

We thank the BMJ editorial committee and the reviewers for their comments and suggestions which helped us to improve the paper

Comments from the BMJ committee

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| <p>1. The decline over time in case fatality 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 addressed 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?</p> | <p>We explored the issue of a shorter length of hospital stay and the impact on case fatality in a sensitivity analysis. After we extended analysis to include stroke cases with a length of hospital stay of 1 day or less, an additional 32,606 admissions for stroke were identified, 0.3% of the total. As expected, with the addition of such a small percentage of cases, analysis of data with these cases resulted in just a small decrease in case fatality and a small increase in event rate, while the trends analysis did not change. In 2001, stroke event rates in men of all ages increased from 334 in the original analysis, (95%CI 330.9-337.7) to 348 in the new analysis, (344.9-351.8), and from 284.5 (281.8-287.2) to 301.6 (298.9 -304.4) in 2010, in women from 273.8 (271.4-276.1) to 281.8 (279.5-284.2) and from 233.7 (231.7-235.8) to 242.6 (240.5-244.7), respectively.</p> <p>Case fatality decreased in 2001 in men from 41.8 to 36.9 (new analysis, 95CI 36.4-37.3) and in 2010 from 26.4 to 22.2 (21.7-22.6), and in women from 44.1 (43.7-44.5) to 38.9 (38.5-39.3) to and 28.5 to 24.2 (23.8-24.5).</p> <p>The inclusion of the extra cases did not affect the conclusions on the contribution of changing event rates and case fatality to changes in mortality rates.</p> <p>We have not amended the manuscript to reflect this, in the spirit of not lengthening it. However, we will do so if you wish.</p> <p>Information on stroke severity was not available in routine medical data.</p> |
| <p>2. 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</p> | <p>We thank reviewers for raising a point about high case fatality rates reported in this study. As now explained in the paper, two factors made our fatality rates seem relatively high. First, we included patients of all ages. Most published studies only included patients with a lower age cut-off, eg MONICA only included people aged under 65. Fatality rates are higher in the elderly; and the elderly comprise a lot of patients. We think that it is right to include the elderly when possible (otherwise, the profile of stroke is incomplete; and the fatality rates reported for 'all ages combined' would be unrealistically low). We included the elderly; but our results also show age-specific rates, which, unlike the age-standardised summary rates, do not depend on arbitrary</p> |

	<p>'standard' populations(see below); interested readers can compare our age-specific rates with those reported in other published work. Secondly, the absolute values of standardised rates are influenced surprisingly much by the choice of 'standard' populations which is inevitably arbitrary (for an excellent demonstration of how much rates can vary depending on the choice of 'standard' populations, see Townsend et al https://academic.oup.com/eurheartj/article/36/40/2696/2293417)</p> <p>As now explained in methods and results, the choice of a standard population, largely arbitrary, made a big difference to the age-standardised case fatality, page 6,9,13.</p> <p>We now present, in Results, estimates of case fatality age-standardised to (1) the internal study population (which is what MONICA did; and, in our view, is the best approach); and (2) the European Standard Population 2013 which some others have used. We show the two alternative standardised rates alongside each other on figure 2.</p> <p>The impact of using different 'standard' populations on the absolute value of standardised rates is, perhaps, not as well understood as it should be, as the Townsend article, above, demonstrates. We have not discussed this in any detail; but we could, if you wish.</p> <p>The discussion is updated to compare case fatality in our study with the MONICA findings, with findings from a large systematic review by Feigin, and findings reported by OXVASC, page 13.</p>
<p>3. Our statistician made the following observations:</p> <p>a. The methods they used are robust, but the authors may want to distinguish proportions from rates.</p> <p>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.</p>	<p>We agree with the BMJ statistician about differences between rates and proportions. We have made changes throughout the manuscript, removing the word 'rate' after case fatality.</p> <p>In Methods section on p.5 we have also amended the definition of case fatality, which now clearly states that it is a proportion: "CF was defined as the proportion of events that were fatal within 30 days after stroke".</p> <p>We have updated the manuscript to avoid making statements and conclusions not directly supported by study findings.</p>
<p>4. Our patient editor noted:</p>	<p>We have added information about patient and public involvement on page 8: "The investigation did not conduct any interaction</p>

