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# Accelerated Accumulation of Multimorbidity After Bilateral Oophorectomy: A Population-Based Cohort Study

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## Abstract

**Objective:** To study the association between bilateral oophorectomy and the rate of accumulation of multimorbidity.

**Patients and Methods:** In this historical cohort study, the Rochester Epidemiology Project records-linkage system was used to identify all premenopausal women who underwent bilateral oophorectomy before age 50 years between January 1, 1988, and December 31, 2007, in Olmsted County, Minnesota. Each woman was randomly matched to a referent woman born in the same year (±1 year) who had not undergone bilateral oophorectomy. We studied the rate of accumulation of 18 common chronic conditions over a median of approximately 14 years of follow-up.

**Results:** Although women who underwent bilateral oophorectomy already had a higher multimorbidity burden at the time of oophorectomy, they also experienced an increased risk of subsequent multimorbidity. After adjustments for 18 chronic conditions present at baseline, race/ethnicity, education, body mass index, smoking, age at baseline, and calendar year at baseline, women who underwent oophorectomy before age 46 years experienced an increased risk of depression, hyperlipidemia, cardiac arrhythmias, coronary artery disease, arthritis, asthma, chronic obstructive pulmonary disease, and osteoporosis. In addition, they experienced an accelerated rate of accumulation of the 18 chronic conditions considered together (hazard ratio, 1.22; 95% CI, 1.14-1.31; $P<.001$). Several of these associations were reduced in women who received estrogen therapy.

**Conclusion:** Bilateral oophorectomy is associated with a higher risk of multimorbidity, even after adjustment for conditions present at baseline and for several possible confounders. However, several of these associations were reduced in women who received estrogen therapy.

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This study was prompted by 2 important areas of uncertainty: the risk and benefits of bilateral oophorectomy for the prevention of ovarian cancer and the role of sex hormones in regulating the aging process. Our group[1-3] and others[4-6] have found that for most women without a cancer indication, the long-term risks of bilateral oophorectomy performed before menopause are greater than the benefits; therefore, the surgery should be limited to women who have a high-risk genetic variant predisposing to cancer.[3,5] However, other authors continue to argue that, in the absence of a randomized clinical trial, the evidence against prophylactic oophorectomy derived from observational studies is not sufficient to change the practice.[7-10]

Studies of the effects of sex steroids, in particular of estrogen, in regulating the aging process in humans have been hampered by the difficulty of measuring aging processes at the cellular, tissue, organ, or system level in vivo.[11] Ferrucci and his team from the Intramural Research Program at the National Institute on Aging have suggested using the accumulation of multimorbidity as a proxy measure for accelerated aging.[12-16]

Using 18 aging-related chronic conditions, we addressed 2 major questions: (1) whether

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bilateral oophorectomy accelerates the accumulation of multimorbidity and (2) whether estrogen therapy (ET) modifies this accumulation.

## PATIENTS AND METHODS

### Bilateral Oophorectomy and Referent Cohorts

The Mayo Clinic Cohort Study of Oophorectomy and Aging-2 (MOA-2) is a recently established population-based cohort study, completely independent from our previous work on this topic.[1,2] We included a cohort of women who underwent bilateral oophorectomy and a cohort of age-matched referent women representative of a geographically defined population. All data collection was through the records-linkage system of the Rochester Epidemiology Project (REP) that has been described extensively elsewhere.[17-20]

We used the electronic index of the REP to identify women whose medical record included a code from the *International Classification of Diseases, Ninth Revision* (*ICD-9*) for either unilateral (65.3x and 65.4x) or bilateral (65.5x and 65.6x) oophorectomy between January 1, 1988, and December 31, 2007. We included women who underwent bilateral oophorectomy or a second unilateral oophorectomy before the onset of menopause and before reaching the age of 50 years, regardless of concurrent or prior hysterectomy. Although hysterectomy is a cause of surgical menopause, women with prior hysterectomy were included because hysterectomy was not considered a cause of ovarian insufficiency. However, we excluded women who underwent oophorectomy for ovarian cancer (primary or metastatic), to treat another estrogen-sensitive malignant disorder (usually breast cancer), or because they had high genetic risk of cancer (eg, carriers of *BRCA1* or *BRCA2* variants).

For each woman included in the bilateral oophorectomy cohort, we defined the date of the surgical procedure as the index date, and we selected via simple random sampling a woman from the Olmsted County population who was born in the same year (±1 year) and had not undergone bilateral oophorectomy before the index date. All women who met these criteria were considered eligible regardless of menopausal status, any possible diseases or risk factors, and of prior hysterectomy or unilateral oophorectomy. The complete medical records of the women with oophorectomy and the referent women underwent extensive manual abstraction by a physician (L.G.-R.) or a trained study nurse to confirm the oophorectomy status and to obtain clinical data. Thus, the final classification of women was based on the findings from medical record review. Figure 1 presents detailed flowcharts for the 2 cohorts. All study procedures were approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center.

### Baseline Conditions and Risk Factors

The complete medical records of women in both cohorts were manually abstracted for demographic, reproductive history, family history of cancer, and life habits information. In addition, the records were searched electronically for all *ICD-9* codes entered by any health care institution participating in the REP before the index date to identify conditions that were already present at baseline. These *ICD-9* codes were used to define the 20 chronic conditions recommended by the US Department of Health and Human Services (DHHS) to study multimorbidity.[21-24] However, we excluded from the DHHS list human immunodeficiency virus infections, autism spectrum disorders, and hepatitis because they were rare in our population and were not considered related to the aging process, and we added anxiety to the DHHS list because it was common in our population and was considered related to the aging process (18 selected conditions).[25] The condition labeled *schizophrenia* was retained because it included other psychoses that were common in the elderly population. To reduce the risk of false-positive diagnoses, only women whose medical record contained at least 2 diagnostic codes for a given condition separated by more than 30 days were considered to have that particular condition. For diagnostic codes entered before 1994, we required a 1-year separation because a finer dating of the codes in our system was impossible during that time frame.[23-25]

