

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: the Kongcun Town Asymptomatic Intracranial Artery Stenosis Study in Shandong, China
AUTHORS	Wang, Xiang; Zhao, Yuanyuan; Ji, Xiaokang; Sang, Shaowei; Shao, Sai; Yan, Peng; Li, Shan; Li, JiFeng; Wang, Guangbin; Lu, Ming; Du, YiFeng; Xue, Fuzhong; Qiu, Chengxuan; Sun, QinJian

VERSION 1 - REVIEW

REVIEWER	Makoto Shiraishi St, Marianna University School of Medicine, Japan
REVIEW RETURNED	11-Jan-2020

GENERAL COMMENTS	<p>The value of this paper is high, the following points are unclear. Therefore, we want this manuscript to be revised.</p> <ol style="list-style-type: none">1. You should indicate a comparison between the cognitive function evaluation and the blood vessel image that can be shown at this time.2. You should clarify the relationship between traditional risk factor and intra- and extracranial stenosis in this study.3. You should discuss that men have a higher smoking rate than women but no difference in vascular stenosis rates.4. Not only vascular stenosis by 3T MRI image but also plaque image should be described in some more detail.5. You should clearly present the grade of flow velocity by TCD and the stenosis by carotid ultrasonography and clarify what extracranial lesions is consistent with that in MRA.
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REVIEWER	Dimitre Staykov Hospital of the Brothers of St. John Eisenstadt, Austria
REVIEW RETURNED	06-Feb-2020

GENERAL COMMENTS	<p>The authors outline a prospective cohort project and have submitted it as a "cohort profile" article. The aim of the current study is to investigate the occurrence of intracranial artery stenosis in a rural region of China and to investigate associated risk factors and also provide long-term follow-up.</p>
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	<p>The study is well outlined. I have several rather minor comments:</p> <ol style="list-style-type: none"> 1. Participants section page 9 row 17: BMI was calculated ... - the calculation should be kilograms divided by height (meters) squared 2. Page 11 row 12: Blood count cannot be measured from serum samples please rephrase to avoid confusion 3. Findings to date page 14 row 45: replace "demonstrate" with "test" because the study has not been completed yet 4. Same page row 59: correct to "less likely to be single" 5. Please report numbers on how many patients did not have sufficient ultrasonic bone window in the present cohort 6. Page 6 row 30: replace "initiate" with "initiated"
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REVIEWER	<p>Arturo Consoli Diagnostic and Interventional Neuroradiologi Department Foch Hospital Suresnes France</p>
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	<p>Authors presented a population-based study focused on the investigation of the prevalence of asymptomatic intracranial artery stenosis and of the associated cardiovascular risk factors in a rural population in the Shandong Province in China.</p> <p>Authors should be lauded for their efforts. The community of Kongcun Town will surely benefit from this study. The Abstract and all the other sections are well written and clearly understandable.</p> <p>The "weak parts" are represented by the fact that only one rural area is included in the study and by the use of the TCD as screening tool, as it has correctly reported by the Authors.</p> <p>The Result section is relatively limited and more details could have been provided, moreover regarding cardiovascular risk factors, and including not only a sex-based distribution but also an age-based analysis.</p> <p>Do Authors plan to report separately the results about MR findings and neuropsychological tests? In that case, this could be specified in the methodology.</p>
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REVIEWER	<p>S D S Ramos The Disabilities Trust, UK</p>
REVIEW RETURNED	16-Feb-2020

GENERAL COMMENTS	<p>In my view, the main limitation of this paper, is that it does not report the results of the neuropsychological assessments, as it is nevertheless implied in the abstract and study design sections. These results must be included in the paper, or otherwise it must be explicitly stated in the present manuscript that they will be reported in a separate paper. Further comments and a list of minor</p>
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amendments are provided in the attached document.

MS Review for BMJ Open

MS ID: bmjopen-2019-036454

TITLE: "Cohort profile: the Kongcun Town Asymptomatic Intracranial Artery Stenosis Study in China"

AUTHORS: Wang, Xiang ; Zhao, Yuanyuan; Ji, Xiaokang; Sang, Shaowei; Shao, Sai; Yan, Peng; Li, Shan; Li, Ji Feng; Wang, Guangbin; Lu, Ming; Du, Yi Feng; Xue, Fuzhong; Qiu, Chengxuan; and Sun, QinJian

Comments to the authors

This article is clear and easy to follow, and details the initial results of a large and detailed population study on asymptomatic intracranial artery stenosis (ICAS). Such results are important to understand the risk factors, impact and course of the condition, and have potential implications for health policy and service provision, as well as public health education.

