

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Interaction of diabetes and smoking on stroke: A population-based cross-sectional survey in China
<b>AUTHORS</b>	Lou, Heqing; Dong, Zongmei; Zhang, Pan; Shao, Xiaoping; Li, Ting; Zhao, Chunyan; Zhang, Xunbao; Lou, Peian

### VERSION 1 – REVIEW

<b>REVIEWER</b>	David Nathanson Department of Clinical science and education, Karolinska institutet, Södersjukhuset Sweden.
<b>REVIEW RETURNED</b>	08-Jun-2017

<b>GENERAL COMMENTS</b>	<p>Referee: 1 Comments to the author</p> <p>This is a cross-sectional survey that evaluates the interaction of type 2 diabetes and smoking on stroke in Chinese adults. The article is well-written and the statistical methods used are appropriate and fits well with the type of data and the scientific questions. However, the novelty of the conclusion yielded from the study (eg that subjects with diabetes who smoke are more likely to develop stroke than non-diabetics who do not smoke) is limited.</p> <p>Major comments</p> <ol style="list-style-type: none"><li>1. The authors have used a definition of stroke that includes both ischemic and haemorrhagic stroke. As smoking and diabetes have a different impact as risk factors for ischemic versus haemorrhagic it is of importance to make a distinction between ischemic stroke and haemorrhagic stroke. Please; if possible, show OR's for stroke divided in ischemic and haemorrhagic stroke.</li><li>2. In most studies evaluating smoking as a risk factor for stroke cigarette smokers are usually defined as current, former and never smokers. The definition of cigarette "smoking" in the present study does not distinguish between current or former smokers which may have implication for "smoking" in this study as a risk factor. This should be addressed and discussed in the discussion section.</li><li>3. The authors states that the present study is a population based study. If so the results must be generalizable to the whole population and therefore the selection of participants in the study must be representative for the entire population. ("Study design and recruitment criterias"): How were the five subdistricts in urban/rural areas selected? Please clarify the criterias for this selection.</li></ol> <p>Minor comments</p>
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	<ol style="list-style-type: none"> <li>1. In fact, there are a few studies assessing the additional effects of smoking on diabetes according to the risk of stroke. Please cite the study by Papademitrou et al (1998 Oct;136(4 Pt 1):734-40), which shows similar results (compared to your study) according to the additional risk of diabetes and smoking on the prevalence of stroke.</li> <li>2. In the section where limitations of the study are described (p. 15) there should be a discussion about the risk of misclassification and recall bias with the current definition of smoking.</li> <li>3. Table 1&amp;2: Please presents the proportions (%).</li> <li>4. Table 2&amp;3: Please add the unadjusted OR's.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

#### Editorial Requests:

The 'strengths and limitations' needs to be re-written. The first three points are not strengths or limitations of your study. As a reminder, this section should contain up to five short bullet points, no longer than one sentence each, that relate specifically to the methods or design of the study reported (see: <http://bmjopen.bmj.com/site/about/guidelines.xhtml#articletypes>).

Response: It had been revised as follow:

- The strengths of this study were that participants of a large sample were randomly selected from the general population of Xuzhou, and many confounding risk factors were adjusted for.
- Owing to the cross-sectional design, we could not determine a causal combined relationship between diabetes, smoking and stroke.
  - We were not able to control for some important and well-known risk factors of diabetes—for example, heart rate and cardiac causes..
- We did not measure fresh fruit consumption, which is causally related to stroke.

Please see the text.

- The quality of English still needs improving in places. We strongly recommend consulting a native English speaker or professional copy-editing service if possible.

Response: It had been done, please see the certificate.

- Please try to work further on improving the rationale for carrying out this study in the introduction section. It still could be clearer why you have decided to focus on the interaction of diabetes and smoking on stroke.

Response: It had been revised as: People with comorbid diabetes and smoking might represent a subgroup with high risk of developing stroke. However, there are a few studies on the interaction of diabetes and smoking on stroke. Please see the text.

- Please provide the proofs for ethical approval as a supplementary file for editors only. Your current ethics statement says that the institution approved your protocol, but it is not clear that it was reviewed by an ethics committee. Please can you revise your ethics statement in the manuscript to make this clearer?

Response: It had been revised as: The study protocol was approved by Xuzhou Center for Disease Control and Prevention. The procedures followed were in accordance with the standards of the ethics committee of Xuzhou Center for Disease Control and Prevention and with the Declaration of Helsinki (1975, revised 2000). Written informed consent was obtained from all participants. Please see the text.

