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Long-term risk of de novo mental health conditions after hysterectomy with ovarian conservation: a cohort study

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Abstract

Objective: The aim of this research was to study the long-term risk of de novo mental health conditions in women who underwent hysterectomy with bilateral ovarian conservation compared with age-matched referent women.

Methods: Using the Rochester Epidemiology Project records-linkage system, we identified a historical cohort of 2,094 women who underwent hysterectomy with ovarian conservation for benign indications at age ≥18 years and with an index date between 1980 and 2002 in Olmsted County, Minnesota. Each woman was age-matched (±1 y) to a referent woman residing in the same county who had not undergone hysterectomy or any oophorectomy before the index date. These two cohorts were followed historically to identify de novo mental health conditions. We estimated hazard ratios (HRs) and 95% confidence intervals (95% CIs) using Cox proportional hazards models adjusted for 20 preexisting chronic conditions and other potential confounders. We also calculated absolute risk increases (ARIs) and reductions (ARRs) at 30 years of follow-up.

Results: Over a median follow-up of 21.9 years, women who underwent hysterectomy at any age experienced increased risks of de novo depression (adjusted HR 1.26; 95% CI, 1.12-1.41; ARI 6.6%) and anxiety (adjusted HR 1.22; 95% CI, 1.08-1.38; ARI 4.7%). The association for depression increased significantly with younger age at hysterectomy, but did not vary significantly by indication. Interactions were not significant for anxiety.

Conclusions: Hysterectomy, even with ovarian conservation, is associated with an increased long-term risk of de novo depression and anxiety, especially when performed in women who are younger.

Key Words: Anxiety – Cohort study – Depression – Epidemiology – Hysterectomy.

Video Summary: http://links.lww.com/MENO/A465.

Over 400,000 hysterectomies with or without bilateral oophorectomy are performed in the United States annually; thus, hysterectomy is the most common major gynecological surgery.[1,2] The risk of increased morbidity and mortality after bilateral oophorectomy with or without concurrent hysterectomy has been established. In particular, bilateral oophorectomy has been associated with increased risk of anxiety, depression, and dementia.[3,4] Emerging research has demonstrated that hysterectomy with both ovaries conserved may also be associated with long-term, harmful effects.[5-8] The association may be explained by a cause–effect inversion, by a confounding by indication, or by biological effects of hysterectomy. For example, it has been hypothesized that hysterectomy may have detrimental effects on the ovaries or directly on other organs and systems via ovarian-independent mechanisms.[9-11] A possible endocrine activity of the endometrium, both during pregnancy and in nonpregnant women, has been

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discussed in the more recent literature, including our recent letter in *Menopause*.[12-14]

The association of hysterectomy with mental health outcomes has been debated. Several studies that assessed depressive symptoms immediately before hysterectomy have shown a general improvement in symptoms and quality of life after surgery.[15-17] Women with gynecologic problems and women undergoing hysterectomy, however, have been shown to have lower quality of life than the general population.[18,19] Therefore, short-term improvement after surgery may indicate normalization of symptoms that were acutely worsened by the gynecologic condition. Indeed, most of the studies that showed an improvement were based on patient recall or on a preoperative evaluation performed within weeks before the surgery.

A study based on a national insurance database in Taiwan demonstrated an increase in depression in women who underwent hysterectomy with ovarian conservation, after excluding women with a preoperative diagnosis of depression.[20] In addition, two longitudinal studies from Australia have shown consistently higher risks of depressive symptoms in women undergoing hysterectomy compared with perimenopausal and postmenopausal women.[21,22] The risk of depression was higher in women who underwent a concurrent bilateral oophorectomy compared with hysterectomy with ovarian conservation.[21,22] In addition, menopause in itself may be a time of vulnerability to depression[23]; however, depression improved over time regardless of surgical status in a longitudinal study of the menopausal transition.[16]

Hysterectomy with ovarian conservation has been previously associated with the risk of dementia[8,24]; however, in some studies it was not possible to clearly separate hysterectomy with and without a concurrent bilateral oophorectomy.[25,26] A 2018 study on a rat model suggested that hysterectomy with ovarian conservation may have a specific detrimental effect on the working memory cognitive domain.[14] The authors suggested that hysterectomy, with or without ovarian conservation, may have important effects on brain aging and endocrine aging.[14] Other studies have suggested an association of hysterectomy with substance abuse disorders, particularly in relation to the postoperative use of narcotic pain medications.[27-29] We are not aware of previous studies of the association between hysterectomy and schizophrenia or psychosis. As shown in detail by the results of this study, the cumulative incidence during the follow-up was higher for depression and anxiety but lower for dementia, substance abuse disorders, and schizophrenia or psychosis.

The aim of this study was to investigate the long-term associations of hysterectomy with bilateral ovarian conservation with a broad range of aging-related mental health conditions, after accounting for preoperative mental health diagnoses and several potential confounders.[30]

METHODS

Study population and overall study design

A subset of women was identified from the Mayo Clinic Study of Uterine Disease and Health (MCSUD), as described elsewhere.[31-34] This subset comprised 2,094 Olmsted County, Minnesota resident women who underwent hysterectomy with ovarian conservation for a benign indication at age $\geq$18 years and with an index date between January 1, 1980 and December 31, 2002 (23 y). All data for this study were obtained using the Rochester Epidemiology Project (REP) medical records-linkage system that includes the complete inpatient and outpatient records of all the major medical care providers in Olmsted County, Minnesota. Details about the REP and about the Olmsted County population have been reported elsewhere.[35]

As described previously, the procedural codes for hysterectomy and the diagnostic codes for surgical indication were extracted from the REP electronic indices to identify the women who underwent hysterectomy.[33] Our ascertainment of hysterectomy was formally validated.[33] The manual review of a random sample of 100 women with a procedural code for hysterectomy confirmed that all women had undergone hysterectomy with full details about the surgery and the pathology (100% positive predictive value). In addition, the type of hysterectomy (abdominal vs vaginal) also had a 99% predictive value.[33] Finally, our exclusion of bilateral oophorectomy has also been validated in a previous study.[36]

The date of hysterectomy was considered the index date. For each woman who underwent hysterectomy, we used simple random sampling to identify one referent woman matched by age ($\pm$1 y) who resided in Olmsted County on the index date, and who had not undergone a hysterectomy or oophorectomy (unilateral or bilateral) before the index date. Women who did not authorize the use of their medical records for research were excluded. All research activities were approved by the institutional review boards at Olmsted Medical Center and Mayo Clinic.

