Author's response to reviews

Title: Effect of socioeconomic status on three-year mortality after first-ever ischemic stroke: Nanjing Stroke Registry

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Author's response to reviews: see over
To: BioMed Central Editorial Team

RE: MS: 1396144789100769 - Effect of socioeconomic status on three-year mortality after first-ever stroke: Nanjing Stroke Registry

Dear Editor:

Thank you for giving us the extensive review and feedback on our manuscript. We’ve made the suggested revisions and invited an editor who is a native speaker of English to edit the manuscript. These responses appear below. We hope the revised manuscript will now satisfy both the reviewer and the editors. We look forward to hearing from you.

Reviewer 1

1. The researchers restricted the study to ischemic stroke and excluded 1,394 patients with hemorrhagic strokes. An explanation for this exclusion should be offered. I am unclear why 63 percent of the 2,200 patients had hemorrhagic strokes. In the United States, hemorrhagic strokes account for only about 20 percent of all strokes.

Answer: We explain it as suggested. Because of different etiological mechanism and clinical manifestation from ischemic stroke, intracranial hemorrhage (n=563) and subarachnoid hemorrhage (n = 61) are excluded in the present study. For example, higher total cholesterol levels are associated with increased risk of ischemic stroke but are protective factors of hemorrhagic stroke. Moreover, an inverse relationship was found regarding all lipids levels across the tertiles of the SES index. Finally, it’s probable that low-SES will be regarded as protective factors of hemorrhagic stroke. Obviously, if patients with hemorrhagic stroke are included in the present study, the final results will become confusing. (See Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology. 2004; 63(10):1868-1875. / Panagiotakos DB, Pitsavos C, Manios Y, Polychronopoulos E, Chrysohou CA, Stefanadis C. Socio-economic status in relation to risk factors associated with cardiovascular disease, in healthy individuals from the ATTICA study. Eur J Cardiovasc Prev Rehabil. 2005; 12(1):68-74.)

We don’t clarify the composition of 1394 patients excluded. Actually, in the early stage of the study, CT and/or MRI scan were less available and these examinations were too expensive to be afforded by every stroke patients. So, 1394 patients should include 770 stroke patients lack of CT/MRI scan, 61 patients with subarachnoid hemorrhage and 563 patients with intracranial hemorrhage. We have added these information in the revised paper. (See Page 5, line13-23)

2. It is unclear how information on SES was obtained. On page 5, the text indicates that "a structured interview was used to assess risk factors and SES by 2 trained neurologists." But on 6 page, it is stated that information on SES was obtained by record linkage.

Answer: We correct it as suggested to: “Structured interview was used to assess risk
factors and final diagnosis of stroke was made to finish primary registration by 2 qualified neurologists based on the World Health Organization (WHO) definition [17].” (See Page 5, Line 10-12)

3. On page 5, it is stated that subjects who smoked 20 or more cigarettes per day were classified as current smokers. Does this mean that persons smoking less than 20 cigarettes per day were classified as nonsmokers? If so, the broad classification of smoking status would likely result in residual confounding. Answer: We have redefined smoking (See Page 6, Line 5-6) and recalculated hazard ratios of smoking status in Table 2.

4. Throughout the Results and Discussion section, there are many instances where "stroke mortality" is mentioned. But the principal outcome is supposed to be overall mortality, so I am unclear about this. Answer: We have corrected “stroke mortality” to “three-year mortality after first stroke” in the results and discussion section. (See Page 3, Line 13; Page 10, Line 8-9; )

5. I am unclear about the hazard ratios and how they were calculated. In 15 years of using the Cox proportional hazard model, I do not recall obtaining any hazard ratios much higher than 2.00. In this paper, there is a relative risk of 82.43 for the lowest income category. But the reference group for this variable -highest income had just two deaths. The standard errors must be very high. Answer: In order to increase the precision of the Hazard Ratios, we reclassified the patients to guarantee even distribution of deaths in every category of SES. (See Page 6, Line 15-26)

6. Table 2. Some of the hazard ratios change drastically between the unadjusted and adjusted models. For example, for myocardial infarction the hazards ratio drops from 2.74 (unadjusted model) to 0.16 (adjusted model). This would mean that subjects with a myocardial infarction would have an 84 percent lower risk of dying. In the adjusted models, there are too many variables/categories for just 166 deaths. Answer: We have reclassified the patients mentioned above. Please see the answers to Q5. After recalculated, hazard ratios remain stable between the unadjusted and adjusted models.