### Outcome Conditions and Multimorbidity

For each woman, the diagnostic indices of the REP were also searched electronically for all *ICD-9* codes entered into the medical record by any health care institution participating in


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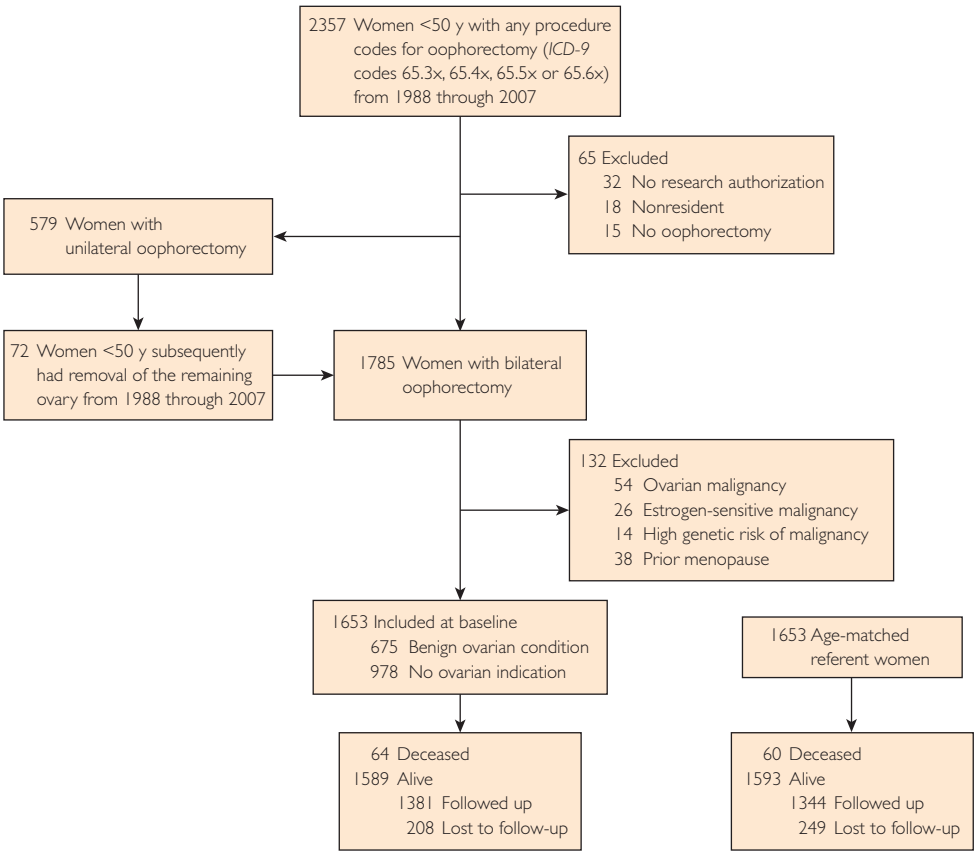


**FIGURE 1.** Flowchart of the 2 study cohorts. The oophorectomy cohort was selected by review of the medical records for women with a procedure code for oophorectomy. The referent cohort was selected via simple random sampling of women from the Olmsted County population who were born in the same year (±1 year) as women in the oophorectomy cohort and had not undergone bilateral oophorectomy. A total of 72 women with unilateral oophorectomy had subsequent removal of their remaining ovary before age 50 years from 1988 through 2007 and were included in the bilateral oophorectomy cohort. Survivors were followed up to the most recent contact with the system or the end of the study (December 31, 2014). Causes of death were available for 57 of 64 deceased women with bilateral oophorectomy and for 54 of 60 deceased referent women. Women lost to follow-up did not receive care within the system during the last 3 years of study (January 1, 2012, through December 31, 2014) and were censored at the last recorded contact.

the REP on or after the index date. In addition, we obtained death certificates for deceased women, and we considered all causes of death (underlying, intermediate, immediate, and other contributing conditions), as described elsewhere.[1] Again, we used the *ICD-9* codes to define 18 outcome conditions. We required 2 diagnostic codes as detailed previously; however, for women who died, one diagnostic code listed anywhere on the death certificate was sufficient. The time of onset of a given condition was the time when the second of the 2 codes for the same condition was entered in the medical record (meeting the time gap criteria outlined previously) or the time of death if the condition was first diagnosed at the time of death.

## Statistical Analyses

We estimated the hazard ratio (HR) for each of the 18 chronic conditions considered one at a time using Cox proportional hazards models

with age as the time scale.[26] Women who had a specific condition before the index year were excluded from that specific analysis (only de novo outcomes were counted). Women were censored at death, at the end of the study (December 31, 2014), or at the time of last contact with the system (lost to follow-up). We used robust sandwich covariance estimates to account for women who were included in both cohorts (referent women who underwent bilateral oophorectomy after the index date). The assumption of proportional hazards was assessed by graphical methods and by introducing a time-dependent coefficient in the Cox models.[26] None of the models violated the proportional hazards assumption.

The accumulation of multimorbidity was represented graphically using Aalen-Johansen curves (a multistate generalization of cumulative incidence curves; unadjusted curves considering all 18 conditions equally). We also computed HRs using Andersen-Gill regression models with age as the time scale.[26-28] None of the models violated the proportional hazards assumption. For a visual comparison of the accumulation of multimorbidity both before and after the index date, the graphs also illustrate the accumulation of multimorbidity in the 10 years preceding the index date. However, the data before the index date were not included in the calculation of the HRs.

In each analysis (for the 18 conditions separately and for the accumulation of conditions), we calculated unadjusted HRs and HRs adjusted using inverse probability weights derived from a logistic regression model including all 18 chronic conditions present at baseline, years of education (0-12, 13-16, and >16 years), race/ethnicity (white vs other), body mass index (calculated as weight in kilograms divided by height in meters squared; <30 vs ≥30 kg/m$^2$), cigarette smoking (current or former vs never), age at baseline (continuous), and calendar year at baseline (continuous). We used inverse probability weights to balance the oophorectomy and referent cohorts at baseline on potential confounders, and we assessed the balance obtained using the standardized difference of means (absolute value).[29,30]

Analyses were conducted overall and in strata defined by age at surgery (≤45 vs 46-49 years), by surgical indication (benign ovarian condition vs no ovarian indication), and by postoophorectomy oral or transdermal ET (within age strata; through the 46th birthday vs discontinued before age 46 years; or through the 50th birthday vs discontinued before age 50 years).[1,2] Extensive details about the type and duration of ET were abstracted manually from drug prescriptions and clinical notes. Adjustments using inverse probability weights were performed separately for each stratum to ensure balance of characteristics at baseline.