Ascertainment of chronic conditions present at the index date

Chronic conditions present at the index date were obtained electronically from the diagnostic indices of the REP. We considered 18 chronic conditions used by the Department of Health and Human Services (DHHS) to define multimorbidity, but added to the list also anxiety and obesity (total of 20 conditions listed in Supplemental Digital Content 1, http://links.lww.com/MENO/A466).[37-39] The modified DHHS list comprises the 5 mental health conditions studied in this paper and 15 other chronic conditions: depression, anxiety, substance abuse disorders (drugs and alcohol), dementia (and other disorders of cognition), schizophrenia and psychosis; hyperlipidemia, hypertension, diabetes, obesity, cardiac arrhythmias, coronary artery disease, congestive heart failure, stroke, arthritis, cancer (all types), asthma, chronic obstructive pulmonary disease, osteoporosis, chronic kidney disease, and hepatitis. Women were required to have at least two diagnostic codes for a given condition separated by more than 30 days to reduce the risk of false-positive diagnoses. Before 1994, a finer dating of the codes was not available; thus, a 1-year separation of codes was required. We included all

chronic conditions documented in the records-linkage system at any time before the index date.

Ascertainment of mental health conditions during follow-up

The primary outcomes of the study were the five mental health conditions included in the modified DHHS list. The mental health outcomes were obtained electronically from the REP indices, and required at least two diagnostic codes separated by more than 30 days (or more than 1 y) as described above. To include those conditions that were first identified at death (such as depression-related suicide or accidental death due to substance abuse), a single diagnostic code found anywhere on a death certificate was, however, also sufficient.

Statistical analysis

Each mental health condition was evaluated separately, and women with that condition diagnosed before the hysterectomy (or index date for referent women) were excluded from the analysis to consider only de novo conditions. The duration of follow-up was calculated from the index date to the earliest of four endpoints: diagnosis of the specific mental health outcome, date of death, last contact within the REP, or the end of the study (December 31, 2015). Cumulative incidence curves were estimated using the Kaplan–Meier method, and absolute risks were derived from the adjusted Kaplan–Meier curves at 15 and 30 years. Differences between the two cohorts were measured using the absolute risk increase (ARI) or reduction (ARR), obtained by subtracting the two absolute risks. In addition, Cox proportional hazards models were used to estimate hazard ratios (HRs) and corresponding 95% CIs using age as the time scale and with women entering the risk set at their respective index ages.

The Kaplan–Meier curves and the Cox models were adjusted using inverse probability weights derived from a logistic regression model, including 20 preexisting chronic conditions, years of education ($\leq$12, 13-16, $>$16, unknown), race (white vs nonwhite), and age and calendar year at index date (continuous). Robust sandwich covariance estimates were used in the Cox models to account for women included in both cohorts (referent women with subsequent hysterectomy), and for the use of estimated weights.

Analyses were performed for all women combined, and stratified by age at hysterectomy (18-35, 36-50, and $>$50 y) and by surgical indication (leiomyomas, menstrual disorders, and uterine prolapse). Formal tests of interaction across strata were performed. The inverse probability weights were derived separately within each stratum to maximize the balance of the adjustment variables. We performed four sets of sensitivity analyses to (1) exclude women with any of the 20 chronic conditions before the index date; (2) censor women at the time of subsequent unilateral or bilateral oophorectomy (both women with hysterectomy and referent women) or hysterectomy (referent women); (3) additionally adjust for number of children (0, 1, 2, $\geq$3 children, unknown); and (4) additionally adjust for number of medical contacts during follow-up treated as a time-dependent continuous variable (and excluding the medical contacts in the first 6 mo after index date). Analyses were performed using the SAS version 9.4 software package (SAS Institute, Inc., Cary, NC), and tests of statistical significance were conducted at the 2-tailed alpha level of 0.05.

RESULTS

Description of the hysterectomy and referent cohorts

Between 1980 and 2002, 2,094 women underwent hysterectomy with ovarian conservation for a benign indication. A total of 529 women (25.3%) were age 18 to 35 years at the time of hysterectomy, 1,294 (61.8%) were 36 to 50 years, and 271 (12.9%) were older than 50 years (Supplemental Digital Content 2, http://links.lww.com/MENO/A467). The median age at index date was 40.0 years (interquartile range [IQR] 35.0-44.0). Indications for hysterectomy with ovarian conservation included uterine leiomyomas (n=827, 39.5%), prolapse (n=425, 20.3%), menstrual disorders (n=534, 25.5%; including heavy and irregular menstrual bleeding), and other noncancer indications (n=308, 14.7%). Vaginal hysterectomy was performed in 1,709 women (81.6%).

The median length of capture in the records-linkage system before the index date was 22.5 years (IQR 13.7-32.2) for women with hysterectomy and 19.3 (IQR 8.2-27.0) for referent women. The median length of follow-up after the index date was 21.9 years (IQR 14.2-28.7) for both cohorts combined, 22.5 years (IQR 15.2-28.8) for women with hysterectomy, and 21.3 years (IQR 13.7-28.6) for referent women. Therefore, the median age at the end of follow-up was 62.0 years (IQR 55.0-71.0) for both cohorts combined, 62.0 years (IQR 55.0-72.0) for women with hysterectomy, and 62.0 years (IQR 54.0-71.0) for referent women. Overall, the median density of medical contacts during follow-up was 7.3 per year (IQR 4.3-11.4) for the women with hysterectomy and 6.2 per year (IQR 3.6-9.9) for referent women (excluding contacts in the first 6 mo after the index date). When we truncated the follow-up at the first diagnosis of de novo depression, the median length of follow-up and the median density of contacts were, however, virtually identical for women with or without hysterectomy. The same pattern was observed for de novo anxiety (data not shown). A total of 293 women (14.0%) died in the hysterectomy cohort and 306 (14.6%) in the referent cohort.

