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Dear Dr. Godlee,

Re: Association of Bilateral Salpingo-Oophorectomy with All-Cause and Cause-Specific Mortality (BMJ-2021-067528)

We thank the Editors and Reviewers for their detailed and thoughtful commentary on our original manuscript. We have made substantial revisions and endeavored to address each of the comments thoroughly. We believe that these revisions represent significant improvements to the manuscript, and that it is stronger overall. All modifications to the manuscript are noted in blue, with line numbers referring to the clean resubmitted version.

Randomized controlled trials evaluating long-term mortality outcomes after bilateral salpingo-oophorectomy are not possible. Rigorous observational research, despite its inherent limitations, is therefore essential in informing practice on this important and controversial topic. In the present study, we meticulously addressed the limitations of existing literature through our specific research design and approach to statistical analysis, and directly acknowledged outstanding gaps that require resolution.

Our findings have not been published elsewhere. Our manuscript is not under consideration by any other journal and will not be submitted elsewhere while under review at *The BMJ*. Please do not hesitate to contact me should you require anything further.

Sincerely,

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Editors, Comment 1: 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.

Author Response: We agree with this feedback and have tempered our language throughout the manuscript and particularly in the Discussion and Conclusion sections. We have also been careful to acknowledge the inherent limitations of observational research, and the strategies we employed in both study design and analysis to mitigate these as best as possible.

Modified Text:

- Abstract, Page 3, Lines 54-57: "In this observational study, BSO appeared to be associated with increased all-cause mortality in women <50, but not ≥50 years. While ovarian conservation at non-malignant hysterectomy may warrant consideration in premenopausal women without an indication for BSO, this strategy may not offer a survival benefit in postmenopausal women."
- Summary Box, Page 4, Lines 69-70: "Our study suggests that BSO may be associated with increased rates of all-cause and non-cancer death in women <50, but not ≥50 years."
- Summary Box, Page 4, Lines 73-75: "In contrast to emerging hypotheses, and although unmeasured confounding remains possible, our study suggests that BSO may not be detrimental to survival when performed at the time of non-malignant hysterectomy in women of postmenopausal age."
- Discussion, Page 14, Lines 299-300: "Compared to ovarian conservation, BSO appeared to be associated with significantly increased all-cause mortality in women <50 but not ≥50 years."
- Discussion, Page 15, Lines 307-308: "Our study suggests that BSO may be associated with increased all-cause death in women of premenopausal age."
- Discussion, Page 15, Lines 37-320: "Considering the strong methodology employed in this work and by Mytton et al., consistency of published literature on this association, and presence of a plausible mechanism, caution may be warranted when considering BSO in young women, namely those without a clinical indication for the procedure."
- Discussion, Page 15, Lines 321-322: "Our study also suggests that BSO may not be associated with all-cause death in women of postmenopausal age."
- Discussion, Page 16, Lines 343-345: "Since age serves as a population-level surrogate for the onset of menopause, these findings provide some support to assertions that BSO could potentially be harmful in premenopausal, but not postmenopausal women."
- Conclusion, Page 19, Lines 399-406: "Our study is consistent with existing literature in suggesting that BSO may be associated with increased all-cause mortality in women of premenopausal age. We found no significant association between BSO and all-cause mortality in women of postmenopausal age. Our findings apply specifically to women undergoing hysterectomy for non-malignant indications, and unmeasured confounding remains a limitation of this work and existing studies. Caution is warranted when considering BSO in premenopausal women without an indication for the procedure, and additional research on other potential trade-offs of BSO in postmenopausal women is required."

Editors, Comment 2: To the point above, please consider toning down the conclusions such as "Ovarian preservation should be adopted in premenopausal women...".

Author Response: We have made the indicated changes, as described in detail above.

Location of Modified Text: See Editors, Comment 1.

Modified Text: See Editors, Comment 1.

Editor, Comment 3: 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, 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.

Author Response: Information on metabolic factors such as BMI, smoking, alcohol use, and physical activity were not available in the databases used for this study. However, we were able to capture comorbidities that are often highly correlated with these factors, such as hypertension, diabetes, cardiovascular disease, and chronic obstructive pulmonary disease, with a high degree of accuracy using validated registries of affected Ontarians. Controlling for these downstream comorbidities likely mitigated potential confounding from the metabolic factors described. Our effect estimates are also generally consistent in direction and magnitude to other studies in the literature that were able to control for such factors[1-4]. Nevertheless, we agree that this is a limitation and have expanded the Discussion section to directly acknowledge this, and to describe the anticipated effect of not adjusting for these covariates in the analysis.

References:

1) Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7(10):821-8.
2) Gierach GL, Pfeiffer RM, Patel DA, Black A, Schairer C, Gill A, et al. Long-term overall and disease-specific mortality associated with benign gynecologic surgery performed at different ages. Menopause. 2014;21(6):592-601.
3) Wilson LF, Pandeya N, Byles J, Mishra GD. Hysterectomy status and all-cause mortality in a 21-year Australian population-based cohort study. Am J Obstet Gynecol. 2019;220(1):83 e1- e11.
4) Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009;113(5):1027-37.

Modified Text:

- Discussion, Page 18, Lines 378-381: "Second, our health administrative data sources lacked information on family history, intraoperative findings, genetic predisposition to malignancy, and metabolic factors such as body habitus, smoking, alcohol use, and physical activity, which may contribute to residual confounding in other age strata as well. The importance of these factors may change as women age; thus it is difficult to predict the direction or magnitude of possible bias in each stratum. If young women

selecting BSO are also predisposed to malignancy or more likely to have an adverse metabolic profile, then the increased rate of all-cause mortality observed in this population could be potentially be explained by unmeasured confounding. We aimed to limit confounding by: restricting our cohort on age and surgical approach to ensure all patients had an opportunity for exposure to BSO; excluding patients with prior breast cancer or codes indicating genetic susceptibility to malignancy; and using overlap weighting to adjust for as many relevant covariates as possible, including downstream surrogates for unmeasured confounders wherever possible. We also performed sensitivity analyses with a plausible negative control."

Editors, Comment 4: Figure 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).

Author Response: We have repeated this secondary analysis using the full age range (30-70 years); the findings are similar and present the same message as our original secondary analysis in the restricted age range (45-54 years) and our primary stratified analysis in four larger age categories (<45, 45-49, 50-54, ≥55 years).

We purposefully restricted our secondary analysis to women aged 45-54 years because: (1) biologically, this is where we hypothesized any change in the association of BSO with all-cause mortality would occur; and (2) statistically, approximately 50% of the total study population falls into this 10-year age range, so we anticipated tighter confidence intervals when quantifying the hazard ratio for BSO at each year of age in this group. As this was an *a priori* decision with a clear rationale, we have retained our original restricted secondary analysis, but have also added the expanded analysis as a supplement.

Modified Text:

- Methods, Statistical Analyses, Page 10, Lines 204-207: "To assess for a change in the association between BSO and mortality around the age of menopause, we performed secondary analyses in women 45-54 years at surgery; this subgroup was selected because we hypothesized that any such transition would occur in this age range, and there was a sufficiently large number of patients to generate precise effect estimates."
- Methods, Statistical Analyses, Page 10, Lines 211-212: "We repeated this for cause-specific death, and in an exploratory fashion within the full study population (30-70 years)."
- Results, Additional Analyses, Page 14, Lines 288-289: "Findings were similar in exploratory analyses performed in the entire study population (Appendix 9)."
- Supplemental Information, Page 16: Addition of Appendix 9

Editors, Comment 5: It's a pity they do not have data on HT. And I wonder if they could provide data about death from cerebrovascular disease.

Author Response: We agree that it is unfortunate that we lacked data on hormone therapy. However, our original manuscript acknowledges this limitation in great depth and explains why

our analysis is still clinically meaningful: it provides population-average estimates that reflect real-world use of hormone therapy.