We performed 3 sets of sensitivity analyses in which (1) we censored at the time of bilateral oophorectomy referent women who underwent bilateral oophorectomy after the index date but before age 50 years, (2) we removed all women who had any of the 18 conditions at baseline, and (3) we removed women who had undergone hysterectomy before the index date (in both cohorts) or had reached menopause before the index date (only for referent women). Finally, in a set of secondary analyses, we compared women who underwent bilateral oophorectomy (with prior or concurrent hysterectomy) to women who underwent hysterectomy with ovarian conservation in the time period 1988-2002 (time frame of overlap of the 2 cohorts). The women who underwent hysterectomy with ovarian conservation were derived from a separate cohort study described elsewhere.[31] All analyses were completed using SAS statistical software version 9.4 (SAS Institute) and R statistical software version 3.1.1 (R Foundation for Statistical Computing), and tests of statistical significance were conducted at the 2-tailed $\alpha$ level of .05.

## RESULTS

### Study Sample

The median follow-up was 14.5 years (interquartile interval, 10.3-19.1) for the 1653 women who underwent bilateral oophorectomy and 14.4 years (interquartile interval, 10.4-19.3; $P$=.87) for the 1653 referent women. Women who underwent bilateral oophorectomy were less educated, were more frequently white, had higher body mass index, and had smoked more pack-years of cigarettes than referent women at the time of bilateral oophorectomy (or index date; Supplemental Table 1, available online at http://www.mayoclinicproceedings.org). In case-control

analyses comparing the 18 chronic conditions present at the time of oophorectomy or the index date, women who underwent bilateral oophorectomy were more likely to have previous diagnoses of depression, anxiety, substance abuse disorders, hyperlipidemia, hypertension, diabetes, cardiac arrhythmias, asthma, and chronic obstructive pulmonary disease. In addition, bilateral oophorectomy was associated with an increased number of preceding chronic conditions (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org).

In each of our adjusted analyses, we used inverse probability weighting to balance the oophorectomy and referent cohorts on these risk factors and chronic conditions at index date, thus minimizing their effects as potential confounders. Supplemental Figure 1 illustrates the degree of adjustment obtained using inverse probability weights overall and in women who underwent bilateral oophorectomy at age 45 years or younger. In summary, the 2 cohorts were not highly imbalanced before the adjustments (standardized difference of means <25% of the SD for most variables), and the adjustments improved the balance successfully (standardized difference of means <5% of the SD).[29]

### Cumulative Incidence of the 18 Conditions Considered Separately

Our primary cohort analyses for the 18 chronic conditions considered separately are presented in Supplemental Table 3 (mental health conditions), Supplemental Table 4 (cardiovascular and metabolic conditions), and Supplemental Table 5 (other somatic conditions) (available online at http://www.mayoclinicproceedings.org) overall and in strata by age at oophorectomy, by indication, and by ET (within age strata). The key findings are also represented graphically in Figure 2. In overall adjusted analyses, we observed significant associations between bilateral oophorectomy and de novo diagnoses of 7 of the 18 conditions: depression, anxiety, hyperlipidemia, diabetes, arthritis, asthma, and chronic obstructive pulmonary disease (HRs ranging between 1.19 and 1.43; all *P* values ≤.01). In adjusted analyses restricted to women who underwent bilateral oophorectomy at age 45 years or younger, we observed an increased risk for all of the 18 conditions except cancer, and the increased risk was significant for 8 of the 18 conditions: depression, hyperlipidemia, cardiac arrhythmias, coronary artery disease, arthritis, asthma, chronic obstructive pulmonary disease, and osteoporosis (HRs ranging between 1.23 and 2.08; all *P* values <.05). Finally, in adjusted analyses restricted to women who underwent bilateral oophorectomy at age 46 to 49 years, we observed significantly increased risk for 6 of the 18 conditions: depression, anxiety,

