GYNECOLOGY

Hysterectomy status and all-cause mortality in a 21-year Australian population-based cohort study

Louise F. Wilson, MEpi; Nirmala Pandeya, PhD; Julie Byles, PhD; Gita D. Mishra, PhD

BACKGROUND: Hysterectomy is a common surgical procedure, predominantly performed when women are between 30 and 50 years old. One in 3 women in Australia has had a hysterectomy by the time they are 60 years old, and 30% have both ovaries removed at the time of surgery. Given this high prevalence, it is important to understand the long-term effects of hysterectomy. In particular, women who have a hysterectomy/oophorectomy at younger ages are likely to be premenopausal or perimenopausal and may experience greater changes in hormone levels and a shortened reproductive lifespan than women who have a hysterectomy when they are older and postmenopausal. Use of menopausal hormone therapy after surgery may compensate for these hormonal changes. To inform clinical decisions about postsurgery management of women who have a hysterectomy prior to menopause (ie, average age at menopause 50 years), it is useful to compare women with a hysterectomy to women with no hysterectomy and to stratify the hysterectomy status by whether or not women have had a bilateral oophorectomy, or used menopausal hormone therapy.

OBJECTIVE: We sought to investigate whether women who had a hysterectomy with ovarian conservation or a hysterectomy and bilateral oophorectomy before the age of 50 years were at a higher risk of premature all-cause mortality compared to women who did not have this surgery before the age of 50 years. We also sought to explore whether use of menopausal hormone therapy modified these associations.

STUDY DESIGN: Women from the midcohort (born 1946 through 1951) of the Australian Longitudinal Study on Women's Health were included in our study sample (n = 13,541). Women who reported a hysterectomy (with and without both ovaries removed) before the age of 50 years were considered exposure at risk and compared with women who did not report these surgeries before age 50 years. To explore effect modification by use of menopausal hormone therapy we further stratified hysterectomy status by menopausal hormone therapy use. Risk of all-cause mortality was assessed using inverse-probability weighted Cox regression models.

RESULTS: During a median follow-up of 21.5 years, there were 901 (6.7%) deaths in our study sample. Overall, there was no difference in all-cause mortality between women who reported a hysterectomy with ovarian conservation (hazard ratio, 0.86; 95% confidence interval, 0.72−1.02) or women who reported a hysterectomy and bilateral oophorectomy (hazard ratio, 1.02; 95% confidence interval, 0.78−1.34) and women with no hysterectomy. When stratified by menopausal hormone therapy use, women with hysterectomy and ovarian conservation before the age of 50 years were not at higher risk of all-cause mortality compared to no hysterectomy, regardless of menopausal hormone therapy use status. In contrast, among nonusers of menopausal hormone therapy only, women who reported a hysterectomy-bilateral oophorectomy before the age of 50 years were at a higher risk of death compared to women with no hysterectomy (hazard ratio, 1.81; 95% confidence interval, 1.01−3.25).

CONCLUSION: Hysterectomy with ovarian conservation before the age of 50 years did not increase risk of all-cause mortality. Among non-menopausal hormone therapy users only, hysterectomy and bilateral oophorectomy before the age of 50 years was associated with a higher risk of death.

Key words: Australia, bilateral oophorectomy, hysterectomy, mortality, survival analysis

Introduction

Hysterectomy is a common surgical procedure, predominantly performed when women are between 30 and 50 years old.[1] Australia has high rates of hysterectomy, second only to the United States and Canada.[1] It is estimated that 1 in 3 women in Australia in their 60s has had a hysterectomy;[2] approximately 30% of women also have a bilateral oophorectomy at the time of surgery.[3] The most common indications for hysterectomy in younger women are uterine leiomyomata (fibroids), endometriosis, and dysfunctional uterine bleeding.[4] Women with a genetic or perceived risk for ovarian cancer, or with a personal history of endometriosis or ovarian cysts, are more likely to have a bilateral oophorectomy.[5] The Royal Australian and New Zealand College of Obstetricians and Gynecologists recommends that caution should be exercised in performing prophylactic bilateral oophorectomy in women <65 years of age (who are not at increased genetic risk of ovarian cancer).[6] However, results from a small survey in Australia showed substantial variation between practitioners' views on the age they would routinely recommend removal of both ovaries at the time of hysterectomy for benign indications, with 50% recommending removal at age 55 years.[7]

Our previous research has shown associations between hysterectomy (with and without bilateral oophorectomy) and poorer physical[8] and mental[9] health. Hysterectomy has also been associated with chronic diseases such as diabetes,[10] stroke,[11] and certain cancers.[12,13] For diabetes, stroke, and poorer physical health, young age at surgery increases this risk.[8,10,11] Given the high prevalence of hysterectomy in women now entering their 60s and 70s, it is important to investigate whether this surgery is also associated with premature mortality.