With respect to specific causes of death, our dataset contains a variable for cardiovascular mortality (composite of death due to cerebrovascular diseases and ischemic heart diseases). Analysis of this outcome was consistent with our other findings: specifically, cardiovascular mortality was significantly increased for women <45 years (HR 1.47, 95% CI 1.07-2.03, p=0.019), non-significantly increased for women 45-49 years (HR 1.24, 95% CI 0.86-1.80, p=0.25), and not increased for women 50-54 (HR 0.91, 95% CI 0.55-1.50, p=0.71) and ≥55 years (HR 0.95, 95% CI 0.84-1.07, p=0.83). Because estrogen plays a role in cardiovascular health, these findings are biologically plausible. This data has been added as a supplement.

Modified Text:

- Methods, Statistical Analyses, Page 11, Lines 217-221: "To explore the potential impact of unmeasured confounding, we performed overlap weighted survival analyses for (1) death due to cardiovascular disease, thought to exist on the causal pathway; and (2) death due to upper gastrointestinal tract cancer, not thought to exist on the causal pathway but strongly associated with smoking and alcohol use, as a negative control (Appendix 4)."
- Results, Additional Analyses, Page 14, Lines 292-294: "BSO was associated with an increase in death due to cardiovascular disease in women <45 years (HR 1.47, 95% CI 1.07-2.03, p=0.019), and not significantly associated with death due to upper gastrointestinal tract cancer in any age strata (Appendix 11)."
- Supplemental Information, Page 18: Addition of Appendix 11

Editors, Comment 6: 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.

Author Response: Hysterectomy is one of the most commonly performed surgical procedures worldwide[1-3]; as such, decisions on whether to perform BSO at the time of hysterectomy are encountered on a regular basis. We have highlighted this in the Introduction section to emphasize the importance of the study.

Data on quality of life, in addition to mortality outcomes, may help guide decision-making with respect to BSO at the time of non-malignant hysterectomy; however, existing literature on this topic is limited[4-8]. Most studies have been performed predominantly in women 45-55 years, and have not found differences in postoperative quality of life or sexual function between those undergoing hysterectomy with BSO and those undergoing hysterectomy alone; however, few accounted for baseline function at the time of hysterectomy and none controlled for other confounding factors[4-8]. We have therefore highlighted the need for improved data on quality of life, particularly in postmenopausal women, in the Discussion section.

References:

1) McPherson K GG, Scott M. International Variations in a Selected Number of Surgical Procedures. In. Paris: OECD Publishing; 2013.

2) Wright JD, Herzog TJ, Tsui J, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. *Obstet Gynecol.* 2013;122(2 Pt 1):233-241.
3) Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ.* 2017;356:j372.
4) Chen X, Guo T, Li B. Influence of prophylactic oophorectomy on mood and sexual function in women of menopausal transition or postmenopausal period. *Arch Gynecol Obstet.* 2013;288(5):1101-1106.
5) Rodriguez MC, Chedraui P, Schwager G, Hidalgo L, Perez-Lopez FR. Assessment of sexuality after hysterectomy using the Female Sexual Function Index. *J Obstet Gynaecol.* 2012;32(2):180-184.
6) Sozeri-Varma G, Kalkan-Oguzhanoglu N, Karadag F, Ozdel O. The effect of hysterectomy and/or oophorectomy on sexual satisfaction. *Climacteric.* 2011;14(2):275-281.
7) Aziz A, Bergquist C, Brannstrom M, Nordholm L, Silfverstolpe G. Differences in aspects of personality and sexuality between perimenopausal women making different choices regarding prophylactic oophorectomy at elective hysterectomy. *Acta Obstet Gynecol Scand.* 2005;84(9):854-859.
8) Aziz A, Bergquist C, Nordholm L, Moller A, Silfverstolpe G. Prophylactic oophorectomy at elective hysterectomy. Effects on psychological well-being at 1-year follow-up and its correlations to sexuality. *Maturitas.* 2005;51(4):349-357.

Modified Text:

- Introduction, Pages 5-6, Lines 99-101: "Hysterectomy is performed for over 400,000 women in the United States and 10,000 women in the United Kingdom annually, and additional data on the role of BSO is needed. We therefore examined the association between BSO and all-cause and cause-specific death in a population-based cohort undergoing non-malignant abdominal hysterectomy, and evaluated how this association varied based on age at surgery."
- Discussion, Pages 16-17, Lines 346-353: "Decisions on whether to ultimately perform opportunistic BSO at non-malignant hysterectomy must weigh the potential benefits and harms of the procedure. BSO is known to reduce ovarian cancer incidence and ovarian cancer mortality at any age. If BSO is also associated with increased all-cause mortality, then this alone may outweigh the benefit of ovarian cancer risk reduction. If BSO is not associated with all-cause mortality, then other factors such as quality of life and sexual function merit consideration; existing studies examining these outcomes in the context of non-malignant hysterectomy are limited, and further research is required."

Editors, Comment 7: 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/)?

Author Response: Bilateral salpingectomy is indeed an emerging practice worldwide. Surgeons routinely performed hysterectomy either with or without BSO prior to 2010, but began to adopt bilateral salpingectomy after publication of the tubal hypothesis in 2010[1,2] which postulated that

high-grade serous cancers may originate in the fallopian tube, and thus bilateral salpingectomy alone may reduce the risk of ovarian cancer[3].

Opportunistic bilateral salpingectomy is an attractive alternative to BSO, because it may offer the benefit of ovarian cancer risk reduction without the loss of ovarian endocrine function. However, the magnitude of ovarian cancer risk reduction associated with bilateral salpingectomy relative to BSO remains unclear[4-8], and further research is required before bilateral salpingectomy can replace BSO as the standard of care for ovarian cancer risk reduction. We have reviewed this in the Discussion section of the manuscript.

References:

1) McAlpine JN, Hanley GE, Woo MM, et al. Opportunistic salpingectomy: uptake, risks, and complications of a regional initiative for ovarian cancer prevention. *Am J Obstet Gynecol.* 2014;210(5):471 e471-411.
2) Sandoval C, Fung-Kee-Fung M, Gilks B, Murphy KJ, Rahal R, Bryant H. Examining the use of salpingectomy with hysterectomy in Canada. *Curr Oncol.* 2013;20(3):173-175.
3) Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol.* 2010;34(3):433-443.
4) Boerner T, Long Roche K. Salpingectomy for the Risk Reduction of Ovarian Cancer: Is It Time for a Salpingectomy-alone Approach? J Minim Invasive Gynecol. 2021;28(3):403-8.
5) Falconer H, Yin L, Gronberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. J Natl Cancer Inst. 2015;107(2).
6) Madsen C, Baandrup L, Dehlendorff C, Kjaer SK. Tubal ligation and salpingectomy and the risk of epithelial ovarian cancer and borderline ovarian tumors: a nationwide case-control study. Acta Obstet Gynecol Scand. 2015;94(1):86-94.
7) Lessard-Anderson CR, Handlogten KS, Molitor RJ, Dowdy SC, Cliby WA, Weaver AL, et al. Effect of tubal sterilization technique on risk of serous epithelial ovarian and primary peritoneal carcinoma. Gynecol Oncol. 2014;135(3):423-7.
8) Cusimano MC, Ferguson SE, Moineddin R, Chiu M, Aktar S, Liu N, et al. Ovarian Cancer Incidence and Death in Average-Risk Women Undergoing Bilateral Salpingo-Oophorectomy at Benign Hysterectomy. Am J Obstet Gynecol. 2021.

Modified Text:

- Discussion, Page 17, Lines 353-357: "Opportunistic bilateral salpingectomy (BS; the surgical removal of both fallopian tubes alone) is an attractive alternative to BSO that does not impact ovarian endocrine function and may still prevent high-grade serous cancers that arise in the fallopian tube; however, additional studies are required to establish the magnitude of ovarian cancer risk reduction offered by BS compared to BSO."

Editors, Comment 8: 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)?

Author Response: We agree with these suggestions and have made the appropriate substitutions throughout the manuscript.

