# PEER REVIEW HISTORY

## ARTICLE DETAILS

| TITLE (PROVISIONAL) | The association between domain-specific sedentary behavior and endometrial cancer: A systematic review and meta-analysis |
|---|---|
| AUTHORS | Yuan, Lei; Ni, Jingyi; Lu, Wen; Yan, Qin; Wan, Xiaoping; Li, Zhen |

## VERSION 1 – REVIEW

| REVIEWER | Friedenreich CM<br>Department of Cancer Epidemiology and Prevention Research, CancerControl Alberta, Alberta Health Services,, Cancer Epidemiology and Prevention Research |
|---|---|
| REVIEW RETURNED | 21-Nov-2022 |

| GENERAL COMMENTS | General Comments:<br>The authors have conducted a very careful and comprehensive systematic review and meta-analysis on the association between domain-specific sedentary behaviour and endometrial cancer risk. The systematic review was appropriately conducted with registration in PROSPERO and following all appropriate PRISMA and MOOSE guidelines for reporting and study conduct. There were no concerns raised with the study conduct, presentation of findings, interpretation of results and conclusions. The only issue found were some English language issues that can be resolved through a careful edit by an English first language editor. Some minor suggestions are provided here.<br><br>Specific Comments:<br>1. Ensure that plural form of verbs are used when appropriate. For example, in the abstract, line 42, it should read "criteria were" rather than "was".<br><br>2. Introduction - a reference should be added to support the sentence on line 72-75.<br><br>3. Significance - throughout the paper, ensure that the words "statistical" or "statistically" are included before "significance" and use the words non-statistically significant rather than "insignificant".<br><br>4. Split infinitives - please avoid the use of split infinitives such as on page 6, line 124, "to quantitatively assess". Please revise to "to assess quantitatively".<br><br>5. Patient and public involvement statement - Please revise to "This issue is not applicable...".<br><br>6. Page 14, line 328: capitalize the 'N" in North America.<br><br>7. Page 16, line 350 - changing "combing" to "combining" |
|---|---|

| | 8. Page 16, lines 357-358: use the plural for study, i.e. "studies" conducted in North America, studies with large sample size, etc. |
| | |
| | 9. Discussion, line 365: consider deleting the statement about "borderline significancy" and just focus on the statistically significant findings in your meta-analysis. |
| | |
| | 10. Several instances of the words "large sampled study" were found which should be revised to "a study with a large sample size". |
| | |
| | 11. Several instances of singular rather than plural nouns were found such as on page 18, line 412, "novel analytic method" rather than "methods" or line 432 "different study population" rather than "populations". |

| REVIEWER | Lauren C. Bates-Fraser |
| | The University of North Carolina at Chapel Hill School of Medicine |
| REVIEW RETURNED | 03-Jan-2023 |

| GENERAL COMMENTS | Overall this meta-analysis addresses an important research question and I commend the authors for taking on a challenging but critical exploration into domain specific sedentary behavior and endometrial cancer risk. My major concerns include: 1. the need to define high vs. low sedentary behavior throughout the manuscript as well as tailoring the conclusion based on the limitations of available literature, 2. the need to update the search (conducted in March 2021 which is 22 months ago), and 3. some clarification regarding specific comments provided below: |
| | |
| | What is known: |
| | 1. What kinds of detrimental effects (i.e., define what you mean here). |
| | 2. Consider mentioning that some inconsistency is due to variation in measurement (objective vs. subjective self-report). |
| | 3. Define what you mean by domains. Consider giving an example. |
| | 4. Consider also including sleep (24-hour activity behaviors) in your discussion of lifestyle factors. |
| | |
| | New findings: |
| | 1. Define what you categorize as "high" (what cut-off are you using? How many hours?) |
| | 2. Please add data to this statement. What is a "borderline significant"? I assume you mean a trend, but it would be helpful to have data with this statement. |
| | |
| | Abstract: |
| | P-values missing from abstract. |
| | |
| | Introduction: |
| | Some of the references are a little out-dated. For example, there is a 2022 meta-analysis that discusses sedentary behavior and endometrial cancer risk: https://link.springer.com/article/10.1007/s10654-022-00873-6 |
| | |
| | The search was last conducted in March 2021. Please update the search to include more recent data. For example, this study may qualify: https://www.jstage.jst.go.jp/article/jea/31/12/31_JE20200145/_article/-char/ja/ |

Lines 144-146 please define the difference between physical inactivity and physical activity

Lines 156-157 please define "highest versus lowest". How are these being defined? How many hours of sedentary behavior in each category?