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AJOG at a Glance

Why was this study conducted?

To investigate whether an Australian cohort of women who reported a hysterectomy, with and without a bilateral oophorectomy before the age of 50 years were at higher risk of premature all-cause mortality compared to women who did not report this surgery before age 50 years, and whether use of menopausal hormone therapy (MHT) modified this association.

Key findings

Women who reported a hysterectomy and ovarian conservation before the age of 50 years were not at higher risk of all-cause mortality, irrespective of whether or not they used MHT. However, mortality was higher in women who reported a hysterectomy and bilateral oophorectomy prior to age 50 years and did not use MHT.

What does this add to what is known?

This is the first study in an Australian population to investigate hysterectomy status and all-cause mortality.

Most studies comparing bilateral oophorectomy to no bilateral oophorectomy (irrespective of hysterectomy status in the exposure and/or comparator group) suggest an increase in risk of all-cause mortality when bilateral oophorectomy is performed at younger ages,[14–17] and among never users of menopausal hormone therapy (MHT),[15,18] although the results are not consistent.[19] Previous studies comparing hysterectomy (irrespective of oophorectomy status) to no hysterectomy or natural menopause have found no association with all-cause mortality.[20,21] To our knowledge, only 1 study has compared hysterectomy with ovarian conservation to no hysterectomy and found an increased risk of all-cause mortality at younger ages, but no modification by ever use of MHT.[17]

Causal mechanisms underlying the associations between hysterectomy and disease and mortality outcomes may principally relate to changes in hormone levels precipitated by the surgery. In particular, women who have a hysterectomy/oophorectomy at younger ages are likely to be premenopausal or perimenopausal and may experience greater changes in hormone levels and a shortened reproductive lifespan than women who have a hysterectomy when they are older and postmenopausal. Use of MHT for women with a hysterectomy and bilateral oophorectomy is recommended from the time of surgery until at least the age of 50 years to compensate for the abrupt reduction in hormone levels;[22] to our knowledge there are no commensurate recommendations on MHT use for women with a hysterectomy with ovarian conservation postsurgery, despite evidence that a hysterectomy alone may also precipitate hormone changes and early ovarian failure.[23,24]

To inform clinical decisions about postsurgery management of women who have a hysterectomy prior to the average age of menopause (ie, 50 years), it is useful to compare women with a hysterectomy to women with no hysterectomy and to stratify hysterectomy status by whether or not women have had a bilateral oophorectomy, or used MHT.

Using data from a midaged cohort of women born between 1946 through 1951 in the Australian Longitudinal Study on Women's Health (ALSWH) (also known as Women's Health Australia) we investigated whether women who had a hysterectomy with ovarian conservation or hysterectomy and bilateral oophorectomy by the age of 50 years were at higher risk of premature all-cause mortality (ie, death before the age of 75 years)[25] compared to women who did not have this surgery before 50 years of age; and we explored whether these associations differed by MHT use.

Materials and Methods

Study population

Our study used data from ALSWH, a prospective, population-based study designed to explore factors that influence women's physical and mental health across key life stages. Recruitment methods and response rates have been described in detail elsewhere.[26,27] The study commenced in 1996 and included 3 cohorts of women born in 1973 through 1978, 1946 through 1951, and 1921 through 1926. Participants within each cohort were randomly selected from the Medicare Australia database (covering all Australian citizens and permanent residents, including refugees and immigrants), except for women in rural and remote areas who were sampled at twice the rate of women in urban areas to allow statistical comparisons between these groups. The ALSWH has been granted ethics clearance by the Universities of Newcastle and Queensland (ethics approvals H0760795 and 2004000224). All participants provided informed, written consent at each survey. Our analysis included data from the 1946 through 1951 birth cohort. The 1996 baseline survey (survey 1) was completed by 13,715 women when they were aged 45–50 years. Seven follow-up surveys (surveys 2–8) took place in 1998 (47–52 years, n = 12,338), 2001 (50–55 years, n = 11,226), 2004 (53–58 years, n = 10,905), 2007 (56–61 years, n = 10,638), 2010 (59–64 years, n = 10,011), 2013 (62–67 years, n = 9151), and 2016 (65–70 years, n = 8622).

Hysterectomy status and MHT use

At each survey, participants were asked whether they had ever had: (1) a hysterectomy, or (2) both ovaries removed. Our exposure group included all of the women who reported a hysterectomy and/or both ovaries removed at baseline (ie, before the age of 50 years). If a woman was aged ≤50 years at a subsequent survey and reported an incident hysterectomy and/or removal of both ovaries, she was also included in the analysis (n = 154 hysterectomy only,

n = 60 hysterectomy and both ovaries removed, reported at survey 2). A woman was considered unexposed if she reported a hysterectomy when she was age >50 years.