There are a few points that need expansion and clarification before the paper can be recommended for publication:

1. It would be useful if the authors could describe in more detail the criteria that distinguish asymptomatic from symptomatic ICAS, particularly given that one of the inclusion criteria to take part in the study was being "free of history of stroke" (p. 7).
2. The authors should expand on the characteristics of Asian populations that make them particularly at risk for this condition. What can we, more generally, learn about ICAS by studying Asian populations?
3. On page 7 (ln. 28-46), the authors refer to health promotion work developed by the School of Public Health at Shandong University and the town government and local health professionals. The authors should comment on the extent to which these initiatives could have led to a more healthy cohort in Kongcun compared to cohorts from other parts of China and the rest of the World.
4. Please provide more detail about the procedure. In particular, clarify how many testing sessions were required to complete the full assessment, and whether or not participation required an overnight stay in hospital.
5. The abstract and the "Phase 2" section of the study design imply that the present manuscript reports the results of neuropsychological assessments. It is not until the results section that it becomes apparent that only a portion of the results of all the assessments conducted during Phase 2 are included in this manuscript, and that it does not cover the neuropsychological assessments. The paper should be revised to either include these results, or to explicitly state in the abstract, study design and / or results section that neuropsychological assessment results will be reported in a separate paper.
6. Some of the results regarding sex differences are statistically significant, but the effect sizes appear to be small (e. g. differences in Total cholesterol, BMI, etc.). Some of the charts in figure 2 appear to suggest that these differences only become apparent for groups of a certain age. To what extent could the differences be due to the underlying differences in age found between the male and female cohorts?
7. The overall results suggest that the prevalence of ICAS increases with age, however, men and women seem to show a different pattern. Please comment on the possible interaction between age and sex on ICAS prevalence.
8. The results suggest that although women have a healthier lifestyle (less likely to smoke and to consume alcohol), they also have poorer

	<p>health outcomes (more likely to be obese, have diabetes and hyperlipidemia). Please comment on the possible reasons and implications of these findings.</p> <p>Minor amendments</p> <p>p. 3, ln. 40-41 and throughout the manuscript – Replace “subjects” with “participants”, “individuals” or “patients”.</p> <p>p. 3, ln. 44-45 – Add percentage in brackets after “2027”.</p> <p>p. 8, ln. 12 – Add comma after “previously”.</p> <p>p. 8, ln. 20 – Delete the word “briefly”.</p> <p>p. 8, ln. 40-41 – Add “a” in the sentence “... all participants underwent a structured questionnaire...”.</p> <p>p. 8, ln. 45-50 – Add citations for all the standardised measures used.</p> <p>p. 9, ln. 14-18 – Delete the calculation of BMI, as this is general knowledge, particularly for the target readers.</p> <p>p. 11, ln. 17 – Replace “5” with “five”.</p> <p>p. 11, ln. 40-46 – Edit the sentence to read: “From April to October 2018, participants who screened positive, and a group of age- and sex-matched controls who had screened negative for ICAS by TCD in Phase 1, underwent the Phase 2 assessment...”</p> <p>p. 12, ln. 35-36 – Replace “affection” with “mood”.</p> <p>p. 12, ln. 51 – Replace “AVLT” with “RAVLT”.</p> <p>p. 14, ln 25-28 – Edit the sentence to read: “... participants would benefit from participating in this project because healthcare advice was provided...”</p> <p>p. 14, ln. 33-36 – Move sentence “All participant-related information was de-identified from the database to preserve privacy.” to the section describing ethics and informed consent.</p> <p>p. 14, ln. 54-56 – Delete the sentence “The mean age of the 2311 participants was 57.6 years, and 53.4% were women.”, as this is already reported on table 1.</p> <p>p. 14, ln. 57-60 – Edit the sentence to read: “Compared to men, women were older, less educated, less likely to be single, and had higher levels of total cholesterol...”</p> <p>p. 23, Table 1 – ln. 19 – Replace “states” with “status”.</p> <p>p. 23, Table 1 – ln. 22 – Delete the word “status” after “single”.</p> <p>p. 23, Table 1 footnote – The use of SD as an abbreviation for standard deviation is standard, so this can be deleted from the table caption. Edit footnote a) to read: “P values are for the test of differences between male and female.” Edit footnote b) to read: “The number of participants with missing values were one for marriage states...”. In the manuscript, comment on whether or not corrections for multiple comparisons were used (e.g. Bonferroni).</p> <p>p. 26, Figure 1 – Replace the word “test” with “assessment” in the boxes starting with “153”. Replace the word “subjects” with more appropriate terminology (e. g. “participants”). Make consistent use of capital letters (e. g. “Cognitive impairment”). Replace “Ischaemia” with “Ischaemic”.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. You should indicate a comparison between the cognitive function evaluation and the blood vessel image that can be shown at this time.

