

## 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>	Synergism between the metabolic syndrome components and cancer incidence: results from a prospective nested case-control study based on the China Health and Retirement Longitudinal Study (CHARLS)
<b>AUTHORS</b>	Li, Lin; Meng, Fang; Xu, Dongkui; Xu, Lingkai; Qiu, Junlan; Shu, Xiaochen

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Matteo Neri Univerità G. D'Annunzio Chieti, Medicine and Aging Sciences
<b>REVIEW RETURNED</b>	15-Mar-2022

<b>GENERAL COMMENTS</b>	<p>In this study the Authors have shown that the Metabolic Syndrome (MetSyn) is associated to the occurrence of cancer in a Chinese population. The importance of the study to me relies on the use of the “harmonized “ criteria (2009), that consider not only overt metabolic disturbances but also more subtle changes, thus supporting the rolse of MetSyn per se; the The Auhtors have convincingly demonstrated their hypothesis. I have some minor comments to offer to this simply yet cleverly designed study.</p> <p>General comments:</p> <ol style="list-style-type: none"> <li>1. An important concept raised by the present and other observations is that ,differently to what commonly thought, not only obesity but even rather subtle metabolic disturbances may give rise to cancer. This may have important implications in the prevention of cancer and should be adequately highlighted</li> <li>2. A more detailed analysis of the mechanisms underlying the role of MetSyn in cancer generation, and their reflection on the need of at least three components of the Syndrome would be welcome</li> <li>3. Participants were asked: “Have you ever been diagnosed with cancer or malignant tumor (excluding minor skin cancers) by a doctor?” This may rise the issue of an asynchronous ocurrence of MetSyn and cancer. If so, please include in limitations</li> <li>4. Generalizability of the study also with respect to non_Asian populations should be discussed as a limitation</li> </ol> <p>Specific comments:</p> <p>Presence of comorbidities should be described Do you have data on physical exercise? Please add</p>
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<b>REVIEWER</b>	André Sousa Laboratório de Biotecnologia Médica e Industrial
<b>REVIEW RETURNED</b>	02-May-2022

<b>GENERAL COMMENTS</b>	This manuscript aims to explore the influence that metabolic
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	<p>syndrome has on cancer incidence based on a case-control study. Overall, the study is very interesting and represents novel results when compared to different studies in the field. The manuscript is very easy to read, although it has some English issues. The results are very clear and easy to understand.</p> <p>Nevertheless, some corrections/suggestions should be considered so the manuscript would be much improved for publication:</p> <p>Major corrections:</p> <ul style="list-style-type: none"> <li>• The abstract is not very clear in terms of workflow, introduction, and English correction. I strongly recommend rewriting it, and I leave some suggestions: The paragraph “objectives” do not have a clear introduction to the theme of the manuscript, and the objective is not described at all; the following 3 subtopics (design, setting, and participants) seems to be all methodology, which I highly recommend to mix in the same subtopic; the results are very confusing, and it has to be rewritten (example, the first sentence, I recommend to write “We observed elevation in cancer risk associated with MetSyn in a significant way when the number of MetSyn components were over three...”); the conclusion has also to be rewritten because it is very confusing.</li> <li>• The discussion part also needs to be improved. In the first paragraph, some sentences are repeated in other parts of the manuscript (for example page 21 lines 17-21, which was in the abstract part and seems very confusing, as previously described in the last topic); in the second paragraph, the strengths and limitations were described in other parts of the manuscript, and they do not have to be listed again; the third paragraph is very confusing and it has to be rewritten; from fourth to seventh paragraphs the message is clear and they are well written; the last paragraph lacks in a conclusion considering the objective of the work. In general, the discussion is a bit confusing and needs to improve in English. Additionally, I strongly recommend highlighting what are the 3 most common MetSyn factors that can lead to cancer development determined by this work, or if the work did not allow to verify that, explain the idea that can be any of the 5 factors.</li> </ul> <p>Minor corrections:</p> <ul style="list-style-type: none"> <li>• In the list of abbreviations, page 3, the abbreviation explanation is not regular. Some of the expressions start with capital letters (example: American Heart Association) and others with small letters (example: confidence intervals). Please, standardize the way of writing.</li> <li>• Page 5, line 38: there is a typo with the word “relatively”.</li> <li>• Page 6, line 8: the correct way to refer to diabetes is “type 2 diabetes mellitus”, please correct it.</li> <li>• Page 6, line 56: rewrite as “exploring the number threshold and combinative...”</li> <li>• Page 8, lines 51-52: the word measure appears two times in the same sentence. I recommend changing too, for example, “The anthropometric measurements also were assessed”</li> <li>• Page 10, line 31: the comma after “informed consent” should be substituted by a dot.</li> <li>• Page 18, line 28-29: the sentence “as a unique MetSyn component”, the proposition a should have been written as “an” since there is a vowel next to it.</li> </ul> <p>Suggestions:</p> <ul style="list-style-type: none"> <li>• The title seems a bit confusing. I suggest “Synergism between the metabolic syndrome components and cancer incidence: results from a prospective nested case-control study based on the China Health</li> </ul>
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	<p>and Retirement Longitudinal Study (CHARLS)".</p> <ul style="list-style-type: none"> <li>• The keywords should be in alphabetic order.</li> <li>• Page 6, line 26: I think the text becomes richer if you add the cutoff values of the 5 risk factors.</li> <li>• Page 7, line 10: since the next section is described the methods used in the writing of the manuscript, which does not correlate only with patients, I suggest removing the word "patients" from de section and leaving only methods or even "methodology".</li> </ul>
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<b>REVIEWER</b>	Ibrahim AlZaim American University of Beirut
<b>REVIEW RETURNED</b>	14-May-2022

