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ORIGINAL RESEARCH ARTICLE

All-cause and cardiovascular mortality after hysterectomy and oophorectomy in a large cohort (HUNT2)

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Abstract

Introduction: Hysterectomy and bilateral oophorectomy are common major surgical procedures that have been associated with increased mortality risk. We aimed to assess the association of hysterectomy and/or bilateral oophorectomy with all-cause and cardiovascular mortality in a Norwegian population.

Material and methods: Cohort study with data from The Trøndelag Health Study (HUNT2) linked to the Norwegian Cause of Death Registry, with follow-up from 1996 until 2014 or death. The unexposed group ($n = 18\,673$) included women with both their ovaries and uterus intact, while the two exposed groups included women with hysterectomy alone ($n = 1199$), or bilateral oophorectomy with or without hysterectomy ($n = 907$). We compared mortality in exposed vs unexposed groups and adjusted for relevant covariates by Cox regression. Further, we performed analyses stratified by age at surgery (≤39, 40–52, ≥53 years) and subgroup analyses among women ≤52 years of age at inclusion.

Results: Among the 47 312 women in HUNT2 (1995–1997), 20 779 provided complete information regarding gynecological surgery and previous health. The hysterectomy group had increased all-cause mortality (hazard ratio [HR] 1.30, 95% confidence interval [CI] 1.06–1.58) and cardiovascular mortality (HR 1.47, 95% CI 1.09–1.97). We found no significant association between bilateral oophorectomy and all-cause or cardiovascular mortality in the total population. However, among women ≤52 years at inclusion, cardiovascular mortality was increased in the hysterectomy group (HR 2.71, 95% CI 1.19–6.17) with a similar, but less precise estimate in the bilateral oophorectomy group (HR 2.42, 95% CI 0.84–6.93).

Conclusions: Hysterectomy was associated with increased all-cause and cardiovascular mortality, whereas bilateral salpingo-oophorectomy was not. Among women ≤52 years at inclusion, both hysterectomy and bilateral oophorectomy were associated with a twofold increased risk of cardiovascular mortality, but the results were imprecise. Women after hysterectomy and/or bilateral salpingo-oophorectomy

Abbreviations: BSO, bilateral salpingo-oophorectomy; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HT, hormone therapy; HDL, high-density lipoprotein.

constitute a group with increased cardiovascular mortality that may need closer attention to cardiovascular disease risk from the healthcare system to ensure timely and effective preventive interventions.

KEYWORDS
cardiovascular disease, cohort study, hysterectomy, mortality, ovariectomy

1 | INTRODUCTION

Cardiovascular disease (CVD) is the number one cause of death in the Western world.[1] Women develop heart disease about 10 years later than men, and endogenous estrogen may provide a protective effect in premenopausal individuals.[2]

Premenopausal bilateral salpingo-oophorectomy (BSO) results in abrupt loss of estrogen.[3] This decline may affect CVD risk, morbidity and mortality,[4–7] and natural or surgical menopause in the 40s has been associated with increased CVD risk[8,9] and increased all-cause and cardiovascular mortality.[9] Hysterectomy may accelerate the menopausal transition[10] and previous studies have reported associations between hysterectomy and CVD, but the findings are divergent. A recent meta-analysis concluded that hysterectomy is related to CVD but stated that CVD risk factors were inconsistently adjusted for across the different studies.[11] A higher CVD risk even before surgery may be part of the explanation.[12] Most of the previous studies were conducted in Northern America,[6,13–16] Canada[4] or Australia,[5,7] where hysterectomy and BSO rates are substantially higher than in Scandinavian countries.[17] There is Scandinavian data on increased prevalence of metabolic syndrome and CVD risk in women who had hysterectomy with or without BSO before 50 years,[18] increased incidence of ischemic heart disease in women with oophorectomy or hysterectomy at young ages[19,20] and increased intima media thickness in women who reached menopause at young ages and never used hormone therapy (HT).[21] Additionally, Olesen et al. recently concluded that BSO may be associated with cardiovascular mortality in women, based on results from the Danish Nurse Cohort, but the results were not statistically significant.[22] We need robust data on all-cause and cardiovascular mortality among Scandinavian women with hysterectomy and BSO, since they may differ from women who undergo these surgeries on the American or Australian continents.

