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**Title:** Endometriosis as a risk factor for premature cardiovascular disease: a population-based cohort study

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**Reviewer 1:** Jamie Kroft

**Institution:** Obstetrics and Gynecology, Sunnybrook Health Sciences Centre  
General comments (author response in bold)

This is a large population-based retrospective cohort study of patients with endometriosis compared to patients without the disease, examining whether there is an increased risk of cardiovascular hospitalization.

Strengths of this paper are the large cohort size, the universal nature of the administrative data used and the statistical analysis.

There are some limitations that should be addressed prior to publication. The cohort of patients with endometriosis was established based on codes used by the authors that were not validated within Ontario. In their discussion, they state that the codes were validated in Sweden but I think it would be helpful to have more information about how they validated the codes used for the study population. Since OHIP codes were used as part of this project, which would not be a part of the Swedish study, more description would be helpful to ensure the study cohort is valid.

**These have been recently validated by a group in Canada – please see reference of abstract in text (publication pending).**

As well, a major limitation is that the endometriosis group has a much higher rate of hysterectomy, bilateral oophorectomy and early menopause. These are known risk factors for cardiovascular disease. The authors note this, but I am not sure why they don't include these as potential confounders in the analysis. These should be adjusted for in the multivariate analysis. If the reason that cardiovascular disease is higher in endometriosis patients is because of early menopause/BSO, then it would be this factor we should be investigating, rather than endometriosis as an independent risk factor. The authors jump to a cause and effect conclusion but at this stage endometriosis is an association with a known risk factor that hasn't been adjusted for.

**Given that females diagnosed with endometriosis in our study developed premature menopause (premature ovarian insufficiency) after enrollment (not prior to endometriosis diagnosis), we do not believe premature menopause is a confounder. Rather, we believe that hysterectomy, bilateral oophorectomy and early menopause come after endometriosis and before CVD, and are hence in the causal pathway to CVD. As such, these variables should not be adjusted for. However, as these variables may be part of the causal effects of endometriosis on CVD, a mediation analysis has been conducted to estimate their indirect effect.**

One last question is in Figure 4 the legend states it is a comparison of Hazard ratios between exposed and unexposed groups for each age range, but there is only one hazard ratio/confidence intervals in each graph, not two. Is one group missing here?

**As this figure plots hazard ratios, the hazard itself is comparing the endometriosis group (exposed) to the unexposed population.**

Thanks very much for this interesting submission.

**Reviewer 2:** Mathew Leonardi MD PhD, Gynecologic Surgeon Sonologist, Assistant Professor

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General comments (author response in bold)

Endometriosis as a risk factor for premature cardiovascular disease: a population-based cohort study

Abstract

- Well written

Introduction

- Line 24: I might avoid stating that three studies have evaluated the association. This is not a systematic review, and the literature could change between submission and decision.

**This text has been revised as follows “To date, there are limited data on the association...”**

Methods

- The authors may need to elaborate on why endometriosis diagnosis prior to the study window is a reason for exclusion. How would the authors even know if diagnostic codes for endometriosis were applied to the patients before 1993 if that was the beginning of the study interval?

**Data from the ICES dataset is only available starting in 1992, and the first few years are not as complete as subsequently. This is why 1993 was chosen as a starting year for data collection.**

- Did the authors consider excluding controls if they had visits for pelvic pain?

**This was considered, however diagnostic codes for pelvic pain alone have been demonstrated to not be correlated with endometriosis.**

- Why were these three gynecologic conditions considered and not others? E.g. infertility?

**Fibroids, infertility, and pelvic pain were considered gynecologic conditions which may present similarly to endometriosis. There are numerous other gynecologic conditions which may also contribute, but were felt to be less likely related to the effect of endometriosis. This is now also addressed in our discussion.**

- I am unable to access the Appendices so maybe this is clear from that, but were there certain surgical procedures that did or maybe should have resulted in exclusion of individuals from being a control/unexposed individual? E.g. hysterectomy?

**While some of these patients may indeed have had other surgical procedures, they would still be exposed to endometriosis related risk factors. An analysis was carried out for those diagnosed with premature menopause (premature ovarian insufficiency)- which includes bilateral oophorectomy. However, a simple hysterectomy may not remove all endometriosis nor its risk factors; as such these patients were not excluded.**

- Is diabetes really considered a form of cardiovascular disease? Should an emergency visit for diabetes really count?