<b>GENERAL COMMENTS</b>	<p>Li et al. in their manuscript titled "Association of components of metabolic syndrome with cancer incidence in a synergistic way: results from a prospective nested case-control study based on the China Health and Retirement Longitudinal Study (CHARLS)", provide evidence that the combination of components of MetS rather each component in its uniqueness drive an increased risk for the development of cancer. Although not strikingly novel, the manuscript is clear and on point. I urge the authors to double-check for grammar mistakes and sentence structures.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> <li>1. Introduction, page 7, line 35: biological mechanisms underlying the association between MetS and increased cancer incidence have evolved to include proximal adipose tissue inflammation and disturbed metabolism as a key instigator of neoplastic alterations in healthy tissues. Such mechanisms must be briefly highlighted in this section.</li> <li>2. Results, page 18, table 3: A comment regarding the non-significance of the OR of elevated triglycerides as a unique MetS component in the IPTW model is warranted.</li> <li>3. Results, page 19, line 10: Kindly provide the stratified analyses according to which system cancer belonged in the revised version of the manuscript.</li> <li>4. Discussion, page 22, line 33: Authors ought to highlight the reasons for reduced HDL to play an important role in secondary cancer risk through speculating some possible underlying mechanisms.</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

**Reviewer: 1**

Prof. Matteo Neri, Univerità G. D'Annunzio Chieti, Ospedale Policlinico SS Annunziata

**Comments to the Author:**

In this study the Authors have shown that the Metabolic Syndrome (MetSyn) is associated to the occurrence of cancer in a Chinese population. The importance of the study to me relies on the use of the "harmonized " criteria (2009), that consider not only overt metabolic disturbances but also more subtle changes, thus supporting the rolse of MetSyn per se; The Auhtors have convincingly demonstrated their hypothesis. I have some minor comments to offer to this simply yet cleverly designed study.

**General comments:**

1. An important concept raised by the present and other observations is that, differently to what commonly thought, not only obesity but even rather subtle metabolic disturbances may give rise to cancer. This may have important implications in the prevention of cancer and should be adequately highlighted.

**Response:**

Thanks a lot for pointing this out! We had added it into the conclusion of the Abstract and the last paragraph in the Discussion as well.

2. A more detailed analysis of the mechanisms underlying the role of MetSyn in cancer generation, and their reflection on the need of at least three components of the Syndrome would be welcome.

**Response:**

The mechanism and the reflection had been supplemented, as you can see in the second paragraph in the Introduction and the second paragraph in the Discussion

3. Participants were asked: "Have you ever been diagnosed with cancer or malignant tumor (excluding minor skin cancers) by a doctor?" This may rise the issue of an asynchronous occurrence of MetSyn and cancer. If so, please include in limitations.

