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ORIGINAL STUDY

Early and surgical menopause associated with higher Framingham Risk Scores for cardiovascular disease in the Canadian Longitudinal Study on Aging

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Abstract

Objective: In women, the risk of cardiovascular disease (CVD) is higher in the postmenopausal period. The effect that menopausal type, natural versus surgical, or the age at natural menopause has on CVD needs further investigation. To this end, we assessed the association between menopausal type and timing and the 10-year office-based Framingham Risk Score (FRS) in women from the Canadian Longitudinal Study on Aging.

Methods: We included women aged 45 to 85 years from the Canadian Longitudinal Study on Aging Comprehensive cohort of seven Canadian provinces who were menopausal at the time of recruitment and had no prior CVD. Poisson regressions were used to evaluate the association between menopausal characteristics and the FRS. Natural menopause was defined as the cessation of menstrual periods for at least 1 year in women with no history of hysterectomy. Surgical menopause was defined as hysterectomy with or without oophorectomy prior to natural menopause. As main covariates, we examined age, education, province of residency, and hormone therapy.

Results: A total of 10,090 women (8,200 natural menopausal and 1,890 surgical menopausal) were eligible for the study. In the multivariable model, surgical menopause was associated with a higher mean FRS compared with natural menopause (CVD risk 12.4% vs 10.8%, $P < 0.001$). Compared with women with age at natural menopause from 50 to 54 years (CVD risk 10.2%), natural menopause before age 40, 40 to 44, or 45 to 49 had a higher CVD risk (12.2%, 11.4%, and 10.6%, respectively, $P < 0.001$).

Conclusions: Our study supports an association between menopausal type and timing on CVD risk prediction and highlights the need to be judicious about surgical menopause. Preventative interventions for CVD should be considered in surgical menopausal women and women with an age at natural menopause less than 45 years.

Key Words: Age at natural menopause – Cardiovascular disease – Epidemiology – Menopause – Risk factors – Women's health.

Video Summary: http://links.lww.com/MENO/A701.

Cardiovascular disease (CVD) is the global leading cause of women's mortality.[1] Sex-specific data indicate that CVD mortality has decreased for both men and women in the last three decades, especially in the greater than 65 years age group; however, there is stagnation among younger women (less than 55 y).[2] Identifying female-specific CVD risk factors could lead to earlier recognition and increased screening of at-risk women.[3,4] Menopause and postmenopausal status are frequently presented as CVD risk factors, because CVD prevalence in postmenopausal women is significantly higher than the prevalence in premenopausal women.[3-5] However, after adjusting for age, studies have not been able to demonstrate a convincing relationship between postmenopausal status and CVD.[4-6] In contrast, certain menopausal characteristics, menopausal type, and natural menopausal timing have been associated with CVD risk.[3,5-7] Within menopausal type, surgical menopause (hysterectomy with or without bilateral oophorectomy) has been associated with a higher CVD risk when compared with natural menopause.[3,5-7] Additionally, earlier age at natural menopause (ANM), specifically less than 45 years, has been associated with increased CVD risk when compared with a later ANM.[6,8,9]

However, there have been methodological gaps in assessing the direction of causality and some argue that relationship between CVD and early ANM may be due to reverse causality.[10] That is, women with a CVD event before age 35 are more likely to have an ANM less than 45 years.[10] It is also possible that women who undergo surgical menopause may have other concurrent CVD risk factors including hypertension, diabetes, high cholesterol, and obesity.[3,11,12] The objective of our study is to estimate the 10-year CVD risk Framingham Risk Score according to menopausal type, natural versus surgical, and natural menopausal timing in women without prior known CVD from the Canadian Longitudinal Study on Aging.