Statistical analysis
Was adjustment for study quality made? If so, please report. If not, consider including.

I appreciate that conducting a meta-analysis on the primary outcome of this study is challenging due to the variation in reporting between studies and the lack of standardization in reporting for sedentary behavior. I recommend the author's consider using a 3-level meta-analysis to account for variation. The 3 sources of variance taken into account included: variance at the level of the subject (Level 1), variance between effect sizes extracted from the same study (Level 2), and variance between studies (Level 3). See this article: https://www.tqmp.org/RegularArticles/vol12-3/p154/p154.pdf

Results:
Reasons for article exclusion could be more clear. For example, what does "methodology n=20" mean?
Line 260 and also in abstract the total sample is missing a comma. Should be written as 882,686.
Same comment for every number reported.
Line 270 please report references for study quality measurements.
Lines 275-278 language is informal and includes a run-on sentence. Please revise for example: Twelve studies have investigated impacts of sedentary behavior during work on endometrial cancer, and five of them reported significant association between occupational sedentary behavior and increased risk of endometrial cancer.7 18 19 25 27 However, five studies did not observe a similar significant effect.12 13 22 23 26 28 29

Line 281 missing p-value

Please include the type of sedentary behavior measurement used in the studies in the results sections. How many were self-report? How many were objective?

Line 363: needs to define what "higher levels of total sedentary behavior" means. Further, is this 55% increase based on the data of N=2 studies? That is a major limitation and needs to be highlighted.

Lines 363-366 needs to include data to support claims.

394: first mention of diet here. Please include diet discussion in the introduction or remove from this section as it is too late to introduce the topic without explanation as to how diet contributes to lifestyle risk.

Lines 458-460: this is a major limitation, and a huge concern in the interpretation of these data. A meta-analysis ultimately informs policy development, and the lack of reporting as to what is "high" and what is "low" needs to be addressed in this manuscript. The authors need to include reporting of what is defined as "high" vs. "low" in order to improve the interpretation of these data.

| | Conclusion: Please consider revising the conclusion to highlight the major limitations of these data. The conclusions are strong considering the lack of studies, variation in reporting, and potential limitations. |
|---|---|
| | Table 1: Formatting of headings needs to be addressed. "Number of participants" is not formatted correctly. |
| | Physical activity and BMI not reported in the table. Additionally, classification of "high" vs "low" sedentary behavior should be included in the table. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer #1:

General comments

The authors have conducted a very careful and comprehensive systematic review and meta-analysis on the association between domain-specific sedentary behaviour and endometrial cancer risk. The systematic review was appropriately conducted with registration in PROSPERO and following all appropriate PRISMA and MOOSE guidelines for reporting and study conduct. There were no concerns raised with the study conduct, presentation of findings, interpretation of results and conclusions. The only issue found were some English language issues that can be resolved through a careful edit by an English first language editor. Some minor suggestions are provided here.

Response: We thank the reviewer very much for the encouraging comments. We have revised the paper according to your comments and suggestions as following.

Specific comments to the authors

1. Ensure that plural form of verbs are used when appropriate. For example, in the abstract, line 42, it should read "criteria were" rather than "was".

Response B1: We have revised "criteria was" as " criteria were".

2. Introduction - a reference should be added to support the sentence on line 72-75.

Response B2: We thank the reviewer very much for the suggestion. We have added references in the revision, as 'It is suggested that this phenomenon may be explained, at least partly, by changing environmental and lifestyle risk factors in these regions, such as the epidemic of obesity, lack of physical activity, and long-time sitting.3,4' (See Lines 73-76).

3. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. Br J Sports Med. 2022;56(2):101-106. doi:10.1136/bjsports-2020-103640

4. Yasin HK, Taylor AH, Ayakannu T. A Narrative Review of the Role of Diet and Lifestyle Factors in the Development and Prevention of Endometrial Cancer. Cancers. 2021;13(9):2149. doi:10.3390/cancers13092149

3. Significance - throughout the paper, ensure that the words "statistical" or "statistically" are included before "significance" and use the words non-statistically significant rather than "insignificant".

Response B3: We have changed the wording in the revision.

4. Split infinitives - please avoid the use of split infinitives such as on page 6, line 124, "to quantitatively assess". Please revise to "to assess quantitatively".

Response B4: We have revised the wording of the statement (See Lines 123-124).

5. Patient and public involvement statement - Please revise to "This issue is not applicable...".

Response B5: We have revised the statement accordingly (See Line 249).

6. Page 14, line 328: capitalize the 'N" in North America.

Response B6: We have replaced "n" by "N" (See Line 337).

7. Page 16, line 350 - changing "combing" to "combining"

Response B7: We apologize for the typo. We have replaced "combing" by "combining" (See Line 360).

8. Page 16, lines 357-358: use the plural for study, i.e. "studies" conducted in North America, studies with large sample size, etc.

Response B8: We have revised the wording as suggested (See Lines 367-368), and also have carefully checked throughout the paper.

9. Discussion, line 365: consider deleting the statement about "borderline significancy" and just focus on the statistically significant findings in your meta-analysis.

Response B9: We thank the reviewer very much for the comment. We want to clarify the reason of using the statement of "borderline significancy" when describing part of our results (See Line 375), is that apart from statistical significancy, we also want to focus on the strength of the associations. The RRs were elevated for leisure-time domain even though they were not statistically significant, and our interpretation of results relied on both significancy and the strength of the associations. Please see the following reference for my rationale for this position.

Amrhein V, Greenland S, McShane B. Scientists rise up against statistical significance. Nature. 2019 Mar;567(7748):305-307. doi: 10.1038/d41586-019-00857-9.

10. Several instances of the words "large sampled study" were found which should be revised to "a study with a large sample size".

Response B10: We have revised "large sampled study" to "a study with a larger sample size" (See Line 419), and have carefully checked and improved the presentation throughout the paper.

11. Several instances of singular rather than plural nouns were found such as on page 18, line 412, "novel analytic method" rather than "methods" or line 432 "different study population" rather than "populations".

Response B11: We have changed the singular nouns into plural nouns in the revision (See Lines 432, 452 and 454).

Reviewer #2:

General comment

Overall this meta-analysis addresses an important research question and I commend the authors for taking on a challenging but critical exploration into domain specific sedentary behavior and endometrial cancer risk. My major concerns include: 1. the need to define high vs. low sedentary behavior throughout the manuscript as well as tailoring the conclusion based on the limitations of available literature, 2. the need to update the search (conducted in March 2021 which is 22 months ago), and 3. some clarification regarding specific comments provided below.

Response: We thank the reviewer for the insightful comments. Detailed responses to the specific comments (including the major concerns) are listed below.

Specific comments to the authors

A. Study Importance Questions

1. What is known: What kinds of detrimental effects (i.e., define what you mean here); Consider mentioning that some inconsistency is due to variation in measurement (objective vs. subjective self-report); Define what you mean by domains. Consider giving an example; Consider also including sleep (24-hour activity behaviors) in your discussion of lifestyle factors.

2. New findings: Define what you categorize as "high" (what cut-off are you using? How many hours?); Please add data to this statement. What is a "borderline significant"? I assume you mean a trend, but it would be helpful to have data with this statement.

Response C1: We thank the reviewer for the insightful comments, although the previous section 'Study Importance Questions' combining both aspects have been deleted by the request of the editor. We have added explanations accordingly in the manuscript and responses in specific sections as follows.

B. Abstract:

P-values missing from abstract.

Response C2: Due to limited space, p-values were not reported in the abstract. But we have added the p-values in the main text.

