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The association of age at menopause and all-cause and cause-specific mortality by race, postmenopausal hormone use, and smoking status

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ABSTRACT

While a mean age at menopause of 51 years has been reported in the United States (U.S.), some U.S. women experience menopause before age 45, possibly increasing risk of cardiovascular mortality; however, the role in all-cause and cerebrovascular-related mortality is unclear. The purpose of this study was to investigate the association between age at menopause and all-cause and cause-specific mortality by race, hormone replacement therapy (HRT) use, and smoking status. REasons for Geographic and Racial Differences in Stroke (REGARDS) is a population-based study of 30,239 participants aged ≥45 years enrolled between 2003 and 2007 of whom 14,361 were postmenopausal women. Age at menopause was defined as < 45 (early) or ≥45. All-cause and cause-specific mortality were ascertained through 2013. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CI) for the association between age at menopause and mortality, adjusting for baseline measures. Of 11,287 eligible women (6403 white; 4884 black), mean menopause age was 45.2 (SD 7.9) with 1524 deaths over 7.1 years. Significant interactions were detected between early age at menopause (39%) and HRT use in association with all-cause mortality ($p < 0.01$), mortality from coronary heart disease ($p = 0.06$), and mortality from all other causes ($p = 0.04$). An association between early age at menopause and all-cause mortality was observed among ever-HRT users (HR = 1.31, 95% CI: 1.10–1.56), but not never-HRT users (HR = 1.01, 95% CI: 0.85–1.20). There were no differences in associations examined by race or smoking status. Increased all-cause mortality risk was observed for ever-HRT users with menopause before age 45.

1. Introduction

Although a mean age at menopause of 51 years has been reported in the United States (U.S.) (American Congress of Obstetricians and Gynecologists, 2011), some U.S. women experience early menopause (< age 45 years) resulting in a large population at risk for adverse effects including mortality, with considerable public health impact. After menopause, the risk of coronary heart disease (CHD) is elevated

Abbreviations: BMI, body mass index; BWHS, Black Women's Health Study; CI, confidence interval; CHD, coronary heart disease; CVD, cardiovascular disease; ECG, electrocardiogram; FDA, Food and Drug Administration; HR, hazard ratio; HRT, hormone replacement therapy; MI, myocardial infarction; MRR, mortality rate ratio; NDI, National Death Index; NAMS, North American Menopause Society; REGARDS, REasons for Geographic and Racial Differences in Stroke; RR, relative risk; SD, standard deviation; U.S., United States

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(Tunstall-Pedoe, 1998). Menopause due to surgery (bilateral oophorectomy or hysterectomy) (Colditz et al., 1987; Gordon et al., 1978; Parker et al., 2009) has been associated with an increased risk of CHD events compared with natural menopause. Additionally, menopause at < 40 years of age has been found to be associated with an increased risk of mortality from CHD, but no association has been observed with stroke or cardiovascular mortality (Gong et al., 2016).

Estrogen deficiency and hormonal menopause prior to age 51 are associated with premature morbidity (osteoporosis and cardiovascular, neurological, and psychiatric diseases) and mortality (Shuster et al., 2010), although the association of age at menopause with mortality by type of menopause is less clear (Jacobsen et al., 2003; Mondul et al., 2005; Ossewaarde et al., 2005). Some studies have reported elevated CHD risk for women with natural menopause at < 45 years of age (Hu et al., 1999; Wellons et al., 2012) and elevated all-cause mortality risk for those with natural menopause at < 40 years of age (Gong et al., 2016). With regard to the relation between postmenopausal hormone replacement therapy (HRT) use and cardiovascular disease (CVD), a consensus is lacking regarding the long-term risks and benefits, and routine use of HRT is not currently recommended for primary or secondary prevention of heart disease (Gartlehner et al., 2017). Differences in the risk-benefit profile between treatment formulations were assessed by a 2017 review that reported statistically significantly increased risk for stroke among women using estrogen (79 more cases), and estrogen plus progestin therapy (53 more cases) compared with placebo (Gartlehner et al., 2017). Additionally, a 2015 review reported a low risk of stroke for oral estrogen use with HRT initiation before age 65 (National Collaborating Centre for Women's and Children's Health (UK), 2015). Further evidence is needed for HRT and CVD, although HRT use is approved by the U.S. Food and Drug Administration (FDA) for treatment of menopausal symptoms and considered by the American College of Obstetricians and Gynecologists (2013) 2013–2014 guidelines for women with good cardiovascular health profiles who are not at risk of associated events and depending on the timing of menopause (Food and Drug Administration, 2019; Gartlehner et al., 2017).