METHODS

Study sample

Canadian Longitudinal Study on Aging (CLSA) is a population-based cohort study of adults aged 45 to 85 years at recruitment with follow-up planned for at least 20 years or until death. Slightly over 15,000 women across Canada's 10 provinces were recruited at baseline between 2010 and 2013. In the current study, we used data from CLSA comprehensive cohort, including computer-assisted in-home interviews and data collected at 11 study sites in 7 provinces: Alberta, British Columbia, Manitoba, Newfoundland and Labrador, Nova Scotia, Ontario, and Quebec. Details about CLSA design, recruitment, and study procedures have been described elsewhere.[13] We selected women who were menopausal at the time of recruitment and had no prior CVD (either reported angina, heart disease, myocardial infarction, stroke, transient ischemic attack, or peripheral vascular disease).

Human subjects

Institutional review for this project was obtained from all seven provinces that the baseline data was collected from. The Research Ethics Boards that approved the study were University of Victoria for British Columbia, University of Calgary for Alberta, University of Manitoba for Manitoba, McMaster University for Ontario, McGill University and Université de Sherbrooke for Quebec, Memorial University of Newfoundland for Newfoundland and Labrador, and Dalhousie University for Nova Scotia. Written informed consent was obtained from all participants.[13]

Cardiovascular risk

We calculated the 10-year office-based Framingham Risk Score (FRS) for CVD risk based on age, sex, body mass index (BMI), diabetes status, systolic blood pressure (SBP), treatment for hypertension, and smoking. Women were excluded if they were missing one or more items on the FRS. The office-based FRS estimates 10-year risk of CVD outcomes (comprised of coronary death, myocardial infarction, coronary insufficiency, angina, ischemic stroke, hemorrhagic stroke, transient ischemic attack, peripheral artery disease, and heart failure)[14] and has been validated in different populations.[15,16] Age was self-reported, sex was recorded by the interviewer. Height and weight were measured following standard protocols and BMI was calculated as weight in kg/ (height in m)^2. Diabetes was defined as 1) self-reported diabetes, and/or 2) self-reported medication use for diabetes, and/or 3) observed medication at home visit that the participant confirmed to use for diabetes. For SBP, we used the average of 6 measures while excluding the first measure. SBP data for 115 participants were missing. Blood pressure treatment was defined as: 1) self-reported hypertension medication use; or 2) observed medications at home visit, or 3) both. Smoking status was self-reported and participants were divided into two categories: those who currently smoked (any quantity) and those not currently smoking.

Menopause-related variables

Women were asked whether they had gone through menopause (defined as ''menstrual periods stopped for at least 1 y and did not restart''). Women who indicated having gone through natural menopause were asked at what age they went through menopause. Age at natural menopause was categorized into five groups: less than 40 years (premature ovarian insufficiency-POI), 40 to 44 (early), 45 to 49, 50 to 54, and 55 years and older. The age group 50 to 54 years was set as the reference group since it reflects median ANM of 51 years in women from the CLSA.[17] For those who were missing ANM and did not report having had hysterectomy, we substituted reported age at hormone therapy (HT) start, if available (n = 58). Women who underwent hysterectomy before natural menopause were considered as surgical menopause; however, information is not available on the age at which the uterus was removed or whether they also had oophorectomy.

Covariates

Covariates were selected based on precedent literature[6,8,9] and possible confounding effects on the relationships of interest. As main covariates, we examined age, education,

study site (province of residency), and use of HT. Education was self-reported and categorized into three groups based on the highest education level completed: primary completed or less, secondary completed, postsecondary completed. Age was calculated by deducting the birthdate from the interview date, and the study site was recorded by the interviewer. HT use was self-reported and was categorized into those who had used HT and those who had never used HT.