Modified Text:

- Title, Page 1, Lines 1-2: "Association of Bilateral Salpingo-Oophorectomy with All-Cause and Cause-Specific Mortality"
- Abstract, Page 2, Lines 31-33: "Objective: To determine if BSO, compared to ovarian conservation, is associated with all-cause or cause-specific death in women undergoing hysterectomy for non-malignant disease; and to determine how this association varies based on age at surgery."
- Abstract, Page 2, Lines 37-39: "Participants: Women (aged 30-70 years) undergoing non-malignant hysterectomy, stratified into premenopausal (<45 years), menopausal transition (45-49 years), early menopausal (50-54 years), and late menopausal (≥55 years) groups."
- Abstract, Page 3, Lines 54-57: "Conclusion: In this observational study, BSO appeared to be associated with increased all-cause mortality in women <50, but not ≥50 years. While ovarian conservation at non-malignant hysterectomy may warrant consideration in premenopausal women without an indication for BSO, this strategy may not offer a survival benefit in postmenopausal women."
- Summary Box, Page 4, Lines 61-63: "Data on the potential long-term health effects of bilateral salpingo-oophorectomy (BSO) are inconsistent, particularly in postmenopausal women, and therefore practice guidelines on use of BSO at the time of hysterectomy for non-malignant disease are limited."
- Summary Box, Page 4, Lines 64-66: "Observational studies that enroll a large representative sample of women undergoing non-malignant hysterectomy, use validated data sources, and have adequate power in older age strata, are required to reliably quantify the risks of BSO."
- Introduction, Page 5, Lines 78-80: "Bilateral salpingo-oophorectomy (BSO; the surgical removal of both ovaries and fallopian tubes) has traditionally been offered at the time of hysterectomy for non-malignant disease to prevent ovarian cancer later in life, but is now being increasingly avoided due to recognition of potential harm from the loss of ovarian hormone production."
- Introduction, Page 6, Lines 101-104: "We therefore examined the association between BSO and all-cause and cause-specific death in a population-based cohort undergoing non-malignant abdominal hysterectomy, and evaluated how this association varied based on age at surgery."
- Methods, Study Design & Population, Page 6, Lines 114-116: "We included adult women (30-70 years) in Ontario, Canada, undergoing abdominal hysterectomy (open, laparoscopic, robotic-assisted) for a non-malignant indication from January 1, 1996, to December 31, 2015."
- Methods, Statistical Analyses, Pages 10-11, Lines 213-217: "To ensure our findings were robust, we: (1) generated traditional multivariable Cox proportional hazard models for all outcomes; and (2) re-ran these models with BSO as a time-varying exposure to account for patients who underwent BSO after hysterectomy; after the index date, only patients who underwent BSO for non-malignant indications (i.e. other than an ovarian mass or cancer) were able to transition from unexposed to exposed."

- Discussion, Page 14, Lines 297-299: "In this population-based cohort study of over 200,000 women undergoing non-malignant hysterectomy, the association of BSO with mortality varied based on the age at which surgery was performed."
- Discussion, Page 15, Lines 310-312: "Work by Mytton et al. is most comparable to ours in its overall design, methodologic approach, and contemporary nature. This study included 113,679 women 35-45 only, undergoing non-malignant hysterectomy in England from 2004-2014."
- Discussion, Page 15, Lines 322-326: "Similar findings have been reported in the Mayo Clinic Cohort Study, Breast Cancer Detection Demonstration Project, and Western Australia Data Linkage Study, which compared women undergoing hysterectomy with BSO to non-surgical referent women; and in the Women's Health Initiative, which compared women undergoing BSO and ovarian conservation at the time of non-malignant hysterectomy (Table 3)."
- Discussion, Page 17, Lines 358-361: "Our study addresses the main limitations of previous work. We included a population-based cohort of all women undergoing non-malignant abdominal hysterectomy in Ontario, whose outcomes should be generalizable to patients with similar demographic and socioeconomic characteristics managed in other jurisdictions and settings."

Editors, Comment 9: 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?

Author Response: Ontario's two largest minority populations are those with South Asian (from India, Pakistan, Bangladesh, Sri Lanka) and Chinese origin. Because Ontario databases do not include specific variables on ethnicity, surname algorithms have been developed as a proxy and validated against self-reported ethnicity to identify both of these population groups; this approach is commonly employed in jurisdictions that lack such information[1,2].

The ICES algorithm classifies Ontario residents as either South Asian, Chinese, or General Population. The General Population category includes any Ontario resident not identified as South Asian or Chinese; this predominantly includes residents of any other ethnicity (e.g. White, Black, etc.), and potentially a small number of residents of South Asian or Chinese ethnicity who were not correctly identified by the surname algorithm. Although "General Population" is the standard terminology used at ICES, we agree that it is confusing for readers who are unfamiliar with the algorithm; a more appropriate term for this category would be "Other". We have therefore made this change throughout the manuscript and have provided additional details on the categorization of ethnicity in the Methods section.

References:

1) Word DL, Perkins RC: Building a Spanish surname list for the 1990's: a new approach to an old problem Washington, DC, U.S. Census Bureau; 1996.

2) Shah BR, Chiu M, Amin S, Ramani M, Sadry S, Tu JV. Surname lists to identify South Asian and Chinese ethnicity from secondary data in Ontario, Canada: a validation study. BMC Med Res Methodol. 2010;10:42.

Modified Text:

- Methods, Covariates, Page 8, Lines 146-149: "Demographic characteristics included age, rural/urban residence, era of surgery (1996-2000, 2001-2005, 2006-2010, 2011-2015), residential income quintile, ethnicity (Chinese, South Asian, Other), and immigration status (long-term resident, immigrant)."
- Methods, Covariates, Page 8, Lines 154-157: "Ethnicity was assigned using validated surname lists that accurately identify Chinese (99.7% specificity; 80.2% sensitivity) and South Asian individuals (99.7% specificity, 50.4% sensitivity), Canada's two largest visible minority groups; all other residents were classified as Other."

Editor, Comment 10: Please comment on the completeness of the Ethnicity covariate, and please describe the accuracy of the Ethnicity identification using Ref#24.

Author Response: The covariate for Ethnicity was derived from a validated surname algorithm as described above. Because Ontario residents are classified into South Asian, Chinese, or General Population (i.e. Other) categories, the variable was 100% complete.

Compared to self-reported ethnicity as a reference standard, the Chinese surname algorithm has 99.7% specificity and 80.2% sensitivity, and the South Asian surname algorithm has 99.7% specificity and 50.4% sensitivity. This indicates that virtually all patients identified as Chinese or South Asian are indeed of those ethnicities; however, some proportion of Chinese or South Asian individuals will be missed and classified into the General Population (i.e. Other) group.

All variables generated in administrative data will have some degree of misclassification, and given how challenging it is to obtain ethnicity information from such sources, the measures of accuracy described above are positive. It is also important to recognize that misclassification of ethnicity is likely non-differential with respect to BSO status; thus adjustment would be expected to still reduce confounding bias due to that covariate. We have added additional details on the accuracy and completeness of the ethnicity covariate to the Methods section.

Modified Text:

- Methods, Covariates, Page 8, Lines 154-157: "Ethnicity was assigned using validated surname lists that accurately identify Chinese (99.7% specificity; 80.2% sensitivity) and South Asian individuals (99.7% specificity, 50.4% sensitivity), Canada's two largest visible minority groups; all other residents are classified as Other."
- Methods, Statistical Analyses, Page 11, Lines 227-230: "Complete case analyses were performed as data were rarely missing (0.04% for area of residence; 0.27% for area-level income quintile)."

Editor, Comment 11: Patient & Public Involvement. Please add reason(s) for not involving members of the public in your own words (e.g. funding or training restrictions, COVID, access

to software, etc.). Also it may be that speaking to patients inspired this review; if this was the case, it is fine to add (e.g. 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.