Hysterectomy and BSO are common surgeries, also in Scandinavian countries, and any relation to increased mortality is of concern. The Trøndelag Health study (HUNT) is a large Norwegian population based cohort study, and we aimed to assess all-cause and cardiovascular mortality in women who had undergone BSO and/or hysterectomy compared with those who had their uterus and ovaries intact. Secondarily, we aimed to assess these associations in women with surgery at different ages and for those below the age of natural menopause at inclusion in HUNT2. We hypothesize that women who report these surgeries will have an increased risk of cardiovascular mortality, and that the risk is greater with younger age at surgery.

Key message

Women below menopausal age reporting a previous hysterectomy and/or bilateral salpingo-oophorectomy, had an increased risk of cardiovascular mortality. These women might benefit from assessment of their personal cardiovascular risk profile.

2 | MATERIAL AND METHODS

The HUNT study is a longitudinal, population-based study carried out in the Nord-Trøndelag region, Norway. It is a collaboration between HUNT Research Center (Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology NTNU), Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. All adult inhabitants aged 20 years and above have been invited in four surveys (HUNT1–4) at approximately 10-year intervals. We have included women from HUNT2 (1995–1997) where they were asked about pelvic surgery. The surveys include questionnaires, blood sampling and clinical measurements. The population in Nord-Trøndelag is considered to be generally representative of the Norwegian population.

Exposure to hysterectomy or BSO was self-reported in the HUNT2 questionnaire by the questions: "Have you had your uterus removed?" and "Have you had both your ovaries removed?" If yes, the women were asked: "At what age did you have your uterus removed?" or "At what age did you have both your ovaries removed?" Partial or unilateral oophorectomy was reported by the question; "Have you had parts of or one ovary removed?"

We classified women into three groups based on their exposure at inclusion. Women were included in the hysterectomy group if they reported hysterectomy and their age at hysterectomy. Women who had both ovaries removed with or without hysterectomy, and reported their age at BSO, were included in the BSO group. Those who had their uterus and ovaries removed in two separate surgeries ($n = 72$) were included in the BSO group, and age at BSO was registered as age at surgery. The unexposed group consisted of women who had their uterus and both ovaries intact. We did not have access to exposure after inclusion, so any women who had gynecological surgery after inclusion in HUNT2 would still be treated as unexposed in the analyses.

The main outcome was death during follow-up (from 1996 to 2014), as registered in the Norwegian Cause of Death Registry (NCoDR). Information from NCoDR and HUNT2 was linked using the 11-digit unique personal identification number that is allocated to all Norwegian citizens, and at the time of linkage the registry data from NcoDR was available until 2014. NCoDR covers all deaths in Norway and deaths of Norwegians who die abroad. Doctors are required to complete a death certificate, where they can include up to three diagnoses describing the causal chain leading to death. The coverage of NCoDR was ≥98.0%[23] in the whole study period. We calculated all-cause mortality by counting all registered deaths during follow-up, whereas cardiovascular deaths covered all deaths with at least one diagnosis of CVD in the causal chain. To be able to discover possible associations of hysterectomy and BSO with any CVD, we defined CVD broadly as any diagnosis included in ICD-10 chapter 9, diseases of the circulatory system (I00-I99).

Due to prior studies showing increased mortality in women after BSO at young ages, we performed subgroup analyses stratified by age at surgery (≤39, 40–52 and ≥53 years of age). These age groups were chosen a priori as menopause before age 40 is defined as premature ovarian failure, whereas 53 years is the average age of natural menopause in Norway.[24] A previous study has shown that the increased risk for cardiovascular disease after BSO and hysterectomy attenuated with age, indicating a stronger short-term risk.[6] To assess this mechanism further, we also performed subgroup analyses of women that were below the age of natural menopause (≤52 years of age) at inclusion in HUNT2. This approach was used to explore the associations between surgery and mortality in sub-samples with substantially shorter time since BSO and/or hysterectomy. These analyses allowed us to assess the mortality risks for younger women specifically.