**Response:**

The chronology of diagnosis of metabolic syndrome and cancer is clearly defined and documented in the present study, i.e., diagnosis of MetSyn at baseline of the cohort and diagnosis of cancer during the follow-up of cohort, by which the causal reference could possibly drawn. However, considering the self-report nature of this study, we still include it in limitations.

4. Generalizability of the study also with respect to non\_Asian populations should be discussed as a limitation

**Response:**

This point was added as a limitation. Thanks for the comments!

**Specific comments:**

Presence of comorbidities should be described

**Response:**

Distribution of comorbidities between cases and controls after match was analyzed and presented in '3. selection of cancer-free concurrent control and matching' in Methods.

Do you have data on physical exercise? Please add

**Response:**

Data on physical exercise was not included in the present analysis due to too many missing values, which would have biased the results a lot if it had been included.

## **Reviewer: 2**

Dr. André Sousa, Laboratório de Biotecnologia Médica e Industrial

### **Comments to the Author:**

This manuscript aims to explore the influence that metabolic syndrome has on cancer incidence based on a case-control study. Overall, the study is very interesting and represents novel results when compared to different studies in the field. The manuscript is very easy to read, although it has some English issues. The results are very clear and easy to understand.

Nevertheless, some corrections/suggestions should be considered so the manuscript would be much improved for publication:

### **Major corrections:**

- The abstract is not very clear in terms of workflow, introduction, and English correction. I strongly recommend rewriting it, and I leave some suggestions: The paragraph “objectives” do not have a clear introduction to the theme of the manuscript, and the objective is not described at all; the following 3 subtopics (design, setting, and participants) seems to be all methodology, which I highly recommend to mix in the same subtopic; the results are very confusing, and it has to be rewritten (example, the first sentence, I recommend to write “We observed elevation in cancer risk associated with MetSyn in a significant way when the number of MetSyn components were over three...”); the conclusion has also to be rewritten because it is very confusing.

### **Response:**

Considering all of the comments from the reviewer, we went through and rewrote quite a part of the abstract with the help of a very good English speaker. We hope that we had presented it more clearly and professionally so that readers could better understand them. However, in order to be consistent with the style of the journal, we prefer to keep the 3 subtopics, which would also make what we want to express clearer. If there are still some problems that have not been solved, we are willing to revise them again. Thanks for the chance!

- The discussion part also needs to be improved. In the first paragraph, some sentences are repeated in other parts of the manuscript (for example page 21 lines 17-21, which was in the abstract part and seems very confusing, as previously described in the last topic); in the second paragraph, the strengths and limitations were described in other parts of the manuscript, and they do not have to be listed again; the third paragraph is very confusing and it has to be rewritten; from fourth to seventh paragraphs the message is clear and they are well written; the last paragraph lacks in a conclusion considering the objective of the work. In general, the discussion is a bit confusing and needs to improve in English. Additionally, I strongly recommend highlighting what are the 3 most common

MetSyn factors that can lead to cancer development determined by this work, or if the work did not allow to verify that, explain the idea that can be any of the 5 factors.

**Response:**

According to reviewer's comments, we went through the whole discussion several times and rewrote some part of it: the first paragraph was rephrased, the second paragraph was deleted, the third and the last paragraphs were modified. Also, we added what are the 3 most common MetSyn components as suggested, which you can see in the first paragraph in Discussion. If there are still some language problems that have not been solved, we are willing to revise them again. Thanks for the chance!

**Minor corrections:**

- In the list of abbreviations, page 3, the abbreviation explanation is not regular. Some of the expressions start with capital letters (example: American Heart Association) and others with small letters (example: confidence intervals). Please, standardize the way of writing.

**Response:**

Corrections were done as suggested. Thanks for the comments!

- Page 5, line 38: there is a typo with the word "relatively".

**Response:**

Corrections were done. Thanks!

- Page 6, line 8: the correct way to refer to diabetes is "type 2 diabetes mellitus", please correct it.

**Response:**

Corrections were done accordingly. Thanks for pointing it out!