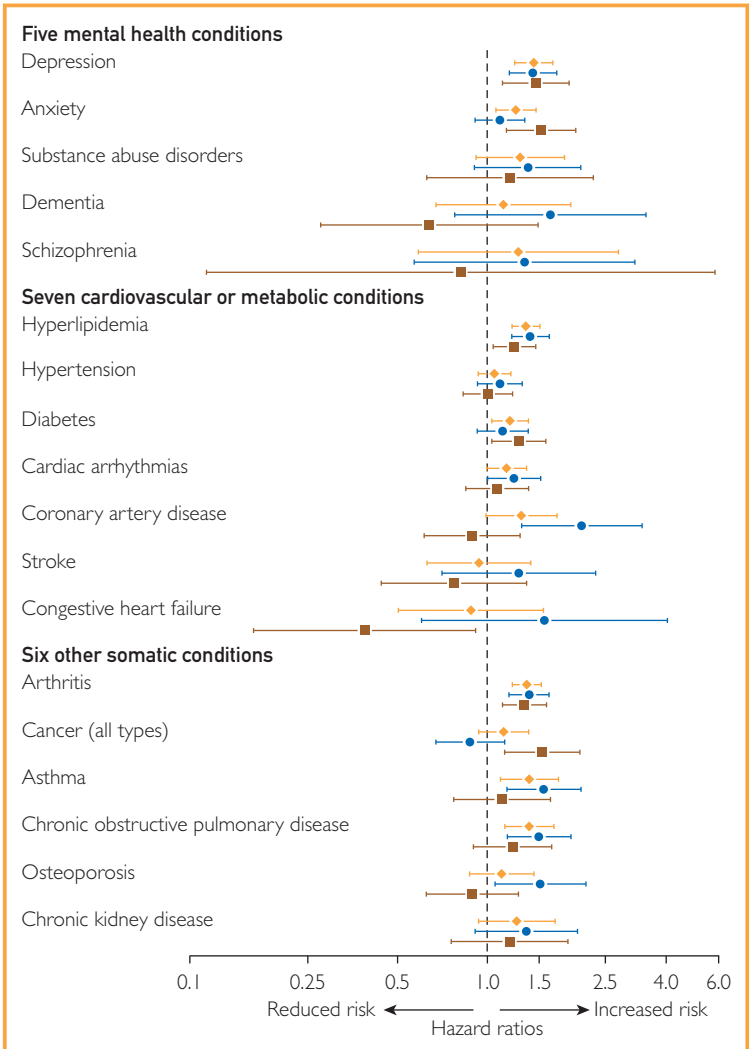


**FIGURE 2.** Adjusted hazard ratios and 95% CIs for each of the 18 chronic conditions considered separately. Analyses are presented as overall (orange diamonds) and in strata by age at oophorectomy (blue circles for age ≤45 years and brown squares for age 46-49 years). The hazard ratios were calculated using Cox proportional hazards models with age as the time scale and were adjusted for the 18 conditions present at index date, for education, race/ethnicity, body mass index, cigarette smoking, age, and for calendar year using inverse probability weights.

hyperlipidemia, diabetes, arthritis, and cancer (HRs ranging between 1.24 and 1.53; all $P$ values $\leq$.02) and significantly reduced risk for congestive heart failure ($P$=.03).

### Interaction Analyses for Individual Conditions

In analyses of interaction by age, women who underwent bilateral oophorectomy at age 45 years or younger had significantly higher risk of coronary artery disease ($P$=.006), congestive heart failure ($P$=.03), and osteoporosis ($P$=.04) compared with women in the 46- to 49-year age stratum; however, they experienced a significantly lower risk of cancer (of all types; $P$=.008). In analyses of interaction by ET, women in the younger age stratum who received ET through the target age (>45 years) experienced a significantly reduced risk of osteoporosis ($P$=.03) compared with women who did not receive ET. Finally, in analyses of interaction by surgical indication, women who underwent oophorectomy because of a benign ovarian condition experienced a significantly higher risk of coronary artery disease ($P$=.03), congestive heart failure ($P$=.01), and chronic obstructive pulmonary disease ($P$=.02) compared with women with no ovarian indication (see footnotes in Supplemental Tables 3-5).

### Accumulation of Multimorbidity

Although women who underwent bilateral oophorectomy already had a higher mean number of conditions at baseline, they experienced an accelerated accumulation of multimorbidity after the surgery (Table, Figures 3 and 4). In each of the 3 panels in Figure 3, the curve for the referent women increased smoothly with age, whereas the curve for the oophorectomy cohort showed an abrupt increase shortly after the index date and continued to diverge thereafter.

### Interaction Analyses for Accumulation of Multimorbidity

In our primary analyses presented in Figure 4, women who underwent oophorectomy at younger ages had a higher risk of accumulation of multimorbidity; however, the strata by age were not significantly different. Women who underwent oophorectomy at younger ages and received ET had a reduced association; however, the strata by ET were not significantly different either among women who underwent bilateral oophorectomy at age 45 years or younger or at age 46 to 49 years. There was also no significant difference between strata for surgical indication, calendar year period, or cigarette smoking (see footnotes in the Table).

### Sensitivity Analyses

The rate of accumulation remained similar in all 3 sets of sensitivity analyses reported in the Table: the first in which the 84 referent women who underwent bilateral oophorectomy after the index date but before age 50 years were censored; the second restricted to women who did not have any of the 18 conditions at baseline; and the third restricted to women who had not undergone hysterectomy (in both cohorts) or natural or medically induced menopause (only referent women) before the index date. In addition, none of the tests for interaction by age at oophorectomy, ET, or surgical indication yielded significant results in the 3 sets of sensitivity analyses (see footnotes in the Table). Finally, the secondary analyses comparing women who underwent bilateral oophorectomy with women who underwent hysterectomy with ovarian conservation derived from a separate cohort yielded an adjusted HR of 1.09 (95% CI, 1.03-1.16; $P$=.004) for the overall group and 1.08 (95% CI, 1.01-1.16; $P$=.02) for women who underwent oophorectomy at age 45 years or younger (data not shown).

## DISCUSSION

### Principal Findings

In our MOA-2 study, women who underwent bilateral oophorectomy before menopause experienced a higher risk for 7 of the 18 chronic conditions under study and an accelerated accumulation of multimorbidity. Most of the associations with individual conditions were stronger in women who underwent bilateral oophorectomy at younger ages, and several of the associations were reduced in women who received ET in the younger age stratum. Similarly, the rate of accumulation of multimorbidity was higher in the younger stratum and was reduced in women who received ET in the younger age stratum. However, the statistical power was limited for several of the interaction analyses. Some of the findings that did not reach statistical significance

**TABLE. Accumulation of Multimorbidity (18 Chronic Conditions Considered Equally) Overall and in Strata by Age at Oophorectomy, Estrogen Therapy (ET), Surgical Indication, Calendar Year Period, and Cigarette Smoking (Only De Novo Outcomes)**