A history of cancer was collected from the Cancer Registry of Norway by linkage with the personal identification number. Based on the strong relation between gynecological cancer and both pelvic surgery and mortality, we categorized ovarian, uterine, cervical and other gynecological cancers as well as non-gynecological cancers in the "history of cancer" variable. In addition, we performed a sensitivity analysis where all participants with gynecological cancer were excluded.

Trained staff at the HUNT examination stations obtained blood samples and clinical measurements. Height and weight were measured with the participant wearing light clothes and no shoes. Body mass index was calculated as weight (in kg) divided by the squared value of height (in m^2). Blood pressure was measured three times according to a standardized procedure using an automatic oscillometric method (Dinamap, Critikon, FL). The cuff size was adjusted to the arm circumference. Waist circumference was measured at the height of the umbilicus while the participant was standing. Women were defined as physically inactive if their leisure-time physical activity during an average week included no high-level (sweaty/breathless) and less than 1 hour low-level activity (not sweaty/breathless). Marital status, daily smoking, age at menarche, as well as history and age of myocardial infarction (MI), angina, stroke and diabetes, were self-reported. Hormone therapy (HT) use was defined as self-reported current use of pills or patches containing estrogen. These covariates were based on questionnaire data and physical examination at inclusion in HUNT2, and could not be treated as time-dependent covariates.

All serum analyses were performed in non-fasting samples at the Central Laboratory, Levanger Hospital, Nord-Trøndelag Hospital Trust. All analyses were performed on a Hitachi 911 auto analyzer. Serum total and high-density lipoprotein (HDL) cholesterol were analyzed using enzymatic colorimetric methods (Boehringer Mannheim, Germany).

2.1 | Statistical analyses

All statistical tests were done in STATA. We described continuous or dichotomous variables with mean and standard deviations or proportions, and compared groups with independent sample *t*-tests or chi-square tests as appropriate. The two exposed groups were compared with the reference group from the time of participation in the HUNT2 survey to death with Kaplan–Meier plots and assessed with Log-Rank test. To adjust for relevant covariates, we conducted Cox regression analysis with covariate data from the start of follow-up including age, history of cancer (categorized as listed above), body mass index, smoking, diabetes, HDL cholesterol, total cholesterol, physical inactivity, blood pressure, not having paid work and current use of HT. The women were followed from inclusion in HUNT2 until death or end of follow-up in 2014. Due to the large size of the dataset the assumption of proportional hazard was assessed graphically from Kaplan–Meier and log–log survival curves, and considered satisfactory (Appendix S1).

2.2 | Ethics statement

Participation in HUNT2 was voluntary and each participant signed a written consent regarding participation in the study and use of their data for later research, including linking to other registries. Our study was evaluated and approved by The Regional Committee of Health and Research Ethics (REC) of Mid Norway (2010/2779 4.2009.94). The project was first accepted on April 15, 2009, with reference number 4.2009.94. Application to add data from the Cancer Registry of Norway was accepted October 22, 2010 (ref. 2010/2779).

3 | RESULTS

A total of 47 312 women aged ≥20 years were invited to participate in HUNT2 (1995–1997): 603 were deceased or had changed residency, 11 429 did not participate in HUNT2, and 4975 did not answer the second questionnaire covering pelvic surgery, resulting in an eligible population of 30 265 women. Of these, 8601 were excluded because of missing or incomplete information regarding pelvic surgery, and a further 885 were excluded due to unilateral or partial oophorectomy. Thus, our study population consisted of

20 779 women. In total, 18 673 women had both their ovaries and uterus intact (unexposed group), 1199 had undergone hysterectomy alone (hysterectomy group) and 907 had undergone BSO with or without hysterectomy (BSO group). Inclusion of participants is shown in Figure 1.

