11-Sep-2021
BMJ-2021-067528 entitled "Association of Surgical Menopause with All-Cause and Cause-Specific Mortality"

Dear Dr. Cusimano,

Thank you for sending us this paper and giving us the chance to consider your work. We sent it out for external peer review and discussed it at the manuscript committee meeting.

Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again.

The reviewers' comments are at the end of this letter.

The editors' comments are listed below:

We hope that you will be willing to revise your manuscript and submit it within 4-6 weeks.When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your revision may be sent again for review.

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If accepted, your article will be published online at bmj.com, the canonical form of the journal. Please note that only a proportion of accepted analysis articles will also be published in print.

I hope you will find the comments useful. Please don't hesitate to contact me if you wish to discuss this further.

Yours sincerely
Nazrul Islam, MBBS, MSc, MPH, PhD
Research Editor, The BMJ
nislam@bmj.com

Report from The BMJ’s manuscript meeting

At the manuscript meeting the Editor makes the final decisions on accepting original papers submitted to the journal. At the manuscript meeting each article is discussed by The BMJ’s international team of research editors and one statistician. When making decisions we take into account each paper’s originality, scientific merits, and interest to a general readership in comparison with other submitted papers. We take reviewers’ reports fully into account too, but the final decision on acceptance or rejection of a paper rests with the editors.

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee: Wim Weber (Chair), Gary Collins (Statistical advisor), Nazrul Islam, Elizabeth Loder, Joseph Ross, Di Wang., Emma Rourke (BMJ Medicine), Sophie Cook (BMJ Medicine)

Paper: BMJ-2021-067528
Decision: put points

Detailed comments from the meeting:

* First, please respond point-by-point to the reviewers' comments.

* The Editors appreciate the use of advanced statistical modeling to answer these important research questions, but it still is an observational study, and therefore, please revise the causal language throughout the manuscript.

* To the point above, please consider toning down the conclusions such as "Ovarian preservation should be adopted in premenopausal women...".

* Previous studies adjusted for other covariates (e.g., BMI, smoking, alcohol use). Please elaborate if these were available in the database. If these were available, please justify for not adjusting for these. If not, please elaborate on the effects of not adjusting for these in the analysis, and/or acknowledge these limitations more specifically in the limitations section.

* Fig 2 depicts the hazard ratios nicely, but is restricted to age <55. Please use the full age range for this analysis (i.e., age >= 55y).

* One Editor commented: it’s a pity they do not have data of HT. And I wonder If they could provide data about death from cerebrovascular disease.

* To put the rationale of the study in global context, might you consider adding some data on how often these procedures are still being done around the world, and any existing data on the quality of life after these procedures.

* One Editor commented: There are clinical considerations for salpingectomy with or without oophorectomy at the time of hysterectomy? I believe this is an emerging practice. Could the authors elaborate on in reference to this paper (https://pubmed.ncbi.nlm.nih.gov/33038519/)

* Another Editor commented: I don’t much like the terms benign hysterectomy or surgical menopause. Can the authors say hysterectomy for non-malignant disease and just refer to BSO rather than surgical menopause (particularly as we don’t know about HRT)?

* Ethnicity groupings are confusing. The use of "General population" indicates the South Asian and Chinese ethnic population are not part of general population. Please consider using a more appropriate term for this group. Does it include White, Black, Mixed, and Other? Does it also include Unknown or missing ethnicity?

* Please comment on the completeness of the Ethnicity covariate. Also, please describe the accuracy of the Ethnicity identification using Ref# 24.

PPI
Please add the reason(s) for not involving members of the public in your own words (e.g.) funding or training restrictions, access to software, COVID etc, also it may be that speaking to patients inspired this review if this was the case it is fine to add that although there was no direct PPI in this paper due to____we did speak to patients about the study and we asked a member of the public to read our manuscript after submission. Please place the PPI declaration at the end of the methods.