- Page 6, line 56: rewrite as "exploring the number threshold and combinative..."

**Response:**

Corrections were done accordingly. Thanks!

- Page 8, lines 51-52: the word measure appears two times in the same sentence. I recommend changing too, for example, "The anthropometric measurements also were assessed"

**Response:**

Corrections were done accordingly. Thanks!

- Page 10, line 31: the comma after "informed consent" should be substituted by a dot.

**Response:**

Corrections were done accordingly. Thanks!

- Page 18, line 28-29: the sentence “as a unique MetSyn component”, the proposition a should have been written as “an” since there is a vowel next to it.

**Response:**

Corrections were done accordingly. Thanks!

**Suggestions:**

- The title seems a bit confusing. I suggest “Synergism between the metabolic syndrome components and cancer incidence: results from a prospective nested case-control study based on the China Health and Retirement Longitudinal Study (CHARLS)”.

**Response:**

We changed the title as suggested.

- The keywords should be in alphabetic order.

**Response:**

Corrections were done accordingly. Thanks!

- Page 6, line 26: I think the text becomes richer if you add the cutoff values of the 5 risk factors.

**Response:**

The cutoff values for all of the 5 risk factors were added. Thanks!

- Page 7, line 10: since the next section is described the methods used in the writing of the manuscript, which does not correlate only with patients, I suggest removing the word “patients” from de section and leaving only methods or even “methodology”.

**Response:**

Modifications were done accordingly. Thanks!

**Reviewer: 3**

Dr. Ibrahim AlZaim, American University of Beirut

**Comments to the Author:**

Li et al. in their manuscript titled "Association of components of metabolic syndrome with cancer incidence in a synergistic way: results from a prospective nested case-control study based on the China Health and Retirement Longitudinal Study (CHARLS)", provide evidence that the combination of components of MetS rather each component in its uniqueness drive an increased risk for the development of cancer. Although not strikingly novel, the manuscript is clear and on point. I urge the authors to double-check for grammar mistakes and sentence structures.

**Response:**

We went through the manuscript and corrected grammar mistakes and rephrased some sentences structures. We hope readers could better understand them. If there are still some language problems that have not been solved, we are willing to revise them again. Thanks for the chance!

**Minor comments:**

1. Introduction, page 7, line 35: biological mechanisms underlying the association between MetS and increased cancer incidence have evolved to include proximal adipose tissue inflammation and disturbed metabolism as a key instigator of neoplastic alterations in healthy tissues. Such mechanisms must be briefly highlighted in this section.

**Response:**

The related biological mechanisms was added in the Introduction. Thanks a lot for the comments!

2. Results, page 18, table 3: A comment regarding the non-significance of the OR of elevated triglycerides as a unique MetS component in the IPTW model is warranted.

**Response:**

Comment was added in the text of table 3! Thanks!

3. Results, page 19, line 10: Kindly provide the stratified analyses according to which system cancer belonged in the revised version of the manuscript.

**Response:**

Stratified analyses according to systems were added in the revised manuscript as Table 4.

4. Discussion, page 22, line 33: Authors ought to highlight the reasons for reduced HDL to play an important role in secondary cancer risk through speculating some possible underlying mechanisms.

**Response:**

The reasons were speculated in the second paragraph in Discussion.



## VERSION 2 – REVIEW

<b>REVIEWER</b>	Matteo Neri Univerità G. D'Annunzio Chieti, Medicine and Aging Sciences
<b>REVIEW RETURNED</b>	22-Jun-2022

<b>GENERAL COMMENTS</b>	I wish to congratulate the Authors for having improved greatly the paper.
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<b>REVIEWER</b>	André Sousa Laboratório de Biotecnologia Médica e Industrial
<b>REVIEW RETURNED</b>	17-Jun-2022

<b>GENERAL COMMENTS</b>	The manuscript has considerably improved during the revision. Thus, this version has the quality of being published in the current form.
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<b>REVIEWER</b>	Ibrahim AlZaim American University of Beirut
<b>REVIEW RETURNED</b>	22-Jun-2022

<b>GENERAL COMMENTS</b>	The authors have clearly answered my comments and I thus have no further concerns over the publication of this manuscript.
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