The women in the hysterectomy and BSO groups were older (mean 60 and 64.5 years of age, respectively) compared with the unexposed group (43 years of age) (Table 1). Age-adjusted clinical characteristics are presented in Table 2. After age adjustment, and compared with the unexposed group, the women in the hysterectomy group were more likely to have a history of cancer, angina and diabetes. They also had higher body mass index, systolic blood pressure and lower HDL cholesterol. Women in the BSO group were more likely to have a history of cancer and diabetes, be physically inactive, and have higher systolic blood pressure and lower levels of HDL cholesterol. On the other hand, they had lower total cholesterol and were less likely to smoke daily (Table 2).

There was a significant proportion of missing information on HT use, and we therefore analyzed differences between women with and without HT data (Appendix S2). Age-adjusted mortality in the group with missing data was similar to the group who did not use HT. We also analyzed clinical characteristics of the 8601 women excluded due to missing data on pelvic surgery (Appendix S3).

Median follow-up time was 17.3 years (minimum/maximum 0.04–18.38 years) for unexposed women, 17.1 years (minimum/maximum 0.32–18.37 years) for the hysterectomy group and 16.9 years (minimum/maximum 0.15–18.36 years) for the BSO group. Person-years and number of deaths are presented in Table 3.

After adjusting for age, the all-cause mortality was increased by 26% (HR 1.26, 95% CI 1.11–1.44) in the hysterectomy group compared with women who had intact internal genitalia. After full adjustment, the increase was 30% (HR 1.30, 95% CI 1.06–1.58). The association increased in strength by older age at hysterectomy (Table 3).

Women with hysterectomy had a 23% higher cardiovascular mortality (HR 1.23, 95% CI 1.02–1.49) compared to the unexposed group. Cardiovascular mortality was 47% higher (HR 1.47, 95% CI 1.09–1.97) after full adjustment. The association was strongest when hysterectomy was performed at the youngest and oldest ages (Table 3).

All-cause mortality was increased by 24% (HR 1.24, 95% CI 1.09–1.42) in the BSO group compared with the group with no pelvic surgery after age adjustment, but no association was seen after full adjustment (HR 1.00, 95% CI 0.80–1.24). All-cause age-adjusted mortality was increased in the women who had BSO at ages ≤39 years or ≥53 years, but these associations were attenuated after full adjustment (Table 3).

We found no statistically significant association with cardiovascular mortality after BSO. However, we observed a slightly increased risk for the whole group (HR 1.13, 95% CI 0.83–1.55), with a higher risk in women who had BSO at ages ≤39 years (52% increased risk [HR 1.52, 95% CI 0.84–2.77]) and ≥53 years (41% increased risk [HR 1.41, 95% CI 0.91–2.17]). Again, these findings were not statistically significant (Table 3).