Conditions present at baseline and adjustments

At baseline (index date), women in the hysterectomy group were more likely to have previous diagnoses of depression, anxiety, hyperlipidemia, obesity, asthma, and chronic obstructive pulmonary disease compared with referent women (Supplemental Digital Content 1, http://links.lww.com/MENO/A466). Women who underwent hysterectomy also had fewer years of education and higher gravidity and parity at baseline compared with the referent group (Supplemental Digital Content 2, http://links.lww.com/MENO/A467). These differences were most pronounced

for the youngest women. The two overall cohorts were not highly imbalanced on baseline characteristics before the adjustments using inverse probability weights (each standardized difference of means was <25% of the SD), and the adjustments improved the balance successfully (each standardized difference of means was <5% of the SD after weighting). The range of the weights used in the overall analysis was 0.6 to 2.5 for the women who underwent hysterectomy and 0.6 to 2.8 for the referent women.

Results of overall analyses

Supplemental Digital Content 3 (http://links.lww.com/MENO/A468) shows the results of univariable analyses for the effect of the major potential confounding variables on the mental health conditions. Tables 1 and 2 show the results of our cohort analyses overall and in strata by age at hysterectomy and by indication. Among women without anxiety or depression at the index date, those who underwent hysterectomy with ovarian conservation experienced a higher risk of de novo anxiety or depression compared with referent women. The incidence curves started to diverge approximately 2.5 years after the index date for depression and 7.5 years for anxiety (Fig. 1). The risk of depression was increased overall (adjusted HR 1.26; 95% CI, 1.12-1.41; Table 1), with a 6.6% ARI at 30 years compared with referent women (Table 3). The risk of anxiety was increased overall (adjusted HR 1.22; 95% CI, 1.08-1.38; Table 1), with a 4.7% ARI at 30 years compared with referent women (Table 3). By contrast, the risks of substance abuse disorders, dementia, and schizophrenia were not significantly increased in women who underwent hysterectomy with ovarian conservation (Table 1).

Results of stratified analyses

The increased risks of de novo depression and anxiety were more pronounced for women who underwent hysterectomy at age 18 to 35 years (Fig. 2). In this younger age group, the risk of depression was increased nearly 50% (adjusted HR 1.47; 95% CI, 1.17-1.86; Table 1), with a 12% ARI at 30 years compared with referent women (Table 3). The risk of anxiety was increased 45% (adjusted HR 1.45; 95% CI, 1.12-1.88; Table 1), with a 10.1% ARI at 30 years compared with referent women (Table 3). The formal tests for interactions across the age strata were statistically significant for depression but not for the other mental health conditions (Table 1, footnote *b*).

The risk of depression was increased significantly in women who underwent hysterectomy for menstrual disorders (adjusted HR 1.30; 95% CI, 1.03-1.63; Table 2) with a 7.4% ARI at 30 years compared with referent women (Table 3), but not for leiomyomas or prolapse. The risks of anxiety, substance abuse disorders, dementia, or schizophrenia did not differ by indication for the hysterectomy (Table 2). The formal tests of interaction by surgical indication were not statistically significant for any of the mental health conditions (Table 2, footnote *c*).

TABLE 1. *Cumulative incidence of mental health conditions overall and in strata by age at hysterectomy with ovarian conservation*

	Hysterectomy			Referent women			Unadjusted models[a]		Adjusted models[b]	
Condition	*N* at risk	Person-years	*N* of events	*N* at risk	Person-years	*N* of events	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Overall										
Depression	1,872	32,540	636	1,950	33,418	506	1.29 (1.15-1.44)	<0.001	1.26 (1.12-1.41)	<0.001
Anxiety	1,941	35,279	554	1,992	35,252	423	1.31 (1.16-1.48)	<0.001	1.22 (1.08-1.38)	0.001
Substance abuse disorders	2,054	43,065	104	2,069	40,905	65	1.51 (1.11-2.04)	0.008	1.35 (0.99-1.85)	0.06
Dementia	2,089	44,221	143	2,091	41,396	132	0.98 (0.78-1.24)	0.87	0.94 (0.74-1.19)	0.59
Schizophrenia and psychosis	2,087	44,356	51	2,082	41,447	47	0.99 (0.67-1.46)	0.94	0.93 (0.62-1.39)	0.73
Age 18-35 y										
Depression	483	7,969	189	511	8,512	130	1.54 (1.23-1.92)	<0.001	1.47 (1.17-1.86)	0.001
Anxiety	494	8,651	168	518	9,084	106	1.67 (1.31-2.11)	<0.001	1.45 (1.12-1.88)	0.005
Substance abuse disorders	520	10,820	41	523	10,201	22	1.74 (1.05-2.90)	0.03	1.27 (0.70-2.29)	0.44
Dementia	529	11,363	15	529	10,487	12	1.24 (0.59-2.58)	0.57	0.66 (0.29-1.53)	0.33
Schizophrenia and psychosis	528	11,397	3	529	10,526	4	0.68 (0.15-3.03)	0.61	0.73 (0.15-3.50)	0.69
Age 36-50 y										
Depression	1,140	20,467	377	1,190	21,095	304	1.28 (1.10-1.48)	0.001	1.25 (1.07-1.45)	0.004
Anxiety	1,192	22,253	332	1,225	22,213	278	1.19 (1.02-1.39)	0.03	1.11 (0.94-1.30)	0.21
Substance abuse disorders	1,265	27,234	53	1,279	26,143	31	1.64 (1.06-2.54)	0.03	1.43 (0.90-2.25)	0.13
Dementia	1,294	28,068	51	1,293	26,583	34	1.44 (0.94-2.22)	0.09	1.37 (0.89-2.12)	0.15
Schizophrenia and psychosis	1,290	28,003	27	1,288	26,486	17	1.52 (0.84-2.74)	0.17	1.34 (0.74-2.45)	0.33
Age >50 y										
Depression	249	4,104	70	249	3,812	72	0.90 (0.65-1.24)	0.51	0.91 (0.65-1.28)	0.59
Anxiety	255	4,375	54	249	3,954	39	1.22 (0.82-1.82)	0.33	1.21 (0.80-1.85)	0.37
Substance abuse disorders	269	5,012	10	267	4,561	12	0.74 (0.33-1.65)	0.46	0.86 (0.37-1.98)	0.72
Dementia	266	4,790	77	269	4,326	86	0.77 (0.57-1.04)	0.08	0.81 (0.59-1.10)	0.18
Schizophrenia and psychosis	269	4,956	21	265	4,435	26	0.69 (0.39-1.22)	0.21	0.71 (0.39-1.28)	0.25