| | Bilateral oophorectomy | | | Referent women | | | Unadjusted models | | Adjusted models[a] | |
|---|---|---|---|---|---|---|---|---|---|---|
| Strata | No. at risk | Person-years | No. of events | No. at risk | Person-years | No. of events | Hazard ratio (95% CI) | *P* value | Hazard ratio (95% CI) | *P* value |
| Primary analyses | | | | | | | | | | |
| Overall | 1653 | 23,940 | 4739 | 1653 | 23,836 | 3828 | 1.23 (1.17-1.30) | <.001 | 1.18 (1.13-1.25) | <.001 |
| Age ≤45 y | 1031 | 15,046 | 2850 | 1031 | 14,723 | 2159 | 1.29 (1.21-1.39) | <.001 | 1.22 (1.14-1.31) | <.001 |
| ET >45 y[b] | 650 | 8229 | 1545 | 603 | 7594 | 1307 | 1.09 (1.00-1.19) | .06 | 1.08 (0.99-1.18) | .08 |
| No ET or ≤45 y | 182 | 1714 | 358 | 161 | 1651 | 231 | 1.49 (1.24-1.80) | <.001 | 1.27 (1.04-1.55) | .02 |
| Age 46-49 y | 622 | 8894 | 1889 | 622 | 9113 | 1669 | 1.16 (1.07-1.25) | <.001 | 1.14 (1.05-1.22) | .001 |
| ET >49 y[c] | 448 | 6022 | 1240 | 427 | 5949 | 1143 | 1.07 (0.98-1.17) | .16 | 1.05 (0.96-1.16) | .26 |
| No ET or ≤49 y | 160 | 1579 | 320 | 155 | 1630 | 304 | 1.08 (0.92-1.28) | .35 | 1.04 (0.88-1.24) | .65 |
| Benign condition[d] | 675 | 9843 | 1925 | 675 | 9735 | 1500 | 1.28 (1.17-1.39) | <.001 | 1.22 (1.12-1.33) | <.001 |
| No indication[e] | 978 | 14,097 | 2814 | 978 | 14,101 | 2328 | 1.21 (1.13-1.29) | <.001 | 1.16 (1.08-1.23) | <.001 |
| Years 1988-1997 | 723 | 13,488 | 2697 | 723 | 13,582 | 2246 | 1.21 (1.13-1.29) | <.001 | 1.19 (1.11-1.27) | <.001 |
| Years 1998-2007 | 930 | 10,452 | 2042 | 930 | 10,254 | 1582 | 1.26 (1.17-1.36) | <.001 | 1.19 (1.10-1.29) | <.001 |
| Smokers | 756 | 10,979 | 2358 | 696 | 10,250 | 1927 | 1.16 (1.08-1.24) | <.001 | 1.13 (1.05-1.22) | .001 |
| Nonsmokers | 897 | 12,962 | 2381 | 957 | 13,586 | 1901 | 1.30 (1.21-1.39) | <.001 | 1.25 (1.17-1.34) | <.001 |
| Sensitivity analyses censoring the 84 referent women who underwent bilateral oophorectomy after the index date[f] | | | | | | | | | | |
| Overall | 1653 | 23,940 | 4739 | 1653 | 22,750 | 3626 | 1.24 (1.18-1.31) | <.001 | 1.19 (1.13-1.26) | <.001 |
| Age ≤45 y | 1031 | 15,046 | 2850 | 1031 | 13,825 | 1993 | 1.31 (1.22-1.41) | <.001 | 1.23 (1.15-1.33) | <.001 |
| ET >45 y[b] | 650 | 8229 | 1545 | 603 | 6892 | 1186 | 1.09 (1.00-1.20) | .0495 | 1.09 (0.99-1.19) | .07 |
| No ET or ≤45 y | 182 | 1714 | 358 | 161 | 1551 | 214 | 1.51 (1.24-1.83) | <.001 | 1.28 (1.04-1.58) | .02 |
| Age 46-49 y | 622 | 8894 | 1889 | 622 | 8926 | 1633 | 1.16 (1.07-1.25) | <.001 | 1.14 (1.05-1.23) | .001 |
| ET >49 y[c] | 448 | 6022 | 1240 | 427 | 5799 | 1119 | 1.06 (0.97-1.16) | .18 | 1.05 (0.96-1.15) | .29 |
| No ET or ≤49 y | 160 | 1579 | 320 | 155 | 1594 | 294 | 1.10 (0.93-1.30) | .29 | 1.05 (0.88-1.25) | .56 |
| Benign condition[d] | 675 | 9843 | 1925 | 675 | 9079 | 1378 | 1.29 (1.18-1.41) | <.001 | 1.24 (1.14-1.35) | <.001 |
| No indication[e] | 978 | 14,097 | 2814 | 978 | 13,671 | 2248 | 1.21 (1.14-1.29) | <.001 | 1.16 (1.09-1.24) | <.001 |
| Sensitivity analyses in women who did not have any of the 18 chronic conditions at baseline[g] | | | | | | | | | | |
| Overall | 659 | 10,191 | 1870 | 888 | 13,097 | 1968 | 1.20 (1.11-1.30) | <.001 | 1.18 (1.09-1.28) | <.001 |
| Age ≤45 y | 420 | 6569 | 1154 | 592 | 8624 | 1184 | 1.25 (1.13-1.39) | <.001 | 1.24 (1.12-1.37) | <.001 |
| Age 46-49 y | 239 | 3621 | 716 | 296 | 4473 | 784 | 1.12 (0.99-1.26) | .06 | 1.11 (0.98-1.25) | .10 |
| Benign condition[d] | 292 | 4562 | 802 | 385 | 5707 | 812 | 1.21 (1.07-1.38) | .003 | 1.18 (1.04-1.34) | .01 |
| No indication[e] | 367 | 5629 | 1068 | 503 | 7390 | 1156 | 1.19 (1.08-1.31) | <.001 | 1.18 (1.07-1.30) | .001 |
| Sensitivity analyses excluding women who underwent hysterectomy or reached menopause before the index date[h] | | | | | | | | | | |
| Overall | 1496 | 21,741 | 4227 | 1383 | 19,845 | 3004 | 1.28 (1.21-1.35) | <.001 | 1.21 (1.15-1.28) | <.001 |
| Age ≤45 y | 919 | 13,465 | 2494 | 932 | 13,254 | 1874 | 1.31 (1.22-1.41) | <.001 | 1.24 (1.15-1.33) | <.001 |
| Age 46-49 y | 577 | 8276 | 1733 | 451 | 6591 | 1130 | 1.22 (1.11-1.33) | <.001 | 1.17 (1.07-1.28) | <.001 |
| Benign condition[d] | 538 | 7939 | 1487 | 590 | 8492 | 1233 | 1.30 (1.18-1.43) | <.001 | 1.24 (1.13-1.36) | <.001 |
| No indication[e] | 958 | 13,802 | 2740 | 793 | 11,352 | 1771 | 1.26 (1.18-1.36) | <.001 | 1.19 (1.11-1.28) | <.001 |

[a]Hazard ratios calculated using Andersen-Gill regression models with age as the time scale and adjusted using inverse probability weights derived from a regression model including all 18 chronic conditions present at baseline, years of education (≤12, 13-16, >16), race (white vs nonwhite), body mass index (<30 vs ≥30 kg/m$^2$), cigarette smoking (current or former vs never), age at baseline (continuous), and calendar year at baseline (continuous). These adjustments were performed separately in each stratum to maximize the balance at baseline. None of the interactions by age was significant.