**While this is true, these were validated and used in the CANHEART study. We agree that diabetes alone as an emergency visit may not be considered a form of cardiovascular disease, and this has been removed from the ED visit composite outcomes. Similarly, given that we included patients with diabetes and hypertension at baseline in our cohort, we have also excluded ED visits for hypertension from the ED visit composite outcome.**

- The multivariate models adjusted for all variables other than other gynecologic conditions. Why?

**These were not adjusted for in our models as their presentation was thought to often be similar to or concurrent with that of endometriosis.**

- Why was no adjustment made for gynecologic procedures?

(<https://www.bmj.com/content/375/bmj-2021-067528>) While one could argue that the procedures are commonly done BECAUSE of endometriosis and therefore not confounders themselves, one may also argue that certain treatments like BSO are inappropriate as a treatment for endometriosis and by controlling for it, the more pure influence of endometriosis on CVD can be gathered.

**Please see explanation above indicating that premature menopause is a likely not a confounder but rather possibly in the causal pathway from endometriosis to CVD. As such we have completed a mediation analysis to address these effects.**

- Beyond surgery, medical treatments for endometriosis are not captured and are a potential confounder.

**Given that treatments for endometriosis occur after a diagnosis and not before, this would likely be an effect modifier rather than a confounder. However, we agree this is a limitation of our study as we did not have the ability to capture this information in our dataset. This is mentioned in our discussion: “We also did not include information on stage of endometriosis or treatments used by many females with endometriosis which may affect the risk of CVD, including NSAIDS, opioids, or hormonal treatment measures such as GnRH agonist suppression, which may induce medical menopause. This is a limitation of administrative health datasets to study endometriosis; unmeasured confounding from these factors may be present.”**

- Was there any intention to assess the interval of time between the label of diagnosed endometriosis and the label of CVD?

**This is now addressed in Figure 4. We present that earlier diagnosis of endometriosis increases risk of CVD.**

## Results

- The average age is quite a bit older than expected. As endometriosis is high likely not a disease that just appears in one's 30s, why do the authors believe analyzing the age at index test diagnosis is relevant? Maybe it would be relevant to bring into the Interpretation the delay in diagnosis (particularly during the era in which the study was completed) and the impact on unexposed inflammatory burden that is present due to lack of treatment.

**This has been added to our discussion: “Unfortunately the delay in diagnosis of endometriosis still remains significant, and women may experience endometriosis symptoms and thus be exposed to untreated inflammation and oxidative stress in the years prior to the assignment of a diagnosis. However, analyzing the age of diagnosis is the closest measurement of length of exposure based on diagnostic coding. An individualized study approach would be required to determine longevity of symptoms, and hence more specific length of risk exposure.”**

- The last part of the Results feels like a throw-away line. I would suggest bringing more written detail here while still referring to the Figure.

**This sentence has been incorporated into the results.**

- Was any consideration made to analyze those who had a surgical diagnosis versus alternative non-surgical diagnoses? What was the point of saying in the Methods, “They were considered to have had a surgical confirmation of disease...” (Page 5, Lines 21-24).

**These are now addressed to ensure no difference in outcomes between medically and surgically diagnosed. A mediation analysis was conducted to determine if there were differences in these patients. This is now in the results section: “The sensitivity analysis indicated that our results did not differ by type of diagnosis of endometriosis (medical vs. surgical) suggesting no misclassification. There was no difference in risk of hospitalization (medically diagnosed aHR 1.14; 95% CI 1.04-1.25 vs. surgically diagnosed aHR 1.14; 95% CI 1.10-1.19) or CVD events between medically or surgically diagnosed endometriosis patients, when compared to those without endometriosis diagnoses (medically diagnosed aHR 1.22; 95% CI 1.13-1.32 vs. surgically diagnosed aHR 1.27; 95% CI 1.23-1.31). However, the risk of ED visits was higher in the medically diagnosed group (medically diagnosed aHR 1.47; 95% CI 1.37-1.58 vs. surgically diagnosed aHR 1.27; 95% CI 1.22-1.32).”**

Interpretation

- Well written

- Exercise is another confounder of importance as endometriosis patients with chronic pain are likely less active.

**This has been added to our discussion: “Our study does not detail personal history for each patient enrolled, including presence of modifiable lifestyle risk factors for CVD such as smoking, diet and exercise.”**

- How do the authors take into account the large time frame and the possibility that diagnosing endometriosis and CVD changed significantly over the time frame?

**Given that there has been significantly improved awareness surrounding endometriosis in the time frame of the study, this may have increased diagnosis. However, this should not affect the comparison of the study population to the unexposed, and if there were an effect would likely bias the results towards the null. Due to word constraints in the article this has not been fully discussed.**