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
1. Are the questions the paper addresses relevant and important to patients and/or carers?
• The study, which identified over 200,000 women undergoing benign hysterectomy, suggests bilateral salpingo-oophorectomy (BSO) should be avoided in women of premenopausal age whenever possible. BSO for ovarian cancer prevention vs. potential harm on the loss of hormone production is of clinical significance and relevance.

2. Are there topics or issues that are missing, or need to be highlighted more?
• Is the data used from the linked health administrative databases held at ICES being deidentified, pseudonymised or anonymised for the use of this study? It would also be great to have ICES in its long form at the first occurrence so that readers know more about this research institute.
• Page 15, line 15: "current guidelines have therefore advised against BSO in premenopausal women" vs. page 15, line 33: "Current guidelines offer no recommendations on whether BSO should be performed or withheld in perimenopausal and postmenopausal women" – this seems slightly contrary.
• Table 3 presents a number of cohort studies examining the association between bilateral salpingo-oophorectomy (BSO) and all-cause death. This study and the last study in table 3 are the only ones that take into account immigration status. What is the significance of including this as a covariate?

• Page 15, line 3: "had sufficient power for both age stratified and cause-specific analyses" – is this a quantitative measure of power that can be included?
• Is it possible to break down the category of ethnicity into smaller groups, rather than just having general population, South Asian and Chinese?

3. Is the treatment or intervention suggested or guidance given something which patients/carers can readily take up? or does it present challenges?
• The article is clearly written and easily understandable by the public. Graphs and tables are neatly presented.

4. Are the outcomes described/measured in the study important to patients/carers? Are there others that should have been considered?
•This study defined premenopausal as <45. Is this in line or similar to the definitions other studies and guidelines referenced in the introduction and the discussion sections? For example, when you say BSO should be avoided in women <45 of age, can you comment on whether that is in line with the current guidelines or not and if "premenopausal" in the current guidelines also refer to <45 of age?

5. Do you have any suggestions that might help the author(s) strengthen their paper and make it more useful for doctors to share and discuss with patients/ carers?
• It is worth giving a one-sentence definition/ description of what BSO is in the introduction.

6. Do you think the level of patient/carer involvement in the study could have been improved? If there was none do you have ideas on how they might have done so?
• Patients and the public were not involved in the design or conduct. It would be best to set up a patient and public involvement group to discuss the use of electronic health records held at ICES.

Additional Questions:
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Please enter your name: Chun Hei Kwok

Job Title: Data Manager

Institution: University of Oxford

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
This is a retrospective study from 1996-2015 and follow up through 2017 evaluating all-cause and cause specific mortality in women undergoing elective hysterectomy, comparing bilateral oophorectomy with conservation of the ovaries in Canada. Overall, this is a well-written paper with statistical methods well thought out. All of the limitations were addressed within the discussion. This will be of great interest to readers.
Only 2 minor comments.
Summary box, second bullet, typo, "enrol"
For women with unilateral salpingo-oopherectomy, how many were there, and what were the indications for the previous surgical procedures?

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Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Chrisandra Shufelt, MD

Job Title: Professor

Institution: Cedars-Sinai Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:
The manuscript by Cusimano et al summarizes the results of a cohort study of the association between bilateral oophorectomy and overall mortality and cause-specific mortality conducted in Ontario, Canada. The question addressed is extremely important and timely. The population-based data resources from Ontario are unique. The methodology is described in detail and the manuscript is clearly written. I have a few suggestions for improvement of the manuscript:

