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Hysterectomy, Oophorectomy and Risk of Dementia: A Nationwide Historical Cohort Study

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Key Words
Dementia · Cohort study · Risk factors · Hysterectomy · Oophorectomy

Abstract
Background: This study aimed to determine whether there is an association between hysterectomy and dementia. ***Methods:*** All female Danish residents born before 1966, alive on their 40th birthday and without a dementia diagnosis prior to 1977 (n = 2,313,388) were followed from January 1, 1977, or the age of 40, whichever came later, until dementia diagnosis, death, emigration or December 31, 2006, whichever came first. The relative risks (RR) for developing dementia in women with hysterectomy/oophorectomy compared to referent women were calculated. ***Results:*** Overall, hysterectomy did not increase the risk of dementia. When stratified by age at dementia diagnosis, hysterectomy was associated with an increased risk for early-onset dementia before the age of 50: hysterectomy alone (RR = 1.38, 95% confidence interval (CI) = 1.07–1.78), with unilateral oophorectomy (RR = 2.10, 95% CI = 1.28–3.45), with bilateral oophorectomy (RR = 2.33, 95% CI = 1.44–3.77). The younger the age at hysterectomy/oophorectomy, the greater was the risk. ***Conclusions:*** Although statistically significant, the association between premenopausal hysterectomy and early-onset dementia is uncertain due to study limitations. Premenopausal bilateral oophorectomy is associated with a higher risk, suggesting a dose effect of premature estrogen deficiency on dementia. The age-dependent effect suggests that the younger brain is probably more vulnerable to estrogen deficiency.

Introduction

Hysterectomy ranks among the most frequently performed operations in developed countries [1]. The lifetime risk of hysterectomy is 25% in the USA and 10% in Denmark [2]. Around 80% of the operations are performed due to benign indications, mainly uterine leiomyomas, dysfunctional uterine bleeding and endometriosis, to improve quality of life [2]. Although the risk of peri- and postoperative complications is high (up to 30%), the mortality rate is up to 1/1,000, and alternative treatments with a lower risk of complications have become available [2], hysterectomy rates have not decreased in the past decade [1, 3]. Bilateral oophorectomy, which is usually performed together with hysterectomy, can be due to a benign ovarian disease or be performed as prophylaxis

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against ovarian cancer [4]. The rates of prophylactic bilateral oophorectomy have increased over time [4].

Hysterectomy without oophorectomy has been shown to accelerate menopause by 3–4 years, presumably because the blood supply to the ovaries is disturbed, leading to loss of ovarian reserve [5]. This premature withdrawal of estrogen can have a deleterious effect on cognitive functions. Women with premenopausal bilateral oophorectomy (surgical menopause) have been shown to suffer cognitive decline after the abrupt onset of menopause, and that hormone replacement therapy (HRT) has a protective effect on their cognitive functions [6, 7]. Although biologically plausible, hysterectomy as a potential risk factor for dementia is an unexplored area. One small longitudinal study found that among homozygous twins, those with hysterectomies were more likely to develop Alzheimer disease (AD), and they had the onset of symptoms at an earlier age [8]. Ovarian status was not mentioned in this study. A large cross-sectional study found no effect of hysterectomy on cognitive function in late life [9].

In this register-based historical cohort study, we tested the hypothesis that hysterectomy is associated with an increased risk for dementia.

Methods

The National Register

The Psychiatric Central Research Register (PCRR) contains nationwide data about all contacts to psychiatric hospital departments since 1969 and the National Patient Register (NPR) all contacts to somatic hospital departments since 1977 [10, 11]. Diagnoses are registered in the PCRR and NPR by WHO International Classification of Diseases (ICD) codes. ICD-8 was used from 1970 to 1993 and ICD-10 since 1994 [12, 13]. Operations were registered in the NPR by Danish Operations and Treatment Classification codes based on the ICD-8 Procedure Coding System from 1977 to 1995 [14]. Since 1996, operations are registered by the Danish version of the Nordic Medico Statistical Committee Classification of Surgical Procedures [15].

