# Association of Surgical Menopause with All-Cause and Cause-Specific Mortality

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# Association of Surgical Menopause with All-Cause and Cause-Specific Mortality

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## ABSTRACT

**Importance:** Bilateral salpingo-oophorectomy (BSO) reduces the risk of ovarian cancer, but results in the cessation of ovarian hormone production, and may be associated with increased mortality in premenopausal women. Routine BSO at hysterectomy remains controversial in postmenopausal women, as ongoing androgen production by the ovaries even after menopause may have clinical benefit.

**Objective:** To determine if BSO, compared to ovarian conservation, is associated with all-cause or cause-specific death in women undergoing benign hysterectomy; and to determine how this association varies based on age at surgery.

**Design:** Retrospective cohort study, with accrual from January 1, 1996, to December 31, 2015, and follow-up to December 31, 2017.

**Setting:** Population-based in Ontario, Canada.

**Participants:** Women (aged 30-70 years) undergoing benign hysterectomy, stratified into premenopausal (<45 years), menopausal transition (45-49 years), early menopausal (50-54 years), and late menopausal (≥55 years) groups.

**Exposures:** BSO versus ovarian conservation.

**Main Outcomes Measures:** Outcomes were all-cause, non-cancer, and cancer death. Within each age stratum, we used overlap propensity score weighted Cox proportional hazard models to examine the association between BSO and mortality outcomes, while adjusting for demographic characteristics, gynecologic conditions, and comorbidities. To account for comparisons in four age strata, $p<0.0125$ was considered statistically significant.

**Results:** We identified 200,549 eligible patients with median follow-up 12 years (interquartile range 7-17); BSO was performed in 19%, 41%, 69%, and 81% of women <45, 45-49, 50-54, and ≥55 years, respectively. BSO was associated with increased rates of all-cause death in women <45 (HR 1.31, 95% CI 1.18-1.45, p<0.001) and 45-49 (HR 1.16, 95% CI 1.04-1.30, p=0.007), but not women 50-54 (HR 0.83, 95% CI 0.72-0.97, p=0.018) or ≥55 years (HR 0.92, 95% CI 0.82-1.03, p=0.16). Findings in women <50 years were driven largely by increased non-cancer death. In secondary analyses exploring an age threshold for ovarian conservation versus removal, the hazard ratio for BSO declined after age 45, and crossed 1 at age 50 years.

**Conclusion:** BSO appears to be associated with increased all-cause mortality in women <50, but not ≥50 years. Ovarian preservation should be adopted in premenopausal women, but may not offer a survival benefit in postmenopausal women.

## SUMMARY BOX

*What is already known on this topic*

- 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 benign hysterectomy are limited.
- Observational studies that enrol a large representative sample of women undergoing benign hysterectomy, use validated data sources, and have adequate power in older age strata, are required to reliably quantify the risks of BSO.

*What this study adds*

- Our study suggests that BSO is 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 a threshold at which the risk-to-benefit ratio of BSO might shift from supportive of ovarian conservation to removal.
- BSO should be avoided in women of premenopausal age. In contrast to emerging hypotheses, BSO does not appear to be detrimental to survival when performed in women of postmenopausal age.

## INTRODUCTION

Bilateral salpingo-oophorectomy (BSO) has traditionally been offered at the time of benign hysterectomy 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 (1, 2). Several observational studies have shown that BSO before age 45 or 50 years is associated with increased all-cause mortality despite reduced rates of ovarian cancer (3-7), and current guidelines have therefore advised against BSO in premenopausal women (8-13).

However, the risk-to-benefit ratio of BSO as women age remains unclear (2). While the ovaries produce estrogen and androgens before menopause, they produce only androgens after menopause, and the clinical significance of this production is debated (12-14). Existing literature on the association between BSO and all-cause mortality after the median age of natural menopause is also controversial: the Nurses' Health Study (15, 16) and a decision analysis (17) have suggested that BSO may be harmful even after age 50 years, but this finding has not been supported by other observational studies (3, 4, 7, 18). Current guidelines offer no recommendations on whether BSO should be performed or withheld in perimenopausal and postmenopausal women (8-13).

Rates of BSO vary markedly between surgeons, indicating ongoing uncertainty in the application of existing evidence (19, 20). 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), used non-surgical controls (3, 4, 6, 7), or had few or no patients in older age strata (5, 6, 15, 16). We therefore examined the association between BSO and all-cause and

cause-specific death in a population-based cohort undergoing benign abdominal hysterectomy, and evaluated how this association varied based on age at surgery.

## METHODS

We performed a population-based retrospective cohort study using linked health administrative databases held at ICES, a non-profit research institute authorized to collect data on all residents of Ontario, Canada, for the purpose of health system evaluation. As Ontarians have universal access to hospital care and physician services, these data are comprehensive. The Research Ethics Board at the University of Toronto provided approval (#38212).

We included adult women (30-70 years) in Ontario, Canada, undergoing abdominal hysterectomy (open, laparoscopic, robotic-assisted) for a benign indication from January 1, 1996, to December 31, 2015. We used validated procedure codes to identify hysterectomy cases from the Discharge Abstract Database (DAD), Same Day Surgery (SDS) database, and Ontario Health Insurance Plan (OHIP) database, which hold records of inpatient surgery, outpatient surgery, and surgeon billing claims, respectively (Appendix 1) (20, 21).

We excluded: (1) non-Ontario residents ineligible for universal health coverage; (2) patients undergoing emergent hysterectomy, due to potential differences in surgical decision making in this setting; (3) patients undergoing hysterectomy for malignant disease; (4) patients with prior breast or gynecologic cancer, or who had undergone surgery for genetic predisposition to malignancy, due to possible confounding by indication in this population; and (5) patients who had previously undergone BSO (Appendix 2-3).

### *Exposure Assessment*

The primary exposure was BSO, defined as removal of all ovarian tissue and corresponding fallopian tubes on the date of hysterectomy (index date). This included BSO in women with both ovaries, and unilateral salpingo-oophorectomy in women with one remaining ovary due to a previous surgical procedure. We used procedure codes from DAD/SDS to identify salpingo-oophorectomy with a sensitivity of 99%, positive predictive value of 98%, and kappa of 99% (Appendix 1) (21). We compared patients undergoing BSO to patients undergoing conservation of one or both ovaries, to reflect loss or retention of ovarian endocrine function respectively (5).

*Outcome Assessment*

The primary outcome was all-cause death. Secondary outcomes were non-cancer and cancer death, selected to understand the pathogenesis of any potential association of BSO with all-cause death. Date of death was obtained from the Registered Persons Database. Causes of death were available to December 31, 2017 from the Ontario Cancer Registry (OCR) and Ontario Registrar General-Death database. Patients were therefore followed from the date of hysterectomy (time 0) to December 31, 2017.

*Covariates*

Covariates were ascertained at the time of the index hysterectomy. Demographic characteristics included age, rural/urban residence, era of surgery (1996-2000, 2001-2005, 2006-2010, 2011-2015), residential income quintile, ethnicity (General Population, Chinese, or South Asian), and immigration status (long-term resident, immigrant). Residential income quintile is a socioeconomic index derived from Canadian census data on median neighbourhood income and

is assigned to patients based on their postal code of residence (22). Immigration status was assigned to patients based on their landing date in Ontario (23) (long-term resident: landing date absent or <1985). Ethnicity was assigned using validated surname lists that accurately identify South Asian and Chinese individuals, Canada's two largest visible minority groups (24).

Clinical characteristics included hysterectomy type (total, subtotal), gynecologic diagnoses at the time of hysterectomy (abnormal uterine bleeding, fibroids, endometriosis, ovarian cysts, premalignant conditions [endometrial hyperplasia, cervical dysplasia], pelvic pain/inflammation, prolapse), overall comorbidity score derived from Aggregated Diagnosis Groups (ADGs) of the Johns Hopkins ACG® System Version 10 (0-5, 6-9, ≥10) (25, 26), specific comorbidities (diabetes, hypertension, cardiovascular disease, chronic obstructive pulmonary disease [COPD], previous malignancy), previous abdominopelvic surgeries (0, 1, 2, ≥3), and previous ovarian surgery. Gynecologic diagnoses and surgical history were obtained from DAD/SDS (Appendix 4) (27-30), and specific comorbidities were obtained from validated registries of affected Ontarians (Appendix 5) (31-34).

*Statistical Analyses*

All analyses were stratified by age group. Because 90% of women experience menopause between the ages of 45-54 years (35, 36) and the median age of menopause is 51 years (37), 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) (38).

We used overlap weighting based on the propensity score (PS) to adjust for differences in patients undergoing BSO and ovarian conservation (39-41). This strategy emphasizes the comparison of patients at clinical equipoise who would have been eligible to receive either

procedure, and is not prone to bias from extreme PS (as often occurs with inverse probability weighting) (39, 41, 42).

We first generated PS separately in each age stratum using logistic regression, modelling BSO as the outcome and all demographic and clinical characteristics described as covariates; exact age within each stratum was modelled as a continuous variable using restricted cubic splines with three knots ($10^{th}$, $50^{th}$, $90^{th}$ percentiles) (43). We then derived overlap weights for each patient, defined as the predicted probability of receiving the opposite treatment (BSO: 1-PS; ovarian conservation: PS) (39). We used standardized differences to compare baseline covariates of exposed and unexposed patients before and after applying overlap weights (44).

We used weighted Cox proportional hazard models to compare the rate of all-cause death by BSO status, censoring at loss to follow-up (i.e. loss of eligibility for provincial health insurance) and end of follow-up (December 31, 2017). We used weighted Fine & Gray subdistribution hazard models to compare the incidence of non-cancer and cancer death by BSO status (45), treating death due to the opposite cause as a competing event, and censoring at loss to follow-up and end of follow-up. We used robust variance estimators to account for weighting, and present hazard ratios (HR) with 95% confidence intervals (CI) (46).

We also plotted weighted cumulative incidence curves for all-cause, non-cancer, and cancer death across BSO status in each age stratum. To test the equality of curves across groups, we used p-values from weighted log-rank tests for all-cause death (47), and from weighted Fine & Gray subdistribution hazard models for non-cancer and cancer death (45, 48).

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 benign indications (i.e. other than an ovarian mass or malignancy) were able to transition from unexposed to exposed.

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. We ran a multivariable Cox proportional hazard model for all-cause death with (1) BSO as the primary exposure; (2) age as a restricted cubic spline with three knots; (3) an interaction term between BSO and age; and (4) all demographic and clinical characteristics as covariates. We then estimated the hazard ratio for BSO at each year of age. We repeated this for cause-specific death.

Datasets were linked using unique encoded identifiers and analyzed at ICES. All statistical tests were two-sided. No significant departures from proportionality were detected based on tests of interaction between BSO status and time, or analyses of Schoenfeld residuals. Because models were run in four strata, we applied a Bonferroni correction such that $p<0.0125$ (0.05/4) was considered statistically significant, and p-values from 0.0125-0.05 were considered marginally significant. Standardized differences $\geq 0.1$ were considered meaningful. Complete case analyses were performed as data were rarely missing (<0.3%). Analyses were performed in SAS v9.4 (SAS Institute Inc., Cary, NC).

**Patient and Public Involvement**

Patients and the public were not involved in the design or conduct of this study.

**RESULTS**

A total of 200,549 women (30-70 years) met inclusion criteria (Appendix 2). BSO was performed in 18.5%, 40.5%, 68.9%, and 80.9% of women <45, 45-49, 50-54, and ≥55 years,

respectively (Table 1). Within each age stratum, patients undergoing BSO were older, had more comorbidities, and more often had a gynecologic indication for BSO than patients undergoing ovarian conservation; differences were less pronounced in older strata. After applying overlap weights, groups were balanced on baseline characteristics, with all standardized differences equal to zero (Appendix 6). Median follow-up was 12 years overall (interquartile range 7-17), and there were 2,268, 1,516, 982, and 2,267 deaths in women <45, 45-49, 50-54, and ≥55 years respectively (Appendix 7).