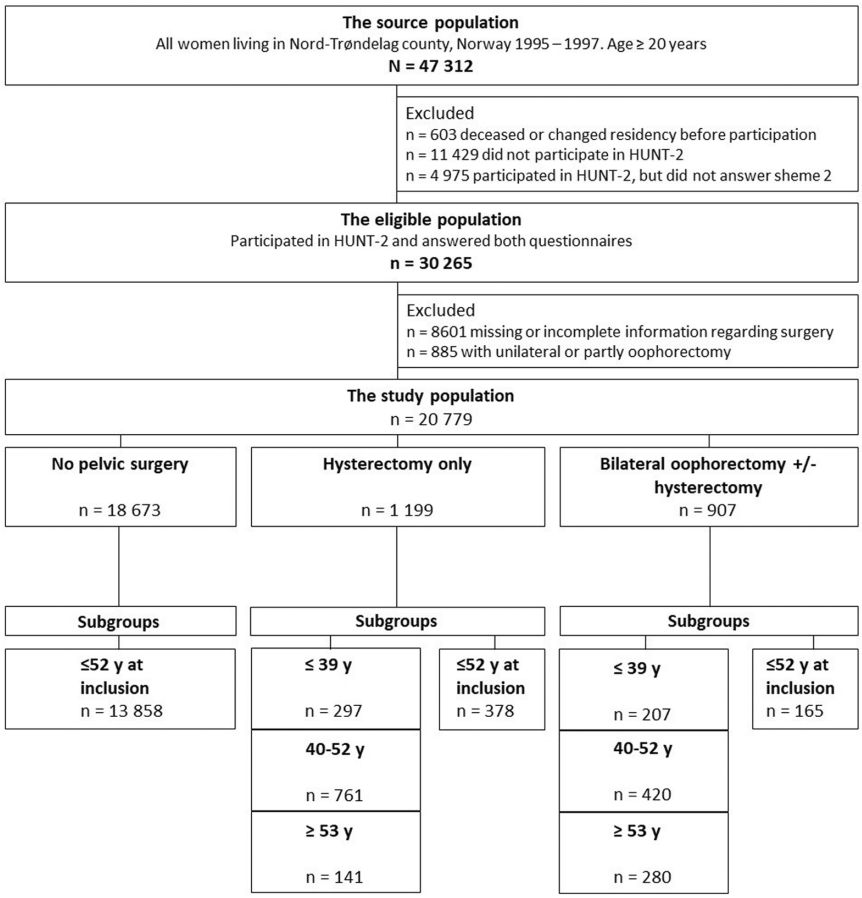

FIGURE 1 Inclusion of participants.

TABLE 1 Clinical characteristics at baseline.

Variable	Ovaries and uterus intact (reference group), *n* = 18 673	Hysterectomy group, *n* = 1199	Oophorectomy group, *n* = 907
Age at HUNT2 (years)	43.0 ± 13.7	60.0 ± 11.6	64.5 ± 11.9
Age at pelvic surgery (years)	Not applicable	46.5 ± 9.8	47.6 ± 11.9
Years since pelvic surgery	Not applicable	15.7 ± 10.6	17.0 ± 11.9
Age at menarche (years)	13.3 ± 1.4	13.4 ± 1.4	13.6 ± 1.5
BMI (kg/m^2)	25.8 ± 4.5	27.4 ± 4.5	27.7 ± 4.5
Systolic blood pressure (mmHg)	130 ± 19	144 ± 24	149 ± 25
Total cholesterol (mmol/L)	5.7 ± 1.3	6.5 ± 1.2	6.6 ± 1.3
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
Married or registered partner	11 280 (60.4)	819 (68.3)	557 (61.4)
Physical inactivity	3002 (16.1)	236 (19.7)	216 (23.8)
Current use of HT[a]	1414 (7.5)	254 (21.2)	220 (24.3)
No paid work	5573 (29.8)	624 (52.0)	627 (69.1)
Daily smoking	5604 (30.0)	294 (24.5)	207 (22.8)
History of myocardial infarction	96 (0.5)	24 (2.0)	23 (2.5)
History of angina	210 (1.1)	86 (7.2)	89 (9.8)
History of cerebral stroke	117 (0.6)	29 (2.4)	38 (4.2)
History of diabetes	257 (1.4)	64 (5.3)	64 (7.1)
History of cancer	442 (2.4)	122 (10.2)	238 (26.2)

Note: Data are mean ± SD or *n* (%).

[a]Hormone therapy.

TABLE 2 Age-adjusted mean differences and odds ratios for continuous and categorical variables measured at baseline.