C. Introduction:

1. Some of the references are a little out-dated. For example, there is a 2022 meta-analysis that discusses sedentary behavior and endometrial cancer risk:

https://link.springer.com/article/10.1007/s10654-022-00873-6

Response C3: We have cited some more recent studies to support the statements in the introduction section as, "It is suggested that this phenomenon may be explained, at least partly, by changing environmental and lifestyle risk factors in these regions, such as the epidemic of obesity, lack of physical activity, and long-time sitting.3,4" (See Lines 73-76); "In addition, although less evidence presented, similar concerns have been raised with regard to physical activity, which has potential protective effect on cancer risk.4,20,21"(See Lines 120-122).

We have also added the mentioned meta-analysis on sedentary behavior and multiple cancers in our revision, as following: "Three previous meta-analyses investigating the association between sedentary behavior and several types of cancers,8" (See Lines 86-87).

3. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. Br J Sports Med. 2022;56(2):101-106. doi:10.1136/bjsports-2020-103640

4. Yasin HK, Taylor AH, Ayakannu T. A Narrative Review of the Role of Diet and Lifestyle Factors in the Development and Prevention of Endometrial Cancer. Cancers. 2021;13(9):2149. doi:10.3390/cancers13092149

20. Saint-Maurice PF, Sampson JN, Michels KA, et al. Physical Activity From Adolescence Through Midlife and Associations With Body Mass Index and Endometrial Cancer Risk. JNCI Cancer Spectr. 2021;5(4):pkab065. doi:10.1093/jncics/pkab065

21. Kitson SJ, Aurangzeb O, Parvaiz J, Lophatananon A, Muir KR, Crosbie EJ. Quantifying the Effect of Physical Activity on Endometrial Cancer Risk. Cancer Prev Res (Phila Pa). 2022;15(9):605-621. doi:10.1158/1940-6207.CAPR-22-0129

8. Hermelink R, Leitzmann MF, Markozannes G, et al. Sedentary behavior and cancer–an umbrella review and meta-analysis. Eur J Epidemiol. 2022;37(5):447-460. doi:10.1007/s10654-022-00873-6

2. The search was last conducted in March 2021. Please update the search to include more recent data. For example, this study may qualify:

https://www.jstage.jst.go.jp/article/jea/31/12/31_JE20200145/_article/-char/ja/

Response C4: We have updated the cut-off date of the literature searching (by 28th February 2023) and found no newly added research. The mentioned study has been included as Miyata et al. (2021) in the original draft.

3. Lines 144-146 please define the difference between physical inactivity and physical activity.

Response C5: We thank the reviewer very much for the comment. We have added the definition of physical inactivity to distinguish it from physical activity, as "Terms associated with physical activity and physical inactivity (insufficient or low levels of physical activity) were also searched since some sedentary behavior studies were conducted in the name of physical activity." (See Lines 144-145).

4. Lines 156-157 please define "highest versus lowest". How are these being defined? How many hours of sedentary behavior in each category?

Response C6: We thank the reviewer for the insightful comments. We are sorry that we did not make a precise expression in the original version. We have improved the statement in the revision as "The highest and lowest values were defined by individual studies with different underlying definitions and different measurements of sedentary behavior. Detailed definition and assessment of sedentary behavior in individual study was summarized in Table S3." (See Lines 202-205).

In addition, relevant limitations have also been discussed as "…it should be emphasized that there could be wide interindividual variation in level of sedentary behavior, with all studies assessing self-reported levels of sedentariness based on questionnaires, interviews, or job titles, and neither of these studies applied repeated measures or corrected for measurement errors. Most included studies compared high versus low level of sedentary behavior and thus, the effect estimate may be inflated

compared to a linear analysis. Moreover, definitions of high versus low levels of sedentary behavior varied greatly in the included studies. For example, the highest level of sedentary behavior in some studies may vary from more than 3 to 8 hours/day, which may decrease the comparability among studies." (See Lines 477-486)

D. Statistical analysis
1. Was adjustment for study quality made? If so, please report. If not, consider including.
Response C7: We have conducted and reported the quality assessment of the studies based on the validated Newcastle-Ottawa Scale (NOS) (See Lines 181-195). In addition, subgroup analysis stratified by study quality was also performed (See Line 222).