*Primary Analyses*

In women <45 years, BSO was associated with an increased rate of all-cause death compared to ovarian conservation (HR 1.31, 95% CI 1.18-1.45, p<0.001). This was driven by a significant increase in the rate of non-cancer death (HR 1.38, 95% CI 1.21-1.58, p<0.001) and marginally significant increase in the rate of cancer death (HR 1.18, 95% CI 1.01-1.39, p=0.044). At 20 years, the weighted cumulative incidence of all-cause death was 6.1% (95% CI 5.6-6.7) for BSO and 4.7% (95% CI 4.4-5.0) for ovarian conservation (Table 2, Figure 1).

In women 45-49 years, BSO was associated with an increased rate of all-cause (HR 1.16, 95% CI 1.04-1.30, p=0.007) and non-cancer death (HR 1.29, 95% CI 1.10-1.52, p=0.002), but not cancer death (HR 1.04, 95% CI 0.89-1.21, p=0.63), compared to ovarian conservation. At 20 years, the weighted cumulative incidence of all-cause death was 6.5% (95% CI 6.0-7.1) for BSO and 5.8% (95% CI 5.3-6.4) for ovarian conservation (Table 2, Appendix 8-9).

In women 50-54 years, BSO was not associated with an increased rate of all-cause (HR 0.83, 95% CI 0.72-0.97, p=0.018), non-cancer (HR 0.81, 95% CI 0.64-1.02, p=0.071), or cancer death (HR 0.87, 95% CI 0.71-1.06, p=0.15) compared to ovarian conservation. At 20 years, the

weighted cumulative incidence of all-cause death was 7.0% (95% CI 6.3-7.7) for BSO and 8.9% (95% CI 7.5-10.5) for ovarian conservation (Table 2, Appendix 8-9).

In women ≥55 years, BSO was not associated with an increased rate of all-cause (HR 0.92, 95% CI 0.82-1.03, p=0.16), non-cancer (HR 1.00, 95% CI 0.85-1.17, p=0.99), or cancer death (HR 0.82, 95% CI 0.69-0.97, p=0.023) compared to ovarian conservation At 20 years, the weighted cumulative incidence of all-cause death was 21.9% (95% CI 20.6-23.2) for BSO and 25.6% (95% CI 22.2-29.3) for ovarian conservation (Table 2, Appendix 8-9).

*Additional Analyses*

Multivariable Cox proportional hazard models treating BSO as a static or time-varying exposure yielded similar results (Table 2, Appendix 10). In secondary analyses exploring a potential age 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

In this population-based cohort study of over 200,000 women undergoing benign hysterectomy, the association of BSO with mortality varied based on the age at which surgery was performed. Compared to ovarian conservation, BSO was associated with significantly increased all-cause mortality in women <50 but not ≥50 years. These findings are biologically plausible: BSO prior to the onset of menopause results in premature deficiency of estrogen, whereas BSO after the onset of menopause will not. Estrogen signalling exerts both genomic and

non-genomic physiologic effects in multiple organ systems, and thus loss of estrogen may contribute to the development or progression of disease (49, 50).

Our study confirms that BSO may be associated with increased all-cause death in women of premenopausal age. Numerous retrospective analyses of prospectively observed cohorts (3, 4, 6, 15, 16) and administrative datasets (3, 5, 7) have reported similar findings, albeit each with distinct limitations (Table 3). 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 benign hysterectomy in England from 2004-2014 (5). Over median follow-up of 6 years, BSO was associated with an increase in all-cause (HR 1.56, 95% CI 1.37-1.81), cardiac (HR 2.00, 95% CI 1.11-3.57), and cancer death (HR 1.85, 95% CI 1.54-2.22) compared to ovarian conservation. We identified similar increases in all-cause and non-cancer death after adjusting for many more potential confounders and ensuring longer follow-up (median 12 years). Considering the strong methodology employed in this work and by Mytton et al., consistency of published literature, and presence of a plausible mechanism, it is possible that the association between BSO and all-cause death in young women may reflect a causal relationship.

Our study also shows that BSO may not be associated with all-cause death in women of postmenopausal age. Similar findings have been reported in the Mayo Clinic Cohort Study (3), Breast Cancer Detection Demonstration Project (4), and Western Australia Data Linkage Study (7), which compared women undergoing hysterectomy with BSO to non-surgical controls; and in the Women's Health Initiative (18), which compared women undergoing BSO and ovarian conservation at the time of benign hysterectomy (Table 3). The Nurses' Health Study is the only cohort study to suggest that the association of BSO with all-cause mortality may not vary with

age: the overall hazard ratio was 1.13 (95% CI 1.06-1.21), and an interaction between BSO status and age (<50, 50-59, ≥60 years) was not significant (p=0.46) (16). This study included a cohort of largely white nurses, had few women ≥50 years (8,969 with 1,166 deaths), and did not control for indications for BSO. Our study was population-based, included over 53,000 women ≥50 years (with 3,249 deaths), and controlled for gynecologic conditions which may act as confounders in older age strata. Both our study and the accumulated literature contrast with the Nurses' Health Study, and suggest that BSO may not be associated with all-cause mortality in older women.

Our study is the first to attempt to identify a threshold at which the risk-to-benefit ratio of BSO might shift from supportive of ovarian conservation to removal. Most studies have run age-stratified analyses without articulating a rationale for the categories chosen, or arbitrarily changed categories in separate publications on the same cohort (15, 16). We provide a clear biological basis for our stratified analyses, but also used restricted cubic splines to explicitly model the how the effect of BSO changed with advancing age. These analyses showed that the hazard associated with BSO appears to decrease after age 45, and approaches the null at around age 50 years. Since age serves as a population-level surrogate for the onset of menopause, these findings support assertions that BSO may be harmful in premenopausal, but not postmenopausal women (4).

Our study also addresses the main limitations of previous work. We included a population-based cohort of all women undergoing benign abdominal hysterectomy in Ontario, whose outcomes should be generalizable to patients managed in other jurisdictions and settings. We used overlap PS weighting, an analytic approach that mimics pragmatic randomized trials by focusing on patients with a realistic probability of receiving either BSO or ovarian conservation.

Our study is the largest to date with prolonged follow-up, and had sufficient power for both age-stratified and cause-specific analyses. In contrast to most studies on this topic, which relied on longitudinal self-reported survey data (4, 6, 15, 16, 18), we observed all patients from the exact date of exposure to BSO and used validated codes to identify BSO, thereby preventing introduction of survival or misclassification bias respectively. Our data sources are of high quality and comprehensive, ensuring accurate and complete outcome ascertainment.

Several limitations require consideration. 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 lifestyle factors, 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. 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. Finally, due to data limitations, we could not explore the influence of the use of hormone therapy on our findings. Existing studies report that the association of BSO with mortality may be pronounced in never-users of hormone therapy (3, 6, 15, 16). However, such analyses are susceptible to confounding; never-users may have contraindications to hormone therapy that are related to mortality (51) or face sociodemographic barriers to its use (52). Since prescription and maintenance of hormone therapy will also vary

between patients and providers after BSO (53), our results reflect the real-world population-average association of BSO with mortality, which itself is meaningful.

## CONCLUSION

Our study, in the context of existing literature, indicates that BSO should be avoided in women of premenopausal age whenever possible. We found no significant association between BSO and all-cause mortality in women of postmenopausal age. Additional research on other potential trade-offs in this age demographic is required.

## ETHICS COMMITTEE APPROVAL

The Research Ethics Board at the University of Toronto (Toronto, Ontario, #38212) provided ethical approval for this study.

## DATA SHARING STATEMENT

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS.

## AUTHOR CONTRIBUTIONS

MCC, NB, and SF contributed to study conception. All authors contributed to study design and data acquisition. MCC, RM, MC, SA, and NL performed statistical analyses. All authors assisted in the interpretation of data. MCC wrote the first draft and created tables and figures. All authors critically revised the manuscript, approved the final version submitted, and agree to be accountable for all aspects of the work.

MCC accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. MCC also attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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All researchers were independent from funders, had access to the data in the study, and take responsibility for the integrity of the data and accuracy of the data analysis.

**TRANSPARENCY DELCARATION**

MCC affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

**COMPETING INTEREST DECLARATION**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: financial support from the American College

of Surgeons for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## DISSEMINATION DECLARATION

We will disseminate findings through peer-reviewed publication, presentations at national and international meetings, and engagement of physicians and medical societies.

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## TABLES

**Table 1.** Baseline characteristics at the time of the index hysterectomy for women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years) and before applying overlap propensity score weights. Gynecologic diagnoses were documented on the admission for hysterectomy, and patients could have multiple diagnoses if relevant.