[b]Women who were taking ET on their 46th birthday, after bilateral oophorectomy (only oral or transdermal). Women who had the particular outcome disease before their 46th birthday, died or were lost to follow-up before their 46th birthday, or had not reached age 46 years as of December 31, 2014, were not included in the corresponding analysis. Follow-up for these analyses was started at age 46 years. None of the interactions by ET was significant in the ≤45-years age stratum.

[c]Women who were taking ET on their 50th birthday, after bilateral oophorectomy (only oral or transdermal). Women who had the particular outcome disease before their 50th birthday, died or were lost to follow-up before their 50th birthday, or had not reached age 50 years as of December 31, 2014, were not included in the corresponding analysis. Follow-up for these analyses was started at age 50 years. None of the interactions by ET was significant in the 46-49 years age stratum.

[d]The benign condition (eg, cysts or endometriosis) was listed by the gynecologist in the medical record at the time of oophorectomy. However, some of these indications are questionable from our current perspective. None of the interactions by surgical indication was significant.

[e]Women without a malignant or benign ovarian condition. Historically, the terms *prophylactic*, *elective*, or *incidental* oophorectomy were used; however, we avoided these terms.

[f]This sensitivity analysis was an alternative way of dealing with referent women who shifted their status from unexposed to exposed during follow-up.

[g]This sensitivity analysis was an alternative method used to reduce confounding caused by the 18 chronic conditions preceding the index date. Analyses were still adjusted for the other potential confounders using inverse probability weighting.

[h]This sensitivity analysis addressed the possible confounding effect of hysterectomy with ovarian conservation preceding the index date or of menopause before the index date (only applicable to referent women).

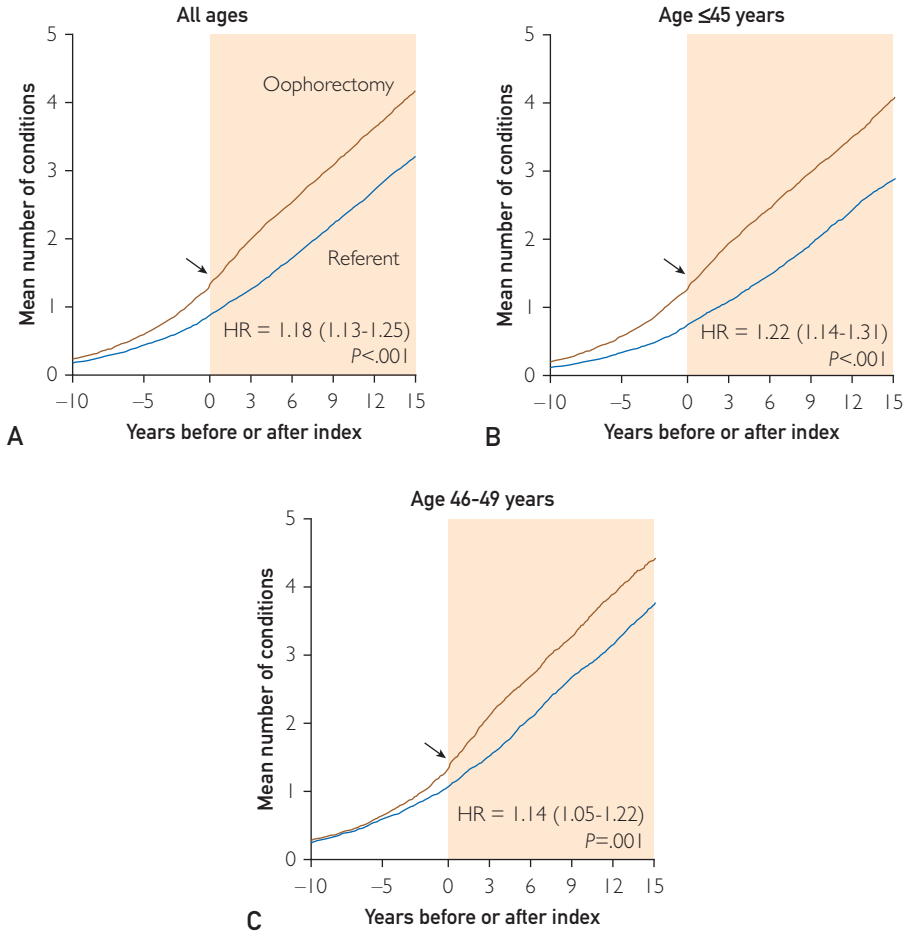


**FIGURE 3.** Accumulation of multimorbidity. The accumulation of chronic conditions is shown as the mean number of conditions over follow-up time (cumulative incidence; Aalen-Johansen curves) for all ages (A), ages 45 years or younger (B), and ages 46 to 49 years (C). The curves are unadjusted; however, the hazard ratios (HR) in the panels were adjusted using inverse probability weights. The shaded area of each graph (events after the index date) illustrates the data collected prospectively in our study and used to calculate the HR. The area not shaded (events before the index date) is only provided for visual comparison, and the data were obtained historically for the women sampled at the index date. The amount of data available before the index date varied across women. In all 3 panels, the curve for women who underwent bilateral oophorectomy showed an abrupt increase shortly after the index date (black arrow) and continued to diverge thereafter.

in our analyses may reach significance with longer follow-up of our cohorts (current follow-up was approximately 14 years).