Variable	Ovaries and uterus intact (reference)	Hysterectomy group		Oophorectomy group	
	Age-adjusted mean (95% CI)	Age-adjusted mean (95% CI)	Age-adjusted mean difference or OR (95% CI)	Age-adjusted mean (95% CI)	Age-adjusted mean difference or OR (95% CI)
Age at menarche (years)	13.3 (13.3–13.3)	13.1 (13.0–13.2)	−0.18 (−0.26 to −0.096)	13.2 (13.1–13.3)	−0.070 (−0.17 to 0.027)
BMI (kg/m^2)	26.0 (25.9–26.0)	26.3 (26.1–26.6)	0.37 (0.095–0.637)	26.3 (26.0–26.6)	0.30 (−0.010 to 0.615)
Systolic blood pressure (mmHg)	131 (131–131)	132 (131–133)	1.4 (0.35–2.5)	135 (133–136)	3.6 (2.4–4.9)
Total cholesterol (mmol/L)	5.78 (5.76–5.79)	5.77 (5.71–5.83)	−0.007 (−0.074 to 0.059)	5.67 (5.60–5.75)	−0.106 (−0.183 to −0.030)
HDL cholesterol (mmol/L)	1.51 (1.51–1.52)	1.47 (1.45–1.50)	−0.042 (−0.065 to −0.017)	1.47 (1.45–1.50)	−0.042 (−0.070 to −0.015)
History of cancer			1.22 (1.05–1.41)		1.84 (1.57–2.15)
History of diabetes			1.62 (1.19–2.20)		1.73 (1.25–2.38)
History of myocardial infarction			0.66 (0.39–1.12)		0.58 (0.34–1.01)
History of angina			1.37 (1.01–1.86)		1.32 (0.97–1.81)
History of stroke			1.04 (0.66–1.65)		1.37 (0.89–2.12)
Being physically inactive			1.17 (1.00–1.37)		1.43 (1.20–1.70)
No paid work			1.48 (1.30–1.67)		2.67 (2.29–3.11)
Married or registered partner			0.53 (0.47–0.61)		0.29 (0.25–0.34)
Current use of HT			1.80 (1.53–2.13)		1.84 (1.52–2.21)
Daily smoking			0.88 (0.76–1.02)		0.81 (0.68–0.96)

Abbreviation: HT, hormone therapy.

TABLE 3 Associations of hysterectomy and bilateral salpingo-oophorectomy (BSO) with all-cause and cardiovascular mortality.

		All-cause mortality			Cardiovascular mortality		
	Person-years	Deaths	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)	Deaths	Age-adjusted HR (95% CI)	Fully adjusted HR (95% CI)
Ovaries and uterus intact (n = 18 673)	318 301	1300	Ref	Ref	498	Ref	Ref
Hysterectomy (n = 1199)	18 259	335	1.26 (1.11–1.44)	1.30 (1.06–1.58)	186	1.23 (1.02–1.49)	1.47 (1.09–1.97)
Hysterectomy ≤39 years (n = 297)	4814	46	1.18 (0.88–1.59)	1.08 (0.72–1.63)	24	1.28 (0.85–1.94)	1.87 (1.08–3.21)
Hysterectomy 40–52 years (n = 761)	11 777	204	1.22 (1.05–1.43)	1.28 (1.01–1.62)	110	1.21 (0.97–1.51)	1.27 (0.88–1.83)
Hysterectomy ≥ 53 years (n = 141)	1668	85	1.49 (1.18–1.88)	2.08 (1.29–3.35)	52	1.30 (0.95–1.78)	1.90 (1.02–3.57)
BSO (n = 907)	13 247	362	1.24 (1.09–1.42)	1.00 (0.80–1.24)	207	1.15 (0.95–1.40)	1.13 (0.83–1.55)
BSO ≤ 39 years (n = 207)	3261	59	1.31 (1.00–1.71)	1.19 (0.77–1.83)	32	1.20 (0.83–1.74)	1.52 (0.84–2.77)
BSO 40–52 years (n = 420)	6379	141	1.11 (0.92–1.33)	0.86 (0.65–1.14)	72	0.95 (0.73–1.24)	0.88 (0.58–1.34)
BSO ≥ 53 y (n = 280)	3607	162	1.40 (1.18–1.68)	1.20 (0.87–1.67)	103	1.37 (1.08–1.74)	1.41 (0.91–2.17)
Women ≤52 years at inclusion (n = 14 401)	249 530	363			74		
Ovaries and uterus intact (n = 13 858)	240 272	328	Ref	Ref	60	Ref	Ref
Hysterectomy (n = 378)	6433	23	1.26 (0.82–1.94)	1.04 (0.61–1.77)	9	2.64 (1.28–5.42)	2.71 (1.19–6.17)
BSO (n = 165)	2825	12	1.60 (0.90–2.86)	1.12 (0.58–2.17)	5	3.57 (1.41–9.00)	2.42 (0.84–6.93)

Note: Age adjustment: Adjusting for age at HUNT2. Full adjustment: Age, cancer, BMI, diabetes, smoking, total & HDL cholesterol, physical inactivity, blood pressure, no paid work, and current use of hormone therapy.