| Characteristic | <45 years | | | 45-49 years | | | 50-54 years | | | ≥55 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No BSO N=78,646 | BSO N=17,816 | Std Diff | No BSO N=32,958 | BSO N=22,467 | Std Diff | No BSO N=8,472 | BSO N=18,741 | Std Diff | No BSO N=4,090 | BSO N=17,359 | Std Diff |
| Age (years) | | | | | | | | | | | | |
| Median (IQR) | 40 (37-43) | 41 (38-43) | 0.19 | 47 (46-48) | 48 (46-49) | 0.35 | 52 (51-53) | 52 (51-53) | 0.23 | 60 (57-65) | 61 (57-65) | 0.00 |
| Era of surgery, *No. (%)* | | | | | | | | | | | | |
| 1996-2000 | 21,337 (27.1) | 6,852 (38.5) | 0.24 | 5,791 (17.6) | 7,474 (33.3) | 0.37 | 1,172 (13.8) | 5,378 (28.7) | 0.37 | 581 (14.2) | 4,637 (26.7) | 0.31 |
| 2001-2005 | 22,656 (28.8) | 4,670 (26.2) | 0.06 | 8,786 (26.7) | 5,936 (26.4) | 0.01 | 2,284 (27.0) | 4,736 (25.3) | 0.04 | 1,313 (32.1) | 4,056 (23.4) | 0.20 |
| 2006-2010 | 19,796 (25.2) | 2,980 (16.7) | 0.21 | 10,292 (31.2) | 4,461 (19.9) | 0.26 | 2,696 (31.8) | 4,086 (21.8) | 0.23 | 1,262 (30.9) | 3,846 (22.2) | 0.20 |
| 2011-2015 | 14,857 (18.9) | 3,314 (18.6) | 0.01 | 8,089 (24.5) | 4,596 (20.5) | 0.10 | 2,320 (27.4) | 4,541 (24.2) | 0.07 | 934 (22.8) | 4,820 (27.8) | 0.11 |
| Area of residence, *No. (%)** | | | | | | | | | | | | |
| Urban | 65,863 (83.7) | 14,935 (83.8) | 0.00 | 28,659 (87.0) | 19,366 (86.2) | 0.02 | 7,299 (86.2) | 16,287 (86.9) | 0.02 | 3,430 (83.9) | 14,810 (85.3) | 0.04 |
| Rural | 12,758 (16.2) | 2,869 (16.1) | | 4,285 (13.0) | 3,091 (13.8) | | 1,171 (13.8) | 2,447 (13.1) | | 658 (16.1) | 2,540 (14.6) | |
| Area-level income quintile, *No. (%)** | | | | | | | | | | | | |
| Quintile 1 (low) | 16,131 (20.5) | 3,716 (20.9) | 0.01 | 5,589 (17.0) | 4,114 (18.3) | 0.04 | 1,298 (15.3) | 2,985 (15.9) | 0.02 | 658 (16.1) | 2,814 (16.2) | 0.00 |
| Quintile 2 | 16,647 (21.2) | 3,669 (20.6) | 0.01 | 6,367 (19.3) | 4,401 (19.6) | 0.01 | 1,593 (18.8) | 3,512 (18.7) | 0.00 | 797 (19.5) | 3,331 (19.2) | 0.01 |
| Quintile 3 | 16,618 (21.1) | 3,774 (21.2) | 0.00 | 6,936 (21.0) | 4,603 (20.5) | 0.01 | 1,685 (19.9) | 3,801 (20.3) | 0.01 | 861 (21.1) | 3,492 (20.1) | 0.02 |
| Quintile 4 | 15,973 (20.3) | 3,625 (20.3) | 0.00 | 7,194 (21.8) | 4,689 (20.9) | 0.02 | 1,876 (22.1) | 4,156 (22.2) | 0.00 | 898 (22.0) | 3,669 (21.1) | 0.02 |
| Quintile 5 (high) | 13,054 (16.6) | 2,973 (16.7) | 0.00 | 6,771 (20.5) | 4,607 (20.5) | 0.00 | 1,998 (23.6) | 4,250 (22.7) | 0.02 | 870 (21.3) | 4,009 (23.1) | 0.04 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Immigration status, *No. (%)* | | | | | | | | | | | | |
| Long-term resident | 69,830 (88.8) | 16,036 (90.0) | 0.04 | 27,878 (84.6) | 19,507 (86.8) | 0.06 | 7,443 (87.9) | 16,683 (89.0) | 0.04 | 3,749 (91.7) | 16,136 (93.0) | 0.05 |
| Immigrant | 8,816 (11.2) | 1,780 (10.0) | | 5,080 (15.4) | 2,960 (13.2) | | 1,029 (12.1) | 2,058 (11.0) | | 341 (8.3) | 1,223 (7.0) | |
| Ethnicity, *No. (%)* | | | | | | | | | | | | |
| General population | 75,670 (96.2) | 17,108 (96.0) | 0.01 | 31,019 (94.1) | 21,213 (94.4) | 0.01 | 8,013 (94.6) | 17,738 (94.6) | 0.00 | 3,914 (95.7) | 16,760 (96.5) | 0.04 |
| South Asian | 1,580 (2.0) | 326 (1.8) | 0.01 | 833 (2.5) | 537 (2.4) | 0.01 | 170 (2.0) | 387 (2.1) | 0.00 | 75 (1.8) | 291 (1.7) | 0.01 |
| Chinese | 1,396 (1.8) | 382 (2.2) | 0.03 | 1,106 (3.4) | 717 (3.2) | 0.01 | 289 (3.4) | 616 (3.3) | 0.01 | 101 (2.5) | 308 (1.8) | 0.05 |
| Hysterectomy type, *No. (%)* | | | | | | | | | | | | |
| Total | 68,418 (87.0) | 16,242 (91.2) | 0.13 | 27,369 (83.0) | 20,428 (90.9) | 0.24 | 7,064 (83.4) | 17,095 (91.2) | 0.24 | 3,396 (83.0) | 16,270 (93.7) | 0.34 |
| Subtotal | 10,228 (13.0) | 1,574 (8.8) | | 5,589 (17.0) | 2,039 (9.1) | | 1,408 (16.6) | 1,646 (8.8) | | 694 (17.0) | 1,089 (6.3) | |
| Abnormal uterine bleeding, *No. (%)* | | | | | | | | | | | | |
| Yes | 48,912 (62.2) | 7,016 (39.4) | 0.47 | 18,955 (57.5) | 10,442 (46.5) | 0.22 | 4,026 (47.5) | 7,390 (39.4) | 0.16 | 769 (18.8) | 3,480 (20.0) | 0.03 |
| No | 29,734 (37.8) | 10,800 (60.6) | | 14,003 (42.5) | 12,025 (53.5) | | 4,446 (52.5) | 11,351 (60.6) | | 3,321 (81.2) | 13,879 (80.0) | |
| Fibroids, *No. (%)* | | | | | | | | | | | | |
| Yes | 37,556 (47.8) | 6,703 (37.6) | 0.21 | 23,884 (72.5) | 14,597 (65.0) | 0.16 | 6,226 (73.5) | 12,729 (67.9) | 0.12 | 1,648 (40.3) | 7,958 (45.8) | 0.11 |
| No | 41,090 (52.2) | 11,113 (62.4) | | 9,074 (27.5) | 7,870 (35.0) | | 2,246 (26.5) | 6,012 (32.1) | | 2,442 (59.7) | 9,401 (54.2) | |
| Endometriosis, *No. (%)* | | | | | | | | | | | | |
| Yes | 20,942 (26.6) | 8,831 (49.6) | 0.49 | 8,176 (24.8) | 7,765 (34.6) | 0.21 | 1,946 (23.0) | 5,105 (27.2) | 0.10 | 615 (15.0) | 3,273 (18.9) | 0.10 |
| No | 57,704 (73.4) | 8,985 (50.4) | | 24,782 (75.2) | 14,702 (65.4) | | 6,526 (77.0) | 13,636 (72.8) | | 3,475 (85.0) | 14,086 (81.1) | |
| Ovarian cyst, *No. (%)* | | | | | | | | | | | | |
| Yes | 8,097 (10.3) | 5,226 (29.3) | 0.49 | 3,655 (11.1) | 6,378 (28.4) | 0.45 | 1,071 (12.6) | 5,042 (26.9) | 0.36 | 676 (16.5) | 5,219 (30.1) | 0.32 |
| No | 70,549 (89.7) | 12,590 (70.7) | | 29,303 (88.9) | 16,089 (71.6) | | 7,401 (87.4) | 13,699 (73.1) | | 3,414 (83.5) | 12,140 (69.9) | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pelvic pain/inflammation, *No. (%)* | | | | | | | | | | | | |
| Yes | 22,919 (29.1) | 7,430 (41.7) | 0.26 | 5,985 (18.2) | 5,687 (25.3) | 0.17 | 1,161 (13.7) | 3,319 (17.7) | 0.11 | 437 (10.7) | 2,181 (12.6) | 0.06 |
| No | 55,727 (70.9) | 10,386 (58.3) | | 26,973 (81.8) | 16,780 (74.7) | | 7,311 (86.3) | 15,422 (82.3) | | 3,653 (89.3) | 15,178 (87.4) | |
| Premalignant disease, *No. (%)* | | | | | | | | | | | | |
| Yes | 4,800 (6.1) | 1,056 (5.9) | 0.01 | 1,369 (4.2) | 1,639 (7.3) | 0.14 | 480 (5.7) | 2,165 (11.6) | 0.21 | 579 (14.2) | 3,690 (21.3) | 0.19 |
| No | 73,846 (93.9) | 16,760 (94.1) | | 31,589 (95.8) | 20,828 (92.7) | | 7,992 (94.3) | 16,576 (88.4) | | 3,511 (85.8) | 13,669 (78.7) | |
| Prolapse, *No. (%)* | | | | | | | | | | | | |
| Yes | 3,108 (4.0) | 349 (2.0) | 0.12 | 1,593 (4.8) | 975 (4.3) | 0.02 | 912 (10.8) | 1,541 (8.2) | 0.09 | 1,722 (42.1) | 4,012 (23.1) | 0.41 |
| No | 75,538 (96.0) | 17,467 (98.0) | | 31,365 (95.2) | 21,492 (95.7) | | 7,560 (89.2) | 17,200 (91.8) | | 2,368 (57.9) | 13,347 (76.9) | |
| Comorbidities (ADGs), *No. (%)* | | | | | | | | | | | | |
| 0-5 | 14,344 (18.2) | 2,073 (11.6) | 0.19 | 7,279 (22.1) | 3,555 (15.8) | 0.16 | 1,730 (20.4) | 2,989 (15.9) | 0.12 | 582 (14.2) | 2,273 (13.1) | 0.03 |
| 6-9 | 41,436 (52.7) | 8,897 (49.9) | 0.06 | 18,049 (54.8) | 11,914 (53.0) | 0.03 | 4,593 (54.2) | 9,966 (53.2) | 0.02 | 2,145 (52.4) | 8,981 (51.7) | 0.01 |
| ≥10 | 22,866 (29.1) | 6,846 (38.4) | 0.20 | 7,630 (23.2) | 6,998 (31.1) | 0.18 | 2,149 (25.4) | 5,786 (30.9) | 0.12 | 1,363 (33.3) | 6,105 (35.2) | 0.04 |
| Hypertension, *No. (%)* | | | | | | | | | | | | |
| Yes | 8,916 (11.3) | 2,145 (12.0) | 0.02 | 6,360 (19.3) | 4,725 (21.0) | 0.04 | 2,197 (25.9) | 5,408 (28.9) | 0.07 | 1,916 (46.8) | 8,091 (46.6) | 0.00 |
| No | 69,730 (88.7) | 15,671 (88.0) | | 26,598 (80.7) | 17,742 (79.0) | | 6,275 (74.1) | 13,333 (71.1) | | 2,174 (53.2) | 9,268 (53.4) | |
| Diabetes, *No. (%)* | | | | | | | | | | | | |
| Yes | 3,437 (4.4) | 950 (5.3) | 0.04 | 1,906 (5.8) | 1,376 (6.1) | 0.01 | 510 (6.0) | 1,358 (7.2) | 0.05 | 518 (12.7) | 2,118 (12.2) | 0.01 |
| No | 75,209 (95.6) | 16,866 (94.7) | | 31,052 (94.2) | 21,091 (93.9) | | 7,962 (94.0) | 17,383 (92.8) | | 3,572 (87.3) | 15,241 (87.8) | |
| Chronic obstructive pulmonary disease, *No. (%)* | | | | | | | | | | | | |
| Yes | 2,826 (3.6) | 874 (4.9) | 0.07 | 1,925 (5.8) | 1,557 (6.9) | 0.04 | 504 (5.9) | 1,308 (7.0) | 0.04 | 400 (9.8) | 1,838 (10.6) | 0.03 |
| No | 75,820 (96.4) | 16,942 (95.1) | | 31,033 (94.2) | 20,910 (93.1) | | 7,968 (94.1) | 17,433 (93.0) | | 3,690 (90.2) | 15,521 (89.4) | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Prior malignancy, *No. (%)* | | | | | | | | | | | | |
| Yes | 745 (0.9) | 206 (1.2) | 0.02 | 476 (1.4) | 373 (1.7) | 0.02 | 139 (1.6) | 348 (1.9) | 0.02 | 117 (2.9) | 528 (3.0) | 0.01 |
| No | 77,901 (99.1) | 17,610 (98.8) | | 32,482 (98.6) | 22,094 (98.3) | | 8,333 (98.4) | 18,393 (98.1) | | 3,973 (97.1) | 16,831 (97.0) | |
| Cardiovascular disease, *No. (%)* | | | | | | | | | | | | |
| Yes | 1,983 (2.5) | 660 (3.7) | 0.07 | 1,066 (3.2) | 1,060 (4.7) | 0.08 | 338 (4.0) | 1,049 (5.6) | 0.08 | 514 (12.6) | 2,406 (13.9) | 0.04 |
| No | 76,663 (97.5) | 17,156 (96.3) | | 31,892 (96.8) | 21,407 (95.3) | | 8,134 (96.0) | 17,692 (94.4) | | 3,576 (87.4) | 14,953 (86.1) | |
| Prior ovarian surgery, *No. (%)* | | | | | | | | | | | | |
| Yes | 7,213 (9.2) | 4,293 (24.1) | 0.41 | 1,875 (5.7) | 1,845 (8.2) | 0.10 | 353 (4.2) | 837 (4.5) | 0.01 | 92 (2.2) | 397 (2.3) | 0.00 |
| No | 71,433 (90.8) | 13,523 (75.9) | | 31,083 (94.3) | 20,622 (91.8) | | 8,119 (95.8) | 17,904 (95.5) | | 3,998 (97.8) | 16,962 (97.7) | |
| Prior abdominopelvic surgery, *No. (%)* | | | | | | | | | | | | |
| 0 | 38,170 (48.5) | 6,856 (38.5) | 0.20 | 20,567 (62.4) | 14,297 (63.6) | 0.03 | 5,838 (68.9) | 13,342 (71.2) | 0.05 | 3,127 (76.5) | 13,402 (77.2) | 0.02 |
| 1 | 24,244 (30.8) | 5,640 (31.7) | 0.02 | 8,564 (26.0) | 5,555 (24.7) | 0.03 | 1,928 (22.8) | 3,992 (21.3) | 0.04 | 757 (18.5) | 3,084 (17.8) | 0.02 |
| 2 | 10,038 (12.8) | 2,926 (16.4) | 0.10 | 8,564 (26.0) | 1,742 (7.8) | 0.01 | 512 (6.0) | 1,008 (5.4) | 0.03 | 146 (3.6) | 674 (3.9) | 0.02 |
| 3+ | 6,194 (7.9) | 2,394 (13.4) | 0.18 | 1,144 (3.5) | 873 (3.9) | 0.02 | 194 (2.3) | 399 (2.1) | 0.01 | 60 (1.5) | 199 (1.1) | 0.03 |