Statistical analyses

Sample characteristics across menopausal status are described. Means and standard deviations were used to describe continuous variables, and counts and percentages for categorical variables. Poisson regressions were used to calculate mean FRS and 95% confidence intervals (CI) for the association between menopausal type and timing with the outcome measure (ie, continuous FRS). All multivariable models were adjusted by age and age squared (age^2), province, education, and HT. While smoking, BMI, diabetes, and blood pressure are potential confounders, statistical adjustment on these measures would be inappropriate given their inclusion in the FRS calculation. Additional analyses were conducted stratifying the sample by smoking status, use of HT, and obesity (BMI $\geq 30\,\text{kg/m}^2$) to examine effect modification. We applied sampling weights (strata and analytic sampling weight) as per the CLSA manual of procedures to account for the sampling design.

RESULTS

A total of 10,090 menopausal women were included in the study, of which 8,200 (81%) had natural menopause and 1,890 (19%) surgical menopause (Fig. 1). Table 1 describes the sample by menopausal type and timing. The average age of the population studied was 64 years old, with 41% of women in the 55 to 64 years age range. The proportion of women older than 75 years was 16%. Among natural postmenopausal women, 8% had an ANM between age 40 and 44 years (early menopause) and 3% before age 40 (POI). HT was reported by 42% of women, being higher in women with surgical menopause (59.2%), and in those with menopause before age 40 (61.9%). The proportion of women with obesity ($\geq 30\,\text{kg/m}^2$) was 26.5% in women with natural menopause and 34.0% in women with surgical menopause. Women with POI had a higher proportion of obesity compared with those with ANM 50 to 54 years (38.1% vs 25.3%, respectively).

Table 2 shows the bivariate analysis of the mean FRS by exposures and covariates, adjusted by age and age^2. Women who underwent surgical menopause had a greater mean FRS (12.34, 95% CI 11.98-12.69) than those who had natural menopause (10.77, 95% CI 10.61-10.92). In women with natural menopause, an ANM < 40 was related to higher mean FRS (12.38, 95% CI 11.41-13.35) than those with ANM 50 to 54 years (10.19, 95% CI 9.97-10.40). In both groups, all menopausal and natural menopausal women, higher mean
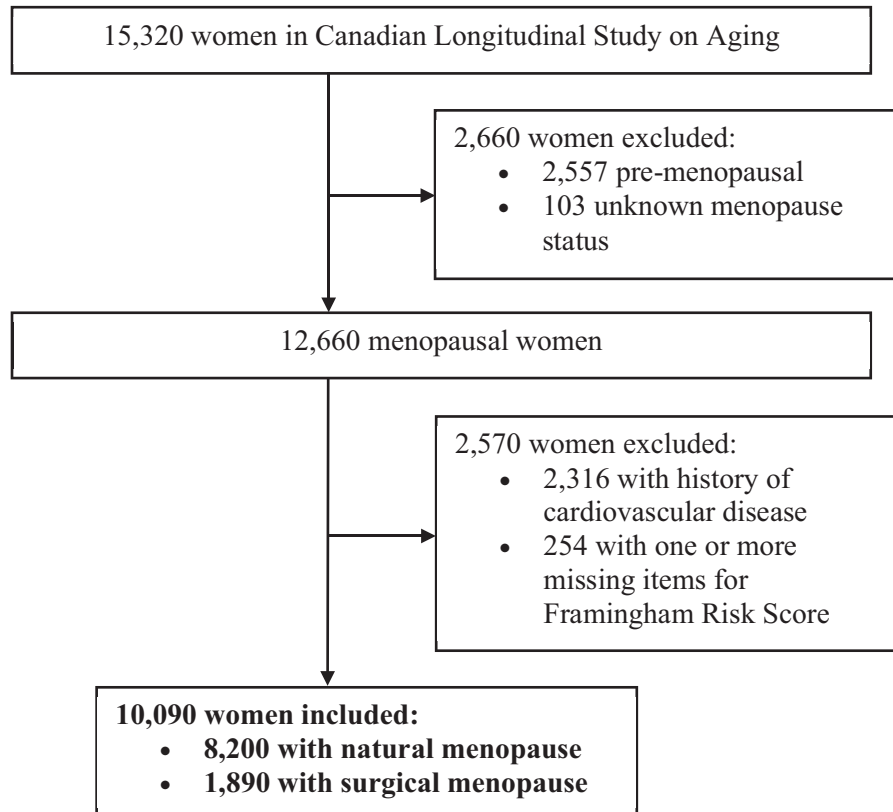

FIG. 1. Flow diagram of participant inclusion.