The Danish Civil Registration System (DCRS) was established in 1968 [16]. It assigns unique national identification numbers to all Danish residents and contains their individual demographic data such as age, gender, emigration and death. The same identification numbers are used in all the Danish national registers, allowing accurate and efficient data linkage between the registers.

Study Sample

The participants were all female Danish residents registered in the DCRS [16], born before 1966, and alive on their 40th birthdays (n = 2,324,171). The women registered with a dementia diagnosis from 1969 to 1977 were excluded (n = 10,783, fig. 1). There was no nonparticipation. The exposure group consisted of women registered with hysterectomy or oophorectomy in the NPR from January 1, 1977, to December 31, 2006. Two consecutive unilateral oophorectomies were classified as bilateral oophorectomies. The referent group comprised women who never had a hysterectomy or oophorectomy and women who had hysterectomy or oophorectomy after dementia onset. A validation study looking at a random sample of hysterectomies performed in the period 1977–1981 showed that there was no significant difference between the number of hysterectomies registered in the NPR and the hospital medical records [17]. In general, the validity of operations registered in the NPR is good with 10% registration errors [18]. A recent study looking at all hysterectomies performed on benign indications in April 2004 found a good agreement between the NPR and the medical records with a kappa between 0.4 and 1.0 [19].

Follow-Up

By register linkage between the DCRS, NPR and PCRR, the study population was followed from January 1, 1977, or the age of 40, whichever came later, until the date of dementia onset, date of death, date of emigration or December 31, 2006, whichever came first. Date of dementia onset was defined as the first day of hospital contact where a dementia diagnosis was recorded in the registers for the first time. Outcome was defined by ICD codes for AD, vascular dementia (VaD), frontotemporal dementia (FTD) and dementia without specification [20]. Positive predictive values are 85.8% for a registered diagnosis of dementia syndrome and 81.0% for AD [20]. The NPR and PCRR can capture about 66% of the expected dementia cases in the population [21]. However, 73% of registered dementia diagnoses in the NPR and PCRR are dementia without specification [21], and the validity of other dementia subtypes except AD is poor [20, 22]. As our data showed that the incidence of dementia diagnoses recorded in the registers is extremely low before the age of 40 (0.01/1,000 person-years), the study population was only followed from the age of 40. Study participants were lost to follow-up only when they died (n = 758,956; 32.8% of the study population) or emigrated (n = 27,360; 1.2% of the study population; fig. 1).

Statistical Analysis

The relative risks (RR) for developing dementia in women with hysterectomy compared to referent women were calculated and stratified by age at dementia diagnosis (40–49, 50–59, 60–69, 70–79, 80 years and above), indication for operations (benign vs. malignant), ovarian status (hysterectomy, unilateral oophorectomy, bilateral oophorectomy) and age at hysterectomy (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90 years and above). As a cohort study, we analyzed data with survival analysis techniques, using Poisson regression with the logarithm of the person-years as an offset. The GENMOD procedure in SAS version 9.1 was used. RR were calculated by log likelihood estimation. Wald's 95% confidence intervals (CI) were used. All RR were adjusted for age and calendar period at dementia diagnosis, both in 1-year groups. The likelihood ratio test was used to test for interactions between variables. In additional analyses, all RR were further adjusted for alcoholism and depression diagnoses registered in the NPR and PCRR prior to dementia onset. Due to the limitations of the registers used in this study, it was not possible to control for other confounders such as education, cardiovascular risk factors, HRT and genetic factors.

The Danish Data Protection Agency approved this study.