One study examined the potential relation between age at menopause and mortality by type of menopause in a cohort of African-American women with consideration of postmenopausal hormone use (Li et al., 2013). In the Black Women's Health Study (BWHS), women with natural menopause (without hysterectomy or bilateral oophorectomy) between ages 40–44 compared with ages 50–54 had a higher all-cause mortality risk (Li et al., 2013). The risk of all-cause mortality was also higher for women with natural menopause without postmenopausal hormone use at ages < 40 and 40–44 compared with ages 50–54; however, mortality risk did not differ by age group among those who used postmenopausal hormones (Li et al., 2013).

Race/ethnicity and smoking may impact age at menopause with early menopause more common among black than white women (Bromberger et al., 1997; MacMahon and Worcester, 1966; Stanford et al., 1987) and among smokers than non-smokers (Hayatbakhsh et al., 2012; Sun et al., 2012) in some, but not all studies (Gold et al., 2001; McKnight et al., 2011). Race/ethnic differences have been observed for overall mortality rates among females, with 2017 U.S. age-adjusted death rates of 728.0 and 642.8 per 100,000 non-Hispanic black and non-Hispanic white females, respectively (Murphy et al., 2018), both for whom the leading cause of death is heart disease (2015) (Centers for Disease Control and Prevention, 2018). Considering these differences, early age at menopause could contribute to the disparate mortality rates.

Given the associations of race and smoking with early menopause (Bromberger et al., 1997; Cooper et al., 1999; Gold et al., 2001; Hardy et al., 2000; Hayatbakhsh et al., 2012; McKinlay et al., 1992; Sun et al., 2012; Torgerson et al., 1994) and the racial/ethnic differences in mortality among females (Murphy et al., 2017), further research is needed to elucidate whether the association of menopausal age with mortality varies by race or smoking status. Results from studies investigating the relationship between age at menopause and all-cause and cause-specific mortality are conflicting (Cooper and Sandler, 1998; Jacobsen et al., 2003, 2004; Jacobsen et al., 1997; Jansen et al., 2002; Lapidus et al., 1985; Mondul et al., 2005; Ossewaarde et al., 2005; Snowdon et al., 1989), and the roles of race and smoking in that relationship have not been sufficiently examined. Two population-based studies have evaluated the relationship between smoking, age at menopause, and mortality (Bellavia et al., 2016; Li et al., 2013), and none have included race.

We examined these associations among women in the REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. The following hypotheses were examined: 1) early age at menopause is associated with increased risk of all-cause and cause-specific mortality after adjustment for sociodemographic and clinical characteristics; 2) the association between early age at menopause and all-cause and cause-specific mortality varies by race, with a stronger association in black than white women; and 3) the association between early age at menopause and all-cause and cause-specific mortality varies by smoking status, with smokers having a stronger association than non-smokers. As a secondary aim, we assessed whether HRT modified the associations between age at menopause and all-cause and cause-specific mortality.

2. Methods

2.1. Study design and population

REGARDS is a national, population-based study investigating geographic and racial/ethnic differences in stroke and cognitive impairment among 30,239 men and women aged ≥45 years enrolled from 2003 to 2007. Details on the design and methods have been published (Howard et al., 2005). Fifty-five percent of participants are women (n = 16,632). A baseline telephone interview collected information on risk factors (smoking status, alcohol consumption, HRT), medical history, demographics, and socioeconomic status. Clinical, physical, and laboratory measurements (height, weight, blood pressure), electrocardiogram (ECG), and medication inventory were obtained at a baseline in-home examination. Written informed consent was obtained from all study participants and Institutional Review Board approval received at participating centers. The analysis included women with natural and induced menopause. We excluded women premenopausal at baseline (n = 1991) and those with implausible (n = 280) (< 25 or > 60 years) (Lanska and Kuller, 1995) or unknown (n = 1614) age at menopause, without ≥1 follow-up visit/call (n = 182), and missing covariates (n = 1278). The final sample included 11,287 women.