TABLE 1. *Population characteristics by menopausal type and natural menopausal timing in women from the Canadian Longitudinal Study on Aging*

Characteristics	Menopausal type			Menopausal timing (ANM)				
	All $N = 10,090$	Natural $N = 8,200$	Surgical $N = 1,890$	<40 $N = 257$	40-44 $N = 664$	45-49 $N = 1,891$	50-54 $= 3,882$	≥55 $N = 1,323$
Age, mean (SD)	64.2 (8.9)	63.9 (8.6)	65.6 (9.7)	64.8 (8.9)	63.2 (9.7)	62.5 (9.5)	63.5 (8.1)	66.2 (7.2)
Age, N (%)								
45-54	1,425 (14.1)	1,134 (13.8)	291 (15.4)	38 (14.8)	139 (20.9)	465 (24.6)	483 (12.4)	0 (0)
55-64	4,183 (41.5)	3,576 (43.6)	607 (32.1)	90 (35.0)	247 (37.2)	691 (36.5)	1,865 (48.0)	643 (48.6)
65-75	2,827 (28.0)	2,276 (27.8)	551 (29.2)	85 (33.1)	168 (25.3)	456 (24.1)	1,032 (26.6)	469 (35.5)
≥75	1,655 (16.4)	1,214 (14.8)	441 (23.3)	44 (17.1)	110 (16.6)	279 (14.8)	502 (12.9)	211 (16.0)
HT, N (%)								
Ever	4,243 (42.2)	3,128 (38.3)	1,115 (59.2)	159 (61.9)	329 (49.7)	744 (39.3)	1,362 (35.1)	485 (36.9)
Never	5,818 (57.8)	5,050 (61.8)	768 (40.8)	98 (38.1)	333 (50.3)	1,147 (60.7)	2,514 (64.9)	828 (63.1)
Study site, N (%)								
Alberta	1,000 (9.9)	810 (9.9)	190 (10.1)	29 (11.3)	66 (9.9)	189 (10)	370 (9.5)	140 (10.6)
British Columbia	2,174 (21.6)	1,806 (22)	368 (19.5)	45 (17.5)	133 (20)	422 (22.3)	888 (22.9)	290 (21.9)
Manitoba	1,035 (10.3)	897 (10.9)	138 (7.3)	27 (10.5)	84 (12.7)	218 (11.5)	413 (10.6)	136 (10.3)
Newfoundland and Labrador	793 (7.9)	632 (7.7)	161 (8.5)	33 (12.8)	62 (9.3)	179 (9.5)	261 (6.7)	90 (6.8)
Nova Scotia	1,013 (10)	764 (9.3)	249 (13.2)	12 (4.7)	62 (9.3)	165 (8.7)	342 (8.8)	149 (11.3)
Ontario	2,150 (21.3)	1,719 (21)	431 (22.8)	47 (18.3)	108 (16.3)	358 (18.9)	842 (21.7)	315 (23.8)
Quebec	1,925 (19.1)	1,572 (19.2)	353 (18.7)	64 (24.9)	149 (22.4)	360 (19)	766 (19.7)	203 (15.3)
Education, N (%)								
Less than secondary	584 (5.8)	421 (5.1)	163 (8.6)	39 (15.2)	43 (6.5)	100 (5.3)	173 (4.5)	56 (4.2)
Secondary	1,908 (18.9)	1,515 (18.5)	393 (20.8)	59 (23.1)	134 (20.3)	355 (18.8)	663 (17.1)	264 (20)
Postsecondary	7,585 (75.3)	6,253 (76.4)	1,332 (70.6)	158 (61.7)	484 (73.2)	1,432 (75.9)	3,043 (78.5)	1,003 (75.8)
BMI, N (%)								
Underweight	100 (1.0)	84 (1.0)	16 (0.9)	4 (1.6)	8 (1.2)	21 (1.1)	38 (1)	12 (0.9)
Normal weight	3,518 (34.9)	2,979 (36.3)	539 (28.5)	71 (27.6)	233 (35.1)	693 (36.7)	1,479 (38.1)	442 (33.4)
Overweight	3,659 (36.3)	2,967 (36.2)	692 (36.6)	84 (32.7)	231 (34.8)	697 (36.9)	1,382 (35.6)	504 (38.1)
Obese	2,813 (27.9)	2,170 (26.5)	643 (34.0)	98 (38.1)	192 (28.9)	480 (25.4)	983 (25.3)	365 (27.6)
Diabetes, N (%)								
No	9,292 (92.1)	7,619 (92.9)	1,673 (88.5)	223 (86.8)	619 (93.2)	1,757 (92.9)	3,638 (93.7)	1,219 (92.1)
Yes	798 (7.9)	581 (7.1)	217 (11.5)	34 (13.2)	45 (6.8)	134 (7.1)	244 (6.3)	104 (7.9)
Smoking, N (%)								
No	9,265 (91.8)	7,533 (91.9)	1,732 (91.6)	220 (85.6)	569 (85.7)	1,680 (88.8)	3,637 (93.7)	1,256 (94.9)
Yes	825 (8.2)	667 (8.1)	158 (8.4)	37 (14.4)	95 (14.3)	211 (11.2)	245 (6.3)	67 (5.1)
Hypertension, N (%)								
No	5,019 (49.8)	4,262 (52.0)	757 (40.1)	109 (42.4)	327 (49.3)	1,023 (54.1)	2,116 (54.5)	616 (46.6)
Yes	5,070 (50.3)	3,938 (48.0)	1,132 (59.9)	148 (57.6)	337 (50.8)	868 (45.9)	1,766 (45.5)	707 (53.4)