Table 1. Overall RR for dementia in women with hysterectomy or oophorectomy compared to referent women

Covariate	Women with dementia	Person-years at risk	RR
Hysterectomy			
Yes	3,534	2,237,497	0.91 (0.84–0.98)
No	91,705	36,255,929	1.00 reference
Unilateral oophorectomy			
Yes	766	622,096	0.99 (0.92–1.07)
No	94,473	37,871,330	1.00 reference
Bilateral oophorectomy			
Yes	2,248	719,410	1.07 (1.01–1.14)
No	92,991	37,774,016	1.00 reference
Indications for hysterectomy[1]			
Unknown indication	174	103,361	1.04 (0.88–1.22)
Benign	2,161	1,731,579	1.06 (0.99–1.15)
Malignant	1,199	402,557	1.00 reference
No hysterectomy	91,705	36,255,929	1.00 reference
Total	95,239	38,493,426	

Covariates are not mutually exclusive. RR are mutually adjusted for hysterectomy, unilateral oophorectomy, bilateral oophorectomy and indication for operation. Furthermore, they were adjusted for calendar period and age at dementia diagnosis, both in 1-year groups. 95% CI are indicated in parentheses.

[1] A formal test for interaction between indications for hysterectomy and hysterectomy regarding risk for dementia was not significant (p = 0.28).

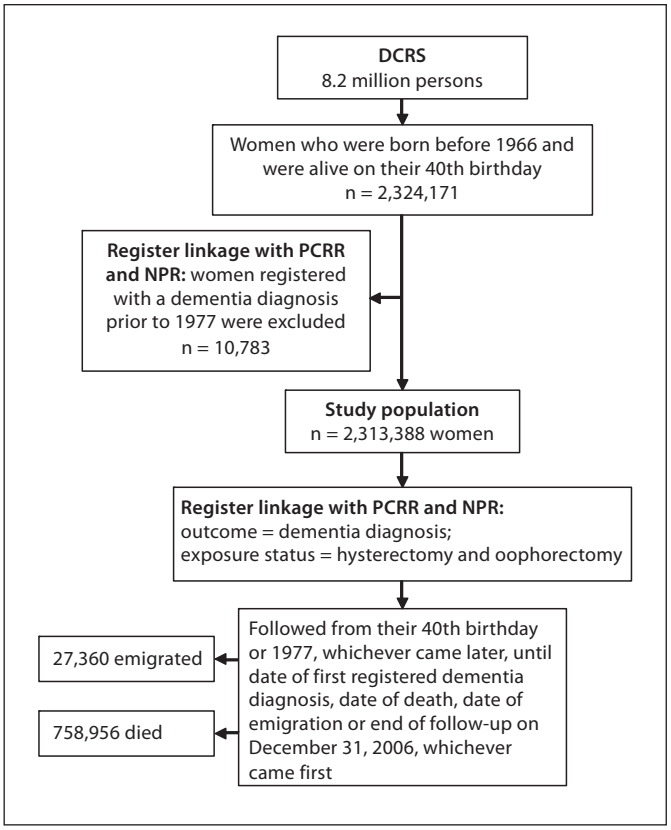

Fig. 1. Flow chart of the study population.

Results

Study Sample

The cohort consisted of 2,313,388 women with 38,493,426 person-years of follow-up. From 1977 to 2006, there were 95,239 incident dementia cases, 176,017 hysterectomies, 71,360 bilateral oophorectomies and 47,152 unilateral oophorectomies. Among the women with hysterectomy, 18,376 (10.4%) also had unilateral oophorectomy and 60,709 (34·5%) had bilateral oophorectomy. The median age for hysterectomy was 47.6 years (25th and 75th percentiles: 42.0 and 56.4), for unilateral oophorectomy 45.0 years (25th and 75th percentiles: 37.9 and 53.3), and for bilateral oophorectomy 57.1 years (25th and 75th percentiles: 49.8 and 66.6).

Risk of Dementia

Overall, women who underwent hysterectomy did not have an increased risk of dementia compared to referent women (table 1). RR stratified by indications for hysterectomy did not show any difference between benign and malignant indications (table 1). When stratified by age at dementia diagnosis, an increased risk for dementia with onset before the age of 50 was seen in women with hysterectomy (RR = 1.58, 95% CI = 1.28–1.95; table 2).