Major comments:
1. I suggest adding to the results of primary analyses the absolute risk increase (ARI) or reduction (ARR) at 20 years. ARI and ARR can also be used to compute the number needed to harm (NNH) or the number needed to treat (NNT).
2. I suggest mentioning that the HR for all-cause mortality in the 50-54 years group is marginally significant in the direction of reduced risk (0.018). Similarly, the HR for cancer mortality in the ≥55 years group is marginally significant in the direction of reduced risk (p = 0.023). These marginal findings support the argument of the investigators that the effects of bilateral oophorectomy are strongly age dependent. The authors may want to mention the debate about a "window of opportunity" or "timing hypothesis" (e.g., Rocca et al, Brain Research 2011).
3. I consider the selection of the reference group (unexposed women) an issue of study design, not a limitation. On page 5, lines 42-52, the authors mention the use of non-surgical controls (they mean referent women) as a limitation. We and others argue that the selection of the referent group depends on the research question. We and others have argued that benign hysterectomy is not an unavoidable fact of life. Therefore, hysterectomy itself is under scientific scrutiny. We and others have shown that having a benign hysterectomy with ovarian conservation is a risk factor for morbidity and mortality (e.g., Laughlin-Tommaso et al, Menopause 2017 and Laughlin-Tommaso et al, Menopause 2019). The problem of the future of gynecological practice goes beyond the decision to remove or not to remove the ovaries. A broader discussion of the issue is reported in Stewart et al, Mayo Clin Proc, 2021 and Rocca et al, Climacteric 2021. As a matter of fact, of 9 studies in Table 3, 4 used non-surgical referent women.

Minor comments:
4. I suggest avoiding the term "surgical menopause" in the title and throughout the manuscript. Surgical menopause is ambiguous as to the endocrine status of a woman. A full discussion of this terminology problem was reported in Rocca et al, Climacteric 2021. I am also arguing that the term bilateral salpingo-oophorectomy should be replaced with bilateral oophorectomy. However, this suggestion is not mainstream (see Rocca et al, Climacteric 2021).
5. I suggest avoiding the adjective "retrospective" to describe a cohort study. Either use simply "cohort study" or "historical cohort study". The problem with the use of the adjective "retrospective" is well illustrated on page 13, lines10-11.
6. When quoting the Mayo Clinic Cohort Study, I suggest quoting two specific reports on cause-specific mortality: Rivera et al, Neuroepidemiology 2009 and Rivera et al, Menopause 2009).
7. Page 6. Line 15. Please spell out the abbreviation ICES the first time it is used.
8. Page 7, line 49-50. The term "general population" is not quite clear from a US perspective. Are most of these persons Whites of European descent?
9. Page 14, line 33-34. There is an extra "the".
10. Page 14, lines 49-50. Add to the sentence "… in other jurisdictions and settings." the specification "with similar demographic and socioeconomic characteristics".

11. Table 3. The Cusimano 2020 study should be labeled as 2021 or “current study” to avoid confusion.
12. Because of the limitations honestly and professionally described on page 15, the authors should recognize that their study is a nice addition to a solid body of literature, rather than the final proof of the truth.

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Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Walter A. Rocca

Job Title: Professor of Epidemiology and Neurology

Institution: Mayo Clinic

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:

Comments:
This is a well written and interesting study investigating the association between hysterectomy with BSO and all-cause and cause-specific women, with hysterectomy with ovarian conservation as the reference. The study methods and results are clearly presented.
I have a few comments for the authors to consider:

(1) The Conclusions statements and "What this study adds" sections state that "BSO should be avoided in women of premenstrual age". This is quite a bold statement, and the authors should be careful with the wording, considering each woman will have a different risk profile and individual circumstances. The authors stated in their limitations that they did not have data on family history and genetic predisposition to malignancy, and therefore they should be very careful in the wording for this statement for women with an increased risk of ovarian cancer.

(2) While the authors have included several potential confounders in their propensity score matching, they have not investigated whether there could be effect modification for some of these variables. In this study, of the women who had a hysterectomy + BSO under the age of 45, 50% had endometriosis and 29% had an ovarian cyst, compared to 27% and 10%, respectively, in the hysterectomy with ovarian conservation group (Table 1). The authors may want to consider effect modification for some of these variables, particularly where indication for surgery is an important factor in the decision making of an individual to have surgery.