2.2. Classification of age at menopause, all-cause and cause-specific mortality

Age at menopause (self-reported age [years] at last menstrual period) was defined as < 45 (early) or ≥45, similar to previous studies (Fioretti et al., 2000; Palmer et al., 2003; Rosenberg et al., 1981). Type of menopause was self-reported at baseline and categorized as natural or induced due to surgery/hysterectomy, radiation, or other conditions. The primary outcomes were all-cause and cause-specific mortality identified through 2013 by report from next-of-kin and online sources (Social Security Death Index, National Death Index) giving ≥7 years average follow-up. Information from medical records, death certificates and interviews with surviving family members was compiled and reviewed by physician-led adjudicators to determine cause of death, which was classified according to ICD-10 coding (Luepker et al., 2003). Cause-specific mortality was categorized into circulatory disease (I00-I19, I26-I59, I70-I99), CHD (I20-I25), stroke (I60-I69), and all other causes, which included accidental and noninjury deaths.

2.3. Covariates

Covariates measured at baseline included demographics, education, medical conditions, behavioral characteristics, and type of menopause. Region of residence was dichotomized as stroke belt (Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, Tennessee) (Lanska and Kuller, 1995) or non-stroke belt (all other states in the contiguous U.S.). Smoking status was characterized as never (≤100 cigarettes in one's lifetime), former (> 100 cigarettes in one's lifetime) or current (active smoking). Body mass index (BMI) (kg/m^2) was classified as normal/underweight (≤24.9), overweight (25–29.9), and obese (≥30.0) (Centers for Disease Control and Prevention, 2017). Self-reported alcohol consumption was defined by the National Institute on Alcohol Abuse and Alcoholism guidelines for women as none or moderate (0–7 drinks/week)/heavy (> 7 drinks/week). HRT use was self-reported and defined as ever-HRT and never-HRT.

History of CVD was determined by ECG or self-reported myocardial infarction (MI), coronary artery bypass surgery, coronary angioplasty, or stenting. History of stroke was defined by self-report of physician diagnosis. Diabetes was defined as self-reported use of diabetic medication or insulin, fasting glucose ≥126 mg/dL, or non-fasting glucose ≥200 mg/dL. Hypertension was defined by self-reported antihypertensive medication use, systolic blood pressure ≥140 mm Hg, or diastolic blood pressure ≥90 mm Hg.

2.4. Statistical analysis

Demographic and clinical characteristics of participants were compared by age at menopause; statistical significance was assessed by chi-square and *t*-tests. Crude incidence rates (95% confidence intervals [CI]) of all-cause and cause-specific mortality were estimated by age at menopause and race, and by smoking status for all-cause mortality only. Cox proportional hazards models were used to estimate hazards ratios (HR) and 95% CIs for the association between early age at menopause and mortality. Survival times were censored at date of death or last completed follow-up.

Interaction terms between the following risk factors and age at menopause were included in the all-cause mortality models to assess variations by race, smoking, and HRT, and in cause-specific mortality models for CHD and all other causes only to assess variations by HRT. In cause-specific mortality analyses, an age*race interaction term was included for stroke because of documented higher stroke incidence for blacks than whites at younger ages (Howard et al., 2011).

The association between early menopause and all-cause and cause-specific mortality was examined without adjustment (Model 1); and with adjustment for age, race, and education (Model 2); model 2 covariates plus medical conditions (CVD and stroke history, BMI, diabetes, and hypertension), and behavioral characteristics (smoking status, alcohol consumption) (Model 3); and model 3 covariates plus type of menopause (Model 4). Smoking-stratified models additionally adjusted for pack-years of smoking. Statistical analyses were conducted using SAS version 9.3 (Cary, NC) (SAS Institute Inc., 2012).