ANM, age at natural menopause; BMI, body mass index; HT, hormone therapy; SD, standard deviation.

FRS scores were observed among those who have never used HT, and those with low education levels.

Table 3 shows the multivariable results. Compared with natural menopause (10.75, 95% CI 10.59-10.90), women with surgical menopause had higher mean FRS (12.37, 95% CI 12.01-12.74). Compared with ANM 50 to 54 (10.20, 95% CI 9.98-10.41), women with ANM < 40 (12.17, 95% CI 11.22-13.12), ANM 40 to 44 (11.41, 95% 10.82-12.00), and ANM 45 to 49 (10.60, 95% CI 10.27-10.92) had higher FRS. In the stratified models (Table 3), surgical menopause and POI remained associated with higher mean FRS in nonsmokers, ever or never HT users, and nonobese women. Early menopause (40-44 y) remained associated in nonsmokers, never HT users, and nonobese women, but not in HT users.

DISCUSSION

Our study assessed the association of menopausal type, surgical versus natural, and ANM timing on the future CVD risk prediction using the FRS in a national sample of Canadian women. Women with surgical menopause had higher mean FRS levels when compared with women with natural menopause. Women with earlier ANM had higher mean FRS levels when compared with women with later ANM. The difference in mean FRS levels was greatest in women with POI (ANM < 40) followed by those with early ANM (40-44 y).