[a]Hazard ratios calculated using Cox proportional hazards models with age as the time scale.
[b]Hazard ratios calculated using Cox proportional hazards models with age as the time scale and adjusted using inverse probability weights derived from a logistic regression model including all 20 chronic conditions present at baseline (index date), years of education (≤12, 13-16, >16, unknown), race (white vs nonwhite), and age and calendar year at baseline (continuous). These adjustments were performed separately in each stratum to maximize the balance at baseline. Overall interactions by age (18-35, 36-50, >50 y) were assessed for each mental health condition: depression $P=0.002$, anxiety $P=0.28$, substance abuse disorders $P=0.20$, dementia $P=0.81$, and schizophrenia and psychosis $P=0.68$.

TABLE 2. *Cumulative incidence of mental health conditions in strata by hysterectomy indication*[a]

	Hysterectomy			Referent women			Unadjusted models[b]		Adjusted models[c]	
Condition	*N* at risk	Person-years	*N* of events	*N* at risk	Person-years	*N* of events	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Leiomyomas										
Depression	726	12,369	223	759	12,449	198	1.13 (0.94-1.37)	0.19	1.12 (0.92-1.35)	0.25
Anxiety	762	13,315	199	772	12,989	161	1.20 (0.98-1.48)	0.07	1.14 (0.93-1.40)	0.22
Substance abuse disorders	807	16,179	33	817	15,468	21	1.50 (0.88-2.57)	0.14	1.36 (0.78-2.36)	0.27
Dementia	824	16,613	59	825	15,628	48	1.14 (0.79-1.65)	0.48	1.11 (0.77-1.61)	0.57
Schizophrenia and psychosis	824	16,663	23	823	15,639	17	1.29 (0.69-2.39)	0.43	1.21 (0.64-2.28)	0.56
Menstrual disorders										
Depression	482	8,585	174	500	8,901	136	1.31 (1.05-1.64)	0.02	1.30 (1.03-1.63)	0.03
Anxiety	497	9,277	156	510	9,504	112	1.43 (1.12-1.81)	0.003	1.24 (0.97-1.60)	0.09
Substance abuse disorders	524	11,367	33	528	11,036	20	1.54 (0.89-2.68)	0.12	1.19 (0.64-2.21)	0.57
Dementia	534	11,849	21	533	11,247	23	0.90 (0.50-1.61)	0.72	0.71 (0.37-1.35)	0.30
Schizophrenia and psychosis	532	11,790	13	532	11,272	7	1.82 (0.73-4.55)	0.20	1.28 (0.46-3.52)	0.64
Uterine prolapse										
Depression	387	6,903	128	403	6,966	105	1.23 (0.96-1.59)	0.11	1.20 (0.92-1.56)	0.17
Anxiety	398	7,380	119	411	7,301	87	1.35 (1.04-1.76)	0.03	1.20 (0.92-1.57)	0.18
Substance abuse disorders	421	9,111	22	417	8,258	12	1.64 (0.81-3.31)	0.17	1.58 (0.77-3.24)	0.22
Dementia	423	9,173	50	425	8,310	46	0.89 (0.60-1.33)	0.58	0.91 (0.60-1.37)	0.65
Schizophrenia and psychosis	423	9,272	13	421	8,323	18	0.62 (0.30-1.25)	0.18	0.55 (0.27-1.13)	0.10

[a]A total of 308 women with other noncancer indications for hysterectomy were not included in the stratified analyses.
[b]Hazard ratios calculated using Cox proportional hazards models with age as the time scale.
[c]Hazard ratios calculated using Cox proportional hazards models with age as the time scale and adjusted using inverse probability weights derived from a logistic regression model including all 20 chronic conditions present at baseline (index date), years of education ($\leq$12, 13-16, $>$16, unknown), race (white vs nonwhite), and age and calendar year at baseline (continuous). These adjustments were performed separately in each stratum to maximize the balance at baseline. Overall interactions by indication (leiomyomas, menstrual disorders, uterine prolapse) were assessed for each mental health condition: depression P=0.12, anxiety P=0.23, substance abuse disorders P=0.55, dementia P=0.21, and schizophrenia and psychosis P=0.44.

Results of sensitivity analyses

In the first set of sensitivity analyses excluding women with any of the 20 preexisting chronic conditions at the index date, the risks of depression and anxiety were still increased in the hysterectomy with ovarian conservation group (n=1,204) compared with referent women (n=1,433; Supplemental Digital Content 4, http://links.lww.com/MENO/A469). Results stratified by age were similar to the results in the full cohort, with some of the more extreme risks found in the younger age stratum (1.5-fold increased risk for depression and 1.7-fold for anxiety, Supplemental Digital Content 4, http://links.lww.com/MENO/A469). Hysterectomy for menstrual disorders was associated with a 1.4-fold increase of both depression and anxiety (Supplemental Digital Content 4, http://links.lww.com/MENO/A469), but there was no association with other mental disorders. The second set of sensitivity analyses censoring women at the time of subsequent oophorectomy (both women with hysterectomy and referent women) or hysterectomy (referent women) showed results similar to the primary analyses (data not shown). Results were also similar to the primary analyses in the third set of sensitivity analyses including number of children as an adjustment variable, and in the fourth set of sensitivity analyses including the number of medical contacts during follow-up (data not shown).

DISCUSSION

Women who underwent hysterectomy with ovarian conservation had a higher long-term risk of de novo diagnosis of depression and anxiety compared with referent women who did not have a hysterectomy at index date. The HRs were significantly higher for women who had hysterectomy at a young age with ARIs between 10% and 12% at 30 years. By contrast, the risks of substance abuse disorders, dementia, and schizophrenia were not significantly increased.

