Author’s response to reviews

Title: Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study.

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Version: 2 Date: 28 November 2007

Author’s response to reviews: see over
Dear Sir/Madame;

Please find attached the revised manuscript (1165593437156610) entitled “Ischemic stroke incidence in Santa Coloma de Gramenet (ISISCOG), Spain. A community-based study”.

The text has been reviewed by a native English speaker with expertise in correcting scientific papers.

Below please find the point by point answers to the referees’ suggestions and comments.

Referee 1

1. Authors should better describe and discuss the age-distribution of incidence as well as of case-fatality and disability.
   
   We have now described and discussed the age-distribution of incidence as well as case-fatality and disability. From page 6, line 21 to page 7, line 3 and page 7 lines 11-21.

2. Study methods include a 90 days follow-up examination of survivors: authors should detail the lost to follow-up.
   
   We have now detailed the survivors lost to follow-up (2 people). Page 7 line 11.

3. Authors should better discuss the possible explanation why their results are at variance with the two previous Spanish studies (Jover-Saenz et al, 1999; Lopez-Pousa et al, 1995).
   
   We have now discussed the possible differences between our study and previous Spanish studies. From page 8, lines 3-15.

4. Authors should discuss the limitations of their study (e.g., control CT scan was performed only in the 56% of patients, etc.)
   
   We do not believe this to be a limitation of the study since the patients who did not receive a control CT scan underwent magnetic resonance imaging. Nonetheless, a paragraph (from page 8, line 32 to page 9, line 2) has now been included to this respect in the Discussion.

Minor comments

1. In the abstract. Results section: last sentence, disability rate should refer to survivors (not to patients in general).
   
   Done
2. In the abstract. Conclusions section: authors should say that rates are "lower than..." instead of simply "low".  
*The text has been changed according to the referee’s suggestion.*

3. In Background: use the term "developed" instead of "industrial" countries.  
*Done*

4. In Background: use the term "efficacy" instead of "effect" of preventive strategies.  
*Done*

5. In Background: use the term "sub-typing" instead of "subtype".  
*Corrected*

6. In Study area and population: use the term "population-based" instead of "based-population".  
*Done*

7. In Results: transthoracic is misspelled.  
*Done*

8. In Discussion: resources is missspelled  
*Corrected*

9. In Discussion: not-admitted is missspelled  
*Corrected*

10. In Discussion: use the term "several" instead of "multiple" factors not assessed....  
*Done*

11. In Table 1: in the title, authors should say age- and sex-specific attack rates.  
*Corrected*

12. In Table 2: in the title, authors should say age- and sex-specific annual incidence rates...  
*Corrected*

13. In table 3: authors should write annual incidence rate cerebral infarction; and adjusted annual incidence rate ischaemic stroke.  
*Done*

**Referee 2**

**Main comments**

1. The main weakness of this study is that it is mostly a descriptive overview of stroke incidence and case-fatality in a Spanish region, but it is unclear what this paper adds to the international literature on stroke. Part of the reason for this
problem is that the paper does not touch on fundamental issues regarding why such study is important or what are the particularities of these studies. Since previous studies have extensively investigated stroke incidence, case-fatality and sub-type distribution, more clarity is needed on the added value of this paper—which main potential could be the particularities of the Spanish region in question.

**We think that this point is answered in the next 2 following points.**

2. In regard to point 1 above, the reasoning of the paper in the introduction is not presented convincingly. Authors present as background the incidence of stroke in Spain and discuss some risk factors for stroke. However, the introduction does not present a clear reasoning of what the motivation and justification for this study is, and why it would be interesting for an international audience. Basically, I suggest authors discuss what the particularities of stroke in Spain are in comparison to other European or world regions, and what the expectations are in this respect. Do authors expect that stroke incidence, subtype distribution, case-fatality and stroke-related disability are different in this region of Spain?

What is the reasoning behind this?