At survey 1, women were also asked if they were currently using MHT (yes/no) and how many years in total they had ever used MHT (never used, <1 year, 1−4 years, 5−10 years, and >10 years). If a woman was not currently using MHT and reported "never used" MHT she was categorized as "not MHT user"; all other women were categorized as "MHT user." If a woman reported incident surgery at survey 2 and MHT use at survey 2 or baseline, she was included in the "MHT user" category.

We created a hysterectomy variable with 3 categories: (1) women who reported having a hysterectomy, but did not report having both ovaries removed, ie, they still retained 1 or both ovaries (hysterectomy−ovarian conservation group); (2) women who reported a hysterectomy and also reported having both ovaries removed (hysterectomy-bilateral oophorectomy group); and (3) women who did not report having either a hysterectomy or both ovaries removed (no hysterectomy group). Women who reported only having both ovaries removed were excluded from the analysis.

We also created a 6-category hysterectomy status/MHT use variable (no hysterectomy/not MHT user, no hysterectomy/MHT user, hysterectomy-ovarian conservation/not MHT user, hysterectomy-ovarian conservation/MHT user, hysterectomy-bilateral oophorectomy/not MHT user, hysterectomy-bilateral oophorectomy/MHT user).

Covariates

We considered covariates for inclusion if we thought they would potentially affect both hysterectomy status and all-cause mortality. We tested for these relationships in univariate models. All covariates were measured at baseline (survey 1).

The age of women was included as a continuous variable. A woman's highest qualification level was categorized as less than high school, high school/trade/diploma, and degree or higher. The remoteness category of a woman's usual place of residence was categorized as major city, inner regional, and outer regional/remote/very remote.[28] Women were asked how they managed on the income available, with response options of impossible, difficult always, difficult sometimes, not too bad, and easy. We dichotomized this variable into impossible/difficult always/difficult sometimes and not too bad/easy. Parity was categorized as: no children, 1 child, 2 children, 3 children, and ≥4 children.

Four health behavior variables were included: smoking status (never smoker, former smoker, current smoker); physical activity level (none, low [<150 minutes], moderate [150−300 minutes], and high [>300 minutes]);[29] alcohol consumption (nondrinker, rarely drinker [<once/mo], low-risk drinker [≤2 drinks/d], risky/high-risk drinker [≥3 drinks/d]);[30] and body mass index (BMI) (calculated from self-reported weight and height and categorized into <18.5 kg/m^2 underweight, 18.5−24.9 kg/m^2 normal weight, 25−29.9 kg/m^2 overweight, and ≥30 kg/m^2 obese).[31]

Women were asked if they had ever been told by a doctor that they had diabetes (high blood sugar) (yes/no) or hypertension (high blood pressure) (yes/no). Women were also asked how they felt about their general health. We included this variable as a marker of overall health and dichotomized the responses into: excellent/very good/good and fair/poor.

Death data

Death was determined by linking participant information to the Australian National Death Index that contains records of all deaths registered in Australia since 1980. Data in the Australian National Death Index is sourced from the Registrar of Births, Deaths, and Marriages in each state and territory, the National Coronial Information System, and the Australian Bureau of Statistics. Survival time was calculated from 1996 (survey 1) through Oct. 31, 2017. We had complete deaths data on all participants.

Statistical analysis

Baseline characteristics (survey 1, 1996) of women were described by hysterectomy status and hysterectomy status/MHT use, with percentages weighted by area of residence to account for oversampling in rural and remote areas in ALSWH.[26] Differences between hysterectomy groups were assessed by the χ^2 test.

We used inverse probability-weighted (IPW) Cox models, with robust error variance, to estimate the effect of hysterectomy status on all-cause mortality. We created time-fixed exposure IPWs to account for the baseline covariates included the model. The advantage of the IPW approach is that (under the assumptions of well-defined exposures, positivity, correctly specified models and no unmeasured confounding or selection bias)[32] it approximates a randomized controlled trial intent-to-treat analysis (ie, with no confounding and no drop-out).[33] To avoid heterogeneity that might be introduced into the weights due to serious illness at baseline, we excluded women from our primary analysis if they died within 2 years of completing survey 1 (n = 44).

To obtain the IPW exposure weights we used multinomial logistic regression models to estimate the numerator and denominator. We created separate IPW weights for hysterectomy status and hysterectomy/MHT use status. The regression model for the numerator included only hysterectomy as the outcome with no covariates. To calculate the denominator all baseline covariates were also included in the model (MHT use was not included as a covariate for hysterectomy status as it was an effect modifier rather than a confounder). Age at survey 1 was included as a continuous variable using restricted quadratic splines[33] and interaction terms that were significant at a P value ≤.1 (highest qualification*hypertension, parity*hypertension, area of residence*general health). Missing values for baseline covariates occurred at a

TABLE 1
Baseline (survey 1) characteristics of participants (n = 13,541) by hysterectomy status