Response: We fully understood the reviewer’s comments and suggestions. We did not report cognitive data because this paper was for “cohort profile” of the journal. In this paper, we aimed to describe the establishment of the study cohort, baseline assessments, some findings from this cohort,

and future plan. However, we agree with the reviewer that cognitive data may be relevant to report because cognitive assessments are relevant part of our study. Thus, we have now added data on global cognitive assessments (MoCA and MMSE) to Table 1. Of note, cognitive tests were performed in KT-aICAS for participants who were diagnosed with aICAS (n = 154) and the matched controls (n = 153). In addition, we notice that the reviewer suggested to report detailed results on different issues in the next comment (No. 2). We suspected that one reason that might have confused the reviewer was that we stated the aims of KT-aICAS in the last paragraph of the "Introduction" section, instead of the aims of this specific "cohort profile" paper (we apologize for this confusion). To avoid such a possible confusion, we have now stated the aims of this paper, and moved the aims of KT-aICAS to "Cohort description" (see page 6, lines 17-22; page 7, lines 1-14).

2. You should clarify the relationship between traditional risk factor and intra- and extracranial stenosis in this study.

Response: As we explained in our response to comment No. 1, we did not address this issue because the main aim of this paper is to describe the KT-aICAS study. However, we totally agree with the reviewer that this is an important issue to address, and we have recently reported the relationship between traditional risk factor and intra- and extracranial stenosis in a separate paper, and we now cited this paper [1].

3. You should discuss that men have a higher smoking rate than women but no difference in vascular stenosis rates.

Response: We thank the reviewer for the suggestions. Although compared with men, women were less likely to smoke and consume alcohol, they were more likely to be obese, having diabetes and hyperlipidemia in our study, which may partially explain the lack of sex difference in prevalence of aICAS. We have added a brief discussion on this in revised manuscript (see page 16, lines 5-9).

4. Not only vascular stenosis by 3T MRI image but also plaque image should be described in some more detail.

Response: We thank the reviewer for the comments. We do have a plan to report the characteristics of vessel plaque image evaluated by 3T MRI in a separate paper (refer to our response to comment No. 1). We have supplemented some descriptions in revised manuscript (see page 16, lines 12-14).

5. You should clearly present the grade of flow velocity by TCD and the stenosis by carotid ultrasonography and clarify what extracranial lesions is consistent with that in MRA.

Response: We agree with the reviewer, and we have now added the data about carotid stenosis by carotid ultrasonography to Table 1. So far we have not yet classified the grade of flow velocity by TCD and degree of stenosis by carotid ultrasonography. We plan to report these data in a separate paper once the data are ready. In addition, neck MRA detection were not performed due to limited research funds. So, we do not have the data on extracranial lesions in MRA.

Reviewer 2:

1. Participants section page 9 row 17: BMI was calculated ... - the calculation should be kilograms divided by height (meters) squared.

Response: We thank the reviewer for kindly pointing out this mistake, which has now been revised [note: description of BMI calculation was deleted following the suggestion from reviewer 4 (minor comment point No. 7)] (see page 10, lines 2-4).

2. Page 11 row 12: Blood count cannot be measured from serum samples please rephrase to avoid confusion.

Response: We thank the reviewer for the kind comments. We measured complete blood count in the whole blood, and we have now rephrased it in revised manuscript (see page 12, line 2).

3. Findings to date page 14 row 45: replace “demonstrate” with “test” because the study has not been completed yet.

Response: We agree that the whole KT-aICAS project, as a prospective cohort study, is still ongoing. However, the two-phase procedure to detect aICAS was indeed successfully implemented in the baseline assessments (Oct 2017-Oct 2018). Thus, in your view, replace “demonstrate” with “have demonstrated” in revised manuscript (see page 15, line 16).

4. Same page row 59: correct to “less likely to be single”.

Response: We thank the reviewer. We added “likely” to the sentence in revised manuscript (see page 15, line 21).

5. please report numbers on how many patients did not have sufficient ultrasonic bone window in the present cohort.

Response: In total, 437 (21.5%) participants showed poor temporal window. We have added this number in revised manuscript (see page 16, line 20).