3. Results

Excluded participants (n = 1278) were compared with those included (n = 11,287) (Table A). A higher proportion of excluded individuals were black, had diabetes, or died; a lower proportion reported current use of estrogen medication or weekly use of moderate/heavy alcohol.

Among the 11,287 women who met eligibility criteria, mean age at baseline was 64.8 years and 43.3% were black (Table 1). Mean age (± SD) at menopause was 45.2 (7.9) years (44.9 [8.1] for black women; 45.5 [7.8] for white, and 49 [5] for natural menopause; 40 [8] for induced). The mean age of women reporting menopause at age < 45 and age ≥ 45 was 37 (5) and 51 (4) years, respectively. More than one-third of women (n = 4357; 39%) experienced early age at menopause. These women were more likely than those without early menopause to be black, current smokers, ever-HRT users, reside in the stroke belt, report more pack-years smoked, and have induced menopause, diabetes, hypertension, and history of CVD or stroke. Women with early age at menopause were less likely to be college graduates and report weekly use of moderate/heavy alcohol.

3.1. Risk of all-cause mortality with age at menopause, overall and by smoking status and race

There were 1524 deaths over a mean follow-up period of 7.1 years. Mean time to death was 5.3 years: 5.2 and 5.4 among women with and without early age at menopause, respectively (p = 0.04). In unadjusted models, all-cause mortality risk was increased among women with early age at menopause compared to those without (HR = 1.17, 95% CI: 1.06–1.30) (Table 2). The association was fully attenuated in Model 3 (HR = 1.03, 95% CI: 0.93–1.14); however, re-emerged after further adjustment for type of menopause and was modified by ever-HRT use (Model 4, HR = 1.15, 95% CI: 1.02–1.29; interaction p < 0.01). Interaction terms were also included in the all-cause mortality models to assess variations between age at menopause and race (p = 0.14) and smoking (p = 0.57) and although not statistically significant (p < 0.10 was considered statistically significant), results were stratified due to a priori hypotheses.

Among current, never, and ever smokers, age at menopause was not associated with all-cause mortality. For white women, early age at menopause was associated with an increased risk of all-cause mortality in the fully adjusted model (HR = 1.22, 95% CI: 1.03–1.44). No associations were observed among black women.

3.2. Risk of all-cause mortality with age at menopause by use of HRT

At baseline, 6675 women ever used HRT and 4580 women never used HRT, with 738 and 776 deaths, respectively (Table 3). Among ever-users, early age at menopause was associated with an increased risk of all-cause mortality in the fully adjusted model (HR = 1.31, 95% CI: 1.10–1.56). There was no association observed among never users. When stratified by smoking status and race, associations were observed between age at menopause and all-cause mortality among ever-users who were former smokers (HR = 1.58, 95% 1.18–2.12) and white (HR = 1.39, 95% CI = 1.13–1.73). Among never-HRT users, early age at menopause was associated with elevated all-cause mortality risk for current smokers (HR = 1.48, 95% CI: 1.01–2.16).

3.3. Risk of cause-specific mortality overall with age at menopause and by race

Early age at menopause was associated with an increased CHD mortality risk although modified by HRT use (HR = 1.50, 95% CI: 1.17–1.93, interaction p = 0.06) (Table 4). As described in the methods, cause-specific mortality analyses for stroke also included an age*race interaction term (p = 0.06). Similar associations were observed among black (HR = 1.42; 95% CI: 1.01–1.99) and white (HR = 1.76; 95% CI: 1.20–2.57) women. No overall associations were observed for mortality from circulatory disease, stroke, and all other causes. An interaction between use of HRT and age at menopause was observed with mortality from all other causes (p = 0.04), but not circulatory disease or stroke.

4. Discussion

We observed a 15% increased risk of all-cause mortality among women with early age at menopause compared to those without in the REGARDS study, after adjustment for covariates including type of

Table 1
Baseline characteristics of women in the REGARDS study overall and by age at menopause, 2003–2007.