Baseline covariates	Hysterectomy-ovarian conservation, n = 2472 n (%)[a]	Hysterectomy-bilateral oophorectomy, n = 851 n (%)[a]	No hysterectomy, n = 10,218 n (%)[a]	$P > \chi^{2}$[b]
Age at entry, n = 13,541				
45 y	493 (16.3)	129 (4.3)	2042 (79.4)	<.0001
46 y	485 (16.9)	168 (5.4)	2142 (77.7)	
47 y	445 (16.5)	169 (5.9)	1981 (77.6)	
48 y	476 (18.2)	164 (6.2)	1932 (75.6)	
49 y	534 (19.1)	208 (7.1)	2018 (73.7)	
50 y	39 (25.0)	13 (14.6)	103 (60.4)	
Body mass index, n = 13,019				
Underweight	34 (15.1)	16 (6.2)	179 (78.7)	<.0001
Normal weight	1073 (15.3)	313 (4.6)	5225 (80.1)	
Overweight	712 (18.8)	262 (6.6)	2784 (74.6)	
Obese	561 (23.0)	224 (8.5)	1636 (68.5)	
Smoking status, n = 13,110				
Never smoker	1234 (16.8)	399 (5.3)	5344 (77.8)	<.0001
Former smoker	667 (17.2)	216 (5.1)	2853 (77.7)	
Current smoker	493 (20.1)	213 (9.0)	1691 (70.9)	
Alcohol consumption, n = 13,420				
Nondrinker	415 (20.1)	162 (7.4)	1453 (72.4)	<.0001
Rarely drinker	802 (18.2)	331 (7.6)	3083 (74.2)	
Low-risk drinker	1112 (16.4)	308 (4.6)	5046 (79.0)	
Risky/high-risk drinker	119 (16.9)	38 (3.7)	551 (79.4)	
Physical activity level, n = 13,439				
No activity	330 (17.8)	128 (7.0)	1220 (75.2)	.4286
Low level	1099 (17.2)	408 (6.1)	4618 (76.7)	
Moderate level	331 (18.5)	101 (5.3)	1393 (76.3)	
High level	689 (17.5)	207 (5.4)	2915 (77.1)	
Highest qualification level, n = 13,408				
Degree or higher	199 (9.4)	46 (2.0)	1630 (88.6)	<.0001
High school/trade/diploma	821 (16.9)	274 (5.7)	3734 (77.4)	
Less than high school	1423 (20.7)	522 (7.5)	4759 (71.7)	
Difficulty managing on income, n = 13,461				
Not too bad/easy	1314 (16.5)	406 (4.9)	5876 (78.6)	<.0001
Impossible/difficult all or some of time	1144 (19.0)	441 (7.3)	4280 (73.7)	
Remoteness category, n = 13,538				
Major cities	853 (17.1)	274 (5.5)	3812 (77.4)	.001
Inner regional	925 (17.4)	346 (6.8)	3885 (75.8)	
Outer regional/remote/very remote	694 (20.6)	231 (6.5)	2518 (73.0)	

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TABLE 1
Baseline (survey 1) characteristics of participants (n = 13,541) by hysterectomy status *(continued)*

Baseline covariates	Hysterectomy-ovarian conservation, n = 2472 n (%)[a]	Hysterectomy-bilateral oophorectomy, n = 851 n (%)[a]	No hysterectomy, n = 10,218 n (%)[a]	$P > \chi^{2}$[b]
No. of children, n = 12,871				
None	126 (11.6)	82 (7.0)	829 (81.4)	<.0001
1	181 (15.3)	74 (5.2)	878 (80.5)	
2	902 (17.2)	300 (6.0)	3740 (76.8)	
3	702 (19.6)	206 (4.9)	2740 (75.5)	
≥4	453 (21.7)	141 (6.5)	1517 (71.9)	
Diabetes, n = 13,483				
No	2355 (17.3)	816 (5.8)	9931 (76.9)	<.0001
Yes	103 (25.7)	31 (9.5)	247 (64.8)	
Hypertension, n = 13,471				
No	1861 (16.7)	635 (5.7)	8152 (77.6)	<.0001
Yes	594 (20.8)	210 (6.5)	2019 (72.7)	
Perception of general health, n = 13,385				
Excellent/very good/good	2039 (16.6)	676 (5.4)	9150 (78.0)	<.0001
Fair/poor	403 (24.7)	164 (9.8)	953 (65.5)	
MHT user, n = 13,529				
No	1477 (14.4)	148 (1.4)	8240 (84.2)	<.0001
Yes	990 (26.2)	702 (18.5)	1972 (55.3)	

MHT, menopausal hormone therapy.

[a] Percentages are weighted for participants' area of residence at baseline (1996); [b] Probability greater than χ^{2} (test of significance).