Minor Essential Revisions
1. In the abstract, NIHSS should be spelled out Done.
2. In the abstract, the sentence "Such a trend still persisted in some indicators of SES (e.g., occupation and income) even after controlled for." is unclear and should be reworded. Answer: The whole abstract has been reworded. (See Page 3)
3. First paragraph of Results. Information on the number of patients is repeated from page 5. Answer: We have modified the repeated information in result section. (See Page 8, Paragraph 1)
4. First paragraph of Results. The sentence, "All the participants' mean age was 71 years." was unclear and should be reworded. Answer: We have corrected it as suggested to “The mean age of the enrolled patients was 71.0±11.2 years (median 71.0 years; range 23 – 100 years.)” (See Page 8, Line
5. **Second paragraph of Results. The sentence, "The proportion of hypertension..." should be reworded.**

Answer: We corrected it to “The proportion of some cerebrovascular risk factors (e.g., hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, myocardial infarction) in death group was significantly higher than in survival group ($p<0.001$).”

(See Page 8, Line 9-12)
Reviewer 2

General; main strengths of the paper
1. This is the first study (to my knowledge and according to the authors) on socio-economic inequalities in stroke mortality in China.
   Answer: Yes, we agree with the reviewer.
2. It uses a large data registry with linkage to detailed information on the socioeconomic status of patients.
   Answer: Yes, we agree with the reviewer.

Major compulsory revisions
3. The key results of the paper are presented in table 2. This table uses only two types of regression models to estimate the association between SEP factors and stroke. While no control variables are included in the first model, the second model includes a wide array of variables that have very distinct relationships to SES and stroke. These variables include:
   a. basic demographic variables, such as age and sex, which are commonly considered as confounders in the association between SEP indicators and health outcomes;
   b. other SEP variables, which should be included only if the aim is to determine the independent effects of different components of SEP (e.g. education vs. income);
   c. behavioral variables, such as smoking and drinking, which should be included only if the aim is to determine the extent to which the association between SEP and health outcomes can be attributed to inequalities in these health behaviors;
   d. physiological variables and disease parameters, which should be included only if the aim is to determine whether there are variations according to SEP in the disease processes leading to stroke death.
   Thus, it would be highly informative if (but only if!) multivariate modeling is done in a step-wise way, adding to each subsequent model a set of different type of variables. The basic model should include age and sex only. I strongly recommend the authors to follow this step-wise approach.
   Answer: We have modified our regression models as suggested. First of all, we include age and sex in the first model. Second, we added smoking, an important behavior variable closely associated with stroke prognosis. Finally, all factors (including age, sex, smoking, hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation, myocardial infarction, prior TIA and NIHSS) were considered.

4. The authors recognize that this hospital-based study excludes persons who my have had stroke but did not reach the hospital, either because they died before reaching the hospital, or before the stroke incident was too mild for the patient. The authors fail to discuss whether this selection bias strongly differs according to socioeconomic position. If persons from lower classes would be admitted to hospitals only if they have relatively severe forms of stroke, this may artificially increase estimates of socio-economic differences in stroke mortality. The authors should discuss this possibility of differential selection bias and its potential effects on their inequality estimates. Might this explain why the inequalities in survival are exceptionally large?
   Answer: Most possible stroke patients were readily identified by their family,
healthcare workers or doctors in community hospitals. Actually, people from lower SES are more likely to see the doctor in hospitals because 3-level medical care system has been established in China (including rural areas). And because medication and examinations were charged the same in hospitals in Nanjing in accordance with regulations issued by authorities concerned, stroke patients could choose the hospital where they wanted to go. Hazard ratios had decreased to a reasonable extent after Stepwise Cox proportional models were modified.

5. In the methods section, the authors describe a regression model with a restricted set of variables. Results according to this model are however not given in table 2 or in the text of the Results section. In any case, I recommend the alternative approach given under point 3.

Answer: We have changed it as suggested. Please see the answers to Q3.

6. The discussion section is difficult to follow on page 10 above, and especially page 11 above/mid. I suggest to shorten the summary on page 10 (and focus on SEP differences) and to replace the two paragraphs on page 11 with new paragraphs that aim to forward possible explanations of the large inequalities in stroke that are observed in this study. What is the possible role of health care? See also my comment 4 on the role of possible artifacts.