Comparison with other studies

Our findings are consistent with findings from other cohort studies and national databases that assessed the long-term risks of anxiety and depression both before and after hysterectomy.[20-22] Depressive symptoms and anxiety in the immediate preoperative period may be caused by the gynecologic condition or by the concerns about the surgery itself. Vandyk et al attempted to distinguish longer term anxiety (persistent or chronic anxiety) from shorter term anxiety, and found that women who had longer term anxiety were more likely to develop depressive symptoms within 6 months after the surgery.[40] Our study focused on long-term anxiety and depression occurring both before and after hysterectomy. To avoid confusion with the short term anxiety or depressed mood that may have been associated with the gynecological condition or surgery itself, we obtained depression and anxiety diagnoses that women received at any time before or after the index date from their medical records.

Contrary to some previous studies, we did not observe a significantly increased risk of dementia after hysterectomy.[8,24] Our power to detect a difference in the risk of dementia in these relatively young cohorts was, however, limited. The overall age of the end of follow-up was approximately 62 years. A longer follow-up of these cohorts is needed to further address this association. Hysterectomy with ovarian conservation was associated with the risk of substance abuse

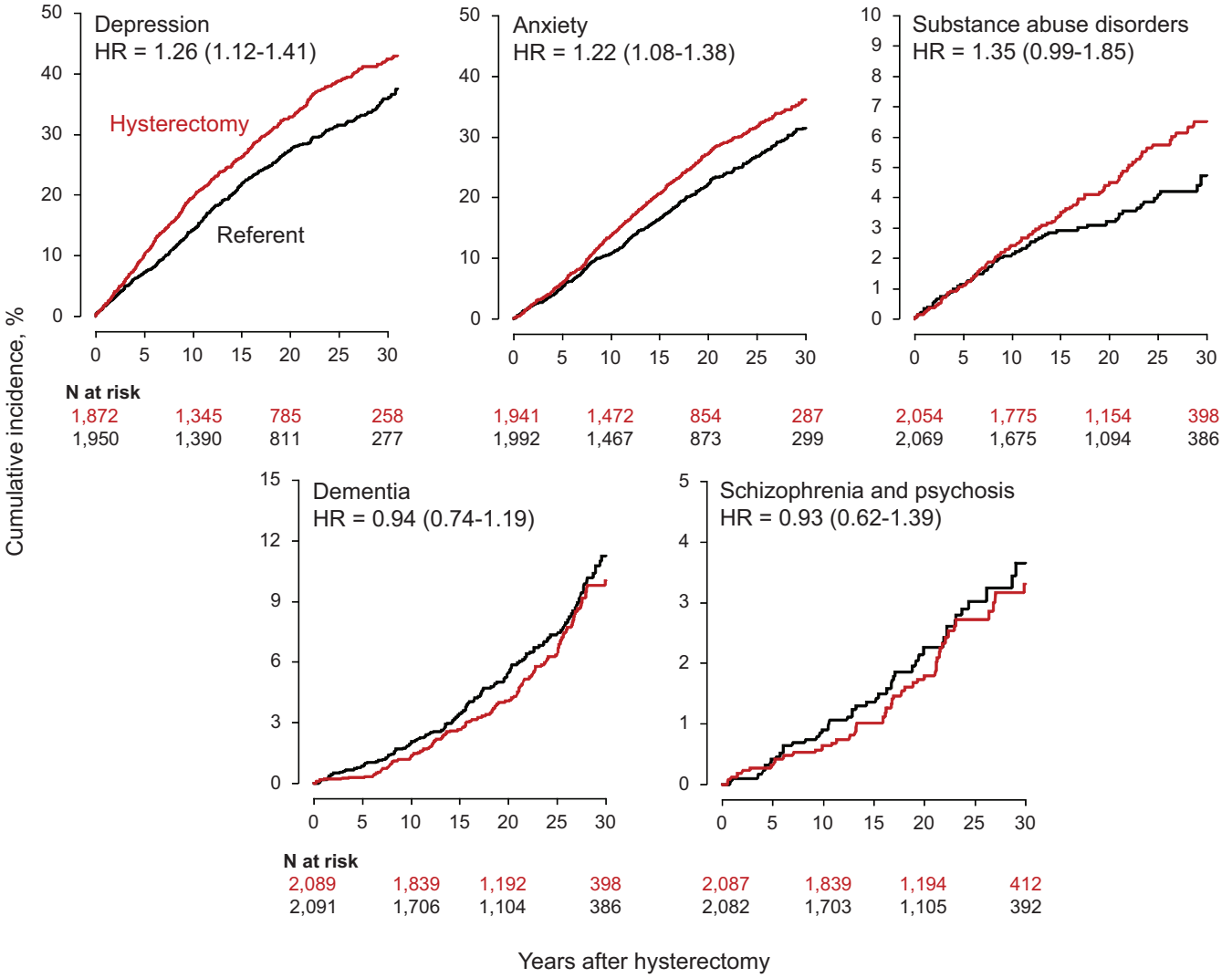

FIG. 1. Cumulative incidence curves for mental health conditions in women who underwent hysterectomy with ovarian conservation compared with referent women (all ages). The curves were adjusted using inverse probability weights derived from a logistic regression model including all 20 chronic conditions present at baseline, years of education (≤12, 13-16, >16, unknown), race (white vs nonwhite), and age and calendar year at baseline (continuous). The number of women at risk varied across conditions because we excluded women with the specific condition on the index date. Note the different scales used for the *y*-axis to better show differences.

disorders in the unadjusted analyses; however, the statistical significance was lost in adjusted analyses. Because the hysterectomies included in the study were performed before 2002, they preceded the recent trend in overutilization of opioid treatments after surgeries.[27-29]

Possible interpretations of the findings

The association between hysterectomy with ovarian conservation and depression or anxiety may be caused by a cause–effect inversion. It is possible that some women did suffer from anxiety, depression, or other mental health conditions, which contributed to the decision to undergo a hysterectomy (cause–effect inversion). Indeed, we reported in this study that depression and anxiety diagnosed before the index date were more common in women who underwent hysterectomy (Supplemental Digital Content 1, http://links.lww.com/MENO/A466). Our primary analyses, however, excluded women affected by depression at index date when considering de novo depression as the outcome. The same was done when considering de novo anxiety as the outcome. Finally, in our first set of sensitivity analyses, we removed all women with any of the 20 chronic conditions recommended by the DHHS, thus eliminating the possible overlap or misclassification of anxiety, depression, or other mental disorders diagnosed before the index date (Supplemental Digital Content 4, http://links.lww.com/MENO/A469). Therefore, our findings in the majority of women do not seem to be explained by a cause–effect inversion.