When stratified by ovarian status, an increased risk for early-onset dementia before the age of 50 was still observed among women who had undergone hysterectomy without oophorectomy (table 3). Within the group with dementia onset before the age of 50, there was a trend of increasing risk of dementia with younger age at hysterectomy (table 4). A test for linear trend was significant (p = 0.001, model adjusted for age and calendar year at dementia diagnosis). Since the NPR only started to register operations in 1977, information about hysterectomy and oophorectomy before the age of 50 was missing for numerous women with dementia onset after the age of 60 (table 4).

We took a closer look at the group of the 96 women with hysterectomy and dementia onset before the age of 50 (table 2) in order to find possible explanations for the

Table 2. RR for dementia in women with hysterectomies compared with referent women, stratified by age at dementia diagnosis

Age at dementia diagnosis[1]	Hysterectomy	Person-years	Women with dementia	Incidence rate per 10,000 person-years	RR
40–49 years	yes	583,340	96	1.65 (1.35–2.01)	1.58 (1.28–1.95)
	no	10,377,474	1,012	0.98 (0.92–1.04)	1.00 reference
50–59 years	yes	816,923	259	3.17 (2.81–3.58)	0.98 (0.86–1.11)
	no	8,849,448	2,679	3.03 (2.91–3.14)	1.00 reference
60–69 years	yes	506,591	463	9.14 (8.34–10.01)	0.94 (0.86–1.04)
	no	7,543,145	6,527	8.65 (8.45–8.87)	1.00 reference
70–79 years	yes	241,907	1,185	48.99 (46.27–51.86)	0.96 (0.90–1.02)
	no	5,979,582	27,424	45.86 (45.32–46.41)	1.00 reference
≥80 years	yes	88,736	1,531	172.53 (164.10–181.40)	0.99 (0.91–1.02)
	no	3,506,280	54,063	154.19 (152.90–155.49)	1.00 reference

RR are adjusted for calendar period and age at dementia diagnosis, both in 1-year groups. 95% CI are indicated in parentheses.
[1] A formal test for interaction between age at dementia diagnosis and hysterectomy regarding risk for dementia was significant (p = 0.001).

Table 3. RR for dementia in women with hysterectomies compared with referent women, stratified by age at dementia diagnosis and ovarian status

Ovarian status[1]	Age at dementia diagnosis				
	40–49 years	50–59 years	60–69 years	70–79 years	≥80 years
Hysterectomy and bilateral oophorectomy	2.33 (1.44–3.77)	1.27 (1.01–1.60)	0.96 (0.82–1.11)	1.00 (0.93–1.08)	1.01 (0.91–1.07)
Hysterectomy and unilateral oophorectomy	2.10 (1.28–3.45)	0.88 (0.61–1.26)	0.90 (0.69–1.18)	0.80 (0.64–1.00)	1.06 (0.85–1.32)
Hysterectomy only	1.38 (1.07–1.78)	0.89 (0.76–1.05)	0.94 (0.82–1.07)	0.92 (0.83–1.02)	0.96 (0.87–1.04)
Bilateral oophorectomy only	2.36 (0.76–7.34)	0.75 (0.31–1.80)	1.03 (0.67–1.59)	0.85 (0.68–1.07)	1.08 (0.93–1.25)
Unilateral oophorectomy only	1.18 (0.71–1.96)	1.08 (0.78–1.50)	0.83 (0.62–1.13)	1.14 (0.97–1.33)	0.92 (0.81–1.05)
Referent group	1	1	1	1	1

RR are adjusted for calendar period and age at dementia diagnosis, both in 1-year groups. 95% CI are indicated in parentheses.
[1] A formal test for interaction between ovarian status and age at dementia diagnosis regarding risk for dementia was significant (p = 0.003).