In the sub-analyses including only women ≤52 years at inclusion, time since surgery was 8.4 years (SD 6.7) in the BSO group and 7.1 (SD 5.4) in the hysterectomy group. In these sub-groups, cardiovascular mortality was increased in the BSO group (age-adjusted HR 3.57, 95% CI 1.41–9.00) compared with the group with intact uterus and ovaries. Although not statistically significant, the HR was also increased after full adjustment (HR 2.42, 95% CI 0.84–6.93). A similar and significant association (HR 2.71, 95% CI 1.19–6.17) was seen in the hysterectomy group (Table 3).

We performed a sensitivity analysis where all participants with gynecological cancer were excluded. In this analysis we have included 20 312 participants: 18 436 unexposed, 1153 with hysterectomy and 723 with BSO. The associations remained similar after this exclusion (Appendix S4), except that the age-adjusted association between BSO and overall mortality was attenuated.

4 | DISCUSSION

In the total cohort, women with hysterectomy had an increased risk of all-cause and cardiovascular mortality, whereas those with BSO did not. However, cardiovascular mortality seemed to be increased in participants who had BSO at ages ≤39 or ≥53 years. In women below the age of natural menopause at inclusion, BSO and hysterectomy were both associated with increased cardiovascular mortality.

Our findings are in line with the study of Gierach et al., who demonstrated higher short-term mortality risk related to benign gynecologic surgery in young individuals.[6] BSO before the age of 45 has been associated with increased all-cause[25] and cardiovascular mortality,[16] whereas both risks seem to be reduced by HT. Further, in 2016, Roeter et al.[26] and Muka et al.[9] published reviews and meta-analyses consistently demonstrating higher risks of CVD and cardiovascular mortality in women with lower ages at menopause. Appiah et al.[12] found adverse left ventricular structure and function in women with premenopausal BSO compared with natural menopause;[27] however, in line with others,[15,28] they concluded that increased pre-surgical CVD risk rather than the gynecologic surgery itself was the predisposing factor.[27] In accordance with studies with baseline data,[12] we found that women with BSO and/or hysterectomy had a slightly increased CVD risk at inclusion compared with unexposed women. However, full adjustment for CVD risk factors strengthened the association between BSO ≤39 years and cardiovascular mortality in the present study, implying that the increased cardiovascular mortality is perhaps not only caused by pre-surgical risk. However, our baseline data were collected after exposure, so we cannot make any conclusions regarding causality in this study. Interestingly, we also observed increased cardiovascular mortality in women with BSO ≥53 years. Postmenopausal ovaries still produce some estrogen, and a 2015 Cochrane review reported a halving of CVD and cardiovascular mortality in women who used HT within 10 years after natural menopause.[29] These findings indicate an impact of estrogen on CVD risk beyond menopause. In view of the theory that lower age at menopause implies higher CVD risk, we would expect a gradient towards the weakest relation between BSO ≥53 years and cardiovascular mortality. The lack of an association between BSO at 40–52 years and cardiovascular mortality is therefore difficult to explain, but small subgroups and residual confounding may be part of the explanation.

The excess all-cause mortality in the hysterectomy group was of the same magnitude as the increased cardiovascular mortality, implying that cardiovascular deaths may largely explain the increased all-cause mortality.

