluation of BP/ DM and HLP which are the common risk factors. If a past medical history of MI or stroke was identified, then a consult with neurologist or cardiologist is performed.

5) Should the authors discuss the possible link of their findings with the healthy migrants effect?

Authors’ response: We do not expect to have the healthy migration effect as the Hajj population attending this 30-day religious trip is a transitory derived group from a reference population for a short period of pilgrimage.

Responses to Reviewer 2: Norberto Cabral

1) The authors ascertained all first ever strokes occurred during Hajj ceremony at the end of 2007 and beginning of 2008 (47 days). They compared, in the same time, the incidence among Iranian pilgrims (17/92,974) in the Mecca and Medina with a database in the Iranian city of Mashhad (12/334,348). However, they didn’t adjust their crude rates to standardized population. In the table 2, they found a crude rate of 18/100,000 (10-26) in Hajj sample and 12/100,000 (5-19) in Mashhad City. I adjusted to SEGI world population (2000), and the incidence was 84/100,000 (49-135) in Hajj and 153/100,000 (109-208) in Mashhad. As they showed in the figure 1, age distribution was very different between the samples, which explains the higher incidence in MSIS. Even though those crude rates were statistically different in some age strata but the study has interest for Muslim countries. So, the external validity of this study is narrow.

Authors’ response: As we stated in the methods, our aim was to compare the first ever stroke in Hajj pilgrims with the MSIS population in a specific time limit. In this revised version, because of the different population pyramids, we adjusted the crude incidence rates to a standard population for comparing two incidence rates. For this purpose, we adjusted two population to a standard population. We used the aggregation of these two population and their strata for respectively, standard population and its strata standard population. We used direct method of adjustment for calculating adjusted incidence rates. Consequently, we calculated the adjusted incidence rates for each population and by gender. After adjustment the incidence was 9/100,000 in Hajj and 16/100,000 in MSIS.

With respect to your comment on the external validity, we added the following to the discussion:
Islam has 1.6 billion followers in the world, comprising over 23% of the world population. Due to the religious rules, attending in Hajj ceremony, at least for once, is an aim for Muslims. Iran is one of the 22 Member States of the WHO Eastern Mediterranean Region (EMRO). These Member States, with a population of nearly 583 million people, are by large Muslims. Therefore, the findings of this study may be considered of value for the EMRO countries in preparation for the Hajj ceremony.

2) Abstract: results, line 11: ...than the Mashhad population; the same in line 17.
Authors’ response: revised

3) Enhance that ascertainment in Hajj ceremony was retrospectively done.
Authors’ response: added to the last paragraph of the methodology

4) Introduction: Objective 1: ... of first ever stroke;
Authors’ response: Revised

5) Methods: How many people had in each caravan?
Authors’ response: Each Caravan included about 100-200 pilgrims. Added

6) Could you specify whether the GP asked specifically if the patient had already had a previous stroke?
Authors’ response: The past medical condition including the previous history of stroke was asked before the trip by the caravan GP.

7) Line 20: Iranians pilgrims. Please, could you clarify if MSIS data was done prospectively? or not? Is it a population-based study?
Authors’ response: MSIS study was a population based prospective cohort study. Added to methodology

8) What means a CT only case?
Authors’ response: Added: A “CT only” strokes was suspected for cases in which a patient, with no clinical sign and symptom, had neuroimaging changes compatible with stroke.13

9) Results: How many first ever strokes were ascertained by GPs in Hajj ceremony?
Authors’ response: GPs referred all of the cases suspected of having stroke. 17 cases had FES.

10) In general, CVT is not included in stroke epidemiological studies. Please, exclude These two cases.
Authors’ response: We included these two cases to have a fair comparison to the MSIS where we enrolled CVT cases. Ischemic stroke and CVST are important types of stroke. In the Hajj group, these cases occur due to a non-indicated use of oral contraceptive.

11) How many “possible” and “CT only” cases were excluded?
Authors’ response: There is no cases with possible or CT only
12) Discussion: The results Hajj pilgrims need to be compared with MSIS data and not with general population.

Authors’ response: All changes has been done

We hope that the editorial board will be satisfied that we have answered the question and concerns raised by the reviewers and we wish to thank the reviewers again for taking the time to review the manuscript. It is only through thoughtful and constructive criticism that the quality of this manuscript, we hope has been improved.

Thank you very much again

Sincerely,

Amir Azarpazhooh, DDS, MSc, PhD, FRCD(C)