28-Jan-2019

Dear Dr. Seminog

Manuscript ID BMJ-2018-047575 entitled "Determinants of the decline in mortality from acute stroke in England: linked national database study of 811 029 adults"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are pleased to offer publication in the BMJ as long as you are able to revise to our satisfaction as outlined below.

We hope very much that you will be willing and able to revise your paper and we are looking forward to reading the revised version in due course.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

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John Fletcher
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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were:Elizabeth Loder (Chair), Tobias Kurth (Statistician), Tiago Villanueva, Jose Merino, Wim Weber, John Fletcher.

Decision: Put points

Detailed comments from the meeting:

1. John Fletcher declared that he had worked in the same institution in the past as some of the authors and was favourably inclined towards them.

2. We all liked you careful approach to using national data and thought you had presented your results clearly.

3. The decline over time in case fatally is plain to see. We did wonder how much of this might be due to a trend over time towards increased referral and investigation of patients with TIA and or minor non-disabling strokes. You have adressed this to some extent by excluding short admissions in your analysis. We would like you to explore this phenomenon a little more in some sensitivity analyses if possible. Perhaps you could explore the trends in people with shorter and longer stays? Do you have any information on severity at admission that could be used?

4. In the discussion please can you draw in some comparisons with other countries? Some editors from other countries agreed with the reviewer comment that the case fatality rate after 30 days in 2001 looked a little high.

5. Our statistician made the following observations:
a. The methods they used are robust, but the authors may want to distinguish proportions from rates.
b. While the analyses on potential explanations of the decline are interesting, I think the authors make too much out of it. As they did not set up causal models, they can hardly state that a factor was contributing to the decline.

6. Our patient editor noted:
Please contribute a PPI declaration for this paper. It is also customary to thank the data participants who made the study possible. Please include a statement of your plans for disseminating the results of your research.

7. Please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is an interesting and useful study on determinants of the trend in mortality from acute stroke in England using HES and ONS death data. However, there are a few major issues requiring discussion and further attention:
1. The authors claimed this is a population-based study, however strictly speaking it is not. This is only hospital episodes study and likely to under-estimate all the rates as shown in the established population based stroke registers that estimate in the UK there are about 10% stroke patients who are community patients and not admitted to hospitals. Also, another dataset, the Sentinel Stroke National Audit Programme (SSNAP), may be more suitable for this type analysis with more specific and detailed data on stroke although it is hospital based. Can the authors discuss these point.
2. Although useful confirmatory data to previous studies, the paper only provided facts on mortality, events and case fatality. They are all closely linked outcomes and basically quite similar and hence, highly correlated. The paper lacks any risk factors for stroke therefore is somewhat superficial in explaining the determinants of these trends. Also, there are no primary and secondary prevention treatment data at all, which makes the analysis and conclusion regarding care unjustified and incomplete.
3. The section on 'study population and selection criteria'. It's not 'population-based mortality' as there are stroke patients who are not admitted. Regarding the definition of event, 'Events were identified

as a hospital admission for stroke, or as a death with stroke as the underlying cause without a corresponding hospital admission for stroke in the preceding 30 days", however, what about stroke patients not admitted and patients admitted to hospital due to other cause of disease but had stroke while in the hospital? All these were likely to contribute to the potential biases of the study findings. Also, why only use 30 days case fatality? What about 7 days, 6 months and 1 year case fatalities to further investigate links with acute care and longer term care?
4. The new methods or messages from this paper are not strong, the advantage being mainly the use of whole country linked data which has been reported before. The relevance to practitioners should be clearer.
5. Reference 27 appears to be missing.
6. The strengths and limitations says this is the largest study of stroke morbidity..., although unclear what morbidities are presented here?

Additional Questions:
Please enter your name: Charles Wolfe

Job Title: Professor of Public Health

Institution: KCL

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
This study used population-based UK administrative data to estimate stroke mortality rates, event rates and case-fatality rates between 2001 and 2010. The main findings were that stroke mortality decreased

over time, and that this was primary attributable to declines in case fatality. Stroke event rates declined over time in most age groups other than those aged 35 to 54 years.
Comments:
1. The findings are interesting and could represent an important contribution to the literature in this area.
2. This is a nice use of high-quality population-based administrative data with complete ascertainment of hospitalizations and deaths that avoids the biases associated with selective case selection and incomplete outcome ascertainment.
3. Stroke hospitalizations (with length of stay more than one day) were used as a proxy for stroke events. It is not unusual for people with non-disabling stroke to have a short length of stay or not be admitted all, and changes in admission thresholds for non-disabling stroke over time could explain some of the observed changes in event rates and case fatality rates. Suggest addressing this more fully in the limitations section.
4. The observed 30-day stroke case fatality rates of over 40% in 2001 and over 26% in 2010 are much higher than reported in other studies (typically ~20%). This suggests that more severe strokes are over-represented in this study. Can the authors comment on why the case fatality rates were so high, and how this might affect the interpretation and generalizability of their findings?
5. The discussion around the decline in stroke case fatality rates could be placed more clearly in the context of what is known about predictors of survival after stroke, e.g. stroke severity, intensive vs palliative approaches to care, etc. The authors suggest that use of thrombolysis might account for some of the decline in stroke case fatality, however, this seems unlikely as thrombolysis is not expected to have any short-term mortality benefits. Stroke severity is the strongest predictor of case fatality. Although this study does not have information on stroke severity or on stroke type (with greater severity and case fatality with hemorrhagic than ischemic stroke), it is conceivable that there have been declines in stroke severity over time, for example, through improved anticoagulation of atrial fibrillation.
6. The statement in the concluding paragraph that "hospitals were instrumental in reducing the rates of stroke mortality through improvements in survival" is speculative, as it is not clear that hospital-based interventions accounted for the declines in stroke case fatality.
7. Minor comment: ICD-10 code I62 represents subdural hematoma and is not usually included in studies of stroke.

Additional Questions:
Please enter your name: Moira Kapral

Job Title: Professor, Department of Medicine and Institute of Health Policy, Management, and Evaluation

Institution: University of Toronto

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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