Some inherited genetic variants or epigenetic modifications, or some early life events or behaviors may have

TABLE 3. *Absolute risk of de novo mental health conditions overall and in strata by age at hysterectomy and by indication*

Condition	Hysterectomy		Referent women		Absolute risk difference, %[b]	
	Absolute risk at 15 y, %[a] (95% CI)	Absolute risk at 30 y, %[a] (95% CI)	Absolute risk at 15 y, %[a] (95% CI)	Absolute risk at 30 y, %[a] (95% CI)	15 y	30 y
Overall						
Depression	26.2% (24.2-28.4)	42.4% (39.7-45.3)	21.8% (19.8-23.9)	35.8% (33.1-38.8)	4.4%	6.6%
Anxiety	20.6% (18.8-22.6)	36.2% (33.5-39.1)	16.4% (14.7-18.3)	31.5% (28.8-34.4)	4.2%	4.7%
Substance abuse disorders	3.5% (2.8-4.5)	6.5% (5.3-8.0)	2.9% (2.2-3.8)	4.7% (3.6-6.2)	0.6%	1.8%
Dementia	2.7% (2.0-3.5)	10.5% (8.7-12.7)	3.5% (2.7-4.4)	11.2% (9.4-13.4)	−0.8%	−0.7%
Schizophrenia and psychosis	1.0% (0.6-1.6)	3.3% (2.4-4.5)	1.4% (0.9-2.0)	3.7% (2.7-5.0)	−0.4%	−0.4%
Age 18-35 y						
Depression	31.8% (27.5-36.6)	47.5% (42.1-53.2)	22.0% (18.1-26.6)	35.5% (30.2-41.4)	9.8%	12.0%
Anxiety	25.0% (21.0-29.5)	43.1% (37.6-49.1)	18.3% (14.8-22.6)	33.0% (27.8-38.9)	6.7%	10.1%
Substance abuse disorders	5.8% (3.9-8.5)	9.9% (7.1-13.6)	5.2% (3.3-7.9)	7.9% (5.3-11.7)	0.6%	2.0%
Dementia	0.3% (0.1-1.7)	4.8% (2.6-8.7)	1.1% (0.4-2.8)	7.2% (4.3-11.9)	−0.8%	−2.4%
Schizophrenia and psychosis	0.0% (0.0-0.0)	1.1% (0.3-3.4)	0.9% (0.3-2.6)	0.9% (0.3-2.6)	−0.9%	0.2%
Age 36-50 y						
Depression	25.2% (22.7-28.0)	40.5% (37.0-44.1)	21.6% (19.2-24.3)	34.2% (30.8-37.9)	3.6%	6.3%
Anxiety	20.2% (18.0-22.8)	34.0% (30.7-37.5)	17.3% (15.1-19.8)	31.8% (28.5-35.3)	2.9%	2.2%
Substance abuse disorders	2.9% (2.0-4.0)	5.1% (3.8-6.8)	2.4% (1.7-3.6)	3.3% (2.4-4.7)	0.5%	1.8%
Dementia	1.0% (0.6-1.8)	6.4% (4.5-8.9)	1.0% (0.5-1.8)	5.4% (3.7-7.8)	0.0%	1.0%
Schizophrenia and psychosis	0.5% (0.2-1.2)	2.6% (1.7-4.2)	0.4% (0.1-1.0)	2.3% (1.3-3.9)	0.1%	0.3%
Age >50 y						
Depression	20.5% (15.5-26.7)	40.4% (32.8-49.2)	22.2% (16.9-28.9)	48.5% (38.5-59.5)	−1.7%	−8.1%
Anxiety	14.0% (9.8-19.6)	34.0% (26.0-43.6)	11.6% (7.8-17.0)	32.6% (22.5-45.8)	2.4%	1.4%
Substance abuse disorders	2.0% (0.8-5.0)	7.9% (3.8-15.8)	3.1% (1.4-6.6)	8.3% (3.3-20.2)	−1.1%	−0.4%
Dementia	14.5% (10.4-20.0)	41.3% (33.4-50.2)	19.3% (14.5-25.4)	53.3% (43.7-63.5)	−4.8%	−12.0%
Schizophrenia and psychosis	5.4% (3.0-9.5)	12.1% (7.6-18.8)	7.3% (4.5-12.0)	18.7% (12.0-28.4)	−1.9%	−6.6%
Leiomyomas[c]						
Depression	25.0% (21.9-28.5)	38.9% (34.5-43.6)	23.1% (20.0-26.6)	36.4% (31.9-41.3)	1.9%	2.5%
Anxiety	20.7% (17.8-24.0)	33.0% (28.9-37.6)	17.1% (14.4-20.3)	31.2% (26.9-36.0)	3.6%	1.8%
Substance abuse disorders	2.8% (1.8-4.3)	6.3% (4.3-9.3)	2.6% (1.7-4.1)	3.5% (2.2-5.4)	0.2%	2.8%
Dementia	3.5% (2.4-5.1)	11.3% (8.4-15.1)	3.4% (2.2-5.1)	11.1% (8.0-15.3)	0.1%	0.2%
Schizophrenia and psychosis	1.2% (0.6-2.3)	3.9% (2.4-6.4)	1.6% (0.9-2.8)	2.7% (1.6-4.5)	−0.4%	1.2%
Menstrual disorders[c]						
Depression	27.6% (23.6-32.1)	43.1% (38.1-48.6)	24.1% (20.2-28.6)	35.7% (30.5-41.4)	3.5%	7.4%
Anxiety	22.4% (18.7-26.7)	37.9% (32.7-43.7)	18.3% (14.9-22.3)	33.3% (28.2-39.2)	4.1%	4.6%
Substance abuse disorders	4.9% (3.2-7.2)	7.0% (4.9-10.0)	3.7% (2.3-6.0)	7.0% (4.5-10.9)	1.2%	0.0%
Dementia	1.6% (0.8-3.4)	6.2% (3.9-9.8)	2.5% (1.4-4.6)	9.3% (6.2-13.9)	−0.9%	−3.1%
Schizophrenia and psychosis	1.2% (0.5-2.7)	3.1% (1.7-5.6)	0.4% (0.1-1.8)	3.8% (1.9-7.4)	0.8%	−0.7%
Uterine prolapse[c]						
Depression	25.2% (20.9-30.1)	40.9% (35.1-47.4)	20.9% (16.9-25.8)	39.4% (32.7-47.0)	4.3%	1.5%
Anxiety	19.6% (15.7-24.2)	36.2% (30.3-42.9)	14.9% (11.4-19.2)	34.9% (28.5-42.4)	4.7%	1.3%
Substance abuse disorders	2.9% (1.6-5.3)	6.9% (4.2-11.2)	2.6% (1.4-5.0)	4.3% (2.1-8.6)	0.3%	2.6%
Dementia	3.8% (2.3-6.3)	18.6% (13.3-25.5)	5.4% (3.4-8.4)	18.0% (13.2-24.2)	−1.6%	0.6%
Schizophrenia and psychosis	0.7% (0.2-2.4)	4.0% (2.0-7.7)	2.3% (1.2-4.7)	6.7% (4.0-11.3)	−1.6%	−2.7%