2. I appreciate that conducting a meta-analysis on the primary outcome of this study is challenging due to the variation in reporting between studies and the lack of standardization in reporting for sedentary behavior. I recommend the author's consider using a 3-level meta-analysis to account for variation. The 3 sources of variance taken into account included: variance at the level of the subject (Level 1), variance between effect sizes extracted from the same study (Level 2), and variance between studies (Level 3). See this article: https://www.tqmp.org/RegularArticles/vol12-3/p154/p154.pdf
Response C8: We thank the reviewer for the suggestion. We agree that the mentioned multilevel analyses are suitable for data with multi-level structure, given three different variance components are considered (sampling variance at the first level, within-study variance at the second level, and between-study variance at the third level). Therefore, three-level meta-analysis is a strong method for dealing with interdependency of effect size, especially for cases with large heterogeneity or geographically nested design.
However, the statistical method we used is common with proved performance and robustness and has been widely used (Borenstein, et al. 2009; Higgins & Green, 2011), leading to a better comparability with previous work. More evidence on the performance and robustness of multilevel meta-analytic models using data sets of different sizes is needed (Assink & Wibbelink, 2016). Meanwhile, our study extracted individual estimation from each study, therefore the within-study variance may not exist. Since two modeling strategies share the same rationale (Borenstein, et al. 2009), the more sophisticated logarithms might lead to higher uncertainty of the pooling (wider confidence intervals). Moreover, our result of pooling is deemed with moderate heterogeneity, the robustness of the pooled associations was shown in multiple subgroups and sensitivity analyses.
Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. 1st ed. Wiley; 2009. doi:10.1002/9780470743386
Higgins JPT, Green S (Editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Updated March 2011]. The Cochrane Collaboration, 2011. Available from Www.Handbook.Cochrane.Org.
Assink, M., & Wibbelink, C. J. M. (2016). Fitting three-level meta-analytic models in R: A stepby-step tutorial. The Quantitative Methods for Psychology, 12(3), 154-174. https://doi.org/10.20982/tqmp.12.3.p154
E. Results:
1. Reasons for article exclusion could be more clear. For example, what does "methodology n=20" mean?
Response C9: We mean that: twenty papers focused on the methodology of physical activity assessment were excluded. We have improved the statement as "Methodology of physical activity assessment (n=20)" in Figure 1.
2. Line 260 and also in abstract the total sample is missing a comma. Should be written as 882,686. Same comment for every number reported.
Response C10: We are sorry for the incorrect expression of number. We have carefully checked and revised them throughout the paper.
3. Line 270 please report references for study quality measurements.

Response C11: We have added the reference for the study quality measurements (See Line 274), as reported in the Methods section. See also Response C7.

4. Lines 275-278 language is informal and includes a run-on sentence. Please revise for example: Twelve studies have investigated impacts of sedentary behavior during work on endometrial cancer, and five of them reported significant association between occupational sedentary behavior and increased risk of endometrial cancer.7 18 19 25 27 However, five studies did not observe a similar significant effect.12 13 22 23 26 28 29.

Response C12: We thank the reviewer very much for this suggestion. We have revised the statement to "Twelve studies have investigated impacts of sedentary behavior during work on endometrial cancer, and five of them reported statistically significant association between occupational sedentary behavior and increased risk of endometrial cancer.10,24,25,32,34 However, seven studies did not observe a similar significant effect.16,17,29,30,33,35,36" (See Lines 281-285).

5. Line 281 missing p-value

Response C13: We thank the reviewer very much for the comment. We have added p value for all the results reported and have carefully checked throughout the paper.

6. Please include the type of sedentary behavior measurement used in the studies in the results sections. How many were self-report? How many were objective?

Response C14: We have added statement as "All included studies assessed self-reported sedentary levels based on questionnaires, interviews, or occupations (Table S4)." (See Lines 258-260)

7. Line 363: needs to define what "higher levels of total sedentary behavior" means. Further, is this 55% increase based on the data of N=2 studies? That is a major limitation and needs to be highlighted.