### Possible Explanations for the Findings

We propose 3 possible mechanisms to explain the observed associations. First, our findings may reflect confounding by shared genetic predisposition or shared social or environmental risk factors. Genetic variants or risk factors may increase the risk of gynecologic diseases prompting the oophorectomy (eg, ovarian cysts or endometriosis) or prompting hysterectomy accompanied by oophorectomy (eg, uterine fibroids).[32,33] These same genetic variants or risk factors may also independently increase the risk of multimorbidity[34] or accelerated aging.[11] However, our analyses for the accumulation of multimorbidity stratified in women with or without a benign ovarian


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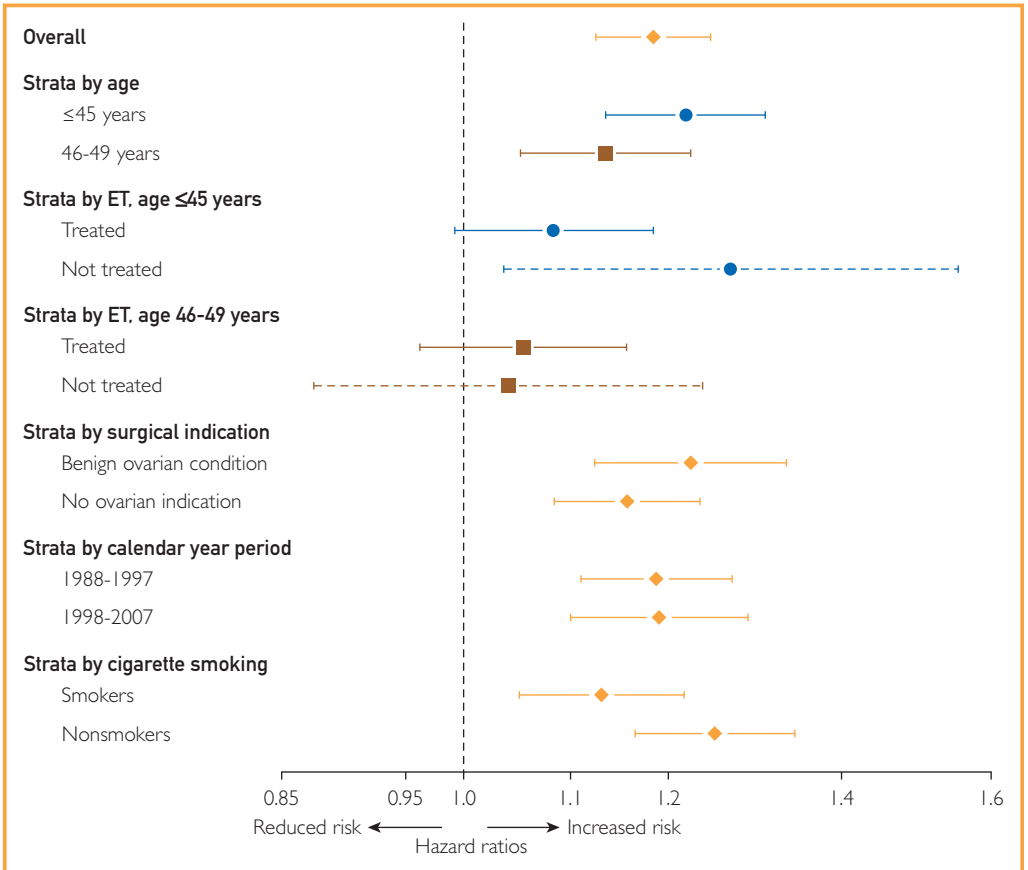


**FIGURE 4.** Adjusted hazard ratios and 95% CIs for the accumulation of multimorbidity (18 chronic conditions combined). Analyses are presented for all ages (orange diamonds) and in strata by age at oophorectomy (blue circles and brown squares), by estrogen treatment within age at oophorectomy strata (solid lines for treated women and dashed lines for untreated women), and in strata by surgical indication, by calendar year period, and by cigarette smoking status at index date for all ages (orange diamonds). The hazard ratios were calculated using Andersen-Gill regression models with age as the time scale and were adjusted for the 18 conditions present at the index date for education, race/ethnicity, body mass index, cigarette smoking, age, and for calendar year using inverse probability weights.

indication did not reveal a significant interaction. In addition, our primary analyses adjusted for the 18 conditions present at baseline using inverse probability weights, and our sensitivity analyses restricted to women free of any condition at baseline do not support a confounding mechanism. We used inverse probability weights to balance the oophorectomy and the referent cohorts at baseline on potential confounders. These methods are a powerful way to bring observational studies closer in interpretation to randomized clinical trials when the intervention (in our case, bilateral oophorectomy) cannot be ethically or feasibly randomized.[29,30]

Second, our findings may suggest that the premature and abrupt loss of estrogen negatively affects multiple fundamental aging mechanisms, leading to harmful effects in multiple cells, tissues, organs, and systems (accelerated aging). Levine et al[11] reported an association between bilateral oophorectomy and a biomarker of aging, the "epigenetic clock," in DNA derived from blood and saliva. Although further work is needed, they concluded that the premature loss of ovarian function may lead to an increase in epigenetic age, a biological marker of accelerated aging. Supplemental Figure 2 (available online at http://www.mayoclinicproceedings.org) illustrates our overall mechanistic

hypothesis linking premature estrogen loss caused by the oophorectomy to the accelerated accumulation of multimorbidity used as a clinical proxy measure for accelerated aging.[12,15,16,35] Some conditions may be affected by estrogen loss more severely or earlier in life than others. Unfortunately, there is no consensus about how many conditions or clusters of conditions, or what severity of conditions, are needed to define accelerated aging and to separate low or moderate accelerated aging. The greater rate of accumulation of chronic conditions with younger age at oophorectomy suggests that the hypothesized protective effects of estrogen may be age dependent and may have a critical age window (timing hypothesis), as already suggested for cardiovascular and neurologic diseases.[1,2,36-40] In support of the role of estrogen, women who underwent bilateral oophorectomy at age 45 years or younger and received ET through the target age experienced a significant attenuation of the risk for osteoporosis compared with women who did not receive ET. However, we did not detect a significant interaction by ET for other outcomes such as hyperlipidemia or diabetes. Finally, we did not find any significant interaction with ET in analyses for the accumulation of multimorbidity. The failure to show significant interactions by ET may be due to limited statistical power, to the variable effect of ET across the chronic conditions, or to the dose and formulation of ET.