[a]Absolute cumulative risk at 15 and 30 years after index date calculated using the Kaplan–Meier method. The estimates were adjusted using inverse probability weights derived from a logistic regression model including all 20 chronic conditions present at baseline (index date), years of education (≤12, 13-16, >16, unknown), race (white vs nonwhite), and age and calendar year at baseline (continuous). These adjustments were performed separately in each stratum to maximize the balance at baseline.
[b]Risk difference calculated as the absolute risk estimate for women who underwent hysterectomy minus the absolute risk estimate for the referent women.
[c]A total of 308 women with other noncancer indications for hysterectomy were not included in the analyses stratified by indication.

predisposed women to manifest gynecological symptoms that prompted the hysterectomy, and independently predisposed the women to develop depression or anxiety after hysterectomy.[41,42] In this scenario, the association would be explained by confounding by indication. In support of a confounding by indication hypothesis is the higher risk of depression in the subset of women who underwent hysterectomy for menstrual disorders compared with leiomyomas or uterine prolapse (Table 2). None of the interactions by indication were, however, statistically significant.

Strong evidence against confounding by indication is provided by our sensitivity analyses restricted to the majority of women who did not have any of the 20 chronic conditions at baseline. In these sensitivity analyses, the HR was higher for menstrual disorders, but was increased also for leiomyomas and uterine prolapse. The formal test for interaction by indication was not significant (Supplemental Digital Content 4, http://links.lww.com/MENO/A469). Also, against a confounding hypothesis is the significant trend of greater HRs with younger age at hysterectomy. This trend is similar to the trend observed for risk of depression, anxiety, and dementia after bilateral oophorectomy, in which there is a direct endocrine effect of the surgery.[3,4] If our findings were due to confounding, they would not be expected to change with age.

Although our study, like any other observational study, cannot determine causality, the higher incidence of depression and anxiety for women who had a hysterectomy at younger age could indicate an impact of the surgery on ovarian function. Some studies have shown that ovarian function