Author Response: We have edited this section to better reflect the degree of patient and public involvement in this study. First, it is important to note that the ICES Public Advisory Council, composed of members of the public from across Ontario, regularly assists ICES with research activities; this group shares feedback on selected studies, provides perspectives on new data opportunities and partnerships, and guides ICES on what research questions matter most to the public. Second, this particular study was conceived via direct patient interaction. Third, prior to study initiation, our design and analysis plan were presented and thoroughly critiqued at the Toronto Health Economics and Technology Assessment Collaborative, a multidisciplinary research collaboration that aims to ensure clinical evidence will be relevant and useful to the public and policy makers.

Modified Text:

- Methods, Patient & Public Involvement, Pages 11-12, Lines 233-240: "This study was conceived via direct patient interaction and the challenges faced in providing data on the relative benefits and risks of BSO in preoperative consent discussions. Additional input was provided: (1) directly by the Toronto Health Economics and Technology Assessment Collaborative, a multidisciplinary research collaboration that aims to ensure clinical evidence will be relevant and useful to both policy makers and the public; and (2) indirectly by the ICES Public Advisory Council, composed of members of the public from across Ontario, which regularly guides ICES on its activities, including the specific types of studies and research questions that will matter most to the public."

Editor, Comment 12: Dissemination. This is mandatory and where you tell readers how you plan to share your work. Ideas: Distribute to clinicians and advocacy groups, use to run a trial where there will be PPI, inform good clinical practice by blog, press release, companion article written with a patient about the results, social media, plain-language summary on a website etc.

Author Response: We have expanded on our existing Dissemination section, to provide additional detail on how we plan to share our research findings.

Modified Text:

- Dissemination Declaration, Page 22, Lines 459-464: "The findings of this study were presented at the American College of Surgeons Clinical Congress, and have been submitted to other national and international meetings. This work will also be distributed to relevant medical societies, as a clinical practice guideline specific to BSO at non-malignant hysterectomy is urgently needed. Direct engagement of physicians is planned via a series of grand rounds presentations at departments of Obstetrics & Gynecology, while patients and the public will be reached via press release and social media."

Editor, Comment 13: Please consider adding an additional analysis using instrumental variable approach, where, for example, the physician's prescribing preference would be used as an instrumental variable (an example here: https://pubmed.ncbi.nlm.nih.gov/26605813/)

Author Response: Both early in study development and again after receiving this query, we considered the use of instrumental variable methods for this research question. We also spoke directly with Dr. Therese Stukel, a senior core scientist at ICES who has special expertise in this analytic method, for detailed guidance and input. While an instrumental variable analysis may remove both measured and unmeasured confounding bias, it was not deemed to be the optimal choice for this study for several key reasons.

First, instrumental variable analysis is more suited to questions of health policy (i.e., "Do physicians with a propensity to perform BSO produce better outcomes?"). This is because the treatment effect identified in instrumental variable analyses may be due to the instrument itself, or due to confounding factors associated with the instrument (i.e., physician specialty, training, level of experience, volume, etc.)[1]. Our core question was instead one of clinical effectiveness (i.e., "What is the effect of providing BSO versus ovarian conservation to a specific patient?"). Overlap weighting based on the propensity score is a contemporary, state-of-the-art method for addressing questions of clinical effectiveness, as it gives a higher weight to patients who could have been assigned to either treatment option, thus targeting the population for which there is the most clinical equipoise[2-3]. Overlap weights also: (1) yield exact balance on the mean of every covariate when propensity scores are derived from a logistic model (as done here); (2) optimize precision of the association between exposure-outcome relative to other balancing approaches; (3) avoid bias due to extreme propensity scores; and (4) retain all patients in the analysis[2-3]. Although this approach does remain susceptible to unmeasured confounding, so too would instrumental variable analysis if there were unmeasured or unknown factors associated with the instrument and the outcome[1].

Second, instrumental variable analysis depends critically on identifying an appropriate instrument which meets several criteria including: (1) the instrument has a causal effect on the exposure of interest; (2) the instrument affects the outcome of interest only through the exposure; and (3) there is no confounding for the effect of the instrument on the outcome[3]. While physician preference has been used as an instrument in other studies, it may not meet criteria in the setting of BSO at the time of non-malignant hysterectomy. Establishing this in itself would be a substantial undertaking, even before the analysis could be completed.

Considering this, we have: (1) Explained why instrumental variable analysis was not chosen; (2) Highlighted the advantages of overlap weighted analyses for studies of clinical effectiveness; (3) Acknowledged the limitations of this approach with respect to unmeasured confounding and the implications on study interpretation; (4) Eliminated all causal language and tempered our conclusions throughout the manuscript, as outlined in earlier.

References:

1) Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. JAMA. 2007;297(3):278-8
2) Li F, Thomas LE, Li F. Addressing Extreme Propensity Scores via the Overlap Weights. Am J Epidemiol. 2019;188(1):250-7.

3) Thomas LE, Li F, Pencina MJ. Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial. *JAMA*. 2020;323(23):2417-2418.
4) Hernan MA, Robins JM. Instruments for causal inference: an epidemiologist's dream? Epidemiology. 2006;17(4):360-72.

Modified Text:

- Summary Box, Page 4, Lines 73-75: "In contrast to emerging hypotheses, and although unmeasured confounding remains possible, our study suggests that BSO may not be detrimental to survival when performed at the time of non-malignant hysterectomy in women of postmenopausal age."
- Methods, Statistical Analyses, Page 9, Lines 176-180: "We used overlap weighting based on the propensity score (PS) to adjust for differences in patients undergoing BSO and ovarian conservation. This strategy emphasizes the comparison of patients at clinical equipoise who would have been eligible to receive either procedure, achieves exact balance on the mean of every covariate included in the PS, and is not prone to bias from extreme PS (as often occurs with inverse probability weighting)."
- Discussion, Pages 17-18, Lines 370-381: "First, we lacked data on preoperative menopausal status, which may confound the association observed in women 45-49 and 50-54 years. If women undergoing BSO are more often postmenopausal at the time of surgery, then our results in these strata may be conservative estimates of the true effect of BSO. Second, our health administrative data sources lacked information on family history, intraoperative findings, genetic predisposition to malignancy, and metabolic factors such as body habitus, smoking, alcohol use, and physical activity, which may contribute to residual confounding in other age strata as well. The importance of these factors may change as women age (20); thus it is difficult to predict the direction or magnitude of possible bias in each stratum. If young women selecting BSO are also predisposed to malignancy or more likely to have an adverse metabolic profile, then the increased rate of all-cause mortality observed in this population could potentially be explained by unmeasured confounding."
- Discussion, Page 18, Lines 381-386: "We aimed to limit confounding by: restricting our cohort on age and surgical approach to ensure all patients had an opportunity for exposure to BSO; excluding patients with prior breast cancer or codes indicating genetic susceptibility to malignancy; and using overlap weighting to adjust for as many relevant covariates as possible, including downstream surrogates for unmeasured confounders whenever possible. We also performed sensitivity analyses with a plausible negative control."
- Discussion, Page 18, Lines 386-389: "We did not pursue instrumental variable analysis as this approach is most suited to questions of health policy, and a valid instrument was not readily apparent for the question of BSO versus ovarian conservation at non-malignant hysterectomy."
- Conclusion, Page 19, Lines 399-406: "Our study is consistent with existing literature in suggesting that BSO may be associated with increased all-cause mortality in women of premenopausal age. We found no significant association between BSO and all-cause mortality in women of postmenopausal age. Our findings apply specifically to women

undergoing hysterectomy for non-malignant indications, and unmeasured confounding remains a limitation of this work and existing studies. Caution is warranted when considering BSO at non-malignant hysterectomy in premenopausal women without an indication for the procedure, and additional research on other potential trade-offs of BSO in postmenopausal women is required. ”

Editor, Comment 14: Please use a sensitivity analysis using negative controls (outcome); an example here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3053408/

Author Response: We have added a sensitivity analysis with death due to upper gastrointestinal tract cancer (composite of death due to esophageal, gastric, liver, biliary cancers) as a negative control. We chose this outcome because it is strongly associated with unmeasured confounders of smoking and alcohol use, and it is not thought to exist on the causal pathway between BSO and all-cause mortality. We did not choose death due to a more common cancer (e.g. colorectal cancer, lung cancer, breast cancer) as a negative control because estrogen may be implicated in the pathogenesis of these cancers, and they have been associated with BSO[1-3].