Using Swedish nationwide healthcare registers, Ingelsson et al. studied CVD and death after hysterectomy and/or oophorectomy.[20] The authors found that both individuals with hysterectomy alone and hysterectomy with oophorectomy ≤50 years had substantially increased CVD risk later in life. The risk in women with hysterectomy with oophorectomy was greater than with hysterectomy alone, but the confidence interval was wide. In contrast to the present study, Ingelsson et al. did not find any significant associations between hysterectomy in women aged 50 or above and CVD. The authors provided robust risk estimates, but no baseline risk was reported.[20] Hence, the authors could not determine whether women with hysterectomy had higher CVD risk prior to surgery or adjust for baseline CVD risk factors. In the present study, the association between hysterectomy and cardiovascular mortality was strengthened after adjustment for CVD risk factors. Falkeborn et al. performed a case–cohort analysis in Swedish women who had undergone hysterectomy and/or oophorectomy.[30] The authors reported a non-significant increased risk after premenopausal oophorectomy and a significant, fourfold increased risk after hysterectomy in women with natural menopause. In line with the present study, the associations with CVD were stronger after hysterectomy than after oophorectomy, and the most pronounced effects were found in women after menopause. In the Women's Health Initiative Study, women with hysterectomy had an increased CVD risk compared with controls, but after adjustments for baseline differences, this risk was attenuated.[28] As part of the CARDIA study, Appiah et al.[12] followed young premenopausal individuals for 25 years to assess associations between hysterectomy and/or BSO and future CVD risk. After full adjustment for baseline CVD risk factors, neither of these surgeries was related to subsequent CVD risk.[12] In the present study, after adjusting for major CVD risk factors at start of follow-up, we still found increased all-cause and cardiovascular mortality in the hysterectomy group, with the strongest associations in the group with hysterectomy ≥53 years. Although earlier menopause due to impaired ovarian blood flow after hysterectomy may represent a biological link to CVD,[10] this does not explain our findings. If that were the case, we would expect to find the highest cardiovascular mortality after BSO and hysterectomy at young ages. We believe that older patients who undergo hysterectomy and/or BSO constitute a group with certain unmeasured characteristics or indications for surgery leading to higher CVD risk.

There are some limitations of our study. The most important is the lack of follow-up data from exposure to the time of participation in HUNT2. This means that our baseline measures do not represent pre-surgical data and that our analyses may be subject to survival bias, with the risk of underestimating the effect of the exposure. Also, most covariates, including the exposure, are self-reported. This introduces the risk of recall bias, and we lack the indication for surgery. However, a history of cancer was attained from a national registry, and we believe the most important distinction is between benign indications or malignancy. This was adjusted for in the cancer covariate, and a sensitivity analysis where all participants with gynecological cancer were excluded did not show major differences from our original results. It is also important to consider the potential for misclassification in the death certificates, but this risk is much lower when using large diagnosis groups, as in the present study, rather than specific diagnoses. Additionally, women who had BSO or hysterectomy after study entry would still be treated as unexposed. Due to the large set of unexposed vs exposed women, we do not believe that this misclassification would have substantial effects on our results. If so, the misclassification would most probably underestimate the association of surgery with mortality. Further, we adjusted for a range of CVD risk factors, some of whom might be both confounders and mediators in the relation between the exposure and cardiovascular mortality. Adjusting for these factors might lead to over-adjustment and, hence, underestimate the association between pelvic surgery and mortality. Nevertheless, associations remained similar in additional models including fewer covariates (Appendix S5). Finally, in the subgroup analyses, the exposed groups were small, and the estimated associations therefore have lower precision.

5 | CONCLUSION

In this population-based cohort study, hysterectomy was associated with increased all-cause and cardiovascular mortality, whereas BSO was not. Among women ≤52 years at inclusion, both hysterectomy and bilateral oophorectomy were associated with a more than twofold increased cardiovascular mortality, but the results were imprecise. Women after hysterectomy and/or BSO constitute a group with increased cardiovascular mortality that may need closer attention to CVD risk from the healthcare system for timely and effective preventive interventions.

AUTHOR CONTRIBUTIONS

TMM: Planned and carried out the data acquisition, interpreted the data and wrote the first draft. TER: Substantial contribution to the interpretation of the data and revising the article. BOÅ: Planned the data acquisition, contributed to the interpretation of the data and revising the article. AHP: Substantial contribution to planning and carrying out the statistical analysis and wrote the paragraph on statistical analysis in the article. AHL: Planned the data acquisition, and contributed to the interpretation of the data and revising the article. NJ: Planned and carried out the data acquisition, interpreted the data and wrote the first draft of the article. All authors revised the paper critically for important intellectual content, approved the final version of the article and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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