Answer: We have revised the paper as suggested. The summary on page 10 is shortened. “The effect of SES on risk of stroke and mortality was an important public issue and had been discussed in the world literature. To the best of our knowledge, the present study was the first detailed assessment undertaken in China. Because the development of economy and education was unbalanced in different part of China, area-level measures couldn’t reflect individuals’ real socioeconomic status. Individual-level measures of SES were chosen in this study. The univariate comparisons showed that in patients of first stroke, the proportion of cerebrovascular risk factors (except smoking status and history of TIA) in death group was significantly greater than in survival group. Stepwise Cox proportional hazards models showed SES (except educational level) significantly correlated with three-year mortality after stroke in the present study.” (See Page 10, Line 2-11)
And we have replaced the two paragraphs on page 11 with new paragraphs. (See Page 11)

Minor essential revisions
7. The language needs improvement at various places.

Answer: Done.

Major discretionary revisions
8. The study is restricted to the 1/3 of stroke cases in the Nanjing Registry due to cerebral infarction. The 2/3 of cases with cerebral hemorrhage is excluded. While this distinction may be logic from a neurological or etiological perspective, from a public health perspective this restriction is a regrettable loss of information. The authors should consider including all stroke cases, in order to present of more comprehensive picture of inequalities in stroke survival in China. One more table may be added.

Answer: We explain it as suggested. Because of different etiological mechanism and clinical manifestation from ischemic stroke, intracranial hemorrhage (n=563) and subarachnoid hemorrhage (n = 61) were excluded in the present study. For
example, higher total cholesterol levels are associated with increased risk of ischemic stroke but are protective factors of hemorrhagic stroke. Moreover, an inverse relationship was found regarding all lipids levels across the tertiles of the SES index. Finally, it’s probable that low-SES will be regarded as protective factors of hemorrhagic stroke. Obviously, if patients with hemorrhagic stroke are included in the present study, the final results will become confusing. (See Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology. 2004; 63(10):1868-1875. / Panagiotakos DB, Pitsavos C, Manios Y, Polychronopoulos E, Chrysohoou CA, Stefanadis C. Socio-economic status in relation to risk factors associated with cardiovascular disease, in healthy individuals from the ATTICA study. Eur J Cardiovasc Prev Rehabil. 2005; 12(1):68-74.)

9. **I recommend combining the two upper educational levels, in order to increase the precision of the Hazard Ratios for this variable. Note that the upper educational level (postgraduate degree) contains only 48 patients and seems to have a deviant level of stroke survival.**

Answer: Done.
Reviewer 3
General
The study investigates the association between SES and mortality after ischemic stroke. The study covers an important topic and is undertaken in a country with a different developmental history than modern western populations. It is rather clearly written and of potential interest to an international audience. However, there are several points for discussion and weaknesses with the study which should be made more clearly.
Answer: Yes, we agree with the reviewer.
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The first comments have to do with selection bias. The population of the study is those hospitalized at Jinling Hospital, Nanjing. However, the authors do not make clear if there are also more hospitals in the area where the study population came from that handles stroke events. If so - are there different taxes in different hospitals, i.e., where the richer people seek some hospitals and the poor people other hospitals?
Answer: In traditional Chinese society, the elderly were taken care of by their offspring in China. Most possible stroke patients were readily identified by their family, healthcare workers or doctors in community hospitals. Because medication and examinations were charged the same in hospitals in Nanjing in accordance with regulations issued by authorities concerned, stroke patients could choose the hospital where they wanted to go.

Do people from lower SES more often seek local traditional doctors than seeking hospitals? If so â€“ how would this affect the results? This would also be a problem with regard to deciding if this is the first-ever stroke or if a patient has been to other hospitals or doctors before â€“ not registered at the Jinling Hospital?
Answer: Actually, people from lower SES are more likely to see the doctor in hospitals because 3-level medical care system has been established in China (including rural areas). Only some patients may seek local traditional doctors. So, it hardly threatens the results. In addition, systematic investigations were performed on every stroke patients in our study. All patients with previous cerebral infarction or hemorrhage were excluded. All available information on every patient was weekly rechecked by expert committee (composed of neurologists and epidemiologists). (See Page 5, paragraph 1; Page 11, Line 25-29).

What about those in the area who die due to a stroke at home (probably most often lower SES groups) â€“ are they taken to Jinling Hospital, Nanjing for an autopsy?
Answer: Unlike western countries, there was a low autopsy rate for some stroke patients who died at home because of cultural constraints.