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prevalence of ≤1% for all variables except parity (5%), BMI (4%), and smoking (3%). To reduce potential bias, we imputed missing values (n = 20 imputations) using the fully conditional method. The imputation model included all covariates, the exposure, outcome, and baseline hazard,[34] as well as auxiliary variables to inform the imputation of BMI.[35] While we included hysterectomy status in the imputation model, we did not use the imputed hysterectomy status in our analysis (n missing for hysterectomy status = 41). Proportional hazard assumptions were checked and satisfied visually through IPW-adjusted survival curves and by testing for the statistical significance of an interaction between hysterectomy and a function of survival time in the model (Supplementary Data S1).[36]

We compared our results from the IPW Cox models with unweighted models that were unadjusted and adjusted for covariates. We also repeated the analysis using only participants with complete information on all covariates (n = 11,558). All analyses were done using software (SAS, Version 9.4 for Windows, SAS Institute Inc, Cary, NC).

Results

After multiple imputations, 13,541 women were included in our analysis. Women were excluded if they reported having both ovaries removed without a hysterectomy at baseline (n = 89), had missing data on hysterectomy status at baseline (n = 41), or died within 2 years of baseline (n = 44). In our study sample, 18% of women reported a hysterectomy with ovarian conservation and 6% reported a hysterectomy and both ovaries removed. Table 1 summarizes the baseline characteristics of included women by hysterectomy status. Table 2 presents the baseline characteristics additionally stratified by MHT use. Women who reported a hysterectomy/oophorectomy at baseline were different from women with no hysterectomy across all covariates reporting poorer health habits, lower education levels, and greater use of MHT (Table 1). When further stratified by MHT use, differences seemed to be mainly driven by hysterectomy status, although for women without a hysterectomy, MHT users were older than not MHT users. MHT users were also more likely to be current smokers (Table 2).

Over a median follow-up period of 21.5 years there were 901 deaths in our

TABLE 2
Baseline (survey 1) characteristics of participants (n = 13,529) by hysterectomy status/menopausal hormone therapy use

Baseline covariates	No hysterectomy/not MHT user, n = 8240 n (%)[a]	No hysterectomy/MHT user, n = 1972 n (%)[a]	Hysterectomy-ovarian conservation/not MHT user, n = 1463 n (%)[a]	Hysterectomy-ovarian conservation/MHT user, n = 1004 n (%)[a]	Hysterectomy-bilateral oophorectomy/not MHT user, n = 114 n (%)[a]	Hysterectomy-bilateral oophorectomy/MHT user, n = 736 n (%)[a]	$P > \chi^{2}$[b]
Age at entry, n = 13,529							
45 y	1813 (71.5)	227 (8.0)	345 (11.8)	146 (4.4)	21 (0.7)	108 (3.6)	<.0001
46 y	1831 (66.2)	309 (11.5)	313 (11.1)	171 (5.9)	21 (0.5)	147 (4.9)	
47 y	1619 (63.8)	362 (13.9)	270 (9.8)	174 (6.6)	28 (1.1)	141 (4.8)	
48 y	1467 (57.3)	465 (18.3)	270 (10.5)	206 (7.7)	19 (0.8)	145 (5.3)	
49 y	1436 (53.1)	580 (20.7)	242 (8.8)	291 (10.3)	24 (0.8)	183 (6.3)	
50 y	74 (43.5)	29 (16.8)	23 (14.3)	16 (10.7)	1 (1.2)	12 (13.4)	
Body mass index, n = 13,010							
Underweight	151 (65.8)	28 (12.9)	19 (8.5)	15 (6.6)	2 (0.3)	14 (5.9)	<.0001
Normal weight	4214 (64.6)	1007 (15.5)	631 (8.9)	440 (6.4)	37 (0.6)	275 (4.0)	
Overweight	2247 (60.9)	537 (13.7)	424 (11.6)	287 (7.2)	38 (0.9)	224 (5.7)	
Obese	1312 (55.5)	324 (13.1)	340 (14.1)	220 (8.9)	30 (1.3)	194 (7.2)	
Smoking status, n = 13,098							
Never smoker	4442 (65.0)	900 (12.9)	777 (10.8)	455 (6.0)	50 (0.8)	348 (4.5)	<.0001
Former smoker	2266 (61.9)	585 (15.9)	374 (9.7)	290 (7.3)	24 (0.5)	192 (4.7)	
Current smoker	1259 (53.3)	430 (17.6)	265 (10.6)	228 (9.5)	36 (1.4)	177 (7.6)	
Alcohol consumption, n = 13,409							
Nondrinker	1173 (59.8)	278 (12.8)	248 (12.4)	165 (7.6)	37 (1.9)	125 (5.6)	<.0001
Rarely drinker	2479 (59.5)	604 (14.8)	471 (10.6)	330 (7.5)	31 (0.7)	299 (6.9)	
Low-risk drinker	4082 (64.4)	962 (14.6)	644 (9.5)	466 (6.9)	35 (0.5)	273 (4.1)	
Risky/high-risk drinker	442 (62.5)	108 (16.9)	83 (12.0)	36 (4.9)	9 (1.0)	29 (2.7)	