There was no significant association of BSO with death due to upper gastrointestinal tract cancer in any age stratum (<45 years: HR 0.93, 95% CI 0.50-1.75; 45-49 years: HR 1.07, 95% CI 0.60-1.92; 50-54 years: HR 1.26, 95% CI 0.57-2.77; ≥55 years: 1.08, 95% CI 0.54-2.17). While such results are reassuring, these findings should not be overstated as they do not prove the exposure-outcome relationship is unbiased. As outlined in the article provided by the Editor, unmeasured confounding may exist even when there is no association between the exposure and negative control outcome; likewise, all confounders may be accounted for and yet a spurious association between the exposure and negative control outcome may be identified[4]. We have added the negative control data to the manuscript and supplemental information, but have also acknowledged that residual confounding may still exist.

References:

1) Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ.* 2017;356:j372.
2) Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol.* 2009;113(5):1027-1037.
3) Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol.* 2013;121(4):709-716.
4) Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology. 2010;21(3):383-8.

Modified Text:

- Summary Box, Page 4, Lines 73-75: “In contrast to emerging hypotheses, and although unmeasured confounding remains possible, our study suggests that BSO may not be detrimental to survival when performed at the time of non-malignant hysterectomy in women of postmenopausal age.”

- Methods, Statistical Analyses, Page 11, Lines 217-221: "To explore the potential impact of unmeasured confounding, we performed overlap weighted survival analyses for (1) death due to cardiovascular disease, thought to exist on the causal pathway; and (2) death due to upper gastrointestinal tract cancer, not thought to exist on the causal pathway but strongly associated with smoking and alcohol use, as a negative control (Appendix 4)."
- Results, Additional Analyses, Page 14, Lines 292-294: "BSO was associated with an increase in death due to cardiovascular disease in women <45 years (HR 1.47, 95% CI 1.07-2.03, p=0.019), and not significantly associated with death due to upper gastrointestinal tract cancer in any age strata (Appendix 11)."
- Discussion, Pages 17-18, Lines 370-381: "First, we lacked data on preoperative menopausal status, which may confound the association observed in women 45-49 and 50-54 years. If women undergoing BSO are more often postmenopausal at the time of surgery, then our results in these strata may be conservative estimates of the true effect of BSO. Second, our health administrative data sources lacked information on family history, intraoperative findings, genetic predisposition to malignancy, and metabolic factors such as body habitus, smoking, alcohol use, and physical activity, which may contribute to residual confounding in other age strata as well. The importance of these factors may change as women age (20); thus it is difficult to predict the direction or magnitude of possible bias in each stratum. If young women selecting BSO are also predisposed to malignancy or more likely to have an adverse metabolic profile, then the increased rate of all-cause mortality observed in this population could potentially be explained by unmeasured confounding."
- Discussion, Page 18, Lines 381-386: "We aimed to limit confounding by: restricting our cohort on age and surgical approach to ensure all patients had an opportunity for exposure to BSO; excluding patients with prior breast cancer or codes indicating genetic susceptibility to malignancy; and using overlap weighting to adjust for as many relevant covariates as possible, including downstream surrogates for unmeasured confounders whenever possible. We also performed sensitivity analyses with a plausible negative control."
- Conclusion, Page 19, Lines 401-403: "Our findings apply specifically to women undergoing hysterectomy for non-malignant indications, and unmeasured confounding remains a limitation of this work and existing studies."
- Supplemental Information, Page 18: Addition of Appendix 11

Reviewer 1, Comment 1: Is the data used from the linked health administrative databases held at ICES being deidentified, pseudonymised, or anonymised for the use of this study?

Author Response: Administrative data held at ICES is deidentified. All direct personal identifiers, including names, health card numbers, and other identifying numbers, are removed promptly after they are collected and replaced by unique encoded identifiers which allow linkage of patients across multiple databases. We have emphasized this in the manuscript.

Modified Text:

- Methods, Study Design & Population, Page 6, Lines 108-111: "We performed a population-based cohort study using deidentified linked health administrative databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences), a non-profit research institute authorized to collect data on all residents of Ontario, Canada, for the purpose of health system evaluation.

Reviewer 1, Comment 2: 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.

Author Response: In 2018, the institute formerly known as the Institute for Clinical Evaluative Sciences formally adopted the initialism ICES as its official name. This change acknowledges the growth and evolution of the organization's research since its inception in 1992, while retaining the familiarity of the former acronym within the scientific community and beyond. We have highlighted the former name of ICES in the manuscript.

Modified Text:

- Methods, Study Design & Population, Page 6, Lines 108-111: "We performed a population-based cohort study using deidentified linked health administrative databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences), a non-profit research institute authorized to collect data on all residents of Ontario, Canada, for the purpose of health system evaluation.

Reviewer 1, Comment 3: This seems slightly contrary: 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".

Author Response: Clinical practice recommendations exist for the use BSO in premenopausal women, but not in postmenopausal women. We have re-written these sentences to make this clearer.

Modified Text:

- Introduction, Page 5, Lines 91-93: "In contrast to the direction provided in premenopausal women, current guidelines offer no recommendations on whether BSO should be performed or withheld in postmenopausal women."

Reviewer 1, Comment 4: 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?

Author Response: The present study is in fact the final study listed in Table 3. We have now re-labelled that study as (Cusimano, 2021) in Table 3 to clarify this.

We included immigration status as a covariate because of a well-documented healthy immigrant

effect in Canada: specifically, immigrants' health and life expectancy is generally better than that of the Canadian-born[1,2]. Since immigration status certainly influences mortality outcomes and could conceivably influence patients' acceptance of BSO, we included it as a covariate in propensity score development.

References:

1) Tu JV, Chu A, Rezai MR, Guo H, Maclagan LC, Austin PC, et al. The Incidence of Major Cardiovascular Events in Immigrants to Ontario, Canada: The CANHEART Immigrant Study. Circulation. 2015;132(16):1549-59.
2) Cheung MC, Earle CC, Fischer HD, Camacho X, Liu N, Saskin R, et al. Impact of Immigration Status on Cancer Outcomes in Ontario, Canada. J Oncol Pract. 2017;13(7):e602-e12.

Modified Text:

- Methods, Covariates, Page 8, Lines 151-154: "Immigration status was assigned to patients based on their landing date in Ontario (long-term resident: landing date absent or <1985), and was included as a covariate to account for the improved health status of immigrants relative to Canadian-born residents."

Reviewer 1, Comment 5: 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?

Author Response: We did not perform a power or sample size calculation as we simply used the maximum number of patients available to us in the previously collected administrative data. We have rephrased this sentence in the manuscript to clarify.

Modified Text:

- Discussion, Page 17, Lines 363-365: "Our study is the largest to date with prolonged follow-up, enabling age-stratified and cause-specific analyses."

Reviewer 1, Comment 6: Is it possible to break down the category of ethnicity into smaller groups, rather than just having general population, South Asian and Chinese?

Author Response: This is unfortunately not possible with the ICES surname algorithms used. Please see response to Editor, Comments 9 and 10, which explains this.

Modified Text: Please see response to Editor, Comments 9 and 10.

Reviewer 1, Comment 7: This study defined premenopausal as <45 years. 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 years 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 years of age?

Author Response: There is no specific age threshold for the premenopausal state, due to population-level variation in the onset of menopause. However, 90% of women experience menopause between 45-54 years, with only 5% experiencing menopause between 40-44 years and the remaining 5% of women experiencing menopause ≥55 years[1-3]. This is why we selected a threshold of <45 years.

The majority of existing studies on outcomes following BSO similarly used a threshold of <45 years in their analyses[3-6]. Furthermore, we specifically defined our four strata for premenopause (<45 years), menopausal transition (45-49 years), early menopause (50-54 years), and late menopause (≥55 years) to match the stages of reproductive aging as outlined by the American Society for Reproductive Medicine[7]. We have clarified this in the manuscript.