* Data were missing for area of residence (N=81, 0.04%) and area-level income quintile (N=545, 0.27%)

Abbreviations: Bilateral salpingo-oophorectomy (BO); interquartile range (IQR); Johns Hopkins Aggregated Diagnosis Groups (ADGs); number (No.) standardized difference (Std Diff)

**Table 2.** Association between bilateral salpingo-oophorectomy and all-cause, non-cancer, and cancer death in women (aged 30-70 years) undergoing benign hysterectomy, stratified by age group (<45, 45-49, 50-54, ≥55 years). Ovarian conservation serves as the referent category. Primary analyses used overlap propensity score weighting, and sensitivity analyses used traditional multivariable Cox proportional hazard models; p<0.0125 (0.05/4) was considered statistically significant, and p-values from 0.0125-0.05 were considered marginally significant.

| Outcome | <45 years | | 45-49 years | | 50-54 years | | ≥55 years | |
|---|---|---|---|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Primary analysis: Overlap propensity score weighted models | | | | | | | | |
| All-cause death | 1.31 (1.18-1.45) | <0.001 | 1.16 (1.04-1.30) | 0.007 | 0.83 (0.72-0.97) | 0.018 | 0.92 (0.82-1.03) | 0.16 |
| Non-cancer death | 1.38 (1.21-1.58) | <0.001 | 1.29 (1.10-1.52) | 0.002 | 0.81 (0.64-1.02) | 0.071 | 1.00 (0.86-1.17) | 0.99 |
| Cancer death | 1.18 (1.01-1.39) | 0.044 | 1.04 (0.89-1.21) | 0.63 | 0.87 (0.71-1.06) | 0.15 | 0.82 (0.69-0.97) | 0.023 |
| Sensitivity analysis: Multivariable models | | | | | | | | |
| All-cause death | 1.30 (1.18-1.45) | <0.001 | 1.17 (1.05-1.30) | 0.006 | 0.86 (0.74-1.00) | 0.044 | 0.97 (0.86-1.09) | 0.57 |
| Non-cancer death | 1.38 (1.21-1.58) | <0.001 | 1.31 (1.11-1.54) | 0.001 | 0.84 (0.68-1.05) | 0.13 | 1.07 (0.91-1.25) | 0.41 |
| Cancer death | 1.20 (1.02-1.41) | 0.029 | 1.06 (0.91-1.24) | 0.43 | 0.88 (0.72-1.07) | 0.18 | 0.85 (0.72-1.01) | 0.072 |

Abbreviations: CI (confidence interval); HR (hazard ratio)

**Table 3.** Cohort studies examining the association between bilateral salpingo-oophorectomy (BSO) and all-cause death.

| Study | Cohort | Follow-Up | Age Group | Sample Size | Deaths | HR (95% CI) | Covariates |
|---|---|---|---|---|---|---|---|
| Rocca, 2006 (3) | Mayo Clinic Cohort Study<br><br>Prophylactic BSO vs. no ovarian surgery | Median 25.0 years | <45 | 1,541 | 262 | 1.67 (1.16-2.40) | Age |
| | | | –HT | 1,462 | 239 | 1.93 (1.25-2.39) | |
| | | | +HT | 1,496 | 252 | 1.27 (0.67-2.39) | |
| | | | 45-50 | 888 | 315 | 1.02 (0.78-1.32) | |
| | | | >50 | 491 | 235 | 0.90 (0.68-1.19) | |
| Parker, 2009 (15) | Nurses' Health Study<br><br>BSO vs. ovarian conservation at time of benign hysterectomy | Maximum 24 years | Overall | 29,380 | 3,197 | 1.12 (1.03-1.21) | Age, parity, diabetes, hypertension, hypercholesterolemia, body mass index, smoking, alcohol intake, exercise, aspirin use, tubal ligation, family history of breast cancer, family history of myocardial infarction <60 years, HT use, oral contraceptive use |
| | | | <45 | NR | 1,627 | 1.06 (0.95-1.80) | |
| | | | 45-54 | NR | 1,300 | 1.15 (1.01-1.32) | |
| | | | ≥55 | NR | 270 | 1.14 (0.85-1.52) | |
| Parker, 2013 (16) | Nurses' Health Study<br><br>BSO vs. ovarian conservation at time of benign hysterectomy | Maximum 28 years | Overall | 30,117 | 4,599 | 1.13 (1.06-1.21) | Age, parity, body mass index, smoking, alcohol intake, exercise, aspirin use, tubal ligation, family history of breast cancer, family history of myocardial infarction <60 years, HT use, oral contraceptive use |
| | | | <50 | 21,094 | 3,433 | 1.13 (1.05-1.22) | |
| | | | –HT | NR | 292 | 1.41 (1.04-1.92) | |
| | | | +HT | NR | 1,695 | 1.05 (0.94-1.17) | |
| | | | 50-59 | 6,241 | 883 | 1.10 (0.93-1.31) | |
| | | | ≥60 | 2,782 | 283 | 1.31 (0.98-1.75) | |
| Jacoby, 2011 (18) | Women's Health Initiative<br><br>BSO vs. ovarian conservation at time of benign hysterectomy | Mean 7.6 (SD 1.6) years | <40 | 7,583 | 446 | 0.90 (0.72-1.13) | Age, parity, ethnicity, education, insurance, health care provider, hypercholesterolemia, hypertension, diabetes, body mass index, smoking, alcohol intake, exercise, myocardial infarction, stroke, coronary revascularization, family history of myocardial infarction or stroke, HT use |
| | | | 40-49 | 11,397 | 661 | 1.00 (0.84-1.19) | |
| | | | ≥50 | 2,934 | 417 | 1.07 (0.84-1.35) | |
| Gierach, 2014 (4) | Breast Cancer Detection Demonstration Project<br><br>BSO vs. no gynecologic surgery | Mean 22.1 years | ≤35 | 50,742 | 13,237 | 1.20 (1.08-1.34) | Landmark analyses at differing ages: Adjusted for BMI, alcohol intake, smoking, HT use, birth cohort |
| | | | ≤45 | 44,971 | 11,894 | 1.10 (1.03-1.17) | |
| | | | ≤55 | 42,053 | 10,862 | 1.01 (0.96-1.06) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Mytton, 2017 (5) | English Hospital Episode Statistics<br><br>BSO vs. ovarian conservation at time of benign hysterectomy | Mean 6.2 (SD 2.8) years | 35-45 | 113,679 | 832 | 1.56 (1.37-1.81)* | Age, deprivation, surgery type, Charlson comorbidity score, number of admissions before hysterectomy |
| Wilson, 2019 (6) | Australian Longitudinal Study<br><br>Hysterectomy with BSO vs. no gynecologic surgery | Median 21.5 years | <50 | 11,069 | 734 | 1.02 (0.78-1.34) | Age, body mass index, smoking, alcohol intake, exercise, education, difficulty managing on income, remoteness category, number of children, diabetes, hypertension, perception of general health |
| | | | –HT | 8,354 | 518 | 1.81 (1.01-3.25) | |
| | | | +HT | 2,708 | 216 | 0.91 (0.67-1.24) | |
| Tuesley, 2020 (7) | Western Australia Electoral Roll<br><br>Hysterectomy with BSO vs. no gynecologic surgery | Median 24.2 years | <35 | 1,013 | 59 | 1.55 (1.20-2.01) | Age at entry, area of residence, area-level socioeconomic status, parity (time-varying), tubal ligation (time-varying) |
| | | | 35-44 | 4,936 | 291 | 1.22 (1.09-1.37) | |
| | | | 45-54 | 8,599 | 414 | 0.87 (0.79-0.96) | |
| | | | 55-64 | 2,963 | 241 | 0.95 (0.84-1.08) | |
| | | | ≥65 | 1,046 | 96 | 0.94 (0.77-1.15) | |
| Cusimano, 2020 | ICES Ontario Databases<br><br>BSO vs. ovarian conservation at the time of benign abdominal hysterectomy | Median 12.0 years | <45 | 96,462 | 2,268 | 1.31 (1.18-1.45) | Demographics: Age, era of surgery, rural/urban residence, area-level income quintile, ethnicity, immigration status<br>Gynecologic: Hysterectomy type, abnormal uterine bleeding, fibroids, ovarian cysts, endometriosis, pelvic pain/inflammation, premalignant disease, prolapse<br>Clinical: Overall comorbidity score, hypertension, diabetes, chronic obstructive pulmonary disease, prior malignancy, cardiovascular disease, prior ovarian surgery, prior abdominopelvic surgery |
| | | | 45-49 | 55,425 | 1,516 | 1.16 (1.04-1.30) | |
| | | | 50-54 | 27,213 | 982 | 0.83 (0.72-0.97) | |
| | | | ≥55 | 26,176 | 2,267 | 0.92 (0.82-1.03) | |

* Mytton et al. reported BSO as the referent group [0.64 (95% CI 0.55-0.73)]; to facilitate comparison, we present the reciprocal.

Abbreviations: Bilateral salpingo-oophorectomy (BSO), CI (confidence interval), HR (hazard ratio), HT (hormone therapy)

## FIGURE LEGENDS

**Figure 1.** Weighted cumulative incidence of all-cause death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

**Figure 2.** Hazard ratios for (a) all-cause, (b) non-cancer, and (c) cancer death, comparing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation at each year of age from 45-54 years in women undergoing benign hysterectomy. Point estimates trend in favour of ovarian conservation in red area, and BSO in blue area; 95% confidence intervals for these point estimates are represented by whiskers.