Reviewer: 1

Reviewer Name: David Nathanson

Institution and Country: Department of Clinical science and education, Karolinska institutet, Södersjukhuset Sweden.

Comments to the author

This is a cross-sectional survey that evaluates the interaction of type 2 diabetes and smoking on stroke in Chinese adults. The article is well-written and the statistical methods used are appropriate and fits well with the type of data and the scientific questions. However, the novelty of the conclusion yielded from the study (eg that subjects with diabetes who smoke are more likely to develop stroke than non-diabetics who do not smoke) is limited.

#### Major comments

1. The authors have used a definition of stroke that includes both ischemic and haemorrhagic stroke. As smoking and diabetes have a different impact as risk factors for ischemic versus haemorrhagic it is of importance to make a distinction between ischemic stroke and haemorrhagic stroke. Please, if possible, show OR's for stroke divided in ischemic and haemorrhagic stroke.

Response: The risk of ischemic and haemorrhagic stroke were also increased by DM2, the OR's were 2.71( 95% CI: 1.72–4.49) and 1.82(95% CI: 1.34–3.35), respectively, after adjusting for confounders. The risk of ischemic and haemorrhagic stroke were all increased by smoking after adjusting for confounders, the OR's were 1.32( 95% CI: 1.12–2.53) and 1.95(95% CI: 1.40–3.41), respectively. It had been added in the result, please see the text.

2. In most studies evaluating smoking as a risk factor for stroke cigarette smokers are usually defined as current, former and never smokers. The definition of cigarette "smoking" in the present study does not distinguish between current or former smokers which may have implication for "smoking" in this study as a risk factor. This should be addressed and discussed in the discussion section.

Response: However, the present study only wanted to observe the interaction of smoking and diabetes on stroke, the cigarette smokers were not categorized as current, former and never smokers. Therefore, when compared our results with others should be carefully. This paragraph had been added in discussion.

3. The authors states that the present study is a population based study. If so the results must be generalizable to the whole population and therefore the selection of participants in the study must be representative for the entire population. ("Study design and recruitment criterias"): How were the five subdistricts in urban/rural areas selected? Please clarify the criterias for this selection.

Response: The sampling method had been revised as "two-stage" probability proportional to size. In the first stage, five subdistricts/townships in urban/rural areas were selected from each region "with probability proportional to size sampling". In the second stage, five communities/villages were selected from each subdistrict/township "with probability proportional to size sampling". Please see the text.

#### Minor comments

1. In fact, there are a few studies assessing the additional effects of smoking on diabetes according to the risk of stroke. Please cite the study by Papademitrou et al (1998 Oct;136(4 Pt 1):734-40), which shows similar results (compared to your study) according to the additional risk of diabetes and smoking on the prevalence of stroke.

Response: Papademetriou and colleagues reported that comparison with nonsmoking patients with no diabetes mellitus or hypertension, patients with diabetes mellitus and hypertension and smoking had a 3-fold increase in the prevalence of peripheral vascular disease and a 3.5-fold increase in cerebrovascular disease. This evidence is strengthened by our results. This paragraph had been added in discussion.

2. In the section where limitations of the study are described (p. 15) there should be a discussion about the risk of misclassification and recall bias with the current definition of smoking.

Response: Fourth, the number of cigarettes smoking was recalled by participants, therefore, therefore, the risk of misclassification and recall bias with the definition of smoking could not be avoid. The sentence had been added in the section of limitations.

3. Table 1&2: Please presents the proportions (%).

Response: it had been done, please see the Table 1&2.

4. Table 2&3: Please add the unadjusted OR's.

Response: it had been done, please see the Table 2&3.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the all changes but marked in red in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

### VERSION 2 – REVIEW

<b>REVIEWER</b>	David Nathanson Department of Clinical science and education, Karolinska institutet, Södersjukhuset Sweden.
<b>REVIEW RETURNED</b>	06-Dec-2017