The authors state that â€œa considerable amount of stroke patients in rural areas were misdiagnosed and couldnÂ´t be treated by local traditional doctors. couldnÂ´t have been enrolled in our registry. These patients couldnÂ´t have been enrolled in our registryâ€”â€œ What is a considerable amount? How might this affect the results?
Answer: Because our study is hospital-based, we are regretsful not to clarify the precise number of these stroke patients. But according to what we mentioned above, people from lower SES are more likely to see the doctor in hospitals because 3-level medical care
system has been established in China (including rural areas). So, it hardly threatens the final result.

2. The authors look at mortality after a first stroke event. What was the proportion lower SES and higher SES at baseline?
Answer: The proportion of lower SES to higher SES was 1.02 at baseline. (See page 8, Line 5-6)

3. The authors have not looked at different time periods with regard to mortality which is often done in these kind of studies, i.e., look at 28-days mortality and more long-term mortality for example after 28 days but within 3 years. The mechanisms behind the deaths are probably different where factors such as co-morbidity and the size of the stroke is of more importance for short-term mortality, while risk factor levels such as for example blood pressure levels are of more importance with regard to long-term mortality. It would be interesting to also see the results based on this categorization.
Answer: We have explained it in page 4, para 2, line 3-4: previous studies indicated most patients were likely to die in the first year after stroke events, and the mortality would remain stable after that [15, 16].

4. Why have the authors chosen to only investigate ischemic strokes and not hemorrhagic strokes, this should be explained in the background section together with other issues mentioned below. I think the Background section is too short as it stands and the references are not in order.
Answer: We explain it as suggested. Because of different etiological mechanism and clinical manifestation from ischemic stroke, intracranial hemorrhage (n=563) and subarachnoid hemorrhage (n = 61) are excluded in the present study. For example, higher total cholesterol levels are associated with increased risk of ischemic stroke but are protective factors of hemorrhagic stroke. Moreover, an inverse relationship was found regarding all lipids levels across the tertiles of the SES index. Finally, it’s probable that low-SES will be regarded as protective factors of hemorrhagic stroke. Obviously, if patients with hemorrhagic stroke are included in the present study, the final results will be confusing. (See Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM. Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology. 2004 Nov 23;63(10):1868-75. / Panagiotakos DB, Pitsavos C, Manios Y, Polychronopoulos E, Chrysohoou CA, Stefanadis C. Socio-economic status in relation to risk factors associated with cardiovascular disease, in healthy individuals from the ATTICA study. Eur J Cardiovasc Prev Rehabil. 2005; 12(1):68-74.) We modified background section as suggested.

5. Blood pressure should be added as a continuous variable and not dichotomized. If possible treatment for hypertension and also BMI should be added as confounders.
Answer: As for blood pressure, we have corrected it as suggested. But because of lack of detailed information about possible treatment for hypertension and BMI in Nanjing Stroke Registry, we are regretful not to add these variables in the present study. (See Page 16, Table 1)

6. The section of potential mechanisms on p.11, last paragraph should be rewritten
and more extensively discuss this issue.

Answer: We have modified it as suggested. (See Page 10, Line 26-31; Page 11, Line 1-13)

7. The study population represents a hospital-based stroke population and not the general population as claimed on p.11 “last paragraph. This should be stated in the Discussion section.

Answer: We modified it as suggested. And we claimed the study population represents a hospital-based stroke population in the discussion section. (See Page 11, paragraph 2, Line 4)

8. How come that the association between educational level and income on the one hand and stroke mortality on the other not only diminishes after adjustment for confounders, but changes direction “do the authors have any comments on that? This should be commented on in the abstract, discussion and conclusions.

Answer: We have modified it as suggested. Firstly, we now used stepwise regression model. According to the new results, the hazards ratios for educational level fail to reach statistical significance in univariate and multivariate models. And we explain it in discussion section. “Education may be a marker of material and psychosocial conditions in adulthood including diet, and stress, and adult receptivity to health-promotion messages and use of preventive care [21]. But owing to its cultural specificity, a week association between education and mortality was observed in this study.” (See page 10, paragraph 3)

9. The manuscript should be sent for linguistic revision as there are missing words and words that are misspelt throughout the manuscript.

Answer: Done.