Comparison with other studies

Several recent studies[6,7,9] have investigated the relationship between menopausal characteristics and CVD risk using the outcome of CVD event or CVD mortality and have findings similar to us. A large pan-European prospective case-cohort study within the European Prospective Investigation into Cancer and Nutrition (EPIC-CVD) defined surgical menopause as having had a hysterectomy, unilateral, or bilateral oophorectomy prior to natural menopause. Surgical menopause was associated with a higher coronary heart disease (CHD) risk compared with natural menopause (HR 1.25, 95% CI 1.10-1.42). However, the risk was attenuated after additional adjustment for age at menopause and intermediates (HR 1.12, 95% CI 0.96-1.29), suggesting that a proportion of the association was explained by cardiovascular risk factors.[6] However, the study did not control for pre-existing CVD which is increased in women undergoing hysterectomy.[12] We excluded women with prior history of CVD, and conducted stratified analyses according to smoking status, use of HT, and obesity. In all women, surgical menopause was associated

TABLE 2. *Bivariate analysis of the mean Framingham Risk Scores by exposures and covariates in women from the Canadian Longitudinal Study on Aging*

Characteristics	Type of menopause sample $N = 10,090$			Age at natural menopause sample $N = 8,017^a$		
	Mean FRS	CI 95%	*P* value	Mean FRS	CI 95%	*P* value
Type of menopause			<0.001			NA
Natural	10.77	10.61-10.92		NA	NA	
Surgical	12.34	11.98-12.69		NA	NA	
ANM[b]			NA			<0.001
<40	NA	NA		12.38	11.41-13.35	
40-44	NA	NA		11.42	10.84-12.01	
45-49	NA	NA		10.62	10.29-10.95	
50-54	NA	NA		10.19	9.97-10.40	
≥55	NA	NA		10.52	10.16-10.87	
HT[c]			0.01			0.001
Ever	10.87	10.66-11.08		10.22	9.99-10.44	
Never	11.23	11.03-11.43		10.73	10.52-10.94	
Age			<0.001			<0.001
45-54	5.46	5.23-5.69		5.33	5.07-5.58	
55-64	8.74	8.54-8.93		8.46	8.26-8.65	
65-75	14.74	14.39-15.10		14.27	13.89-14.65	
≥75	22.76	22.15-23.36		22.14	21.42-22.85	
Study site			<0.001			<0.001
Alberta	10.31	9.88-10.73		9.89	9.42-10.35	
British Columbia	10.25	9.98-10.53		9.80	9.51-10.08	
Manitoba	12.67	12.18-13.17		12.14	11.62-12.65	
Newfoundland and Labrador	11.51	10.98-12.04		10.83	10.29-11.38	
Nova Scotia	11.55	11.06-12.04		10.74	10.20-11.28	
Ontario	11.18	10.87-11.50		10.44	10.10-10.78	
Quebec	10.89	10.58-11.19		10.54	10.20-10.88	
Education[d]			<0.001			<0.001
Less than secondary	12.76	12.16-13.36		12.03	11.34-12.72	
Secondary	12.08	11.72-12-43		11.55	11.16-11.95	
Post-secondary	10.64	10.48-10.80		10.12	9.95-10.29	

Poisson regression analysis, age adjusted apart from the bivariate with the age categories.
ANM, age at natural menopause; CI, confidence interval; FRS, Framingham Risk Score; HT, hormone therapy.
[a]From 8,200 women who had natural menopause, age at menopause was missing in 183.
[b]Age at hysterectomy not available in Canadian Longitudinal Study on Aging.
[c]Information on hormone therapy is missing for 29 in the type of menopause sample and 18 in the age at natural menopause sample.
[d]Information on education is missing for 13 in the type of menopause sample and 11 in the age at natural menopause sample.

with a higher mean FRS compared with natural menopause adjusting for age, study site, education, and HT. In the stratified analysis, the association remained in nonsmokers, ever or never use of HT, obese, and nonobese women. On the contrary, the association was attenuated in smokers, a known independent risk factor for CVD, suggesting that smoking had greater impact on this association than type of menopause.