**Following the suggestions of the referee in the Discussion we explain the interest this study may have for the international literature. We have particularly underlined the collection of case fatality and disability and the possible reasons for the lower incidence of death, the methodologic improvements this study contributes compared to others performed in Spain, and the fact that this study will allow the evaluation of the institutional plan for protocolized health and emergency care for stroke patients (Page 8, lines 9-13).**

3. In the introduction there is an emphasis on risk factors, but the focus of the paper on case-fatality and disability may also point at a role of healthcare related factors. Is there anything in particular about this Spanish region that may explain a possible difference in case-fatality and disability with respect to other European regions? This needs to be discussed in the introduction.

**The population studies was an urban population located a maximum of 20 minutes from an acute care hospital with a department of neurology. The interest here may lay in the influence which the possibility of obtaining specialized health care early following a stroke event may have on case fatality and patient disability. A sentence stating this has been added in the Discussion (page 10, lines 1-3). In addition, we believe that our case ascertainment methods are exhaustive, combining “hot” and “cold” pursuit techniques. We also believe that data collection on case fatality and disability to be correctly registered, despite not having reviewed the death certificates since autopsies are not routinely undertaken in all deaths and the death certificates were signed by the GPs or neurologists (in hospital deaths) participating in the study. This has been stated now in the Discussion.**

4. The strategy developed by the authors to ascertain stroke incidence seems appropriate. However, this study is of the ‘unlinked type’ (information on the denominator and the numerator came from different sources), which may be a
drawback in the estimation of first incident stroke: In particular, when a stroke case is detected and the clinical history reveals that this person had a stroke before the study started, this would no longer be considered a first stroke. However, this person should also be excluded from the denominator, because he or she was not at risk of first stroke at the time the study started. I believe their unlinked method does not take this into account. This could artificially make stroke rates lower than they actually are, for instance in comparison to follow-up studies in which information from the population and the outcome comes from the same source. This may not be a large problem and it may have only a small impact on the results. However, it is essential that authors spend more space in the discussion to discuss the limitations of their study and the possible biases that could arise as a consequence. *We agree with the referee but did not previously know the number of deaths the study population presented and could therefore not exclude the denominator. This has been explained in the part on limitations in the Discussion. (Page 10, lines 4-12).*

5. The main conclusion of the authors is that the incidence and case-fatality of ischaemic stroke is lower in this region of Spain as compared to other world regions. However, the validity of this main conclusion is not fully developed in the paper. Firstly, it is not clear how the present study population compares to the population in other studies, which may have very different age ranges. Authors standardized their rates to the European standard population, but many of the studies presented in Table 3 presumably use a different standard population, e.g., the World population. Furthermore, even after standardization, the age ranges may be so different that comparisons are not fully valid. Since this is the main conclusion of the paper (and the one most likely to be interesting for an international audience), I suggest authors present and discuss Table 3 in more detail in the results section. Issues to address include: Firstly, it is not always clear that the incidence of ischaemic stroke is lower in their study as compared to other studies, specially if confidence intervals are taken into account. Can a more convincing comparison be made? Secondly, how age or other factors influence these conclusions? *We have included the standardized results for the world and European populations to achieve better comparability. We mainly focus on differences between our study and the others from Spain (Page 9, lines 3-15). Anyway, we believe that table 3 is rather self-informative.*

6. Discussion, paragraph 1: From this paragraph it would appear that the rate of stroke in this Spanish region is within the normal ranges of the incidence in Spain as a whole (163-257 for total rate and 132-174 for first ever stroke). Therefore, and particularly taking confidence intervals into account, it is difficult to conclude that in this region the incidence of stroke is lower as compared to Spain as a whole. *We agree with the referee. Even though the overall estimates are lower in our study, confidence intervals overlap and several methodologic differences exist between studies. We have reduced the emphasis of this sentence.*

7. The discussion lacks a more detailed presentation of the limitations of the
study and the possible biases, as well as a more precise discussion of the implications of the study. I suggest authors make an attempt for a more thorough discussion of these issues.