10. In the background section the authors should justify what their study would add to the studies already done on the association between SES and mortality after a stroke “Are there reasons to believe that the associations between SES and stroke mortality would be different in a Chinese population than in a western population? Would the mechanisms be different?”

Answer: We have modified it as suggested. (See page 4, paragraph 1,2)

11. Why was the cut-off level for fasting blood glucose as high as 7.0 mmol/L?

Answer: According to diagnosis criteria issued by WHO, the diagnostic fasting plasma (blood) glucose value has been lowered to > or =7.0 mmol/L. (See Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998; 15(7):539-53.)

12. Please clarify the sentence on p.10, 1st paragraph starting with “And correlation”

Answer: We have reworded page 10, paragraph 1 as suggested.

13. Please clarify the sentence starting with Population-based Sino-MONICA on p.11 last paragraph. Also in the next sentence, which demographic characteristics are the authors referring to?
**Answer:** We have reworded it as suggested to “Population-based Sino-MONICA project [4] in China showed mortality rate of stroke was high by international standards, with higher rates in the north and lower rates in the south.” (See Page 11, Paragraph 2, Line 2-4)

14. **In the conclusion the authors state that after economic reforms there has been a great development in China with regard to GNP, income and so on. I think this should be mentioned also earlier in the Discussion section and shortly in the Background to set some of the background for the study.**

**Answer:** We have modified it as suggested. (See Page 4, Paragraph 2)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

15. **In the abstract the last sentence in the result section “there must be words missing” I don’t understand this sentence.**

**Answer:** We have reworded the result section of the abstract. (See Page 3)

16. **The HRR seems very high with regard to the lowest vs the highest income level could this be due to the fact that there were only 2 deaths in the highest income category?**

**Answer:** In order to ensure precision of the hazards ratios, we combined the last two categories of income level. (See Page 6, Line 15-26)

17. **In table 1 there were no cases of mortality after a stroke event among farmers, however, in table 2, the hazard ratio compared to non-manuals was 5.23?**

**Answer:** We have redesigned stepwise regression mentioned above. (See Page 16, Table 1; Page 17, Table 2; Page 18, Table 3)

18. **In table 1 in the foot notes not should be added after if.**

**Answer:** Done.
Reviewer 4

This is a study evaluating the association between socioeconomic status (SES) and 3-year mortality after stroke in China. The results will be of interest to researchers in this area.

Answer: Yes, we agree with the reviewer.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The analysis is based on data from a hospital-based stroke registry linked with information on SES. It would be helpful to have information on the quality of the data sources. Is there likely to be any misclassification bias?

   Answer: We have explained it as suggested. (See Page 5, Paragraph 1).

2. In the multivariable analysis, only some of the measures of SES were correlated with outcome. The authors should discuss why there might be a discrepancy in the findings based on the measure of SES.

   Answer: We have explained it as suggested. (See Page 10, Paragraph 3)

3. Additional discussion around potential explanations for the association between SES and stroke outcomes, particularly in the Chinese setting, would be welcome. It would also help to know more about the usual delivery of stroke care in China, and potential barriers based on SES.

   Answer: We have discussed it as suggested. (See page 10, paragraph 3; page 11, paragraph 2)

4. The stroke registry was consent-based, which may have led to selection biases. Can the authors provide additional information on how the registry patients compared with typical stroke patients in their area?

   Answer: We have modified it as suggested. In traditional Chinese society, the elderly were taken cared by their offspring in China. Almost all possible stroke patients were readily identified by their family, healthcare workers or doctors in community hospitals. Because medication and examinations were charged the same in hospitals in Nanjing in accordance with regulations issued by authorities concerned, stroke patients could choose the hospital where they wanted to go. Other stroke patients with less severe or silent stroke weren’t hospitalized. In addition, a considerable amount of stroke patients in rural areas were misdiagnosed and couldn’t be treated properly by local traditional doctors. Unlike western countries, there was a low autopsy rate for some stroke patients who died at home because of cultural constraints. These patients mightn’t have been enrolled in our registry, which may finally lead to selection bias.

5. The authors used individual-level measures of SES. A comment on the relative merits of individual vs. area-level SES measures (particularly in China) would be helpful.

   Answer: We explained it as suggested. “Because the development of economy and education was unbalanced in different part of China, area-level measures couldn’t reflect individuals’ real socioeconomic status. Individual-level measures of SES were chosen in this study.” (See Page 10, Line 3-5)