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(continued)

TABLE 2
Baseline (survey 1) characteristics of participants (n = 13,529) by hysterectomy status/menopausal hormone therapy use *(continued)*

Baseline covariates	No hysterectomy/not MHT user, n = 8240 n (%)[a]	No hysterectomy/MHT user, n = 1972 n (%)[a]	Hysterectomy-ovarian conservation/not MHT user, n = 1463 n (%)[a]	Hysterectomy-ovarian conservation/MHT user, n = 1004 n (%)[a]	Hysterectomy-bilateral oophorectomy/not MHT user, n = 114 n (%)[a]	Hysterectomy-bilateral oophorectomy/MHT user, n = 736 n (%)[a]	$P > \chi^{2}$[b]
Physical activity level, n = 13,428							
No activity	979 (59.8)	241 (15.5)	192 (10.4)	137 (7.3)	22 (1.4)	106 (5.6)	.5175
Low level	3733 (62.3)	882 (14.4)	639 (10.1)	458 (7.1)	50 (0.8)	358 (5.3)	
Moderate level	1118 (61.4)	274 (15.0)	197 (11.1)	133 (7.3)	14 (0.6)	87 (4.6)	
High level	2356 (63.2)	558 (14.0)	421 (10.7)	267 (6.7)	28 (0.6)	178 (4.7)	
Highest qualification level, n = 13,397							
Degree or higher	1376 (75.0)	253 (13.5)	122 (5.7)	77 (3.7)	4 (0.2)	42 (1.9)	<.0001
High school/ trade/diploma	3051 (63.5)	683 (14.0)	487 (10.0)	330 (6.8)	29 (0.6)	244 (5.1)	
Less than high school	3735 (56.3)	1020 (15.4)	836 (12.3)	586 (8.4)	80 (1.2)	442 (6.3)	
Difficulty managing on income, n = 13,450							
Not too bad/easy	4801 (64.5)	1072 (14.1)	798 (10.0)	513 (6.5)	51 (0.7)	354 (4.2)	<.0001
Impossible/ difficult all or some of time	3391 (58.6)	887 (15.1)	653 (11.0)	489 (7.9)	62 (0.9)	379 (6.4)	
Remoteness category, n = 13.526							
Major cities	3082 (62.8)	727 (14.6)	507 (10.2)	342 (6.8)	41 (0.8)	233 (4.7)	.004
Inner regional	3119 (61.1)	763 (14.7)	544 (10.2)	381 (7.2)	45 (0.8)	300 (6.0)	
Outer regional/ remote/very remote	2036 (59.2)	482 (13.8)	412 (12.5)	281 (8.0)	28 (0.7)	203 (5.7)	

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TABLE 2
Baseline (survey 1) characteristics of participants (n = 13,529) by hysterectomy status/menopausal hormone therapy use *(continued)*

Baseline covariates	No hysterectomy/not MHT user, n = 8240 n (%)[a]	No hysterectomy/MHT user, n = 1972 n (%)[a]	Hysterectomy-ovarian conservation/not MHT user, n = 1463 n (%)[a]	Hysterectomy-ovarian conservation/MHT user, n = 1004 n (%)[a]	Hysterectomy-bilateral oophorectomy/not MHT user, n = 114 n (%)[a]	Hysterectomy-bilateral oophorectomy/MHT user, n = 736 n (%)[a]	$P > \chi^{2}$[b]
No. of children, n = 12,863							
None	679 (68.0)	150 (13.4)	78 (7.2)	48 (4.4)	7 (0.5)	75 (6.5)	<.0001
1	680 (63.9)	197 (16.6)	103 (8.4)	78 (5.8)	13 (1.2)	61 (4.0)	
2	2980 (62.1)	758 (14.8)	545 (10.4)	356 (6.8)	38 (0.7)	261 (5.2)	
3	2249 (61.8)	490 (13.8)	417 (11.5)	284 (8.0)	24 (0.5)	182 (4.4)	
≥4	1245 (57.7)	271 (14.1)	259 (12.6)	194 (9.1)	22 (1.0)	119 (5.5)	
Diabetes, n = 13,471							
No	8019 (62.3)	1906 (14.6)	1392 (10.3)	960 (7.0)	105 (0.7)	710 (5.1)	<.0001
Yes	197 (55.7)	50 (9.7)	63 (15.3)	38 (9.6)	9 (3.5)	22 (6.2)	
Hypertension, n = 13,459							
No	6643 (63.5)	1505 (14.1)	1121 (10.2)	736 (6.4)	88 (0.8)	546 (5.0)	<.0001
Yes	1565 (56.7)	452 (16.1)	332 (11.3)	261 (9.5)	24 (0.8)	186 (5.7)	
Perception of general health, n = 13,374							
Excellent/very good/good	7469 (64.0)	1677 (14.1)	1253 (10.2)	783 (6.4)	95 (0.7)	580 (4.6)	<.0001
Fair/poor	685 (47.7)	266 (17.7)	191 (12.3)	211 (12.4)	17 (1.0)	147 (8.9)	

MHT, menopausal hormone therapy.