We have made a more detailed presentation of the limitations and implications of the study (Page 10, lines 4-12).

Minor Comments
1. Abstract: Please include information on the size of the population, age and number of cases in the methods section.

We have included more information about this in the Methods and Results section of the abstract.

2. Abstract results: Please present only the European standardized rates—the crude rates are almost the same and are difficult to interpret since they are not standardized.

As suggested we have now included the European (and also world) standardized rates in the Methods section.

3. Abstract: The finding on ‘low recurrent stroke’ is not included in the abstract results. Either this should be described in the results or not mentioned in the conclusions of the abstract.

Conclusions have been updated in the Abstract.

4. There are a number of English language errors in the paper. The paper may need to be reviewed by an English editor.

Done.

Referee 3

Major Revisions
The methods are not fully appropriate. Data are not fully representative. The Discussion and the conclusions are not well balanced and fully supported by the data. The title should be shortened.

We do not agree with the reviewer in several points: We have used the methods proposed by Malmgrem, Bonita Sudow and Warlow in The Lancet (2004;363:1920). The only difference is that the death certificates were not consulted since these had been signed by the physicians participating in the study.

The data are highly representative since we have used the data from the municipal census of December 31, 2001 which is the most exhaustive, reliable and essential source of information in this study. We agree however, that the title is relatively long but the name of the city in which the study was performed in long.

In addition, we think that we have now balanced the Discussion and conclusions.

The following should also be taken into account:
- Authors assert to have followed the criteria for the ideal stroke incidence study but this is not true in terms of standard diagnostic criteria and complete case
ascertainment. Besides, they do not report the latest paper that has been published on this topic in The Lancet (2004;363:1920).

We believe we have used all the criteria proposed by these authors (the 4 criteria covering standard definitions, all the criteria covering standard methods, except for the death certificates since in our country autopsies are not systematically performed in all dead patients and the death certificates were signed by the general practitioners participating in the study or the participating neurologists in the case of hospital death). Moreover, we know the number of survivors at 90 days because the follow up was carried out using the Barthel Index. We also believe that we have used all the criteria regarding standard data presentation.

The reference suggested has now been included.

- The resident population is represented by an equal number of men and women; this result is rather uncommon and should be commented also with reference to the different age groups.

The similarity between the numbers is purely accidental. We realize that these values may seem to be rather uncommon but we used the municipal census of December 31, 2001.

The population is Caucasian of middle-low socio-economic level with high medical advice demand. The proportion of inhabitants older than 65 years is 15.7% (13.6% in men and 17.8% in women).

- Codes of the ICD-9 Classification should have been reported, at least for the ischemic events (433-434, 435, and 436-437). Definitions of stroke types and particularly of cerebral infarction should be given.

Please note that we used the TOAST criteria to classify Stroke ischaemic subtypes, so now we can not include the codes as suggested by the reviewer, since they are not fully comparable.

- The case-finding procedure should be described with more details giving due information on death certificates under this heading. - Data collection methods and the existence of a database should be mentioned.

We have now described the details regarding the death certificates, data collection methods and the existence of a database (Page 5, lines 17-24).

- Statistical analyses need to be fully described together with the methods used. The software used for the analyses should also be reported.

To compute incidence rates and their confidence intervals, row and standardised, we have used the statistical package CIA v1.0 (Professor MJ Gardner & BMJ, 1989). This has now been included in the text (page 6, lines 4-6).

- A figure referring to the age-and sex-specific incidence rates for first-ever stroke should be added.

We thank the referee for the suggestions but perhaps a table would present the information in greater detail without the need for changing a table to a figure. Please inform us.

- The European population needs to be clarified as pertaining to a specific

We believe the new World approach (WHO) is probably not as useful for comparison with older studies.

- The Results and the Discussion should be reorganized according to the above reported issues and due consideration should be given to comparisons with other registers.

We have reorganized the Results and the Discussion as suggested.

We hope the manuscript is now acceptable for publication.

Yours sincerely,

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