<b>GENERAL COMMENTS</b>	<p>This is a cross-sectional survey that evaluates the interaction of type 2 diabetes and smoking on stroke</p> <p>in Chinese adults. The article is well-written and the statistical methods used are appropriate and fits</p> <p>well with the type of data and the scientific questions. However, the novelty of the conclusion yielded</p> <p>from the study (eg that subjects with diabetes who smoke are more likely to develop stroke than non-</p> <p>diabetics who do not smoke) is limited.</p> <p>Major comments</p> <p>1.The authors have used a definition of stroke that includes both ischemic and haemorrhagic stroke. As</p> <p>smoking and diabetes have a different impact as risk factors for ischemic versus haemorrhagic it is of</p> <p>importance to make a distinction between ischemic stroke and haemorrhagic stroke. Please; if possible,</p> <p>show OR's for stroke divided in ischemic and haemorrhagic stroke.</p> <p>Response: The risk of ischemic and haemorrhagic stroke were also increased by DM2, the OR's were</p> <p>2.71( 95% CI: 1.72–4.49) and 1.82(95% CI: 1.34–3.35),respectively, after adjusting for confounders.</p> <p>The risk of ischemic and haemorrhagic stroke were all increased by smoking after adjusting for</p> <p>confounders, the OR's were 1.32( 95% CI: 1.12–2.53) and 1.95(95% CI: 1.40–3.41),respectively.</p>
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It had been added in the result, please see the text.

Comment to response: Thanks for adding these interesting results!

2. In most studies evaluating smoking as a risk factor for stroke cigarette smokers are usually defined as

current, former and never smokers. The definition of cigarette “smoking” in the present study does not

distinguish between current or former smokers which may have implication for “smoking” in this study

as a risk factor. This should be addressed and discussed in the discussion section.

Response: However, the present study only wanted to observe the interaction of smoking and diabetes

on stroke, the cigarette smokers were not categorized as current, former and never smokers. Therefore,

when compared our results with others should be carefully. This paragraph had been added in

discussion.

Comment to response: Now better, however the inserted sentence (p 14, line 7) seems to be unfinished.

Please clarify.

3. The authors states that the present study is a population based study. If so the results must be

generalizable to the whole population and therefore the selection of participants in the study must be

representative for the entire population. (“Study design and recruitment criterias”): How were the five

subdistricts in urban/rural areas selected? Please clarify the criterias for this selection.

Response: The sampling method had been revised as “two-stage” probability proportional to size. In the

first stage, five subdistricts/townships in urban/rural areas were selected from each region “with

probability proportional to size sampling”. In the second stage, five communities/villages were selected

from each subdistrict/township “with probability proportional to size sampling”. Please see the text.

Comment to response: Ok, but it is not clear how the selection was

made. Please clarify the method of selection further so it can be understood and repeated. Is your method robust per the risk of selection bias? - If not - discuss this matter in the section "limitations of the study".

Minor comments

1. In fact, there are a few studies assessing the additional effects of smoking on diabetes according to

the risk of stroke. Please cite the study by Papademitrou et al (1998 Oct;136(4 Pt 1):734-40), which

shows similar results (compared to your study) according to the additional risk of diabetes and smoking

on the prevalence of stroke.

Response: Papademetriou and colleagues reported that comparison with nonsmoking patients with no

diabetes mellitus or hypertension, patients with diabetes mellitus and hypertension and smoking had a

3-fold increase in the prevalence of peripheral vascular disease and a 3.5-fold increase in

cerebrovascular disease. This evidence is strengthened by our results. This paragraph had been added in

discussion.

Comment to response: OK.

2. In the section where limitations of the study are described (p. 15) there should be a discussion about

the risk of misclassification and recall bias with the current definition of smoking.

Response: Fourth, the number of cigarettes smoking was recalled by participants, therefore, therefore,

the risk of misclassification and recall bias with the definition of smoking could not be avoid. The

sentence had been added in the section of limitations.

Comment to response: OK.

3. Table 1&2: Please presents the proportions (%).

	<p>Response: it had been done, please see the Table 1&amp;2.</p> <p>Comment to response:OK.</p> <p>4. Table 2&amp;3: Please add the unadjusted OR's.</p> <p>Response: it had been done, please see the Table 2&amp;3.</p> <p>Comment to response:OK.</p> <p>We tried our best to improve the manuscript and made some changes</p> <p>in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the all changes but marked in red in revised paper.</p> <p>We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.</p> <p>Once again, thank you very much for your comments and suggestions.</p> <p>Comment to response: Thanks for an improved manuscript!</p>
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### **VERSION 2 – AUTHOR RESPONSE**

1..It had been revised in method as : In the first stage, five subdistricts/townships in urban/rural areas were selected "according to the population of each subdistrict/township" from each region with probability proportional to size sampling. In the second stage, five communities/villages were selected "according to the population of each community/village" from each subdistrict/township with probability proportional to size sampling....., please see thre text.

2. the sentence had been revised as :when compared "the association between smoking and stroke of our study" with "that of "others should be carefully. Please see the text.