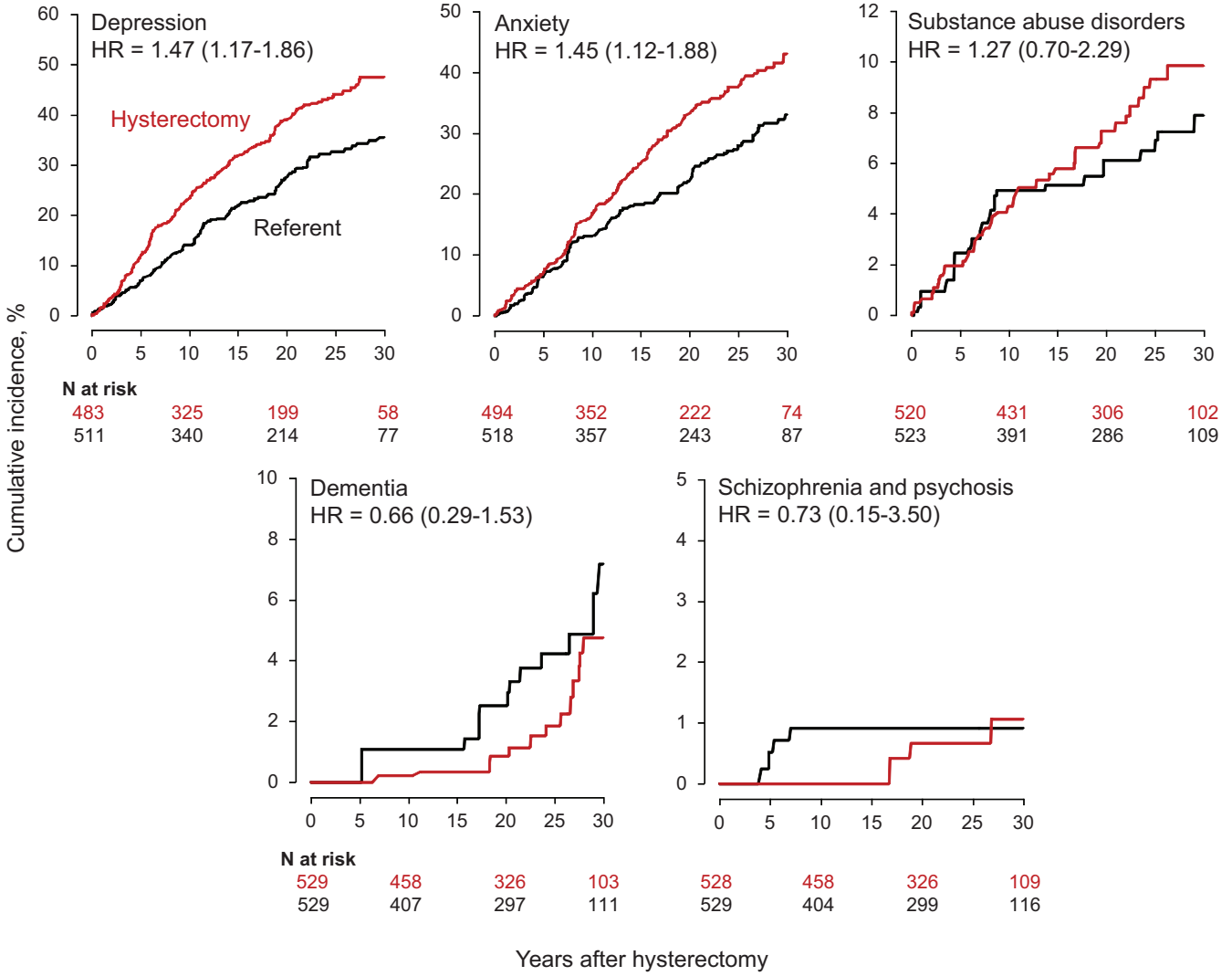

FIG. 2. Cumulative incidence curves for mental health conditions in women who underwent hysterectomy with ovarian conservation at age 18 to 35 years compared with referent women. The curves were adjusted using inverse probability weights derived from a logistic regression model restricted to this age stratum, and including all 20 chronic conditions present at baseline, years of education (≤12, 13-16, >16, unknown), race (white vs nonwhite), and age and calendar year at baseline (continuous). The number of women at risk varied across conditions because we excluded women with the specific condition on the index date. Note the different scales used for the *y*-axis to better show differences.

may decline after hysterectomy.[5,9,10] There is speculation that the decline in ovarian function is mediated either by a decrease in collateral blood flow between the uterus and the ovaries, or by a paracrine effect of the uterus on the ovaries.[5,11-13] It is also possible that hysterectomy affects brain aging and endocrine aging through some yet unknown mechanisms that are not mediated by an ovarian effect.[12-14]

Higher parity has been associated with hysterectomy, with women bearing more than three children reporting higher hysterectomy rates than women with less children and nulliparous women.[43] In our cohort, women who underwent hysterectomy had higher parity, and this difference was more pronounced in women who had hysterectomy at age 18 to 35 years (Supplemental Digital Content 2, http://links.lww.com/MENO/A467). Only 8% of women who underwent hysterectomy at age 18 to 35 were nulliparous, and we do not know whether they desired future fertility. Facing the decision to have a hysterectomy before the end of childbearing could increase depression for some women. Adjustment for parity, however, did not modify our results.

We have controlled or removed the possible confounders and biases to the extent possible; however, the observed associations may be explained by some residual or yet unknown confounding variable. In addition, because we considered several outcome conditions, and conducted stratified analyses and sensitivity analyses, some of the significant findings may be due to chance. If we hypothesize that all the biases and confounding effects have been removed, that the women have a 30-year follow-up, and that the associations are attributable to hysterectomy, we can estimate the number needed to harm (NNH; defined as the inverse of ARI). In women who underwent hysterectomy, the NNH was 15 for

depression and 21 for anxiety. NNH was even lower for women who underwent hysterectomy at age 18 to 35 years: 8 for depression and 10 for anxiety.

Strengths and limitations

Important strengths of this study include the large sample size of women with direct medical record documentation of hysterectomy and bilateral ovarian conservation (n=2,094). The comprehensive nature of the medical records-linkage system also allowed for a significant amount of information to be collected, with no reliance on self-report of mental health diagnoses, hysterectomy, or oophorectomy. In addition, the longitudinal nature of REP allowed us to assess the chronic conditions present at baseline and provided a long follow-up period. We used inverse probability weights to balance the hysterectomy 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, hysterectomy) cannot be ethically or feasibly randomized.[44,45]

There were some limitations to the study. First, the REP indices, although comprehensive, may have missed some diagnoses. This underdiagnosis is particularly important for diagnoses such as mental health disorders that carry a social stigma. Second, electronic records are subject to incorrect coding in daily practice, and overdiagnosis may also have occurred. To address the chance of overdiagnosis, however, two diagnostic codes, separated by more than 30 days (or more than 1 y) were required. Third, several confounders including marital status, desire for future children, alcohol consumption, occupation, physical activity, and income level were not available from electronic abstraction and could not be included in our analyses. Our adjusted models included education, race, age, and calendar year at the index date, and 20 preexisting chronic conditions. If any of the unmeasured potential confounders were associated with the adjustment variables, their effect may have been indirectly controlled. Fourth, despite the long follow-up of the two cohorts (median of approximately 20 y), the women were relatively young at the end of follow-up (median of approximately 62 y); therefore, the study was underpowered to detect dementia and schizophrenia or psychosis. Finally, our findings could be, in part, explained by a surveillance bias because women who underwent hysterectomy may have had more intense contacts with healthcare providers after the hysterectomy.[46] When we truncated the follow-up at the first diagnosis of depression or anxiety, the length of follow-up and the density of medical contacts were, however, virtually identical in women with or without hysterectomy.

CONCLUSIONS

Hysterectomy, even with conservation of both ovaries, is associated with an increased risk of long-term mental health conditions, primarily anxiety and depression. In a subset of women, these associations may be due to a confounding by indication in which preexisting depression and anxiety or preexisting risk factors may have played a role. There is, however, growing evidence that in another subset of women, hysterectomy may have deleterious effects on brain aging and endocrine aging. These effects may be mediated by an effect of hysterectomy on the ovaries, or the uterus may have direct effects on the brain and on other organs or systems that are not mediated by the ovaries.[5,11-14] Further research is needed on the possible direct effects of hysterectomy on mental health and on instruments to screen women before hysterectomy to assess long-term risk.

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