A large body of literature from animal experiments supports the detrimental effects of oophorectomy on several aging processes and on the life span. Bilateral removal of the ovaries in young animals (ovariectomy) is the conventional experimental intervention used to study the effects of premature estrogen deprivation in accelerating the aging of specific tissues or organs (eg, heart, brain, bone) and to study the possible opposing effect of hormonal treatment as a replacement intervention. By contrast, transplant of ovaries from young mice into old mice was reported to significantly increase life span.[41] Only a few selected studies focusing on nonhuman primates are mentioned here because they may be more relevant to women. A number of studies found an acceleration of vascular degeneration following ovariectomy in monkeys.[37,38] Other studies reported an acceleration of brain degeneration following ovariectomy in rodents and monkeys.[39,40] Unfortunately, we are not aware of studies linking ovariectomy to reduced life span in monkeys; however, studies in dogs and mice revealed a reduction in life span following ovariectomy.[42,43]

Third, our findings may suggest either protective effects of ovarian hormones other than estrogen (eg, progesterone, testosterone, or inhibin) or harmful effects of the disruption of the hypothalamus-pituitary-ovarian axis caused by bilateral oophorectomy (increased release of follicle-stimulating hormone and luteinizing hormone). However, the possible effects of these hormones on the cellular processes associated with aging remain unknown.[34]

## Strengths and Limitations

Some methodological features distinguish this MOA-2 study from several previous studies that addressed related questions.[4-6,8] First, information about menopause timing and type, risk factors present at baseline, and the use of estrogen or other hormones during follow-up was abstracted manually from the medical records included in a records-linkage system. Similarly, the 18 conditions used to define the baseline and the outcome conditions were extracted electronically from the REP indexes, without direct involvement of the study patients, thus avoiding recall bias.

Second, because the women were followed up immediately after the oophorectomy or the index year, there was no time gap between the oophorectomy and the recruitment into the study. Third, because the data collection was historical, women did not need to provide a study-specific informed consent but only a general consent to use their medical records for research (Minnesota legal requirements).[17] Therefore, nonparticipation was minimal at baseline and during follow-up.

Fourth, our referent women comprised a population-based sample without restrictions. Other studies compared clinical series of women who underwent bilateral oophorectomy concurrent with hysterectomy to women who underwent hysterectomy with ovarian conservation.[4,5] We avoided using hysterectomy with ovarian conservation as a referent group because hysterectomy itself may modify the risk of morbidity and


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mortality.[6,44] However, for comparison with other studies, we conducted a set of secondary analyses comparing women who underwent bilateral oophorectomy (with prior or concurrent hysterectomy) with women who underwent hysterectomy with ovarian conservation. As expected, the associations were attenuated but remained significant, suggesting that both the hysterectomy and the oophorectomy may contribute to the increased risk.

Our study has limitations that should be considered. First, we may have underestimated the rates of certain conditions that are asymptomatic or do not uniformly come to medical attention. Second, the *ICD-9* codes used to define the baseline and the outcome conditions were assigned during the course of routine medical care and are subject to misclassification. We attempted to reduce the risk of false-positive diagnoses by including only those patients who had at least 2 codes in their medical record for a given condition separated by more than 30 days, as used in other studies.[23,45] Third, we cannot exclude some level of surveillance bias if the women who underwent oophorectomy had more frequent contacts with the medical facilities after the index date.[46] On the other hand, the density of contacts with the medical facilities in Olmsted County is high for women older than age 40 years, regardless of their oophorectomy status.[17]

Fourth, the oophorectomies used to define our historical cohorts took place over 20 years, and surgical and estrogen prescribing practices have changed over time. However, we did not observe any significant difference in the rate of accumulation of multimorbidity for women who underwent bilateral oophorectomy in the 1988 to 1997 vs the 1998 to 2007 decades. Fifth, we cannot exclude that some unmeasured variables (eg, income) may have caused residual confounding or that some of the findings for the 18 conditions considered separately may have been due to chance.

Finally, the statistical power was limited for some of the stratified analyses and for some of the tests for interaction. In addition, there were a number of methodological limitations that could not be addressed in the current sample. We plan to continue to follow up our cohorts and to accumulate additional outcome conditions so that more complex analyses will be possible to address issues such as the clustering of chronic conditions, the severity and duration of conditions, and specific types of cancer. This report is a first step toward understanding the complex effects of bilateral oophorectomy on multimorbidity, but many questions remain unanswered.

## CONCLUSION

Our study findings suggest that bilateral oophorectomy is associated with an accelerated accumulation of multimorbidity defined using a set of 18 chronic conditions, even after adjusting for these same 18 conditions present at baseline and for several possible confounders. However, several of the associations were reduced in women who received estrogen therapy. It has been suggested that the accumulation of multimorbidity may be a clinical proxy measure for accelerated aging. Our findings have both scientific and public health implications. The findings from our study, combined with those from several important preceding studies, provide more definitive evidence against the use of bilateral oophorectomy for the prevention of ovarian cancer in most premenopausal women who are at average risk of ovarian cancer. Although numerous professional societies worldwide have issued guidelines discouraging the practice of prophylactic bilateral oophorectomy in most women, the practice continues. In addition, our findings emphasize the importance of considering aging in a broader perspective, including multiple cellular, tissue, organ, and system levels, and of using multimorbidity as a clinical manifestation of these underlying complex aging mechanisms. Finally, this study should prompt additional research at the laboratory and clinical level to clarify the role of estrogen and other ovarian hormones in regulating the aging process in women.

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## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **DHHS** = Department of Health and Human Services; **ET** = estrogen therapy; **HR** = hazard ratio; ***ICD-9*** = *International Classification of Diseases, Ninth Revision*; **MOA-2** = Mayo Clinic Cohort Study of Oophorectomy and Aging; **REP** = Rochester Epidemiology Project

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