Characteristic	Total (n = 11,287) n (%), mean ± SD	Age at menopause	
		< 45 years (n = 4357) n (%), mean ± SD	≥45 years (n = 6930) n (%), mean ± SD
Age	64.8 ± 8.8	64.7 ± 8.5	64.9 ± 8.9
Race, black	4884 (43.3)	2002 (46.0)	2882 (41.6)**
Death	1524 (13.5)	632 (14.5)	892 (12.9)*
Time to death, years	5.3 ± 2.5	5.2 ± 2.5	5.4 ± 2.5*
Stroke belt region (vs. non-belt)	6483 (57.4)	2759 (63.3)	3724 (53.7)
Education			**
Less than high school	1405 (12.4)	685 (15.7)	720 (10.4)
High school graduate	3169 (28.1)	1325 (30.4)	1844 (26.6)
Some college	3194 (28.3)	1272 (29.2)	1922 (27.7)
College graduate and above	3519 (31.2)	1075 (24.7)	2444 (35.3)
Smoking status			**
Never	5965 (52.9)	2204 (50.6)	3761 (54.3)
Former	3687 (32.7)	1419 (32.6)	2268 (32.7)
Current	1635 (14.5)	734 (16.8)	901 (13.0)
Pack-years smoked	9.74 ± 18.5	11.01 ± 19.9	8.94 ± 17.6**
BMI			
Underweight/normal	2902 (25.8)	986 (22.8)	1916 (27.8)
Overweight	3579 (31.9)	1391 (32.1)	2188 (31.7)
Obese	4748 (42.3)	1957 (45.2)	2791 (40.5)
Moderate/heavy alcohol consumption (vs. none)	3429 (30.4)	1108 (25.4)	2321 (33.5)**
Menopause induced by surgery/other condition (vs. natural)	5154 (45.7)	3473 (79.7)	1681 (24.3)**
Ever use of hormone replacement therapy	6675 (59.3)	2950 (67.9)	3725 (53.9)**
Current use of estrogen medication[a]	1414 (12.5)	754 (17.3)	660 (9.5)**
Current use of progestin medication[a]	300 (2.7)	54 (1.2)	246 (3.6)**
History of cardiovascular disease	1470 (13.0)	675 (15.5)	795 (11.5)**
History of stroke	626 (5.6)	299 (6.9)	327 (4.7)**
Diabetes	2308 (20.4)	1016 (23.3)	1292 (18.6)**
Hypertension	6799 (60.2)	2802 (64.3)	3997 (57.7)**

Abbreviations: vs., versus; BMI, body mass index.
[a] A total of 218 participants reported current use of both estrogen and progestin.
* $p < 0.05$.
** $p < 0.0001$.

Table 2
Age at menopause and all-cause mortality risk among women in the REGARDS study, 2003–2013 (n = 11,287).

	No. of deaths	Event rate/1000 person-years (95% CI)	All-cause mortality			
			Model 1 unadjusted HR (95% CI)	Model 2[a] HR (95% CI)	Model 3[b] HR (95% CI)	Model 4[c] HR (95% CI)
All causes						
< 45 years	632	20.53 (18.96–22.16)	1.17 (1.06–1.30)	1.14 (1.03–1.26)	1.03 (0.93–1.14)	1.15 (1.02–1.29)
≥45 years	892	17.73 (16.58–18.91)	Referent	Referent	Referent	Referent
Smoking status						
Never						
< 45 years	261	16.54 (14.59–18.60)	1.09 (0.93–1.27)	1.06 (0.90–1.23)	0.95 (0.81–1.11)	1.03 (0.86–1.24)
≥45 years	422	15.32 (13.89–16.82)	Referent	Referent	Referent	Referent
Former[d]						
< 45 years	222	21.93 (19.14–24.91)	1.24 (1.04–1.49)	1.19 (0.99–1.43)	1.10 (0.91–1.32)	1.20 (0.97–1.49)
≥45 years	298	17.94 (15.96–20.04)	Referent	Referent	Referent	Referent
Current[d]						
< 45 years	149	30.58 (25.87–35.68)	1.12 (0.90–1.41)	1.17 (0.93–1.47)	1.08 (0.88–1.39)	1.27 (0.96–1.67)
≥45 years	172	27.92 (23.91–32.25)	Referent	Referent	Referent	Referent
Race						
Black						
< 45 years	309	22.19 (19.78–24.73)	1.11 (0.95–1.28)	1.07 (0.92–1.24)	0.97 (0.84–1.13)	1.11 (0.94–1.32)
≥45 years	404	20.03 (18.12–22.03)	Referent	Referent	Referent	Referent
White						
< 45 years	323	19.17 (17.13–21.31)	1.21 (1.05–1.39)	1.24 (1.08–1.43)	1.12 (0.97–1.30)	1.22 (1.03–1.44)
≥45 years	488	16.19 (14.79–17.66)	Referent	Referent	Referent	Referent