The InterLACE consortium,[7] a pooled analysis of individual data from 10 international studies, reported a 20% higher risk of CVD (HR 1.22, 95% CI 1.16-1.28) in women with surgical menopause compared with natural menopause. In addition, compared with natural menopause at 50 to 54 years, women with surgical menopause before 35 (HR 2.55, 95% CI 2.22-2.94) and 35 to 39 years (HR 1.91, 95% CI 1.71-2.14)

TABLE 3. *Multivariable Poisson regression analysis of menopausal characteristics and Framingham Risk Scores in women from the Canadian Longitudinal Study on Aging*

	All women[a] Mean FRS (95% CI)	Smokers[a] Mean FRS (95% CI)	Nonsmokers[a] Mean FRS (95% CI)	Never HT use[b] Mean FRS (95% CI)	Ever HT use[b] Mean FRS (95% CI)	Obese[a] Mean FRS (95% CI)	Nonobese[a] Mean FRS (95% CI)
Type	$N = 10,048^c$	$N = 823$	$N = 9,225^c$	$N = 5,814^c$	$N = 4,234^c$	$N = 2,804^c$	$N = 7,244^c$
Natural[d]	10.75 (10.59-10.90)	14.20 (13.58-14.81)	10.43 (10.28-10.58)	9.89 (9.71-10.08)	12.06 (11.80-12.32)	15.15 (14.78-15.52)	9.25 (9.10-9.39)
Surgical	12.37 (12.01-12.74)	15.12 (13.70-15.54)	12.08 (11.72-12.44)	11.57 (11.02-12.12)	13.70 (13.21-14.20)	16.29 (15.55-17.02)	10.29 (9.94-10.63)
ANM (y)	$N = 7,988^c$	$N = 654$	$N = 7,334^c$	$N = 4,916^c$	$N = 3,072^c$	$N = 2,109$	$N = 5,879^c$
<40	12.17 (11.22-13.12)	15.25 (13.06-17.44)	11.46 (10.48-12.44)	11.62 (10.08-13.17)	13.43 (12.16-14.70)	15.47 (13.67-17.27)	10.46 (9.44-11.48)
40-44	11.41 (10.82-12.00)	12.83 (11.03-14.62)	10.97 (10.41-11.54)	11.07 (10.19-11.95)	12.27 (11.48-13.06)	15.57 (14.35-16.78)	9.71 (9.12-10.31)
45-49	10.60 (10.27-10.92)	14.10 (13.10-15.11)	10.15 (9.83-10.47)	9.93 (9.54-10.33)	11.78 (11.22-12.35)	15.54 (14.73-16.36)	8.96 (8.68-9.25)
50-54[d]	10.20 (9.98-10.41)	13.93 (12.89-14.97)	9.95 (9.75-10.16)	9.50 (9.24-9.75)	11.41 (11.03-11.80)	14.79 (14.23-15.35)	8.72 (8.53-8.90)
≥55	10.52 (10.17-10.87)	14.83 (13.12-16.55)	10.28 (9.93-10.62)	9.81 (9.36-10.25)	11.73 (11.14-12.31)	14.55 (13.72-15.37)	9.10 (8.77-9.44)

Menopausal type and ANM are separate models.
ANM, age at natural menopause by age categories; HT, hormone therapy.
[a]Adjusted for age, study site, education, and hormone therapy.
[b]Adjusted for age, study site, and education.
[c]P value = <0.05.
[d]Reference category.

had higher risk of CVD than those with natural menopause (HR 1.59, 95% CI 1.23-2.05 and HR 1.51, 95% CI 1.33-1.72, respectively).[7] Women who experienced surgical menopause at earlier age (<50 y) and used HT had lower risk of incident CHD than those who were not users of HT.[7] In our stratified analysis, HT did not modify the association between surgical menopause and a higher FRS compared with natural menopause. However, this result needs to be interpreted with caution since CLSA does not have information about the age at hysterectomy, and as suggested in the InterLACE study the age of surgical menopause may modify the effect of HT on the FRS.[7]