References:

1) McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Am J Hum Biol.* 1992;4(1):37-46.
2) Kato I, Toniolo P, Akhmedkhanov A, Koenig KL, Shore R, Zeleniuch-Jacquotte A. Prospective study of factors influencing the onset of natural menopause. *J Clin Epidemiol.* 1998;51(12):1271-1276.
3) Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol. 2006;7(10):821-8.
4) Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. Obstet Gynecol. 2009;113(5):1027-37.
5) Rivera CM, Grossardt BR, Rhodes DJ, Brown RD, Jr., Roger VL, Melton LJ, 3rd, et al. Increased cardiovascular mortality after early bilateral oophorectomy. Menopause. 2009;16(1):15-23.
6) Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. BMJ. 2017;356:j372.
7) Practice Committee of American Society for Reproductive M. The menopausal transition. Fertil Steril. 2008;90(5 Suppl):S61-5.

Modified Text:

- Methods, Statistical Analyses, Page 9, Lines 170-175: "Because 90% of women experience menopause between the ages of 45-54 years (38, 39) and the median age of menopause is 51 years (40), we defined the following strata *a priori*: premenopause (<45 years), menopausal transition (45-49 years), early menopause (50-54 years), and late menopause (≥55 years). These strata are also consistent with the stages of reproductive aging, as proposed by the American Society for Reproductive Medicine (41)."

Reviewer 1, Comment 7: It is worth giving a one-sentence definition/description of what BSO is in the Introduction.

Author Response: We agree and have added this to the manuscript.

Modified Text:

- Introduction, Page 5, Lines 78-81: "Bilateral salpingo-oophorectomy (BSO; the surgical removal of both ovaries and fallopian tubes) has traditionally been offered at the time of hysterectomy for non-malignant disease to prevent ovarian cancer later in life, but is now being increasingly avoided due to recognition of potential harm from the loss of ovarian hormone production."

Reviewer 1, Comment 8: 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.

Author Response: Please see response to Editor, Comment 11. We have modified this section of the manuscript to better reflect the degree of patient and public involvement, and we note that there is in fact an ICES Public Advisory Council (composed of members of the public from across Ontario) which regularly assists ICES with its research activities.

Modified Text: Please see response to Editor, Comment 11.

Reviewer 2, Comment 1: Summary box, second bullet, typo, "enrol"

Author Response: We have corrected the identified typographical error.

Modified Text:

- Summary Box, Page 4, Lines 64-66: "Observational studies that enroll a large representative sample of women undergoing non-malignant hysterectomy, use validated data sources, and have adequate power in older age strata, are required to reliably quantify the risks of BSO."

Reviewer 2, Comment 2: For women with unilateral salpingo-oophorectomy, how many were there, and what were the indications for the previous surgical procedures?

Author Response: Of the 200,549 women in our cohort, 4,018 (2.0%) underwent unilateral oophorectomy prior to hysterectomy. Of the 76,383 women who underwent BSO, 2,611 of these (3.4%) involved a second unilateral oophorectomy at the time of hysterectomy. Our dataset does not contain variables for the specific indication for previous unilateral oophorectomy procedures, but we know they were for benign conditions based on the manner in which our inclusion and exclusion criteria were applied. To ensure this is clear, we moved our patient flow chart to the main manuscript and added these details to the Results section.

Modified Text:

- Figures, Figure 1: Transfer of Figure 1 to manuscript from supplement
- Results, Study Population, Page 12, Lines 244-246: "A total of 200,549 women (30-70 years) met inclusion criteria (Figure 1); 76,383 (38%) underwent concurrent BSO, and only 2,611 of these (3.4%) involved a second unilateral oophorectomy following previous surgery."

Reviewer 3, Comment 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).

Author Response: We have computed the risk difference with 95% confidence intervals for all-cause death in each age stratum. We have also provided the corresponding number needed to harm or harm, if the overall association in relevant survival models was statistically significant. Completing this analysis was time-intensive and required bootstrapping. Our approach is now outlined in the Methods section.

Modified Text:

- Methods, Page 10, Lines 198-203: "We computed the risk difference in weighted cumulative incidence functions between groups at 20 years of follow-up. If the association in survival models was statistically significant, we took the inverse of the risk difference to compute the number needed to treat (NNT) or harm (NNH) by that time point. We generated 95% CIs for risk difference estimates using the 2.5th and 97.5th percentiles of 1000 bootstrapped estimates."
- Results, Primary Analyses, Page 13, Lines 273-264: <45 years: "At 20 years, the weighted cumulative incidence of all-cause death was 6.1% (95% CI 5.6-6.6) for BSO and 4.7% (95% CI 4.4-5.0) for ovarian conservation (Table 2, Figure 1); this corresponded in an absolute risk increase of 1.4% (95% CI 0.8 to 2.1; NNH 71) at 20 years."
- Results, Primary Analyses, Page 13, Lines 269-270: 45-49 years: "At 20 years, the weighted cumulative incidence of all-cause death was 6.5% (95% CI 6.0-7.0) for BSO and 5.8% (95% CI 5.3-6.4) for ovarian conservation (Table 2, Appendix 8-9); this corresponded to an absolute risk increase of 0.7% (95% CI -0.12 to 1.45; NNH 151) at 20 years."
- Results, Primary Analyses, Page 13, Lines 275-276: 50-54 years: "At 20 years, the weighted cumulative incidence of all-cause death was 6.9% (95% CI 6.3-7.6) for BSO and 8.8% (95% CI 7.4-10.3) for ovarian conservation (Table 2, Appendix 8-9); this corresponded to an absolute risk decrease of 1.9% (95% CI -0.43 to -0.36) at 20 years."
- Results, Primary Analyses, Page 13, Lines 281-282: ≥55 years: "At 20 years, the weighted cumulative incidence of all-cause death was 21.7% (95% CI 20.4-22.9) for BSO and 25.3% (95% CI 22.1-28.5) for ovarian conservation (Table 2, Appendix 8-9); this corresponded to an absolute risk decrease of 3.6% (95% CI -7.0 to -0.24) at 20 years."

Reviewer 3, Comment 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).

Author Response: We agree with the above comments. We have made changes to: (1) highlight the marginally significant results; (2) explain that the association of BSO with mortality outcomes may depend on the timing of surgery; and (3) cite work by Rocca et al. with respect to the timing hypothesis specifically.

Modified Text:

- Discussion, Page 14, Lines 299-302: "Compared to ovarian conservation, BSO appeared to be associated with significantly increased all-cause mortality in women <50 but not ≥50 years; in fact, there were marginally significant decreases in all-cause and cancer mortality in women 50-54 and ≥55 years respectively."
- Discussion, Page 14, Lines 304-306: "Estrogen signalling exerts both genomic and non-genomic physiologic effects in multiple organ systems, and thus loss of estrogen at certain critical times may contribute to the development or progression of disease (54-56)."

Reviewer 3, Comment 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 nine studies in Table 3, four used non-surgical referent women.

Author Response: We agree that the selection of the referent group depends on the underlying research question. Understanding whether hysterectomy itself is associated with morbidity and mortality is another important issue in clinical practice. However, we hoped that this study could specifically help guide the narrower decision for opportunistic BSO or ovarian conservation at the time of non-malignant hysterectomy.

Many studies currently cited in practice guidelines or reviewed by physicians to guide this particular decision often enrolled a referent group of women who did not undergo gynecologic surgery (despite the fact that this referent group helps address different clinical question). While this is not a limitation of the individual studies per se, it is a limitation of the literature as a whole with respect to informing practice on our specific clinical question of interest. We have changed our language in describing referent women as suggested, but have still mentioned this as a limitation of the literature as a whole in the Introduction section.

Modified Text:

- Introduction, Page 5, Lines 97-99: "Many studies enrolled selected cohorts, relied on patient recall to establish BSO status, opted for referent women who did not undergo gynecologic surgery, or had few or no patients in older age strata."