6. Page 6 row 30: replace “initiate” with “initiated”.

Response: It was done (see page 6, line 17).

Reviewer 3:

1. The Result section is relatively limited and more details could have been provided, moreover regarding cardiovascular risk factors, and including not only a sex-based distribution but also an age-based analysis.

Response: We thank the reviewer for the valuable comments. The main purpose of this manuscript is to introduce the cohort profile of the KT-aICAS study. However, we agree with the reviewer that this is an important issue to address, and we do have recently reported these data and we now cited our report in the text (see page 16, lines 11-12, reference No. 33) [1].

2. Do Authors plan to report separately the results about MR findings and neuropsychological tests? In that case, this could be specified in the methodology.

Response: Yes, we do. We plan to report separately the results about MR findings and neuropsychological tests in the future. We have now specified this in revised manuscript (see page 7, lines 6-14).

Reviewer 4:

In my view, the main limitation of this paper, is that it does not report the results of the neuropsychological assessments, as it is nevertheless implied in the abstract and study design sections. These results must be included in the paper, or otherwise it must be explicitly stated in the present manuscript that they will be reported in a separate paper. Further comments and a list of minor amendments are provided in the attached document.

Response: We agree with the reviewer that cognitive assessments are important parts of our KT-aICAS project and should be included in this paper. We have now added global cognitive data to Table 1. However, neurocognitive assessments were performed on subsample in phase II of this study, and data on full neuropsychological assessments will be reported in a separate paper. We briefly described this now (see page 6, lines 17-19; page 7, lines 11-14; page 16, 12-14).

1. It would be useful if the authors could describe in more detail the criteria that distinguish asymptomatic from symptomatic ICAS, particularly given that one of the inclusion criteria to take part in the study was being “free of history of stroke” (p. 7).

Response: We defined asymptomatic ICAS (aICAS) as having ICAS without a history of stroke (see page 5, line 9), and symptomatic ICAS as ICAS with a history of stroke (see page 6, line 10). As our

study sample was free of a history of stroke, all participants who were detected with ICAS were classified as having aICAS.

2. The authors should expand on the characteristics of Asian populations that make them particularly at risk for this condition. What can we, more generally, learn about ICAS by studying Asian populations?

Response: We thank the reviewer for the valuable comments. Following the reviewer's comments, we have added a brief information in the "Introduction" with regard to why studying aICAS in Asian population is relevant, and cite related literature in revised manuscript (see page 5, lines 8-17).

3. On page 7 (ln. 28-46), the authors refer to health promotion work developed by the School of Public Health at Shandong University and the town government and local health professionals. The authors should comment on the extent to which these initiatives could have led to a more healthy cohort in Kongcun compared to cohorts from other parts of China and the rest of the World.

Response: We understand the reviewer's concern on this issue. We are not so sure about how much our health promotion work in the local town will make our study cohort healthier. We do believe that our previous work in the town helped for better cooperation (e.g., high participation rate at baseline and possibly high adherence to future follow-ups) from local residents for implementing this project. We briefly commented on this in revised manuscript (see page 8, lines 6-8).

4. Please provide more detail about the procedure. In particular, clarify how many testing sessions were required to complete the full assessment, and whether or not participation required an overnight stay in hospital.

Response: In response to the reviewer's valuable comments, we have now provided more detailed description about the procedure and assessment. Briefly, the whole assessments in the two-phase baseline survey for each participants included two sessions, one session for each phase: Session 1 (Phase 1): the face-to-face survey, clinical examinations, lab test, and TCD examination that were performed on the same day (see page 9, lines 6-9); Session 2 (Phase 2): MRI scan and full neurocognitive assessments were scheduled in a separate day and were performed in the university hospital (see page 12, lines 12-15).

5. The abstract and the "Phase 2" section of the study design imply that the present manuscript reports the results of neuropsychological assessments. It is not until the results section that it becomes apparent that only a portion of the results of all the assessments conducted during Phase 2 are included in this manuscript, and that it does not cover the neuropsychological assessments. The paper should be revised to either include these results, or to explicitly state in the abstract, study design and / or results section that neuropsychological assessment results will be reported in a separate paper.

Response: We thank the reviewer for this comment, and we have now carefully addressed this question, and revised our manuscript accordingly (refer to our response to the reviewer's comment at the beginning).

6. Some of the results regarding sex differences are statistically significant, but the effect sizes appear to be small (e. g. differences in Total cholesterol, BMI, etc.). Some of the charts in figure 2 appear to suggest that these differences only become apparent for groups of a certain age. To what extent could the differences be due to the underlying differences in age found between the male and female cohorts?