POI and early natural menopause have been related to greater CVD risk;[6,9] in some studies even menopause earlier than 49 years old has shown an association with increased CVD risk,[9] as we also found. In the EPIC-CVD study, earlier menopause was linearly associated with higher CHD risk (HR per-year decrease = 1.02, 95% CI 1.01-1.03), adjusted for age, smoking, HT, education, and parity.[6] The InterLACE consortium reported a higher CVD risk in women with POI (HR 1.55, 95% CI 1.38-1.73), early (HR 1.30, 95% CI 1.22-1.39), and relatively early (45-49 y; HR 1.12, 1.07-1.18) menopause adjusted for smoking, HT, BMI, and education.[9]

Obesity and smoking appear to have a significant moderating effect on the relationship between POI and early menopause on CVD incident risk compared with ANM 50 to 54 years. In our stratified analysis, higher mean FRS persisted in women with POI and early menopause who were nonsmokers, and nonobese. However, the association was attenuated in smokers and obese women, suggesting that smoking and obesity independently of ANM had a greater impact on this association than ANM. HT did not modify the association between POI and a higher FRS. That is a higher FRS persisted in women with POI compared with ANM 50 to 54 years independently of HT use. However, absence of information about the underlying diagnosis resulting in POI, time from POI diagnosis and HT initiation, HT regimen, and number of years on HT among other factors limit the interpretation of the finding of no association between HT and FRS in women with POI. Prospective studies on the use of HT in women with POI are needed.[18] In women with early menopause, a higher FRS persisted in those who never used HT compared with ANM 50 to 54 years, but was attenuated in ever users (ie, women with early menopause who use HT have a similar FRS than women with ANM 50-54 y who also use HT).

Strengths and limitations

The CLSA biochemical data on high-density lipoprotein cholesterol and total cholesterol levels needed for the laboratory-based FRS were not available for use at the time of this analysis. Instead, our study used D'Agostino et al's validated office-based FRS which replaced these variables with BMI.[14] However, there are strengths to this alternative. The use of BMI in place of cholesterol values in CVD risk scoring systems may provide a more accurate prediction.[19] It is also a more accessible and inexpensive measurement for patients

to monitor outside of clinics.[19] FRS prediction assumes that individuals are free of CVD at baseline, which was our case. It is possible that our calculations are underestimating our participants' CVD risks, if participants who had CVD were not screened out by the CLSA questions or clinical examinations. At the same time, a strength of our study is that the FRS components were assessed by trained research personnel and used objective medical measurements. Another limitation is that the CLSA did not ask participants whether their hysterectomy included or did not include bilateral oophorectomy, nor the age at hysterectomy. Thus, we were unable to further separate surgical menopausal data by ovarian preservation or age at surgical menopause. Similar to our study, the EPIC-CVD study defined surgical menopause as having had a hysterectomy, unilateral, or bilateral oophorectomy, when age at surgery preceded or was equal to age at menopause.[6] Other studies have shown that even with ovarian conservation, hysterectomy is associated with an increased long-term risk of cardiovascular and metabolic conditions.[20] In fact, symptoms of ovarian insufficiency may occur up to 4 years earlier in women who had hysterectomy with ovarian conservation,[21] and it has been demonstrated that the Anti-Mullerian hormone, an objective marker of ovarian the reserve, decreases 1 year after hysterectomy with ovarian conservation.[22]

CONCLUSIONS

Our study supports an association between menopausal type and natural menopausal timing on prediction of future CVD risk, using the FRS. Surgical menopause is associated with a higher FRS than natural menopause. This association should reinforce efforts to minimize the use of unnecessary surgical menopause.[23] Among natural menopausal women, those who had an ANM of less than 45 years had a higher CVD risk compared with women with ANM at 50 to 54 years. Clinicians should be aware of this association to recognize that surgical menopausal women and women with an ANM less than 45 years may have a higher CVD development risk. Increased and early screening and health promotion interventions for CVD should be considered in women who present with these menopausal characteristics.

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