Response C15: As mentioned in the previous response (See Response C6), the higher levels here represent a general conception of higher exposure as the definition and assessment of sedentary behavior varies across studies. We cannot provide definitions of higher levels of sedentary behavior. In addition, we thank the reviewer very much for the insightful comments on the results for the total domain, which was pooled from limited evidence. We have improved the statement and discuss the relevant limitation in the revision, as following: "Secondly, the small number of studies included in our meta-analysis could lower the statistical power and limit the ability to examine the existence of small study effects and excess significance bias. For total domain of sedentary behavior, only two studies estimated the association with endometrial cancer. In such case, the reliability of the pooling may be influenced, and the results should be interpreted with caution.46" (See Lines 472-477)

46. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. 1st ed. Wiley; 2009. doi:10.1002/9780470743386

F. Discussion:

8. Lines 363-366 needs to include data to support claims.

Response C16: We are sorry that we did not make a precise expression in the original draft. We have added risk estimates to support the claims in the discussion, as following (See Lines 372-378):
"In this systematic review and comprehensive meta-analysis, 55% increased risk of endometrial cancer was observed among individuals with higher levels of total sedentary behavior (RR=1.55, 95% CI: 1.27-1.89), 22% among those with occupational sedentary behavior (RR=1.22, 95% CI: 1.09-1.37), and 34% with borderline significancy among those with leisure-time sedentary behavior (RR=1.34, 95% CI: 0.98-1.83). The overall increased risk disregarding specific domains was 27% (RR=1.28, 95% CI: 1.14-1.43)."

9. 394: first mention of diet here. Please include diet discussion in the introduction or remove from this section as it is too late to introduce the topic without explanation as to how diet contributes to lifestyle risk.

Response C17: We have added relevant evidence in introduction, as following (See Lines 101-104):
"…while occupational sedentary behavior is related to education and socioeconomic variables, leisure-time sedentary behavior is likely linked to lifestyle factors such as diet and obesity.13"

13. Hobbs M, Pearson N, Foster PJ, Biddle SJH. Sedentary behaviour and diet across the lifespan: an updated systematic review. Br J Sports Med. 2015;49(18):1179-1188. doi:10.1136/bjsports-2014-093754

10. Lines 458-460: this is a major limitation, and a huge concern in the interpretation of these data. A meta-analysis ultimately informs policy development, and the lack of reporting as to what is "high" and what is "low" needs to be addressed in this manuscript. The authors need to include reporting of what is defined as "high" vs. "low" in order to improve the interpretation of these data.

Response C18: We thank the reviewer very much for the constructive comments. We agree and have supplemented the relevant statements in the revision. Please refer to the Response C6 and C15.

G. Conclusion:

Please consider revising the conclusion to highlight the major limitations of these data. The conclusions are strong considering the lack of studies, variation in reporting, and potential limitations.

Response C19: We have revised the expression as "Despite the little evidence on domain-specific effect of sedentary behavior on endometrial cancer, we found, in general, higher levels of total and occupational sedentary behavior increase the risk of endometrial cancer. The association between leisure-time sedentary behavior and endometrial cancer is borderline significant. The pooling may be influenced by limited studies and variations in assessment of sedentary behavior and should be interpreted with caution." in the conclusion section (See Lines 495-504).

H. Table 1:

1. Formatting of headings needs to be addressed. "Number of participants" is not formatted correctly.

Response C20: We have changed the 'number of participants' into 'subject' with the reference to a previous systematic review (See Table 1).

Hashizume M, Kim Y, Ng CFS, Chung Y, Madaniyazi L, Bell ML, Guo YL, Kan H, Honda Y, Yi SM, Kim H, Nishiwaki Y. Health Effects of Asian Dust: A Systematic Review and Meta-Analysis. Environ Health Perspect. 2020 Jun;128(6):66001. doi: 10.1289/EHP5312.

2. Physical activity and BMI not reported in the table. Additionally, classification of "high" vs "low" sedentary behavior should be included in the table.

Response C21: Because there is limited space to explain the confounder and classification of sedentary behavior in detail in Table 1, we have summarized relevant information in supplemental tables (Table S3, S4, S7) with descriptions in the main text shown below:

"Detailed data and characteristics of study participants, diagnostic criteria of the outcome, and the assessment of sedentary behavior is provided in Table S3, S4." (See Lines 260-261).

"Details of confounders adjusted by each study are presented in Table S7." (See Lines 277-278).