Response: We thank the reviewer for the valuable comments. We agree with the reviewer that the statistical differences by sex do not necessarily indicate clinical relevance, and this is particularly true when we compare continuous variables in relatively large sample (e.g., BMI and total cholesterol)- even a small difference in mean could be statistically different. For the data in figure 2, the sex differences in certain age groups could be due to sampling errors or multiple reasons (e.g., genetic or

biological, or social environmental factors) as we explained in our responses to comments No. 7 and 8 below.

7. The overall results suggest that the prevalence of ICAS increases with age, however, men and women seem to show a different pattern. Please comment on the possible interaction between age and sex on ICAS prevalence.

Response: We thank the reviewer for the valuable comments. Indeed, the prevalence of aICAS steadily increased in men from 40 years of age, whereas in women the substantial increase occurred after 60 years of age. The reasons for the sex differences in the patterns of age-related prevalence of aICAS are likely to be complicated, but the substantial decrease in estrogen level in postmenopausal women may, at least partly, contribute to the increased prevalence of aICAS after 60 years of age, because estrogen has been proven to be a protective factor for atherosclerosis [2]. We have now added a brief discussion on this in revised manuscript (see page 17, lines 2-8).

8. The results suggest that although women have a healthier lifestyle (less likely to smoke and to consume alcohol), they also have poorer health outcomes (more likely to be obese, have diabetes and hyperlipidemia). Please comment on the possible reasons and implications of these findings.

Response: The sex differences in health among middle-aged, especially elderly people, are well established, but the reasons are not fully understood. Besides the potential effect of sex hormone and lifestyles, the sex differences in age, education, socioeconomic position, and social environment may also contribute to sex differences in health outcomes. We have now briefly discussed this issue in revised manuscript (page 16, lines 2-9). We thank the reviewer for this valuable comment, and we do plan to further address this issue, particularly when follow-up data become available.

Minor amendments

1. p. 3, ln. 40-41 and throughout the manuscript—Replace “subjects” with “participants”, “individuals” or “patients”.

Response: We thank the reviewer for the suggestion. “Subjects” throughout the manuscript has been replaced with “participants”, except one that was used in the declaration of Helsinki.

2. p. 3, ln. 44-45 –Add percentage in brackets after “2027”.

Response: It is done (see page 3, line 15).

3. p. 8, ln. 12 –Add comma after “previously”.

Response: A comma has been added (see page 8, line 21).

4. p. 8, ln. 20 –Delete the word “briefly”.

Response: We deleted the word (see page 9, line 4).

5. p. 8, ln. 40-41 –Add “a” in the sentence “... all participants underwent a structured questionnaire...”.

Response: Yes, it is done (see page 9, lines 8-9).

6. p. 8, ln. 45-50 –Add citations for all the standardised measures used.

Response: We thank the reviewer for the suggestion. Citations for all the standardised measures used has been added (see page 9, line 14, References No. 18 and 19).

7. p. 9, ln. 14-18 –Delete the calculation of BMI, as this is general knowledge, particularly for the target readers.

Response: It is done (see page 10, lines 2-4).

8. p. 11, ln. 17 –Replace “5” with “five”.

Response: Yes, it is done (see page 11, line 21).

9. p. 11, ln. 40-46 –Edit the sentence to read: “From April to October 2018, participants who screened positive, and a group of age- and sex-matched controls who had screened negative for ICAS by TCD in Phase 1, underwent the Phase 2 assessment...”

Response: We thank the reviewer for the suggestion. We have accordingly edited the sentence as suggested (see page 12, lines 12-14).

10. p. 12, ln. 35-36 –Replace “affection” with “mood”.

Response: We thank the reviewer for the suggestion. We had replaced “affection” with “mood” in revised manuscript (see page 13, line 13).

11. p. 12, ln. 51 –Replace “AVLT” with “RAVLT”.

Response: It is done (see page 13, line 18).

12. p. 14, ln 25-28 –Edit the sentence to read: “... participants would benefit from participating in this project because healthcare advice was provided...”

Response: This sentence has been amended. We thank the reviewer for the suggestion (see page 15, lines 6-9).

13. p. 14, ln. 33-36 –Move sentence “All participant-related information was de-identified from the database to preserve privacy.” to the section describing ethics and informed consent.

Response: It is done (see page 8, line 22; page 15, lines 11-12).