(3) Following from comment 2, a proportion of women who have a hysterectomy with BSO will be making a decision between hysterectomy with BSO or no surgery (or an alternative treatment); thus the decision may often not be between hysterectomy with or without BSO. The authors have not assessed the association between hysterectomy with BSO and mortality compared to women without surgery. The conclusions can, therefore, only be applied to women having a hysterectomy for benign indication who are weighing up the risk and benefits of also removing the ovaries as part of this procedure. The authors should consider this in the wording of their conclusions.

(4) The authors should make it clear in the abstract that when the term 'age' is used it is referring to age at surgery.

(5) Page 13, line 15: The authors state that the prior research has limitations, however these are not included in Table 3 as indicated.

(6) In Table 2, the authors should consider listing the adjusting variables used in the sensitivity analysis in a footnote to the table.

(7) In Table 3, the HRs cited for the paper by Tuesley 2020 were those from a sensitivity analysis rather than the main results from that study. This should be corrected to show the study's main results from the study.

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Please enter your name: Karen Tuesley

Job Title: PhD Candidate

Institution: University of Queensland

Reimbursement for attending a symposium?: No

A fee for speaking?: No

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Reviewer: 5

Recommendation:

Comments:
BMJ-2021-067528
Association of Surgical Menopause with All-Cause and Cause-Specific Mortality

This manuscript describes a retrospective cohort study of 200,549 women aged 30-70 years who have undergone benign hysterectomy. The objective was to determine if bilateral salpingo-oophorectomy (BSO) compared to ovarian conservation is associated with mortality (all-cause or cause-specific) in women undergoing benign hysterectomy, and to determine whether/how this varies depending of at age the time of surgery.
The authors stratified age groups to correspond to pre-menopause, menopausal transition, early menopause and late menopause. Primary end point was all- cause death; secondary end point was non-cancer and cancer death. The statistical analyses included overlap weighting based on the propensity score; Cox proportional hazard models.
The authors found that in women < 50 years of age undergoing benign hysterectomy, BSO was associated with increased mortality, whereas this was not the case in women aged 50 or older.

As there previously has been varying data favoring either BSO or ovarian conservation in women undergoing hysterectomy, this study is important as the authors have tried to eliminate some probable causes of bias and to explain some of the differences of outcomes in previous studies. It is biologically plausible that there is a difference between women depending on menopausal stage, thus stratifying into age-groups (as data on menopausal status weren't available) along with analyses of each year of age around the menopausal transition.
Using all-cause mortality is sensible as well as is including the secondary outcome of non-cancer and cancer death. This eliminates issues of competing risks that are unaccounted for.
Generally, the data are in line with similar previous studies, and it is also reassuring that the results are comparable for primary analysis and the sensitivity analysis.

Strengths:
Large number of women studied and long follow up.
Age groups were defined a priori, therefore the results (as to age groups) are less likely to be incidental, but plausible due to a sound hypothesis.
Excluding women with malignant disease or prior breast or gynecological cancer along with surgery for genetic predisposition to malignancy.

Weaknesses:

Age is only a proxy for menopause as this typically varies over 10 years; data on menopause would have improved the weight of the biological plausibility of the results, and may have reduced some of the other unknown confounders.
The propensity score is used to reduce the confounding due to known characteristics/covariates, but not the unknown ones, and perhaps these unknown confounders become noticeable when comparing to some of the similar studies such as the WHI where more covariates of importance for cardiovascular health and mortality were included such as BMI, smoking, exercise, hypertension and diagnoses of cardiovascular disease. Some of these risk factors are also related to early menopause. (In the WHI, the HR was around 1.0, thus suggesting no effect of BSO vs. Ovarian hysterectomy)
So, when correcting for covariates of high importance for mortality in women < 50 years of age, the increased risk of BSO seen in the present manuscript could possibly be explained by confounders. This should be commented on in the discussion.

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Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Louise Schierbeck

Job Title: Dr.

Institution: Nordsjællands Hospital, Hillerød; Department of Cardiology

Reimbursement for attending a symposium?: No

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