[a] Percentages are weighted for participants' area of residence at baseline (1996); [b] Probability greater than χ^{2} (test of significance).

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TABLE 3
Unweighted and inverse probability-weighted hazard ratios and 95% confidence intervals for the effect of hysterectomy status and hysterectomy status/menopausal hormone therapy user on all-cause mortality

Exposure of interest	Deaths	Person-years	Death rate/ 10,000 person-y	Unweighted HR (95% CI) Unadjusted	Unweighted HR (95% CI) Adjusted for baseline covariates[a]	IPW HR (95% CI)
Hysterectomy status						
No hysterectomy	663	214,571.11	30.9	Reference	Reference	Reference
Hysterectomy-ovarian conservation	167	51,858.27	32.2	1.04 (0.88–1.24)	0.88 (0.74–1.05)	0.86 (0.72–1.02)
Hysterectomy-bilateral oophorectomy	71	17,696.39	40.1	1.30 (1.02–1.66)	0.94 (0.73–1.21)	1.02 (0.78–1.34)
Hysterectomy/MHT status						
No hysterectomy/not MHT user	501	173,417.69	28.9	Reference	Reference	Reference
No hysterectomy/MHT user	162	41,153.42	39.4	1.37 (1.15–1.63)	1.12 (0.93–1.34)	1.09 (0.90–1.31)
Hysterectomy-ovarian conservation/not MHT user	93	30,802.94	30.2	1.05 (0.84–1.30)	0.91 (0.73–1.14)	0.93 (0.75–1.17)
Hysterectomy-ovarian conservation/MHT user	74	21,005.33	35.1	1.22 (0.95–1.56)	0.90 (0.70–1.15)	0.78 (0.59–1.04)
Hysterectomy-bilateral oophorectomy/not MHT user	17	2303.80	73.8	2.61 (1.61–4.23)	1.72 (1.06–2.80)	1.81 (1.01–3.25)
Hysterectomy-bilateral oophorectomy/MHT user	54	15,392.59	35.1	1.21 (0.92–1.61)	0.85 (0.64–1.13)	0.91 (0.67–1.24)

CI, confidence interval; *HR*, hazard ratio; *IPW*, inverse probability-weight; *MHT* = menopausal hormone therapy.

[a] Adjusted for age at entry, body mass index, smoking status, alcohol consumption, physical activity level, highest qualification level, difficulty managing on income, remoteness category, number of children, diabetes, hypertension, perception of general health.

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study sample. The median follow-up time did not differ by hysterectomy or hysterectomy/MHT status; however, the interquartile range was higher for the hysterectomy-bilateral oophorectomy/not MHT user group and the hysterectomy-ovarian conservation/MHT user group (Supplementary Data S2).

Across the 3 hysterectomy groups, the hysterectomy-bilateral oophorectomy group had the highest death rate (40.1 per 10,000 person-years) (Table 3). In the unadjusted model, women with a hysterectomy-bilateral oophorectomy had a higher risk of all-cause mortality (unadjusted hazard ratio [HR], 1.30; 95% confidence interval [CI], 1.02–1.66) compared to women with no hysterectomy. Our estimated IPWs for hysterectomy status had a mean of 1.00 (SD 0.23, range 0.19–4.79) indicating a correctly specified model.[37] In the IPW Cox model, compared to women with no hysterectomy, having a hysterectomy-ovarian conservation or a hysterectomy-bilateral oophorectomy was not associated with higher risk of all-cause mortality (IPW HR, 0.86; 95% CI, 0.72–1.02 and IPW HR, 1.02; 95% CI, 0.78–1.34, respectively) (Table 2). The results were similar in the standard survival analysis that adjusted for covariates (Table 3). In the complete case analysis, the adjusted and IPW results were similar to our primary analysis; however, the unadjusted HRs for hysterectomy-bilateral oophorectomy did not reach statistical significance (Supplementary Data S3).