14. p. 14, ln. 54-56 –Delete the sentence “The mean age of the 2311 participants was 57.6 years, and 53.4% were women.”, as this is already reported on table 1.

Response: We understand the reviewer’s comment. We prefer to keep this sentence in the text because the readers will be able to know this very important information without referring the table (see page 15, line 20-21).

15. p. 14, ln. 57-60 –Edit the sentence to read: “Compared to men, women were older, less educated, less likely to be single, and had higher levels of total cholesterol...”

Response: We have edited this sentence. We thank the reviewer for the kind suggestion (see page 15, line 20-22).

16. p. 23, Table 1 –ln. 19 – Replace “states” with “status”.

Response: it is done (see Table 1).

17. p. 23, Table 1 –ln. 22 – Delete the word “status” after “single”.

Response: It is done (see Table 1).

18. p. 23, Table 1 footnote –The use of SD as an abbreviation for standard deviation is standard, so this can be deleted from the table caption. Edit footnote a) to read: “P values are for the test of differences between male and female.” Edit footnote b) to read: “The number of participants with missing values were one for marriage states...”. In the manuscript, comment on whether or not corrections for multiple comparisons were used (e. g. Bonferroni).

Response: We have now edited footnotes of Table 1, as suggested. We thank the reviewer for the suggestion. We did not make correction for multiple comparisons because this paper is mainly descriptive, and the comparisons by in table 1 were aimed to show characteristics of study participants by sex.

19. p. 26, Figure 1 –Replace the word “test” with “assessment” in the boxes starting with “153”.

Replace the word “subjects” with more appropriate terminology (e. g. “participants”). Make consistent use of capital letters (e. g. “Cognitive impairment”). Replace “Ischaemia” with “Ischaemic”.

Response: We thank the reviewer for the suggestion. All the words mentioned above have been replaced in Figure 1.

VERSION 2 – REVIEW

REVIEWER	Sara da Silva Ramos The Disabilities Trust, UK
REVIEW RETURNED	05-Apr-2020

GENERAL COMMENTS	<p>Most of the concerns raised in the previous review have been addressed on this revision of the manuscript. However, there are a few points that still require clarification:</p> <ol style="list-style-type: none">1. The criteria distinguishing asymptomatic from symptomatic ICAS are still not entirely clear. It is noted that the authors now refer to “clinical stroke” (p. 3), however, it would be useful if they could provide an operational definition of what was considered “clinical stroke”, and how a history of clinical stroke was established. Were potential participants asked for their past history, including previously unreported instances of transient ischaemic attack, for example? Were exclusion criteria identified from medical records?2. Regarding the issue of possible effects of the work on health promotion within the region on the results of the present study, it is noted that the authors have now commented on the positive impact this might have had on recruitment (p. 8, ln., 7-8). However, there is still no consideration of the possible effect these health initiatives could have had on health outcomes, including the prevalence of aICAS and risk factors and other outcomes considered. There is acknowledgement that this cohort might not be representative of other rural cohorts, but more detail should be provided on what the differences might be (e. g. could this cohort be more or less healthy compared to cohorts from other parts of China and the rest of the World?).3. The abstract now makes more clear that the results of the neuropsychological assessments are not reported in this manuscript. However, this should also be reflected throughout the paper. For example, the neuropsychological evaluation should not be considered a strength of the present study, as the results are not reported (at present, it is only a strength of the methodology), and that point should be deleted from this section (p. 4, ln. 11-12). The lack of reporting of most of the results relating to cognitive impairment should also be mentioned on other sections of the paper (e. g. p. 7, ln. 11-12; section on strengths and limitations). The authors should, however, include a brief commentary of the results on the MMSE and the MoCA, in particular, explain how these should be interpreted for the Chinese version used in the study, and also what they make of the apparent sex differences (e. g. Are these meaningful, or likely due to the large sample size?).4. The added discussion of the sex, age and sex by age interactions is noted, however, the details of these statistical comparisons should be included in more detail, in the body of the manuscript. The paper
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	<p>would also benefit from explaining in a little more detail the link between oestrogen and the factors under study (i. e. ICAS and its risk factors). What are the key findings from previous research, and to what extent are these corroborated in the present sample?</p> <p>5. The explanation of counter-intuitive findings, which showed that although women have a healthier lifestyle (less likely to smoke and to consume alcohol), they also have poorer health outcomes (more likely to be obese, have diabetes and hyperlipidemia) is inconsistent and somewhat circular. The authors state that “the sociocultural tradition in China, especially in rural regions, could explain the sex differences in behavioural factors” (p. 16, ln. 6-7), but then they add “whereas the differences in health conditions might be partially contributable (sic) to sex differences in factors such as educational achievement, socioeconomic position, lifestyles, and dietary habit” (p. 16, ln. 7-9). This is still not accounting for the inconsistency between the sex differences found in “behavioural factors” (i. e. smoking, drinking) and “health conditions” (i. e. diabetes, etc.), and it is, to some extent, attributing the same possible cause (behaviour) to both behaviours (like smoking and drinking) and health outcomes. “Lifestyles and dietary habit” are also behaviours, so at best, the possibility that women have less healthier lifestyle for aspects that were not measured in the study, such as diet (as opposed to smoking or alcohol intake), should be considered. Finally, the word “contributable” in the sentence just cited, should be replaced with “attributable”.</p> <p>6. The sentence “The mean age of the 2311 participants was 57.6 years, and 53.4% were women.” has not been deleted in the revised version. This is unnecessary, as the mean age is already reported on table 1, and the percentage corresponding to the number of participants of different sex can easily be included on the same table.</p> <p>There appears to be some conflation between the concepts of "public involvement" and "benefits to the public". This section (p. 15, ln. 4-12) should focus on describing how the patients and the public were involved in the development of the study and in the dissemination of the study findings.</p>
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VERSION 2 – AUTHOR RESPONSE