observed association. Thirty-three women in this group also underwent oophorectomy, 16 unilateral and 17 bilateral. The distribution of dementia diagnoses for these 96 women was: 85.4% dementia without specification, 5.2% AD, 6.3% VaD and 3.1% FTD. Seventy-six cases (79.2%) were operated due to benign indications (mainly uterine leiomyomas, abnormal uterine bleedings, endometriosis, benign ovarian tumors and dyspareunia) and 20 cases (20.8%) due to malignant indications (15.6% cervical carcinoma in situ stage 0–1, 3.1% ovarian cancer, 1.0% breast cancer and 1.0% uterine cancer). The median age at hysterectomy in this group was 40.2 years (25th and 75th percentiles: 35.1 and 43.6). The time lapse between hysterectomy and onset of dementia had a median of 6.3 years (25th and 75th percentiles: 1.9 and 11.5). To rule out other causes such as systemic illnesses, psychiatric disorders, brain lesions or encephalitis, all the registered diagnoses in the NPR and PCRR from 1969 to 2006 for the 96 patients were reviewed. It showed that 9 patients were registered also with alcoholism and 7 with depression. When additional analyses were made to adjust for the effect of a registered diagnosis of alcohol abuse and depression, all RR presented in tables 2–4 were essentially unchanged.

Discussion

In our study, hysterectomy with or without oophorectomy was shown to modestly increase the risk for dementia with onset before the age of 50. Since natural menopause occurs at an average age of 51 [23], the women with

Table 4. RR for dementia in women with hysterectomies compared with referent women, stratified by age at dementia diagnosis and age at hysterectomy

Age at hysterectomy[1]	Age at dementia diagnosis				
	40–49 years	50–59 years	60–69 years	70–79 years	≥80 years
20–29 years	1.98 (0.82–4.77)	0.75 (0.19–3.01)			
30–39 years	1.77 (1.28–2.43)	1.10 (0.86–1.42)	0.88 (0.59–1.31)		
40–49 years	1.44 (1.09–1.90)	0.89 (0.74–1.06)	0.95 (0.83–1.08)	0.93 (0.78–1.10)	
50–59 years		1.08 (0.84–1.39)	0.93 (0.79–1.10)	0.96 (0.86–1.06)	0.96 (0.80–1.14)
60–69 years			0.89 (0.71–1.12)	0.98 (0.89–1.09)	0.98 (0.90–1.07)
70–79 years				0.89 (0.71–1.12)	1.03 (0.95–1.11)
80–89 years				0.89 (0.78–1.00)	0.88 (0.77–1.00)
≥90 years					1.08 (0.51–2.26)
Referent group	1	1	1	1	1

RR are adjusted for calendar period and age at dementia diagnosis, both in 1-year groups. 95% CI are indicated in parentheses.
[1] A formal test for interaction between age at hysterectomy and age at dementia diagnosis regarding risk for dementia was significant (p = 0.05).

hysterectomy prior to dementia with onset before the age of 50 were most likely premenopausal or perimenopausal at the time of the operation. It is biologically plausible that hysterectomy alone can cause premature menopause. During hysterectomy, the ovarian branch of the uterine artery is ligated, reducing the blood supply to the ovaries. Studies have shown disturbances in blood flow to the ovaries, a significant decrease in estradiol and a reduction in ovarian follicular reserve following hysterectomies [5]. Moreover, the menstruating endometrium itself may stimulate ovarian functions [24].