- Discussion, Page 15, Lines 322-326: "Similar findings have been reported in the Mayo Clinic Cohort Study (3, 56, 57), Breast Cancer Detection Demonstration Project (4), and Western Australia Data Linkage Study (7), which compared women undergoing hysterectomy with BSO to non-surgical referent women; and in the Women's Health Initiative (18), which compared women undergoing BSO and ovarian conservation at the time of non-malignant hysterectomy (Table 3)."

Reviewer 3, Comment 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).

Author Response: As outlined in our response to Editor, Comment 8, we have replaced any reference to "surgical menopause" with "bilateral salpingo-oophorectomy". We have retained the term "bilateral salpingo-oophorectomy" (rather than "bilateral oophorectomy") as this was the procedure performed, and this is the standard terminology used amongst clinicians in Obstetrics & Gynecology, to whom this article is primarily targeted.

Modified Text: Please see response to Editor, Comment 8

Reviewer 3, Comment 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, lines 10-11.

Author Response: We have removed the term retrospective from the manuscript.

Modified Text:

- Abstract, Page 2, Lines 34-35: "Design: Cohort study, with accrual from January 1, 1996, to December 31, 2015, and follow-up to December 31, 2017."
- Methods, Study Design & Population, Page 6, Lines 108-111: "We performed a population-based cohort study using deidentified linked health administrative databases held at ICES (formerly known as the Institute for Clinical Evaluative Sciences), a non-profit research institute authorized to collect data on all residents of Ontario, Canada, for the purpose of health system evaluation."

Reviewer 3, Comment 6: When quoting the Mayo Clinic Cohort Study, I suggest quoting two specific reports on cause-specific mortality: Rivera et al, Menopause 2009, and Rivera et al, Neuroepidemiology 2009.

Author Response: We have added citations for Rivera et al., Menopause 2009, and Rivera et al., Neuroepidemiology 2009, which showed increased mortality due to cardiovascular diseases and neurological/mental diseases respectively following BSO in women <45 years. While we agree

that both are important studies, we have not elaborated on them significantly in the Discussion section due to our primary focus on all-cause death as an outcome, and the fact that the Mayo Clinic Cohort Study used women in the general population as a reference group and therefore addressed a different research question.

Modified Text:

- Discussion, Page 15, Lines 308-310: "Numerous retrospective analyses of prospectively observed cohorts (3, 4, 6, 15, 16) and administrative datasets (3, 5, 7, 56, 57) have reported similar findings (Table 3), albeit each with distinct limitations."
- Discussion, Page 15, Lines 322-326: "Similar findings have been reported in the Mayo Clinic Cohort Study (3, 56, 57), Breast Cancer Detection Demonstration Project (4), and Western Australia Data Linkage Study (7), which compared women undergoing hysterectomy with BSO to non-surgical referent women; and in the Women's Health Initiative (18), which compared women undergoing BSO and ovarian conservation at the time of non-malignant hysterectomy (Table 3)."

Reviewer 3, Comment 7: Page 6. Line 15. Please spell out the abbreviation ICES the first time it is used.

Author Response: This has been changed. Please see response to Reviewer 1, Comment 4.

Modified Text: Please see response to Reviewer 1, Comment 4.

Reviewer 3, Comment 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?

Author Response: The General Population category includes any resident not identified as South Asian or Chinese. Although "General Population" is the standard terminology used at ICES, a more appropriate term for this category would be "Other" as it includes all other ethnicities. Please see our detailed response to Editor, Comments 9 and 10 on this issue.

Modified Text: Please see response to Editor, Comments 9 and 10.

Reviewer 3, Comment 9: Page 14, line 33-34. There is an extra "the".

Author Response: We have corrected this typographical error.

Modified Text:

- Discussion, Page 16, Lines 339-341: "We provide a clear biological basis for our stratified analyses, but also used restricted cubic splines to explicitly model how the effect of BSO changed with advancing age."

Reviewer 3, Comment 10: Page 14, lines 49-50. Add to the sentence "… in other jurisdictions and settings." the specification "with similar demographic and socioeconomic characteristics".

Author Response: We agree with and have incorporated the suggested change.

Modified Text:

- Discussion, Page 17, Lines 358-361: "We included a population-based cohort of all women undergoing non-malignant abdominal hysterectomy in Ontario, whose outcomes should be generalizable to patients with similar demographic and socioeconomic characteristics managed in other jurisdictions and settings."

Reviewer 3, Comment 11: Table 3. The Cusimano 2020 study should be labeled as 2021 or "current study" to avoid confusion.

Author Response: We have corrected this typographical error.

Modified Text:

- Tables, Table 3, Page 34: Change of Cusimano, 2020 to Cusimano, 2021

Reviewer 3, Comment 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.

Author Response: We agree with this assessment and have been careful to not overstate our findings throughout the manuscript. Please see response to Editor, Comments 1 and 2.

Modified Text: Please see response to Editor, Comments 1 and 2.

Reviewer 4, Comment 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.

Author Response: We have removed this statement from the "What this study adds" section altogether, and have modified the wording of our Abstract and Conclusion section, as this was not our intention. We meant to suggest that ovarian conservation could be considered specifically at non-malignant hysterectomy in women <45 years who have no indication for BSO.

Modified Text:

- Abstract, Page 3, Lines 55-57: "While ovarian conservation at non-malignant hysterectomy may warrant consideration in premenopausal women without an indication for BSO, this strategy may not offer a survival benefit in postmenopausal women."

- Discussion, Page 15, Lines 37-320: "Considering the strong methodology employed in this work and by Mytton et al., consistency of published literature on this association, and presence of a plausible mechanism, caution may be warranted when considering BSO in young women, namely those without a clinical indication for the procedure."
- Conclusion, Page 19, Lines 404-406: "Caution is warranted when considering BSO at non-malignant hysterectomy in premenopausal women without an indication for the procedure, and additional research on other potential trade-offs of BSO in postmenopausal women is required."

Reviewer 4, Comment 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.

Author Response: We could not identify a strong biologic rationale for why the effect of early estrogen withdrawal via BSO would be different for women with or without specific gynecologic diagnoses, except possibly due to unmeasured pre- or postoperative factors (e.g. use of hormone therapy may be more or less likely in patients with certain diagnoses). We were also concerned about the consequences of multiple testing; we have already examined three separate outcomes among four separate age strata, and additionally characterized effect modification by age at surgery in significant detail.

Considering this, we opted against further analyses exploring effect modification by certain gynecologic diagnoses. Such analyses likely go beyond the scope of this observational dataset, would be very difficult to interpret, and should likely not be used to directly influence clinical practice or surgical decision-making regardless.

Modified Text: Not applicable

Reviewer 4, Comment 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.

Author Response: We agree with these comments. The intent of our study was indeed to specifically help inform patients and physicians "weighing up the risk and benefit of removing the ovaries" at the time of a planned hysterectomy for non-malignant indications. The intent of our study was not to compare outcomes between women undergoing hysterectomy with BSO to

women without surgery, and as such, our findings should not be generalized to clinical decisions between hysterectomy with BSO or non-surgical management. We have made changes to the manuscript to ensure that this is clearly specified in our conclusions.

Modified Text:

- Abstract, Page 3, Lines 55-57: "While ovarian conservation at non-malignant hysterectomy may warrant consideration in premenopausal women without an indication for BSO, this strategy may not offer a survival benefit in postmenopausal women."
- Summary Box, Page 4, Lines 73-75: "In contrast to emerging hypotheses, and although unmeasured confounding remains possible, our study suggests that BSO may not be detrimental to survival when performed at the time of non-malignant hysterectomy in women of postmenopausal age."
- Discussion, Page 16, Lines 346-348: "Decisions on whether to ultimately perform opportunistic BSO at non-malignant hysterectomy must weigh the potential benefits and harms of the procedure."
- Conclusion, Page 19, Lines 401-403: "Our findings apply specifically to women undergoing hysterectomy for non-malignant indications."

Reviewer 4, Comment 4: The authors should make it clear in the abstract that when the term 'age' is used it is referring to age at surgery.

Author Response: We have made edits throughout the manuscript to ensure that this is clear, and also modified our manuscript figures to specifically mention age at surgery.