Response to reviewer:

1. The criteria distinguishing asymptomatic from symptomatic ICAS are still not entirely clear. It is noted that the authors now refer to “clinical stroke” (p. 3), however, it would be useful if they could provide an operational definition of what was considered “clinical stroke”, and how a history of clinical stroke was established. Were potential participants asked for their past history, including previously unreported instances of transient ischaemic attack, for example? Were exclusion criteria identified from medical records?

Response: We defined asymptomatic ICAS (aICAS) as ICAS without a history of clinical stroke or transient ischaemic attack (TIA) according to self-report of a physician diagnosis and/or clinical examinations showing typical neurological symptoms, which were determined during the interviews

and clinical examination. We did not refer to any medical records. We revised it in the revised manuscript (see page 7, lines 17-19).

2. Regarding the issue of possible effects of the work on health promotion within the region on the results of the present study, it is noted that the authors have now commented on the positive impact this might have had on recruitment (p. 8, ln., 7-8). However, there is still no consideration of the possible effect these health initiatives could have had on health outcomes, including the prevalence of aICAS and risk factors and other outcomes considered. There is acknowledgement that this cohort might not be representative of other rural cohorts, but more detail should be provided on what the differences might be (e. g. could this cohort be more or less healthy compared to cohorts from other parts of China and the rest of the World?).

Response: Since 2009, the School of Public Health at Shandong University has been working together with the town government and local health professionals to conduct epidemiological surveys every 3 years on health condition of local residents. This might help improve the cooperation of local residents (e.g., high participation rate at baseline and possibly high adherence to future follow-up assessments) for implementing this project. We have made this clear in the revised manuscript (page 8, lines 1-5). However, no medical interventions have been actively implemented in local town. It is unclear to what extent our health surveys may affect health outcomes of local residents. Anyhow, this might make our study cohort differ from other rural cohorts in China. We have now briefly discussed this situation and acknowledged this as a potential limitation of the project (page 20, lines 15-18).

3. The abstract now makes more clear that the results of the neuropsychological assessments are not reported in this manuscript. However, this should also be reflected throughout the paper. For example, the neuropsychological evaluation should not be considered a strength of the present study, as the results are not reported (at present, it is only a strength of the methodology), and that point should be deleted from this section (p. 4, ln. 11-12). The lack of reporting of most of the results relating to cognitive impairment should also be mentioned on other sections of the paper (e. g. p. 7, ln. 11-12; section on strengths and limitations). The authors should, however, include a brief commentary of the results on the MMSE and the MoCA, in particular, explain how these should be interpreted for the Chinese version used in the study, and also what they make of the apparent sex differences (e. g. Are these meaningful, or likely due to the large sample size?).

Response: We fully understand the reviewer's comments. Because this is a "Cohort profile" paper for BMJ Open that aimed to describe our Kongcun Town aICAS project and summarize the key findings so far, we claimed that inclusion of comprehensive neuropsychological assessments on a subsample of the project could be a strength of our Kongcun Town aICAS Project, rather than for the current report. However, to avoid any confusion, we deleted it as the reviewer suggested.