**Figure 1.** Weighted cumulative incidence of all-cause death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

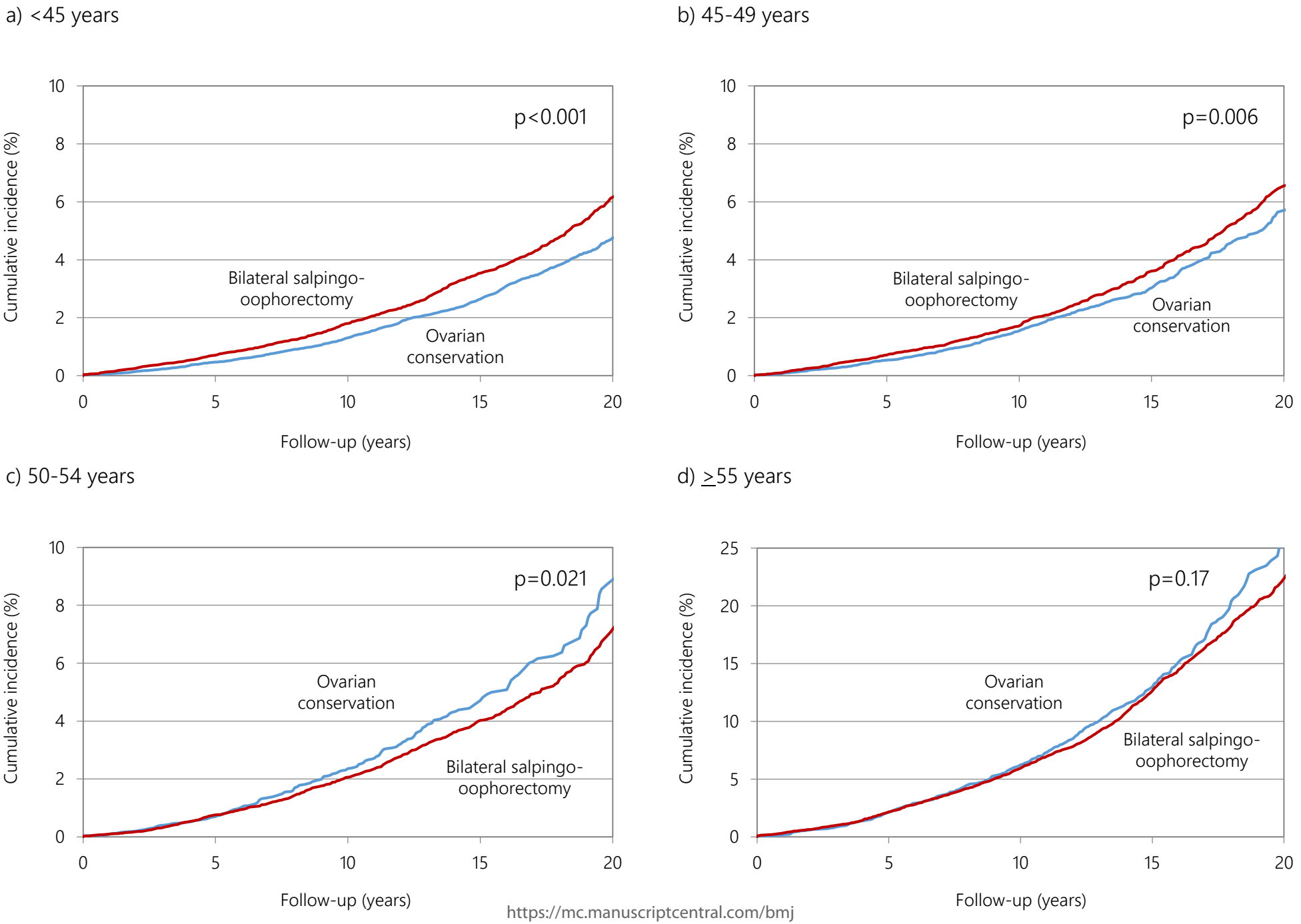
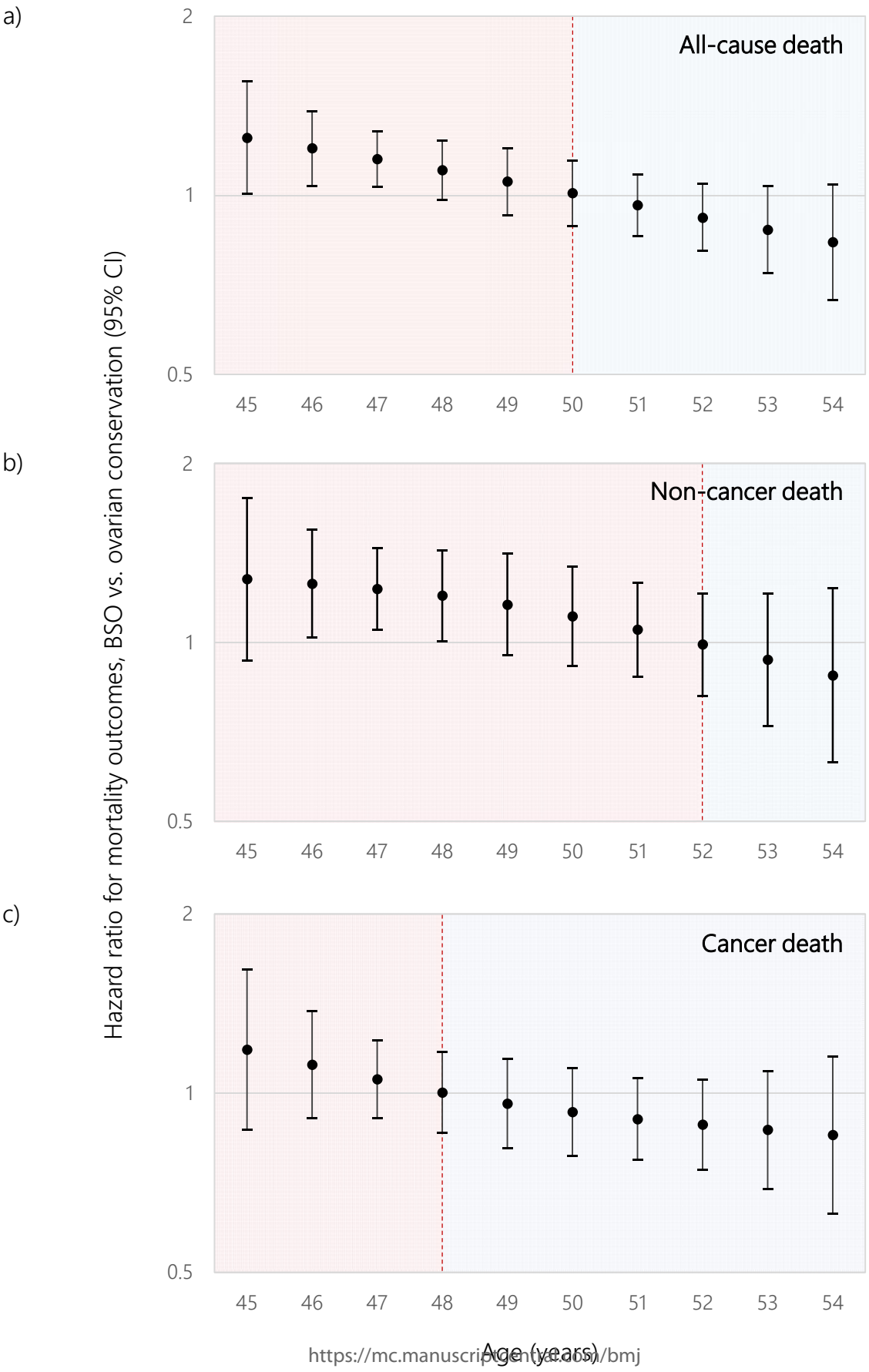


Figure 2. Hazard ratios for (a) all-cause, (b) non-cancer, and (c) cancer death, comparing BSO versus ovarian conservation at each year of age from 45-54 years in women undergoing benign hysterectomy. Point estimates trend in favour of ovarian conservation in red area, and BSO in blue area; 95% confidence intervals for these point estimates are represented by whiskers.



**ONLINE-ONLY APPENDIX**

**Appendix 1.** Codes for hysterectomy and salpingo-oophorectomy.

**Appendix 2.** Flow chart of included patients.

**Appendix 3.** Inclusion & exclusion criteria, with relevant codes.

**Appendix 4.** International Classification of Diseases (ICD)-9 and -10 codes for major gynecologic diagnoses documented on the inpatient or outpatient admission for hysterectomy.

**Appendix 5.** Codes and algorithms used to ascertain specific comorbidities.

**Appendix 6.** Weighted baseline characteristics for women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

**Appendix 7.** Unweighted mortality outcomes for women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

**Appendix 8.** Weighted cumulative incidence of non-cancer death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

**Appendix 9.** Weighted cumulative incidence of cancer death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

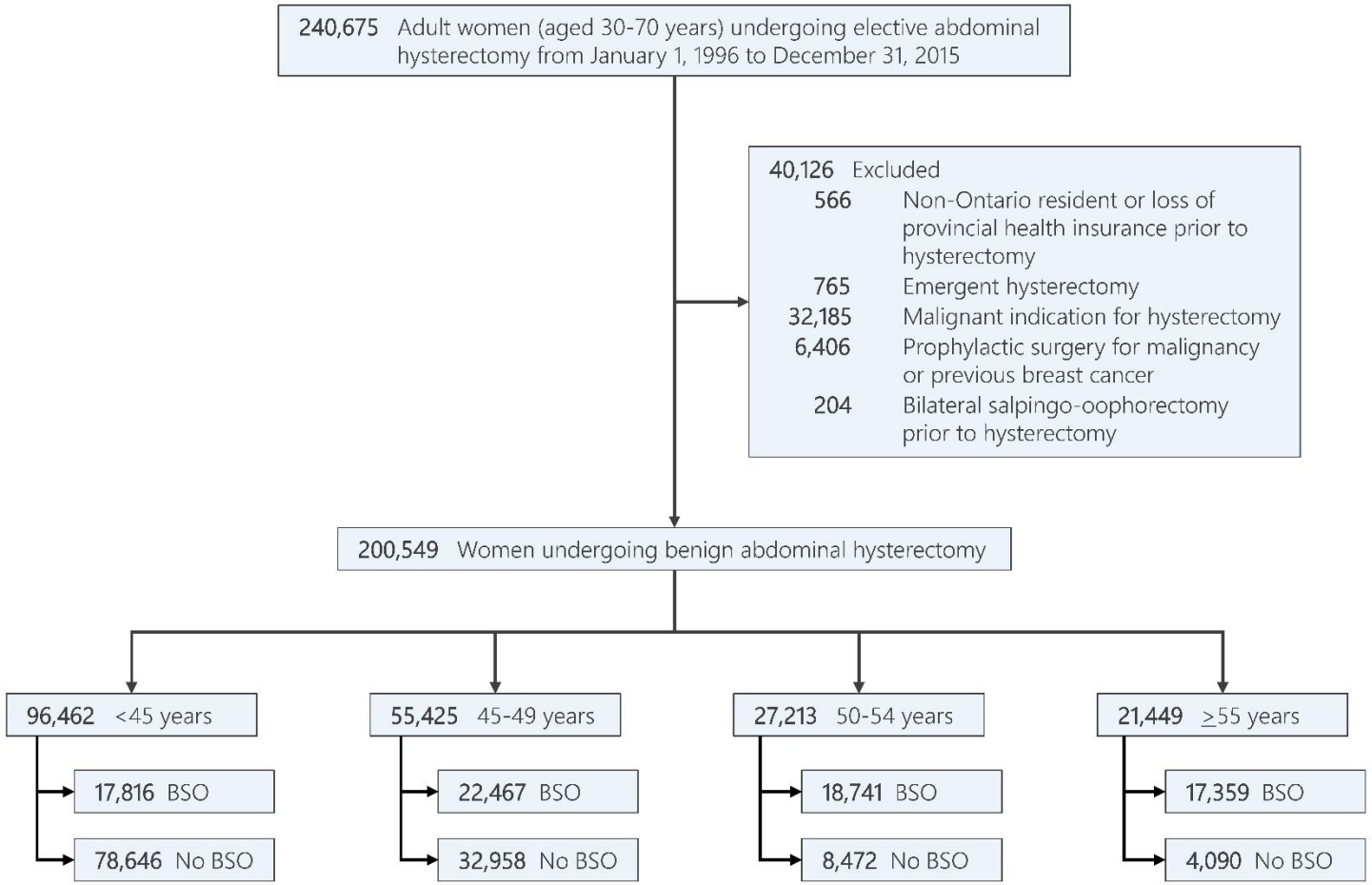
**Appendix 10.** (a) Women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) at some point after hysterectomy, and (b) sensitivity analyses modelling BSO as a time-varying covariate in a traditional multivariable Cox proportional hazards model; ovarian conservation serves as the referent category. All analyses are stratified by age group (<45, 45-49, 50-54, ≥55 years); $p<0.0125$ (0.05/4) was considered statistically significant, and p-values from 0.0125-0.05 were considered marginally significant.