When the hysterectomy status was further stratified by MHT use, the death rate was lowest for no hysterectomy/not MHT user (28.9 deaths/10,000 person years) and highest for hysterectomy-bilateral oophorectomy/not MHT user (73.8 deaths/10,000 person years) (Table 3). In the unadjusted Cox model, compared to women with no hysterectomy/not MHT user, women with a hysterectomy-bilateral oophorectomy/not MHT user had a higher risk of all-cause mortality (unadjusted HR, 2.61; 95% CI, 1.61–4.34); a higher risk was also seen in women with no hysterectomy/MHT user (unadjusted HR, 1.37; 95% CI, 1.15–1.63) (Table 3). Our estimated IPWs for hysterectomy status/MHT use had a mean of 1.00 (SD 0.34, range 0.13–6.11) indicating a correctly specified model.[37] In the IPW Cox model, the higher risk of all-cause mortality only remained in the hysterectomy-bilateral oophorectomy/not MHT user group vs the no hysterectomy/not MHT user group (IPW HR, 1.81; 95% CI, 1.01–3.25), with similar results in the model adjusted for covariates (Table 3).

In the complete case analysis there were some differences between the adjusted and IPW models, with no estimates reaching statistical significance in

the IPW model (Supplementary Data S3). While the direction of the estimates was similar for all hysterectomy status/MHT use groups in the complete case IPW model and imputed IPW model (primary analysis) the higher risk of all-cause mortality seen in the hysterectomy-bilateral oophorectomy/not MHT user group was not statistically significant in the complete case analysis.

Comment

Overall, in our study sample, women who reported having a hysterectomy (with and without bilateral oophorectomy) before the age of 50 years were not at higher risk of all-cause mortality. When we stratified by MHT use, women with hysterectomy-ovarian conservation before the age of 50 years were not at higher risk of all-cause mortality, regardless of their MHT use status. In contrast, women who reported a hysterectomy-bilateral oophorectomy before the age of 50 years and were not MHT users had a higher risk of death compared to women with no hysterectomy and not MHT users.

Although not directly comparable because of the use of different exposure and comparator groups, studies that have compared hysterectomy (with/without oophorectomy) to no hysterectomy[17,20,21] and bilateral oophorectomy (with/without hysterectomy) to no bilateral oophorectomy[14,15,17,21] have also found no overall association with all-cause mortality.

Gierach and colleagues[17] found an overall increased risk of all-cause mortality in women who had a total abdominal hysterectomy with ovarian conservation before the age of 40 years, and women who had a bilateral oophorectomy (with/without hysterectomy) before the age of 45 years, compared to women with no gynecological surgery. All of the women in our study had their surgery before the age of 50 years and we did not find a higher mortality risk. A limitation of our study is that women were not asked about their age at hysterectomy until surveys 7 and 8 (in 2013 and 2016), so we could not explore whether the exact timing of surgery before the age of 50 years may vary the level of risk. Similar to our study, Gierach and colleagues[17] also found no evidence of effect modification by MHT use for women with a hysterectomy with ovarian conservation.

In our study, there were only a small number of women with a hysterectomy-bilateral oophorectomy who did not use MHT prior to baseline (n = 114) and the higher risk was only statistically significant when we included imputed missing data in our analysis. However, our finding of a higher risk of all-cause mortality is consistent with 2 other studies.[15,17] Potential explanations are that women who have a hysterectomy and bilateral oophorectomy before the age of 50 years are most likely premenopausal at the time of surgery. An abrupt reduction in hormone levels that is not compensated through exogenous estrogen within a critical window close to the time of surgery may increase the risk of a range of chronic diseases and have a consequent increase in mortality. Alternatively, the prescription of MHT may have been contraindicated in these women and it could be the underlying indication (and not the absence of MHT or the surgery) that led to the increased mortality. We did not have sufficient numbers of women in the hysterectomy-bilateral oophorectomy/not MHT user group to explore whether late initiation of MHT use might make a difference to mortality outcomes. Future research should investigate this question.

Strengths of our study are that ALSWH is a large community-based prospective study with 21 years of follow-up. All of the women were born within a 5-year time frame, limiting cohort effects in the analysis. Limitations of our study are those inherent in an observational study; the potential presence of residual confounding, measurement error, and reporting bias. All of the exposure and covariate information was collected by self-report; while reporting of hysterectomy has consistently had high validity across studies,[38,39] the validity of self-report of bilateral oophorectomy may be less reliable.[39,40] Misclassification of MHT may also have occurred, although self-reported MHT use has been shown to be a reliable and valid measure.[41,42] As women were not asked the reason for their hysterectomy we could not explore whether different indications may have influenced mortality outcomes. Finally, our study was in a cohort of Australian women born from 1946 through 1951, mostly Caucasian. This limits the generalizability of our findings as hysterectomy/bilateral oophorectomy trends and risk factors may differ by country and birth cohort, and patterns of MHT use have changed over time.

Despite these limitations, this study is the first in an Australian population and contributes to the evidence base on the long-term health outcomes of hysterectomy and bilateral oophorectomy and the potential impact of postsurgery MHT use. Further research is required to investigate whether there are differences in mortality risk by indication for surgery. In addition, investigations in more recent birth cohorts of women are necessary to ascertain the impact of changes in patterns of MHT use, including type, dose, duration, and age at initiation. ■

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