Author’s response to reviews

Title: Stroke in urban and rural populations in north-east Bulgaria: incidence and case fatality findings from a 'hot pursuit' study

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PDF covering letter
RESPONSE TO DR TRUELSON

DR = Discretionary revisions; CR = Compulsory revisions; both as numbered by reviewer

Discretionary revisions

DR 1:
The suggested reference to Malmgren has been included and the intended role of the external comparisons has been made more explicit.

DR 2:
A p value for the seasonal difference has been added as suggested.

DR 3:
The reference to non-linearity has been dropped and the text rewritten to provide a qualitative description of the findings.

Compulsory revisions

CR 1:
‘Verbal autopsies’
We have dropped this term and completely reworked our description of our ascertainment and classification processes, starting with a fresh abstraction from our paper records of new variables describing the nature and quality of the data sources used.

Much of this material is now in the more detailed version of the methods (additional file 1) and in additional files 3 and 4. We trust that the summary descriptions in the primary text are also sufficiently informative.

CR 2
Statistical methods
The specific page reference for deriving the confidence intervals is now given.

The use of a poisson distribution for calculating confidence intervals is now noted in the methods section of the primary text.

CR 3
We assume this reference is the para beginning ‘Median (interquartile…)’. Duplication with preceding text has been removed and the text tidied.

CR 4
It is now stated in the primary text that the investigated sample is of unknown representativeness and the table itself has been transferred to additional file 4.

CR 5
The caption and footnotes for Figure 2 have been rewritten in simpler and more explicit language.

CR 6
The relevant text has been rewritten.

CR 7
We have done more analyses on the differences in case fatality, which we agree are very interesting, and presented them in figure 3. This gives the numeric values and shows their confidence intervals.

CR 8
The discussion has been expanded with references to studies in other central and East European countries (as suggested). We have not been able to locate other published studies comparing urban and rural rates though we are aware that the MONICA north Sweden study (Asplund et al) included a large rural hinterland. We are also aware that in Hungary mortality rates are much higher in rural areas and in the north east but we know of no studies there. Novosibirsk and Uzhgorod were both urban only. Some of the East Asian studies (Japan, China) appear to have been in rural areas but we have not located specific urban rural comparisons. We would be grateful for further leads.

CR 9
We have added some comments about candidate explanations for the differences in incidence and case fatality. However much of the data from our parallel dietary studies is still being analysed and is not yet published.

RESPONSE TO COMMENTS OF DR WOLFE
(Numbering follows that of the reviewer)

1. We agree that the low CT scan proportion means that the information on pathological type is very difficult to interpret. We are happy to consign it to ‘additional information’ (and have done so, along with a ‘health warning’). We disagree however with the more serious point that a low CT scan proportion makes our estimated incidence of total stroke ‘questionable’ or just a ‘ball park estimate’. Because this point about CT scans recurs we would like to comment further on its relevance to the central objectives of this study. As we have made clearer in our revised primary text, our chief concern was to test the implication of the official mortality data and of local clinical opinion that the incidence of total stroke in this region was very high and that it was higher in rural areas than in urban areas. It is not an appropriate answer to this question to suggest that the study might have been done elsewhere in order to achieve a higher CT scan proportion. Alternatively, we doubt if it would have been realistic in research funding terms or indeed ethical to ferry patients up to 70 km by ambulance to Varna over sometimes difficult roads for a CT scan in circumstances where most patients suffering a stroke were not admitted to hospital and many did not receive specialist assessment. Most importantly, we do not agree that the clinical classification of suspect events as stroke or not stroke (when based on adequate clinical information) is likely to be subject to materially important degrees of bias. In a study from Oxfordshire in the early 1980s, of a total of 325 cases of ‘clinically definite first stroke’, subsequently investigated by CT or necropsy, there were 5 ‘false-positives’ and 3 ‘false negatives’ – giving a net upward bias of 2/325 or less than 1 percent (Sandercock et al, BMJ (1985) 290:194). We would immediately concede that our study is conducted in different and less favourable circumstances and that
classifications were sometimes conducted with inadequate clinical information. However, net biases would have to be an order of magnitude larger than those of Sandercock et al before they threatened our main conclusions.

In order to deal more satisfactorily with these issues we have completely re-worked our account of our ascertainment and classificatory processes, starting with the fresh abstraction of additional information from our paper records. We have sought to make good use of the opportunities provided by online publishing and much of this material is now in the more detailed version of the methods (additional file 1) and in additional files 3 and 4. We trust that the summary descriptions in the primary text are also sufficiently informative.

(We note that the other reviewer, Dr Truelsen, whilst sharing the point about pathological types, expresses no concern that our main results may be seriously biased.)

2. Choice of studies for external comparison: We have made more explicit the reasons for our choice of comparison studies in the more detailed version of the Methods (additional file 1). We agree that our findings should also be placed in the context of more recent reports especially from Eastern Europe and we have done this in the revised discussion section of the primary text.

The small size of our denominators is acknowledged but we have already been careful not to overstate the precision of our estimates (Submitted text, discussion section, first para: ‘The point estimates need to be interpreted in the light of their confidence intervals.’)

3. We have clarified that by ‘first in lifetime’ we mean ‘first ever in a lifetime’. In relation to the selection of weights for age standardization: Our choice of the world standard followed from our choice of studies for external comparisons. We would be happy to add rates standardized using the ‘European’ weights if the editor concurs with the reviewer.

4. We agree that we need to discuss our findings in the context of more recent studies and have done this in the discussion section of the revised primary text.

5. We have re-written this para and are happy to accept editorial guidance on whether unpublished material may be included in the references. (We have been awaiting updated official urban / rural mortality data which is expected around now.)

6. Data describing the case-finding and assessment processes is now available in much greater detail in the additional information. Events under 35 were excluded because the expected numbers would not yield sufficiently precise age-specific estimates to justify their inclusion in age-standardised rates.

7. The reviewer appears to have missed the references to the GCS results in the discussion of case fatality on p 11. More is now made of these in the analyses of differences in case fatality (Figure 3).

8. The reviewer is in error in believing that overlapping confidence intervals preclude a significant difference. Two-tailed p values for the rate difference have now been added to the table. Both are highly significant.

9. See 1 above.

10. Repeats some of the points dealt with under 1 and 4 above. With the possible exception of the secular increase in Novosibirsk (reference number 17 in the current text), more recent studies do not extend the range of incidence rates previously reported and therefore do not weaken our main finding: that incidence, especially in
the rural areas is indeed high relative to findings in other European populations. See also 1 above.

11. Assessment procedures previously described as ‘verbal autopsies’. We agree that our previous discussion of these was unsatisfactory (in both the methods and discussion). As noted above this has now been completely reworked. We think this deals adequately with the question of possible upward bias in our ascertainment and classificatory processes (downward biases, if present, would not weaken our conclusions unless they were strongly differential between urban and rural areas).

12. Table 1 is now only in additional information.

13. Table 3 is now only in additional information (and comes with a ‘health warning’ re its interpretability).

14. The caption and footnotes for Figure 2 have been simplified and expanded.