**Appendix 1.** Codes for hysterectomy and salpingo-oophorectomy. Patients required a procedure code for hysterectomy in the Discharge Abstract Database or Same Day Surgery database, and a surgeon billing claim for hysterectomy in the Ontario Health Insurance Plan database, within 6 weeks of each other to be eligible for inclusion.

| Procedure | Technique | DAD/SDS Codes | | OHIP Codes |
|---|---|---|---|---|
| | | Years 1996-2001 | Years 2002+ | |
| Total hysterectomy | Open | 1.RM.89.LA | 80.3 | S710, S757, S758, S759, S763, S769, S810, S816 |
| | Laparoscopic | 1.RM.89.DA, 1.RM.89.AA | N/A | |
| | Robotic | 1.RM.89.^^ + 7.SF.14.ZX | N/A | |
| Subtotal hysterectomy | Open | 1.RM.87.LA | 80.2 | |
| | Laparoscopic | 1.RM.87.DA, 1.RM.87.BA, 1.RM.87.CA | N/A | |
| | Robotic | 1.RM.87.^^ + 7.SF.14.ZX | N/A | |
| Radical hysterectomy | Open | 1.RM.91.LA | 80.5 | |
| | Laparoscopic | 1.RM.91.DA, 1.RM.91.AA | NA | |
| | Robotic | 1.RM.91.^^ + 7.SF.14.ZX | NA | |
| Salpingo-oophorectomy | Unilateral | 1.RB.89.^^, 1.RD.89.^^ [location attribute (L)eft/(R)ight] | 77.2, 77.3 | N/A |
| | Bilateral | 1.RB.89.^^, 1.RD.89.^^ [location attribute (B)ilateral] | 77.41, 77,42, 77.51, 77.52 | |

Abbreviations: CCI (Canadian Classification of Intervention); DAD (Discharge Abstract Database); OHIP (Ontario Health Insurance Plan); SDS (Same Day Surgery database)

**Appendix 2.** Flow chart of included patients.



**Appendix 3.** Inclusion & exclusion criteria, with relevant codes.

| Criteria | Source | Codes |
|---|---|---|
| **Inclusion Criteria** | | |
| 1. Female patient | RPDB | SEX=F |
| 2. Age 30-70 years at index date | RPDB | Based on variables BDATE and BYEAR |
| 3. Record of abdominal hysterectomy in DAD/SDS and OHIP (+/-6 weeks) from January 1, 1996 to December 31, 2015, and performed on an elective basis | DAD<br>SDS | Hysterectomy codes: Supplemental Table 1<br>Admission category variable: ADMCAT=L |
| **Exclusion Criteria** | | |
| 1. Non-Ontario residents ineligible for universal health insurance coverage | RPDB | - IKN=Invalid<br>- First two digits of PRCDDABLK not 35<br>- Death or loss of OHIP prior to index date |
| 2. Suspected emergent hysterectomy | OHIP<br>DAD<br>SDS | - Surgery between midnight and 7AM: E410<br>- Peripartum indication for hysterectomy (PATSERV=51, 53, or 59)[1] |
| 3. Malignant indication for hysterectomy or a prior breast cancer diagnosis | OCR<br>DAD<br>SDS | - Gynecologic cancer diagnosed any time prior or up to six weeks after index date (ICD-9: 179-184; ICD-10: C510-C58, C481, C48.2)<br>- Main indication for index surgical admission was either a cancer diagnosis or a gynecologic neoplasm of uncertain or unknown behaviour: ICD-9: 140-208, 2360, 2362, 2361, 2363; ICD-10: C00-C97, D390, D391, D392, D397, D399<br>- Documentation of prophylactic surgery for malignancy before or on index date (mastectomy, hysterectomy, salpingo-oophorectomy): ICD-9: V50.4, ICD-10 Z40<br>- Breast cancer diagnosis prior to index date: ICD-9: 174; ICD-10: C50 |
| 4. Bilateral salpingo-oophorectomy prior to index date | DAD<br>SDS | Salpingo-oophorectomy codes: Supplemental Table 1 |

Abbreviations: DAD (Discharge Abstract Database); OHIP (Ontario Health Insurance Plan); SDS (Same Day Surgery database); RPDB (Registered Persons Database)

1) Codes derived from: Canadian Institute for Health Information (CIHI). Technical Note: Hysterectomy Readmission. Accessed at: <https://www.cihi.ca/en/technical-note-hysterectomy-readmission-0#P14_938>

**Appendix 4.** International Classification of Diseases (ICD)-9 and -10 codes for major gynecologic diagnoses documented on the inpatient or outpatient admission for hysterectomy. Patients could multiple diagnoses if relevant.

| Indication | Definition | ICD-10 Codes | ICD-9 Codes |
|---|---|---|---|
| **Premalignant Conditions** | | | |
| | Endometrial hyperplasia | N850, N851 | 6213 |
| | Cervical dysplasia | N870, N871, N872, N879 | 6221 |
| | Vaginal dysplasia | N890, N891, N892, N893 | 6230 |
| | Vulvar dysplasia | N900, N901, N902, N903 | N/A |
| | CIS cervix | D060, D061, D067, D069 | 2331 |
| | CIS vagina | D072 | N/A |
| | CIS vulva | D071 | N/A |
| | CIS endometrium/uterus | D070 | 2332 |
| | CIS unspecified female genital organs | D073 | 2333 |
| **Benign Ovarian Cysts** | | | |
| | Benign neoplasm ovary | D27 | 220, 2200 |
| | Follicular ovarian cyst | N830 | 6200 |
| | Corpus luteum cyst | N831 | 6201 |
| | Other & unspecified ovarian cysts | N832 | 6202 |
| | Neoplasm of uncertain or unknown behaviour of ovary | D391 | 2362 |
| **Abnormal Uterine Bleeding**[1] | | | |
| | Heavy menstrual bleeding | | |
| | Excessive/frequent, regular cycle | N920 | 6262 |
| | Excessive/frequent, irregular cycle | N921 | 6262 |
| | Excessive in premenopause | N924 | 6270 |
| | Irregular, other | N925 | 6264, 6266 |
| | Irregular, unspecified | N926 | 6264, 6266 |
| | Abnormal, other | N938 | 6268 |
| | Abnormal, unspecified | N939 | 6269 |
| | Excessive menstruation at puberty | N922 | 6263 |
| | Ovulation bleeding | N923 | 6265 |
| | Postcoital and contact bleeding | N930 | 6267 |
| | Postmenopausal bleeding | N950 | 6271 |
| **Fibroids**[2] | | | |
| | Fibroids | D25 | 218 |
| | Submucous leiomyoma | D250 | 2180 |
| | Intramural leiomyoma | D251 | 2181 |
| | Subserosal leiomyoma | D252 | 2182 |
| | Leiomyoma of uterus, unspecified | D259 | 2189 |
| **Endometriosis** | | | |
| | Uterus | N800 | 6170 |

| | | | |
|---|---|---|---|
| | Ovary | N801 | 6171 |
| | Fallopian tube | N802 | 6172 |
| | Pelvic peritoneum | N803 | 6173 |
| | Rectovaginal septum/vagina | N804 | 6174 |
| | Intestine | N805 | 6175 |
| | Cutaneous scar | N806 | 6176 |
| | Other, unspecified | N808, N809 | 6178, 6179 |
| **Prolapse**[2] | | | |
| | Female urethrocele | N810 | N/A |
| | Cystocele | N811 | N/A |
| | Incomplete uterovaginal prolapse | N812 | 6182 |
| | Complete uterovaginal prolapse | N813 | 6183 |
| | Uterovaginal prolapse, unspecified | N814 | 6184 |
| | Vaginal enterocele | N815 | 6186 |
| | Rectocele | N816 | N/A |
| | Other female genital prolapse | N818 | 6188 |
| | Female genital prolapse, unspecified | N819 | 6189 |
| | Prolapse of vaginal wall | N/A | 6180 |
| | Uterine prolapse | N/A | 6181 |
| | Postoperative vaginal prolapse | N/A | 6185 |
| | Old laceration of pelvic muscle | N/A | 6187 |
| **Pelvic Pain & Inflammation** | | | |
| Inflammation | Salpingitis and oophoritis | N700, N701, N709 | 6140, 6141, 6142 |
| | Inflammatory disease of uterus | N710, N711, N719 | 6143, 6144, 6150, 6151, 6159 |
| | Inflammatory disease of cervix | N72 | 6160 |
| | Parametritis, pelvic cellulitis, pelvic peritonitis, pelvic peritoneal adhesions, other/unspecified female pelvic inflammatory disease | N730, N731, N732, N733, N734, N735, N736, N738, N739 | 6145, 6146, 6147, 6148, 6149 |
| | Pelvic inflammatory disease (tuberculous, syphilitic, gonococcal, chlamydial, other, unspecified) | N740, N741, N742, N743, N744, N748 | 614, 615 |
| | Bartholin's cyst/abscess/disease | N750, N751, N758, N759 | 6162, 6163 |
| | Vaginitis/vulvitis/ulceration | N760, N761, N762, N763, N764, N765, N766, N768, N7680, N7688 | 6161, 61610, 61611, 6164, 6165, 61650, 61651 |
| | Vulvovaginal ulceration and inflammation NEC | N770, N771, N778 | 6168, 6169 |
| Abdominal & pelvic pain | Acute abdomen, RUQ/LUQ, RLQ/LLQ, pelvic/perineal pain, other/unspecified abdominal pain | R100, R1010, R1011, R1012, R1019, R102, R1030, R1032 R1039, R104 | 7890 |
| | Acute, chronic, or other pain | R520, R521, R522, R529 | N/A |
| Menstrual pain | Mittelschmerz | N940 | 6252 |

| | | | |
|---|---|---|---|
| | Dyspareunia | N941 | 6250 |
| | Vaginismus | N942 | 6251 |
| | Premenstrual tension syndrome | N943 | 6254, 6255 |
| | Primary dysmenorrhea | N944 | 6253 |
| | Secondary dysmenorrhea | N945 | 6253 |
| | Dysmenorrhea, unspecified | N946 | 6253 |
| | Other specified conditions associated with female genital organs and menstrual cycle | N948 | N/A |
| | Unspecified condition associated with female genital organs and menstrual cycle | N949 | N/A |

1) Codes for heavy menstrual bleeding have been previously used by Bansi-Matharu et al. (Citation: Bansi-Matharu L, Gurol-Urganci I, Mahmood TA, Templeton A, van der Meulen JH, Cromwell DA. Rates of subsequent surgery following endometrial ablation among English women with menorrhagia: population-based cohort study. *BJOG.* 2013;120(12):1500-1507.)

2) Codes for fibroids and prolapse have been previously used by Reeves et al. (Citation: Reeves GK, Balkwill A, Cairns BJ, Green J, Beral V, Million Women Study C. Hospital admissions in relation to body mass index in UK women: a prospective cohort study. *BMC Med.* 2014;12:45.)

**Appendix 5.** Codes and algorithms used to ascertain specific comorbidities.

| Comorbidity | Source | Relevant Codes | Algorithm & Citation |
|---|---|---|---|
| Previous malignancy | - Ontario Cancer Registry | ICD-10: C00-C97<br>ICD-9: 140-208 | Not applicable |
| Hypertension | - Ontario Hypertension Database<br>- DAD<br>- SDS<br>- OHIP | ICD-9: 401, 402, 403, 404, 405<br>ICD-10: I10, I11, I12, I13, I15<br>OHIP: 401, 402, 403, 404, 405 | Tu et al. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. CMAJ. 2008; 178(11): 1429-1435.<br><br>SN: 72%<br>SP: 95% |
| Diabetes | - Ontario Diabetes Database<br>- DAD<br>- SDS<br>- OHIP<br>- ODB | ICD-9: 250<br>ICD-10: E10, E11, E13, E14<br>OHIP: 250, K030, K045, K046, Q040<br>SUBCLNAM = Insulins; oral anti-glycemics | Lipscombe et al. Identifying diabetes cases from administrative data: a population-based validation study. BMC Health Serv Res. 2018;18(1):316.<br><br>SN: 90.0%<br>SP: 97.7% |
| Chronic obstructive pulmonary disease | - COPD Database<br>- OHIP<br>- DAD<br>- SDS | OHIP: 491, 492, 496<br>ICD-10: J41, J43, J44 | Gershon et al. Identifying individuals with physician diagnosed COPD in health administrative databases. COPD. 2009;6(5):388-394.<br><br>SN: 85.0%<br>SP: 78.4% |
| Previous cardiovascular disease | - DAD<br>- SDS<br>- NACRS<br>- OHIP | Ischemic heart disease<br>ICD-10: I20-I25<br>ICD-9: 410-414<br>OHIP: 410, 412, 413<br><br>Stroke/transient ischemic attack<br>ICD-10: I60, I61, I63 (except I63.6), I64, H34.1, G45 (except G45.4), H34.0<br>ICD9: 362.3, 430, 431, 434 , 436, 435<br>OHIP: 436, 432, 435<br><br>Heart failure<br>ICD-10: I500, I501, I509<br>ICD-9: 428 | Tu et al. The Cardiovascular Health in Ambulatory Care Research Team (CANHEART): Using Big Data to Measure and Improve Cardiovascular Health and Healthcare Services. Circ Cardiovasc Qual Outcomes. 2015;8:204-212. |

| | | | |
|---|---|---|---|
| | | OHIP: 428<br><br>Coronary revascularization<br>CCI: 1IJ50, 1IJ54, 1IJ57GQ, 1IJ76<br>CCP: 4802, 4803, 481<br>OHIP: Z434, G298, R742, R743<br><br>Cardiac catheterization<br>CCI: 3IP10<br>CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4995, 4996, 4997<br>OHIP: Z442 or G297 | |