It has been shown that early menopause in women with Down syndrome is associated with an increased risk for dementia and mortality [25]. A more abrupt form of early menopause, surgical menopause (premenopausal bilateral oophorectomy), has been postulated to have a detrimental effect on cognitive function due to the premature and abrupt withdrawal of estrogen. The evidence to support this hypothesis is limited to a few small, short-term, randomized clinical trials of estrogen treatment that reported a decline in verbal episodic memory in women with surgical menopause, an effect that was reversed by estradiol injections [6]. Results from observational studies are conflicting, and the long-term effect of surgical menopause on cognitive function is unknown [26]. To our knowledge, only one study from the Mayo Clinic in the USA examined the direct association between premenopausal hysterectomy/oophorectomy and the long-term risk of dementia [7]. This large cohort study showed that women who underwent premenopausal bilateral or unilateral oophorectomy had an increased risk of dementia, a risk that was counteracted by estrogen replacement until at least the age of 50. The younger the age at oophorectomy, the higher was the risk. Remarkably, 70% of the women who had unilateral oophorectomy in this study also underwent hysterectomies [7]. Very few studies have been done on isolated unilateral oophorectomy. It is unknown whether isolated unilateral oophorectomy can maintain normal ovarian function. In one retrospective study, among 14 women with polycystic ovary syndrome who underwent unilateral oophorectomy, 7 went on to bear children and none entered menopause 14–18 years after surgery [27]. However, a prospective cohort study showed that hysterectomy was associated with earlier onset of menopause (3.7 years earlier, 96% CI = 1.5–6.0), and hysterectomy with unilateral oophorectomy was associated with an even earlier onset of menopause (4.4 years earlier, 95% CI = 0.6–7.9) [5]. Probably, ovarian function is intact after isolated unilateral oophorectomy but a concurrent hysterectomy can reduce the blood supply to the remaining ovary and lead to premature ovarian failure. Our study supports such a hypothesis, showing that unilateral oophorectomy alone did not have an effect on dementia. Only when hysterectomy was present together with unilateral oophorectomy, was an increased risk seen (table 3). Among women with hysterectomy, we observed a dose effect of the degree of ovarian deficiency on the risk of dementia: the fewer the ovaries, the higher the risk (table 3).

In our study, women with isolated hysterectomy had a modestly increased risk for early-onset dementia (table 3). The effect of hysterectomy plus bilateral oophorectomy on dementia was greater and extended into the group with dementia onset between 50 and 59 years, suggesting a stronger association between surgical menopause and dementia (table 3). The increased risk for dementia with onset before the age of 50 associated with isolated bilateral oophorectomy did not reach statistical significance because there were only 3 cases in this category (table 3). Bilateral oophorectomy alone was not associated with an increased risk of dementia with onset between the age of 50 and 59 (table 3), probably because there were only 5 cases in this group. Consistent with the Mayo Clinic's findings, we observed a trend of an increasing risk for dementia with younger age at hysterectomy (table 4). Although it is not possible to determine how much concomitant bilateral oophorectomy contributed to this trend, it appears that the younger brain is more vulnerable to estrogen deficiency.

Other mechanisms linking surgical menopause and dementia have been suggested [28]. It is possible that complex interactions between premature estrogen withdrawal and other causal mechanisms are responsible for the association between premenopausal hysterectomy/oophorectomy and dementia [28].

Concerning the effect of exogenous estrogen on the risk of dementia, studies using animal models and observational studies strongly support the protective effect of HRT against dementia, but data from placebo-controlled experimental studies have shown that HRT has no effect or does not increase the risk for dementia [6]. Since women in experimental studies were older and received HRT years after menopause whereas observational studies included younger women who received HRT near the time of their menopause, it has been hypothesized that HRT may protect against dementia when started perimenopausally but has no effect or even increases the risk of dementia when started years after menopause [6]. This hypothesis has recently been challenged by an observational study which showed that HRT has a positive effect on certain cognitive functions, but initiation close to menopause was not associated with better cognition [29]. Other factors that could contribute to the discrepancies between observational and experimental studies are the differences in estrogen compounds, routes and modes of administration, and the concomitant use of progestin [6]. While the controversy over the effect of estrogen on dementia in older naturally menopausal women is unsettled, women with surgically induced premature menopause appear to be a particular high-risk group for developing dementia and can potentially benefit from early treatment with HRT.

Our study has limitations. First, patients with dementia who had never been in contact with the hospitals were misclassified as noncase. This differential misclassification could lead to a type I error. Second, although premenopausal hysterectomy and oophorectomy can increase the risk for both AD and VaD, it was not possible to confirm this because the majority of dementia diagnoses in the hospital registers are dementia without specification [20]. A registered diagnosis of dementia without specification could mean dementia of all causes, neurodegenerative or nonneurodegenerative. However, it is most likely that the distribution of dementia subtypes within this group of diagnosis follows the known distribution of subtypes of dementia, with AD and VaD being the two major subtypes accounting for 70–80% of all dementias. In our earlier validation study, we could confirm that at least 30% of the registered diagnoses of dementia without specification were in fact AD [20]. Third, due to the limitations of the registers available to us in this study, we could not control for education, cardiovascular risk factors, HRT and genetic factors.