In addition, given that we did not report the full results of cognitive tests, we have slightly modified the text with regard to cognitive assessments throughout the paper. We have also added brief comments on the results of MMSE and MoCA data in the revised manuscript (see page 16, line 11-15).

4. The added discussion of the sex, age and sex by age interactions is noted, however, the details of these statistical comparisons should be included in more detail, in the body of the manuscript. The paper would also benefit from explaining in a little more detail the link between oestrogen and the factors under study (i. e. ICAS and its risk factors). What are the key findings from previous research, and to what extent are these corroborated in the present sample?

Response: We thank the reviewer for the comments. The prevalence of aICAS increased steadily with age in men (from 2.8% in 40-49 years to 12.9% in over 70 years old) (p for trend <0.001), but in women the prevalence was relatively stable from 40 to 60 years of age (from 8.4 % to 8.1%), and then substantially increase (12.8% in aged ≥70 years) (p for trend=0.141). We have done the test for trends, and we revised it in the revised manuscript (see page 17, line 6-11).

Unfortunately, we do not have data on oestrogens in our Kongcun Town Project, thus we are not able to directly study the link of oestrogens with aICAS and related risk factors. However, we now briefly discussed about the literature with regard to our study findings (see page 17, line 11-17). It appears that our findings are largely consistent with literature and support the potential that estrogens may play an important role in anti-intracranial atherosclerosis.

5. The explanation of counter-intuitive findings, which showed that although women have a healthier lifestyle (less likely to smoke and to consume alcohol), they also have poorer health outcomes (more likely to be obese, have diabetes and hyperlipidemia) is inconsistent and somewhat circular. The authors state that “the sociocultural tradition in China, especially in rural regions, could explain the sex differences in behavioural factors” (p. 16, ln. 6-7), but then they add “whereas the differences in health conditions might be partially contributable (sic) to sex differences in factors such as educational achievement, socioeconomic position, lifestyles, and dietary habit” (p. 16, ln. 7-9). This is still not accounting for the inconsistency between the sex differences found in “behavioural factors” (i. e. smoking, drinking) and “health conditions” (i. e. diabetes, etc.), and it is, to some extent, attributing the same possible cause (behaviour) to both behaviours (like smoking and drinking) and health outcomes. “Lifestyles and dietary habit” are also behaviours, so at best, the possibility that women have less healthier lifestyle for aspects that were not measured in the study, such as diet (as opposed to smoking or alcohol intake), should be considered. Finally, the word “contributable” in the sentence just cited, should be replaced with “attributable”.

Response: We thank the reviewer for the further comments on the issue of sex differences in health outcomes. To be honest, we do not know the exact explanations of the sex differences in health outcomes because the health conditions of middle-aged and elderly people are determined by multiple complex genetic and environmental risk and protective factors over their lifelong period. It is well known that sex differences of certain behavioral factors in our population such as smoking and alcohol consumption are determined by local sociocultural traditions, as we briefly discussed (see page 16, line 4, we added a reference no 33 to support this statement). On the other hand, educational achievement, as a marker/measure of socioeconomic position, is a strong determinant of health. Women received very limited education compared with men, which might contribute to poor health outcomes. We agree with the reviewer that women may have less healthy lifestyle in certain aspects such as diet. Unfortunately, we do not have dietary data to directly compare. We have now added a brief discussion on this issue (page 16, lines 4-7).

We have replaced "contributable" with "attributable" (page 16, line 5-6). We thank the reviewer for kindly pointing out this error.

6. The sentence “The mean age of the 2311 participants was 57.6 years, and 53.4% were women.” has not been deleted in the revised version. This is unnecessary, as the mean age is already reported on table 1, and the percentage corresponding to the number of participants of different sex can easily be included on the same table.

Response: We now deleted this sentence in the revised manuscript (page 15, lines 17-18) and added percentages of participants by sex to Table 1.

7. There appears to be some conflation between the concepts of "public involvement" and "benefits to the public". This section (p. 15, ln. 4-12) should focus on describing how the patients and the public were involved in the development of the study and in the dissemination of the study findings.

Response: We have now carefully revised this section following the BMJ Open's instructions on reporting patient and public involvement in research (https://bmjopen.bmj.com/pages/authors/#reporting_patient_and_public_involvement_in_research) (page 15, lines 4-10).

VERSION 3 - REVIEW

REVIEWER	Sara da Silva Ramos The Disabilities Trust, UK
REVIEW RETURNED	21-May-2020

GENERAL COMMENTS	All issues raised have been addressed in the latter revision, and in my view the manuscript is now suitable for publication.
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