Abbreviations: Canadian Institute for Health Information Discharge Abstract Database (DAD); Canadian Institute for Health Information Same Day Surgery Database (SDS); Canadian Institute for Health Information National Ambulatory Care Reporting System (NACRS); International Classification of Diseases (ICD); Ontario Drug Benefit Database (ODB); Ontario Health Insurance Plan Database (OHIP); sensitivity (SN); specificity (SP)

**Appendix 6.** Weighted baseline characteristics for women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years). Overlap propensity score weighting mathematically produces exact balance for means of covariates included in the original logistic propensity score model.

| Characteristic | <45 years | | | 45-49 years | | | 50-54 years | | | ≥55 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No BSO N=78,646 | BSO N=17,816 | Std Diff | No BSO N=32,958 | BSO N=22,467 | Std Diff | No BSO N=8,472 | BSO N=18,741 | Std Diff | No BSO N=4,090 | BSO N=17,359 | Std Diff |
| Age (years) | | | | | | | | | | | | |
| Mean | 40.19 | 40.19 | 0.00 | 47.40 | 47.40 | 0.00 | 51.93 | 51.93 | 0.00 | 61.21 | 61.21 | 0.00 |
| Era of surgery, *(%)* | | | | | | | | | | | | |
| 1996-2000 | 35.12 | 35.12 | 0.00 | 25.38 | 25.38 | 0.00 | 17.43 | 17.43 | 0.00 | 16.41 | 16.41 | 0.00 |
| 2001-2005 | 26.94 | 26.94 | 0.00 | 27.36 | 27.36 | 0.00 | 27.43 | 27.43 | 0.00 | 30.40 | 30.40 | 0.00 |
| 2006-2010 | 18.30 | 18.30 | 0.00 | 24.11 | 24.11 | 0.00 | 28.35 | 28.35 | 0.00 | 29.22 | 29.22 | 0.00 |
| 2011-2015 | 19.65 | 19.65 | 0.00 | 23.15 | 23.15 | 0.00 | 26.79 | 26.79 | 0.00 | 23.98 | 23.98 | 0.00 |
| Area of residence, *(%)* | | | | | | | | | | | | |
| Urban | 83.78 | 83.78 | 0.00 | 86.34 | 86.34 | 0.00 | 86.46 | 86.46 | 0.00 | 84.02 | 84.02 | 0.00 |
| Rural | 16.22 | 16.22 | | 13.66 | 13.66 | | 13.54 | 13.54 | | 15.98 | 15.98 | |
| Area-level income quintile, *(%)* | | | | | | | | | | | | |
| Quintile 1 (low) | 21.01 | 21.01 | 0.00 | 17.82 | 17.82 | 0.00 | 15.66 | 15.66 | 0.00 | 16.06 | 16.06 | 0.00 |
| Quintile 2 | 20.91 | 20.91 | 0.00 | 19.62 | 19.62 | 0.00 | 19.06 | 19.06 | 0.00 | 19.24 | 19.24 | 0.00 |
| Quintile 3 | 21.14 | 21.14 | 0.00 | 20.74 | 20.74 | 0.00 | 20.01 | 20.01 | 0.00 | 20.84 | 20.84 | 0.00 |
| Quintile 4 | 20.34 | 20.34 | 0.00 | 21.22 | 21.22 | 0.00 | 22.19 | 22.19 | 0.00 | 21.89 | 21.89 | 0.00 |
| Quintile 5 (high) | 16.59 | 16.59 | 0.00 | 20.60 | 20.60 | 0.00 | 23.08 | 23.08 | 0.00 | 21.96 | 21.96 | 0.00 |
| Immigration status, *(%)* | | | | | | | | | | | | |
| Long-term resident | 89.77 | 89.77 | 0.00 | 85.88 | 85.88 | 0.00 | 88.13 | 88.13 | 0.00 | 92.24 | 92.24 | 0.00 |
| Immigrant | 10.23 | 10.23 | | 14.12 | 14.12 | | 11.87 | 11.87 | | 7.76 | 7.76 | |
| Ethnicity, *(%)* | | | | | | | | | | | | |
| General population | 96.12 | 96.12 | 0.00 | 94.39 | 94.39 | 0.00 | 94.58 | 94.58 | 0.00 | 96.06 | 96.06 | 0.00 |
| South Asian | 1.83 | 1.83 | 0.00 | 2.42 | 2.42 | 0.00 | 2.06 | 2.06 | 0.00 | 1.69 | 1.69 | 0.00 |
| Chinese | 2.05 | 2.05 | 0.00 | 3.19 | 3.19 | 0.00 | 3.37 | 3.37 | 0.00 | 2.24 | 2.24 | 0.00 |
| Hysterectomy type, *(%)* | | | | | | | | | | | | |
| Total | 90.59 | 90.59 | 0.00 | 88.55 | 88.55 | 0.00 | 86.98 | 86.98 | 0.00 | 87.57 | 87.57 | 0.00 |
| Subtotal | 9.41 | 9.41 | | 11.45 | 11.45 | | 13.02 | 13.02 | | 12.43 | 12.43 | |
| Abnormal uterine bleeding, *(%)* | | | | | | | | | | | | |
| Yes | 45.86 | 45.86 | 0.00 | 51.85 | 51.85 | 0.00 | 45.10 | 45.10 | 0.00 | 19.60 | 19.60 | 0.00 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | 54.14 | 54.14 | | 48.15 | 48.15 | | 54.90 | 54.90 | | 80.40 | 80.40 | |
| Fibroids, *(%)* | | | | | | | | | | | | |
| Yes | 40.28 | 40.28 | 0.00 | 67.95 | 67.95 | 0.00 | 71.89 | 71.89 | 0.00 | 42.27 | 42.27 | 0.00 |
| No | 59.72 | 59.72 | | 32.05 | 32.05 | | 28.11 | 28.11 | | 57.73 | 57.73 | |
| Endometriosis, *(%)* | | | | | | | | | | | | |
| Yes | 43.46 | 43.46 | 0.00 | 30.30 | 30.30 | 0.00 | 24.41 | 24.41 | 0.00 | 16.01 | 16.01 | 0.00 |
| No | 56.54 | 56.54 | | 69.70 | 69.70 | | 75.59 | 75.59 | | 83.99 | 83.99 | |
| Ovarian cyst, *(%)* | | | | | | | | | | | | |
| Yes | 22.47 | 22.47 | 0.00 | 18.44 | 18.44 | 0.00 | 83.98 | 83.98 | 0.00 | 19.16 | 19.16 | 0.00 |
| No | 77.53 | 77.53 | | 81.56 | 81.56 | | 16.02 | 16.02 | | 80.84 | 80.84 | |
| Pelvic pain/inflammation, *(%)* | | | | | | | | | | | | |
| Yes | 38.89 | 38.89 | 0.00 | 22.24 | 22.24 | 0.00 | 84.93 | 84.93 | 0.00 | 11.29 | 11.29 | 0.00 |
| No | 61.11 | 61.11 | | 77.76 | 77.76 | | 15.07 | 15.07 | | 88.71 | 88.71 | |
| Premalignant disease, *(%)* | | | | | | | | | | | | |
| Yes | 6.26 | 6.26 | 0.00 | 5.85 | 5.85 | 0.00 | 92.87 | 92.87 | 0.00 | 15.87 | 15.87 | 0.00 |
| No | 93.74 | 93.74 | | 94.15 | 94.15 | | 7.13 | 7.13 | | 84.13 | 84.13 | |
| Prolapse, *(%)* | | | | | | | | | | | | |
| Yes | 2.40 | 2.40 | 0.00 | 4.73 | 4.73 | 0.00 | 10.01 | 10.01 | 0.00 | 36.77 | 36.77 | 0.00 |
| No | 97.60 | 97.60 | | 95.27 | 95.27 | | 89.99 | 89.99 | | 63.23 | 63.23 | |
| Comorbidities (ADGs), *(%)* | | | | | | | | | | | | |
| 0-5 | 13.16 | 13.16 | 0.00 | 18.35 | 18.35 | 0.00 | 18.88 | 18.88 | 0.00 | 14.10 | 14.10 | 0.00 |
| 6-9 | 50.99 | 50.99 | 0.00 | 54.31 | 54.31 | | 54.13 | 54.13 | 0.00 | 52.26 | 52.26 | 0.00 |
| ≥10 | 35.85 | 35.85 | 0.00 | 27.34 | 27.34 | | 27.00 | 27.00 | 0.00 | 33.64 | 33.64 | 0.00 |
| Hypertension, *(%)* | | | | | | | | | | | | |
| Yes | 11.95 | 11.95 | 0.00 | 20.31 | 20.31 | 0.00 | 27.04 | 27.04 | 0.00 | 46.58 | 46.58 | 0.00 |
| No | 88.05 | 88.05 | | 79.69 | 79.69 | | 72.96 | 72.96 | | 53.42 | 53.42 | |
| Diabetes, *(%)* | | | | | | | | | | | | |
| Yes | 5.14 | 5.14 | 0.00 | 6.03 | 6.03 | 0.00 | 6.49 | 6.49 | 0.00 | 12.34 | 12.34 | 0.00 |
| No | 94.86 | 94.86 | | 93.97 | 93.97 | | 93.51 | 93.51 | | 87.66 | 87.66 | |
| Chronic obstructive pulmonary disease, *(%)* | | | | | | | | | | | | |
| Yes | 4.66 | 4.66 | 0.00 | 6.55 | 6.55 | 0.00 | 6.33 | 6.33 | 0.00 | 9.98 | 9.98 | 0.00 |
| No | 95.34 | 95.34 | | 93.45 | 93.45 | | 93.67 | 93.67 | | 90.02 | 90.02 | |
| Prior malignancy, *(%)* | | | | | | | | | | | | |
| Yes | 1.15 | 1.15 | 0.00 | 1.57 | 1.57 | 0.00 | 1.74 | 1.74 | 0.00 | 2.93 | 2.93 | 0.00 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No | 98.85 | 98.85 | | 98.43 | 98.43 | | 98.26 | 98.26 | | 97.07 | 97.07 | |
| Cardiovascular disease, *(%)* | | | | | | | | | | | | |
| Yes | 3.43 | 3.43 | 0.00 | 4.00 | 4.00 | 0.00 | 4.38 | 4.38 | 0.00 | 12.80 | 12.80 | 0.00 |
| No | 96.57 | 96.57 | | 96.00 | 96.00 | | 95.62 | 95.62 | | 87.20 | 87.20 | |
| Prior ovarian surgery, *(%)* | | | | | | | | | | | | |
| Yes | 18.40 | 18.40 | 0.00 | 7.09 | 7.09 | 0.00 | 4.36 | 4.36 | 0.00 | 2.36 | 2.36 | 0.00 |
| No | 81.60 | 81.60 | | 92.91 | 92.91 | | 95.64 | 95.64 | | 97.64 | 97.64 | |
| Prior abdominopelvic surgery, *(%)* | | | | | | | | | | | | |
| 0 | 41.66 | 41.66 | 0.00 | 62.89 | 62.89 | 0.00 | 69.40 | 69.40 | 0.00 | 76.38 | 76.38 | 0.00 |
| 1 | 31.30 | 31.30 | 0.00 | 25.31 | 25.31 | 0.00 | 22.36 | 22.36 | 0.00 | 18.51 | 18.51 | 0.00 |
| 2 | 15.49 | 15.49 | 0.00 | 7.89 | 7.89 | 0.00 | 5.94 | 5.94 | 0.00 | 3.71 | 3.71 | 0.00 |
| 3+ | 11.56 | 11.56 | 0.00 | 3.83 | 3.83 | 0.00 | 2.30 | 2.30 | 0.00 | 1.39 | 1.39 | 0.00 |

Abbreviations: Bilateral salpingo-oophorectomy (BSO); standardized difference (Std Diff); Johns Hopkins Aggregated Diagnosis Groups (ADGs)