<p>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.</p>	<p>or intervention with individuals on whom data were obtained. Patients and the public were not involved in the design, analysis or interpretation of this study. The analysis was done on the anonymised data, and therefore we are not able to consult with or disseminate our findings to participants”.</p> <p>Dissemination of research articles is undertaken at departmental level by the Nuffield Department of Population Health (NDPH) Communications Team. They intend to work with the Communications Team to develop a news item regarding this paper that will fully reference the paper and be shared with the BMJ Press Office prior to publication. The news item will be distributed to appropriate external media, and posted on relevant websites (including those of the Department, the Oxford University Medical Sciences Division and related research group websites), and will be shared via Departmental and Divisional Twitter feeds. They will also liaise with other interested parties, such as the funders who support the study authors, to make them aware of the publication and to encourage them to share the results through their own communications channels.</p>
<p>Reviewer 1</p>	
<p>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</p>	<p>The study is a population-based study of mortality, with all stroke deaths in the country included, regardless a place of death. The decline in mortality is the starting point for the study both in terms of its rationale and its execution. To that extent, we think that the ‘population-based’ element is justified. We agree with the reviewer that by using information from inpatient records to calculate stroke event rates, we limited our population to hospitalised patients only, and miss the small proportion of those who were treated wholly outside hospital. We discussed this in a section on study limitations, p.10-11.</p> <p>We did not have access to the SSNAP dataset, but we now mention it in Discussion. However as rightly pointed out by the reviewer, SSNAP, similarly to the linked HES, only covers hospitalised stroke patients, and therefore is not superior to linked HES in this respect (i.e. it, too, does not provide a comprehensive coverage of all stroke cases treated wholly outside hospital in England). Second, SSNAP doesn’t contain information on stroke severity, which is an important limitation of our study too. If an alternative national dataset free from these two limitations existed in England, it might have been a more appropriate dataset for analysis. In our recommendations for</p>

<p>is hospital based. Can the authors discuss these point.</p>	<p>future research, we said that SSNAP data can be used to investigate the contribution of specific factors in explaining the reduction in case fatality, page 19.</p>
<p>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</p>	<p>We have revised the manuscript to remove any assumptions about the contribution of specific aspects of care, including the impact of primary care on reduction in stroke mortality.</p>
<p>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</p>	<p>We have explained in our response to the comment made by the BMJ committee, that this is a population-based study of stroke mortality. In the UK it is a legal requirement to register all deaths, therefore a linked file of electronic patient records and national vital statistics, would provide a comprehensive account of all deaths in the country.</p> <p>Regarding stroke events, people with stroke who were not admitted to a hospital and did not die, are missing from the study. While those patients who were hospitalised for other diseases or causes, and had a stroke while in the hospital, would be included in the analysis if stroke diagnosis was reported as the primary diagnosis on their hospital discharge summary.</p>

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.	
4. 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?	We reported on case fatality at 30 days, because it corresponds with the MONICA study. Exploring trends in shorter and longer case fatality is important, and has been done by others. However, it is beyond the scope of this study, which aimed to report on determinants of reduction in stroke mortality rather than to quantify fatality at different time intervals after admission.
5. 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.	To the best of our knowledge, no other studies have explored the factors influencing changes in stroke mortality rates in England. We have added a section on implications for clinicians, policymakers and researchers, page 14.
6. Reference 27 appears to be missing.	The reference was added.
7. The strengths and limitations says this is the largest study of stroke morbidity..., although unclear what morbidities are presented here?	We thank the reviewer for pointing at the unclear use of terminology, and we changed stroke morbidity to events.
Reviewer: 2	
1. 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-	We revised the manuscript to describe the limitations of using inpatient records to define stroke events, and how changes in hospital admission policies could artificially reduce case fatality rates, if more people with less severe strokes are admitted, p. 11

<p>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.</p>	
<p>2. 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?</p>	<p>We have discussed the high case fatality in the study in our response to the BMJ editorial committee comment above. As demonstrated on figure 2, the choice of a standard population for age-standardisation makes a big difference to the results. However, there is no universal approach to standardisation, and the choice of standard population is often arbitrary. When we used ESP 2013, not the internal study population, to age-standardise case fatality, our estimates changed from above 40% to around 20%, page 9. Also, the fatality rates in age-specific groups, Table 2, show that fatality rates in the younger patients (e.g. those under 65) are much lower than 40%.</p>
<p>3. 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</p>	<p>We thank the reviewer for their helpful comment about thrombolysis, we have revised discussion and removed a part where we have talked about the impact of thrombolysis on short-term mortality in young adults. We have added improved management of atrial fibrillation in a paragraph where we discuss stroke prevention on page 12.</p> <p>Due to the limitations of available data, we were not able to explore the contribution of specific predictors of survival after stroke on reduction in case fatality. However, we have listed this as a priority for future studies, and highlighted the importance of investigating the impact of the organisation of stroke care and specific interventions on the outcomes of stroke.</p>

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.	
4. 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.	We have changed the conclusion, and it now reads as following: “Our findings demonstrated that improved survival of stroke patients is driving the reduction in stroke mortality”, page 16.
5. Minor comment: ICD-10 code I62 represents subdural hematoma and is not usually included in studies of stroke.	Subdural haematoma following trauma is coded elsewhere at ICD10 S06.5, and is rightly excluded by us and by others. There were 40 709 cases of non-traumatic subdural haematoma, presumed to be (non-traumatic) stroke, coded as I62, which constitutes 4.3% of total cases of stroke in the study. We included I62 in analysis, because we wanted to make our results comparable to other studies of stroke mortality. Most epidemiological studies of stroke, including MONICA, used a range of ICD 10 codes, which included I62.