Modified Text:

- Abstract, Page 2, Lines 31-33: "Objective: To determine if BSO, compared to ovarian conservation, is associated with all-cause or cause-specific death in women undergoing hysterectomy for non-malignant disease; and to determine how this association varies based on age at surgery."
- Abstract, Page 2, Lines 37-39: "Participants: Women (aged 30-70 years) undergoing non-malignant hysterectomy, stratified into premenopausal (<45 years), menopausal transition (45-49 years), early menopausal (50-54 years), and late menopausal (≥55 years) groups according to age at surgery."
- Abstract, Page 3, Lines 51-53: "In secondary analyses exploring an age-at-surgery threshold for ovarian conservation versus removal, the hazard ratio for BSO declined after age 45, and crossed 1 at age 50 years."
- Summary Box, Page 4, Lines 69-72: "Our study suggests that BSO may be associated with increased rates of all-cause and non-cancer death in women <50, but not ≥50 years, and is the first to use advanced modelling to attempt to identify an age-at-surgery threshold at which the risk-to-benefit ratio of BSO might shift from supportive of ovarian conservation to removal."
- Methods, Covariates, Page 8, Lines 146-149: "Demographic characteristics included age at surgery, rural/urban residence, era of surgery (1996-2000, 2001-2005, 2006-2010,

2011-2015), residential income quintile, ethnicity (Chinese, South Asian, Other), and immigration status (long-term resident, immigrant).

- Methods, Statistical Analyses, Page 9, Line 170: "All analyses were stratified by age group at surgery."
- Methods, Statistical Analyses, Page 10, Lines 204-205: "To assess for a change in the association between BSO and mortality around the age of menopause, we performed secondary analyses in women 45-54 years at surgery."
- Results, Study Population, Page 12, Lines 246-248: "Performance of BSO also varied with age at surgery: 18.5%, 40.5%, 68.9%, and 80.9% of women <45, 45-49, 50-54, and ≥55 years underwent BSO, respectively (Figure 1, Table 1)."
- Results, Additional Analyses, Page 14, Lines 285-288: "In secondary analyses exploring a potential age-at-surgery threshold for ovarian conservation versus removal, the hazard ratio associated with BSO was highest at age 45 years, gradually declined thereafter, and crossed 1 at age 50 years for all-cause death, 52 years for non-cancer death, and 48 years for cancer death (Figure 2)."
- Discussion, Page 16, Lines 339-341: "We provide a clear biological basis for our stratified analyses, but also used restricted cubic splines to explicitly model how the effect of BSO changed with advancing age at surgery."

Reviewer 4, Comment 5: Page 13, line 15: The authors state that the prior research has limitations, however these are not included in Table 3 as indicated.

Author Response: It was never our intention include all limitations in Table 3, as that table is already quite dense (and there is simply no further space on the page to expand it). The sentence highlighted by the reviewer is indeed confusing, and we have modified it to make it clearer. We have also specifically mentioned the major limitations in the text and directly thereafter provided citations for the corresponding studies.

Modified Text:

- Introduction, Page 5, Lines 95-99: "No study has identified an age threshold at which the risk-to-benefit ratio of BSO may transition from supportive of ovarian conservation to removal. Many studies enrolled selected cohorts (4, 6, 15, 16, 18), relied on patient recall to establish BSO status (4, 6, 15, 16, 18), opted for referent women who did not undergo gynecologic surgery (3, 4, 6, 7), or had few or no patients in older age strata (5, 6, 15, 16)."
- Discussion, Page 15, Lines 307-310: "Numerous retrospective analyses of prospectively observed cohorts (3, 4, 6, 15, 16) and administrative datasets (3, 5, 7, 56, 57) have reported similar findings (Table 3), albeit each with distinct limitations."

Reviewer 4, Comment 6: In Table 2, the authors should consider listing the adjusting variables used in the sensitivity analysis in a footnote to the table.

Author Response: The adjusting variables were all the same variables included in propensity score development. We have added the suggested footnote to clarify this.

Modified Text:

- Tables, Table 2, Page 32: "Covariates were identical to those included in propensity score development: age at surgery (years), rural/urban residence, era of surgery (1996-2000, 2001-2005, 2006-2010, 2011-2015), residential income quintile, ethnicity (Chinese, South Asian, Other), immigration status (long-term resident, immigrant), hysterectomy type (total, subtotal), abnormal uterine bleeding (yes/no), fibroids (yes/no), endometriosis (yes/no), ovarian cysts (yes/no), premalignant conditions (yes/no), pelvic pain/inflammation (yes/no), prolapse (yes/no), Johns Hopkins Aggregated Diagnosis Groups (0-5, 6-9, ≥10), diabetes (yes/no), hypertension (yes/no), cardiovascular disease (yes/no), chronic obstructive pulmonary disease (yes/no), previous malignancy (yes/no), previous abdominopelvic surgeries (0, 1, 2, ≥3), previous ovarian surgery (yes/no)"

Reviewer 4, Comment 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.

Author Response: In their main analysis, Tuesley et al. retained women who underwent hysterectomy or oophorectomy as a part of cancer treatment in their analysis and considered them unexposed to that surgery. In a sensitivity analysis, they censored procedures performed for cancer. We initially included the results of the sensitivity analysis in Table 3 because this seemed most comparable to our study of BSO at hysterectomy for non-malignant indications. However, results were similar in both the main analysis and sensitivity analysis. We have therefore changed Table 3 to present the main analysis. We have also added the overall point estimates (i.e., those not stratified by age).

Modified Text:

- Tables Table 3, Page 34: Change of hazard ratios

Reviewer 5, Comment 1: 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.

Author Response: The Women's Health Initiative (WHI) cohort study did not identify an association between BSO and all-cause death in women <50 years at the time of hysterectomy (HR <40 years: 0.90, 95% CI 0.72-1.13; HR 40-49 years: 1.00, 95% CI 0.84-1.19). While this

may be due to adjustment for smoking status, body mass index, alcohol intake, and exercise, the WHI study also had short follow-up (mean 7.6 years), recruited a selected population ineligible for the WHI randomized controlled trial (78% had used HRT), and was prone to survival bias for enrolling patients years to decades after hysterectomy (mean age at enrollment: 63 years)[123]. We suspect these latter reasons are more likely to explain their null findings. All other major studies have identified an increased rate of all-cause death with BSO performed in women <45 or <50 years, either regardless of HRT use[132,151,153,154] or specifically in those who had never used HRT[15,16,152], and some of these studies also adjusted for the aforementioned factors.

Nevertheless, we certainly agree with the above comments that unmeasured confounding remains possible in our study. We controlled for as many cardiovascular risk factors as possible (e.g. area-level income quintile, hypertension, diabetes, chronic obstructive pulmonary disease) and performed sensitivity analyses using death due to upper gastrointestinal tract cancers as a negative control, but unfortunately had no way of capturing adverse metabolic factors in our administrative datasets. We have therefore further expanded on our explanation of confounding in the Discussion section.

Modified Text:

- Discussion, Pages 17-18, Lines 373-381: "Second, our health administrative data sources lacked information on family history, intraoperative findings, genetic predisposition to malignancy, and metabolic factors such as body habitus, smoking, alcohol use, and physical activity, which may contribute to residual confounding in other age strata as well. The importance of these factors may change as women age (20); thus it is difficult to predict the direction or magnitude of possible bias in each stratum. If young women selecting BSO are also predisposed to malignancy or more likely to have an adverse metabolic profile, then the increased rate of all-cause mortality observed in this population could potentially be explained by unmeasured confounding.
- Discussion, Page 18, Lines 381-386: "We aimed to limit confounding by: restricting our cohort on age and surgical approach to ensure all patients had an opportunity for exposure to BSO; excluding patients with prior breast cancer or codes indicating genetic susceptibility to malignancy; and using overlap weighting to adjust for as many relevant covariates as possible, including downstream surrogates for unmeasured confounders whenever possible. We also performed sensitivity analyses with a plausible negative control."