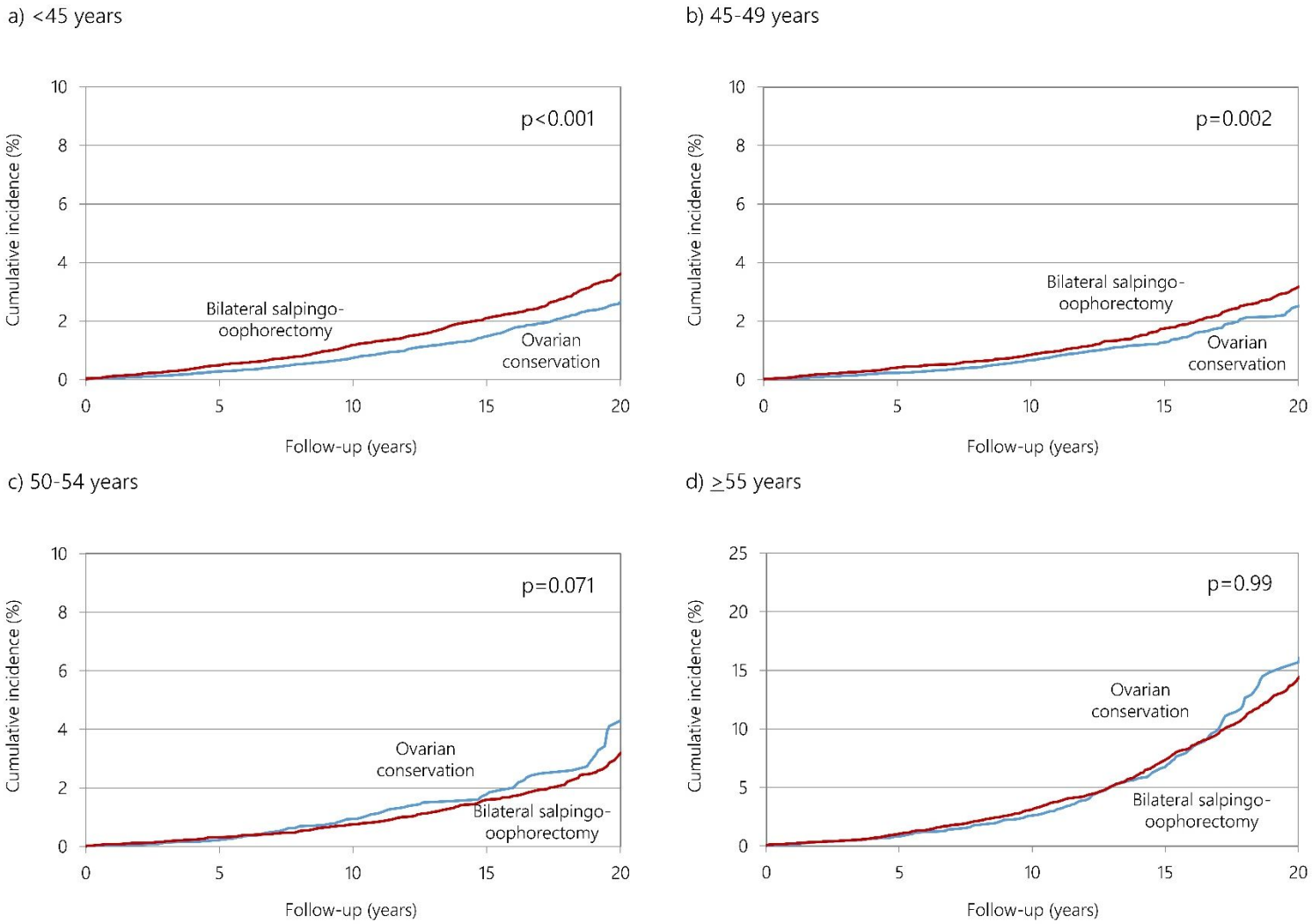
**Appendix 7.** Unweighted mortality outcomes for women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) versus ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).

| Outcome | <45 years | | 45-49 years | | 50-54 years | | ≥55 years | |
|---|---|---|---|---|---|---|---|---|
| | No BSO N=78,646 | BSO N=17,816 | No BSO N=32,958 | BSO N=22,467 | No BSO N=8,472 | BSO N=18,741 | No BSO N=5,153 | BSO N=21,023 |
| Follow-up (years) | | | | | | | | |
| Median (IQR) | 13 (8-17) | 14 (8-18) | 11 (7-15) | 13 (8-18) | 10 (6-14) | 12 (7-17) | 11 (7-14) | 11 (6-16) |
| Status at end of follow-up, *No. (%)* | | | | | | | | |
| Alive | 77,002 (97.9) | 17,192 (96.5) | 32,256 (97.9) | 21,653 (96.4) | 8,211 (96.9) | 18,020 (96.2) | 3,713 (90.8) | 15,469 (89.1) |
| Death* | 1,644 (2.1) | 624 (3.5) | 702 (2.1) | 814 (3.6) | 261 (3.1) | 721 (3.8) | 377 (9.2) | 1,890 (10.9) |
| Non-cancer | 928 (1.2) | 373 (2.1) | 299 (0.9) | 405 (1.8) | 109 (1.3) | 319 (1.7) | 203 (5.0) | 1,117 (6.4) |
| Cancer | 682 (0.9) | 236 (1.3) | 390 (1.2) | 391 (1.7) | 148 (1.7) | 397 (2.1) | 171 (4.2) | 741 (4.3) |

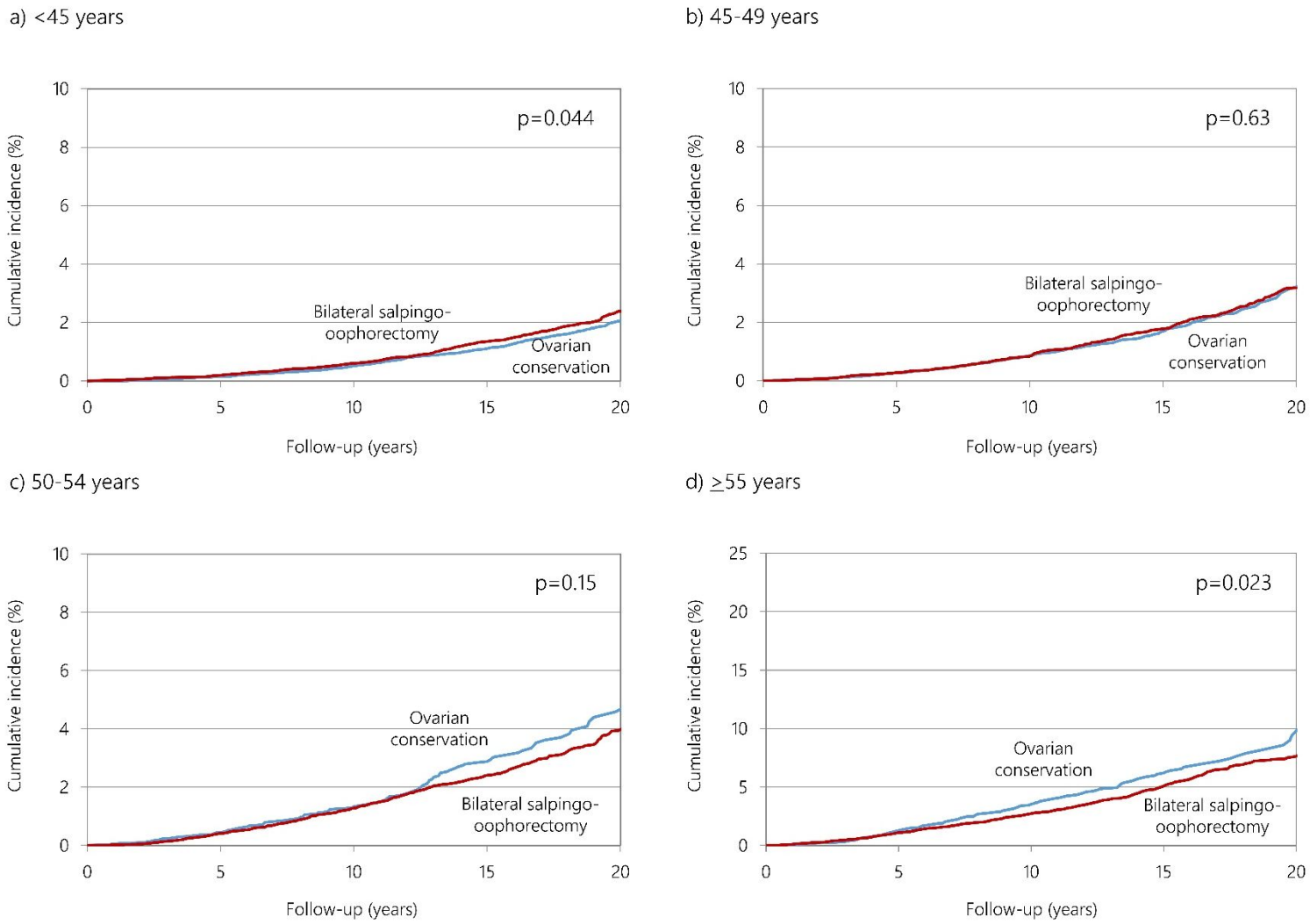
* Data were missing for cause of death (N=124, 1.76% of deaths)

Abbreviations: Bilateral salpingo-oophorectomy (BSO); interquartile range (IQR), number (No.)

**Appendix 8.** Weighted cumulative incidence of non-cancer death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).



**Appendix 9.** Weighted cumulative incidence of cancer death in women (aged 30-70 years) undergoing benign hysterectomy with bilateral salpingo-oophorectomy or ovarian conservation, stratified by age group (<45, 45-49, 50-54, ≥55 years).



**Appendix 10.** (a) Women (aged 30-70 years) undergoing bilateral salpingo-oophorectomy (BSO) at some point after hysterectomy, and (b) sensitivity analyses modelling BSO as a time-varying covariate in a traditional multivariable Cox proportional hazards model; ovarian conservation serves as the referent category. All analyses are stratified by age group (<45, 45-49, 50-54, ≥55 years); p<0.0125 (0.05/4) was considered statistically significant, and p-values from 0.0125-0.05 were considered marginally significant.

a)

| | **<45 years (N=96,462)** | **45-49 years (N=55,425)** | **50-54 years (N=27,213)** | **≥55 years (N=21,449)** |
|---|---|---|---|---|
| Status at index hysterectomy, *No. (%)* | | | | |
| Ovarian conservation | 78,646 (81.5) | 32,958 (59.5) | 8,472 (31.1) | 4,090 (19.1) |
| Bilateral salpingo-oophorectomy | 17,816 (18.5) | 22,467 (40.5) | 18,741 (68.9) | 17,359 (80.9) |
| Any BO after index hysterectomy, *No. (%)*[a] | 2,470 (2.6) | 597 (1.1) | 117 (0.4) | 28 (0.13) |
| BO for benign indications[b] | 1,098 (44.5) | 211 (35.3) | 49 (41.9) | 18 (64.3) |
| BO for ovarian mass or malignancy[b] | 1,372 (55.5) | 386 (64.7) | 68 (58.1) | 10 (35.7) |

[a] Denominator is patients who underwent ovarian conservation at index hysterectomy

[b] Denominator is patients who underwent any BSO after index hysterectomy

b)

| **Outcome** | **<45 years** | | **45-49 years** | | **50-54 years** | | **≥55 years** | |
|---|---|---|---|---|---|---|---|---|
| | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** | **HR (95% CI)** | **p-value** |
| All-cause death | 1.25 (1.13-1.38) | <0.001 | 1.16 (1.04-1.29) | 0.010 | 0.85 (0.73-0.99) | 0.036 | 0.95 (0.84-1.07) | 0.38 |
| Non-cancer death | 1.33 (1.17-1.52) | <0.001 | 1.31 (1.12-1.54) | 0.001 | 0.82 (0.66-1.03) | 0.088 | 1.04 (0.89-1.22) | 0.60 |
| Cancer death | 1.12 (0.95-1.31) | 0.19 | 1.03 (0.88-1.20) | 0.73 | 0.89 (0.73-1.09) | 0.25 | 0.82 (0.69-0.98) | 0.030 |

Abbreviations: CI (confidence interval); HR (hazard ratio)