Lower education is associated with both an increased risk for dementia [30] and a higher rate of hysterectomy on benign indications [31]. A causal effect between education and dementia is controversial. Low education can be a proxy variable for low socioeconomic status, sedentary lifestyle, unhealthy diet, high incidence of metabolic syndrome and cardiovascular disease [32]. Cardiovascular risk factors and cardiovascular disease are recognized risk factors for dementia. The estrogen deficiency state in postmenopausal women is associated with cardiovascular risk factors such as weight gain, hypertension, insulin resistance and dyslipidemia [33]. Surgical menopause is known to increase the risk of cardiovascular disease [34]. Incidence studies have found hypertension and weight cycling to be risk factors for hysterectomy on benign indications, regardless of ovarian status, suggesting that women with isolated hysterectomy are also at risk for cardiovascular disease [24, 35]. Thus, cardiovascular risk factors and cardiovascular disease might be involved in the intermediate pathological pathways linking hysterectomy, oophorectomy, estrogen deficiency and dementia. In the subgroup of the 96 women with hysterectomy and dementia onset before the age of 50 in this study, 91 women were operated due to indications with no contraindication for HRT. The actual risk for dementia could be underestimated if HRT had already been started early

and thereby reduced this risk. Conversely, it cannot be ruled out that HRT increased the risk of dementia in this subgroup. It is unlikely that women with hysterectomy have the extremely rare mutations in familial AD, VaD and FTD. Since 2005, diagnostic genetic testing for autosomal dominant inherited dementia in Denmark has been carried out on a referral basis at the Molecular Genetics Laboratory, Copenhagen University Hospital Rigshospitalet. To date, only 7 families with these rare mutations were identified [36]. However, it is a drawback that apolipoprotein and estrogen receptor gene polymorphisms could not be incorporated as covariates in this study.

We cannot exclude the possibility that hysterectomy and bilateral oophorectomy may also increase the risk of late-onset dementia because of two reasons. First, women with early menopause, spontaneously or surgically, have been found to have an increased risk for cardiovascular disease and mortality [29]. Second, older women who had hysterectomy and oophorectomy before 1977 were massively misclassified as nonexposed in this study (table 4), a nondifferential misclassification that would bias toward nil.

Due to the limitations of this study, the association between hysterectomy and dementia cannot be ascertained. However, this study replicated the age-dependent effect of premature estrogen deficiency on dementia reported from the Mayo Clinic study [7] and showed a dose effect action of premature estrogen deficiency on the risk of dementia. These two findings and the strong association between premenopausal bilateral oophorectomy and dementia support results from earlier studies that showed a negative effect of surgical menopause on the long-term risk of dementia [7].

The results of this study are generalizable for the Danish female population older than 40 years. Although the rates of hysterectomy vary across continents, Denmark and other industrialized countries share important features: 20% of women will have undergone hysterectomy before the age of 55 [1, 3, 37], 80% of hysterectomies are performed for benign indications [1, 3, 37], bilateral oophorectomy is frequently performed in connection with hysterectomy (35–50%) [4, 37], and hysterectomy is associated with low socioeconomic status and cardiovascular risk factors [24, 31, 38]. Possibly, our findings can also be generalized to women older than 40 years in Western industrialized countries.

The findings of our study advocate further investigation about the effect of premature estrogen withdrawal on long-term cognitive decline. Further studies are also needed to confirm and clarify the complex causal mechanisms underlying the association between premenopausal hysterectomy and oophorectomy, cardiovascular disease and dementia. If women with premenopausal hysterectomy and bilateral oophorectomy are confirmed to be at risk for developing dementia, a considerable population of women worldwide will be at increased risk. Any intervention that could modify this potential risk, such as early HRT or a more conservative approach to hysterectomy and oophorectomy, will have an important public health impact.

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