[a] Model 2: Adjusted for demographic characteristics (age, race) & education (less than high school, high school graduate, some college, college graduate).
[b] Model 3: Adjusted for demographic characteristics, education, medical conditions (cardiovascular disease history and stroke, diabetes, and hypertension at baseline) & behavioral characteristics (smoking status [current-former-never], body mass index [BMI] [underweight/normal, overweight, obese], and weekly alcohol consumption [moderate/heavy vs. none]).
[c] Model 4: Adjusted for demographic characteristics, education, medical conditions, behavioral characteristics & type of menopause (surgical/hysterectomy or radiation induced vs. natural).
[d] Models for former and current smokers are also adjusted for pack-years of smoking.

Table 3
Age at menopause and all-cause mortality risk by baseline hormone replacement therapy (HRT) Use, 2003–2013.

	All-cause mortality					
	Women ever using HRT at baseline			Women never using HRT at baseline		
	No. of deaths	Event rate/1000 person-years (95% CI)	HR (95% CI)[a]	No. of deaths	Event rate/1000 person-years (95% CI)	HR (95% CI)[a]
All causes						
< 45 years	366	17.42 (15.68–19.25)	1.31 (1.10–1.56)	261	26.93 (23.76–30.29)	1.01 (0.85–1.20)
≥ 45 years	372	13.38 (12.05–14.77)	Referent	515	23.03 (21.09–25.07)	Referent
Smoking status						
Never						
< 45 years	142	13.18 (11.10–15.44)	1.20 (0.92–1.56)	116	23.35 (19.30–27.78)	0.87 (0.67–1.13)
≥ 45 years	168	11.30 (9.65–13.07)	Referent	253	20.07 (17.67–22.61)	Referent
Former[b]						
< 45 years	138	19.63 (16.49–23.04)	1.58 (1.18–2.12)	82	26.84 (21.35–32.95)	0.95 (0.69–1.33)
≥ 45 years	139	13.88 (11.67–16.28)	Referent	157	24.00 (20.39–27.90)	Referent
Current[b]						
< 45 years	86	26.83 (21.46–32.79)	1.19 (0.80–1.78)	63	37.77 (29.03–47.65)	1.48 (1.01–2.16)
≥ 45 years	65	22.25 (17.17–27.98)	Referent	105	32.73 (26.77–39.28)	Referent
Race						
Black						
< 45 years	138	17.45 (14.66–20.48)	1.23 (0.92–1.65)	169	28.20 (24.11–32.60)	1.05 (0.84–1.31)
≥ 45 years	114	13.24 (10.92–15.77)	Referent	286	24.89 (22.09–27.85)	Referent
White						
< 45 years	228	17.41 (15.22–19.74)	1.39 (1.13–1.73)	92	24.88 (20.06–30.21)	0.95 (0.72–1.26)
≥ 45 years	258	13.44 (11.85–15.13)	Referent	229	21.07 (18.43–23.89)	Referent

Abbreviations: hormone replacement therapy, HRT.
[a] Adjusted for: demographic characteristics, education, medical conditions, behavioral characteristics & type of menopause.
[b] Models for former and current smokers are also adjusted for pack-years of smoking.

menopause. This association was modified by HRT use. Although early age at menopause was associated with risk of all-cause mortality among white women, differences by race were not statistically significant. There were no associations among black women or by smoking status.

Among women who used HRT, risk of all-cause mortality with early age at menopause was increased significantly overall as well as for former smokers and white women, but not for never or current smokers or black women. Among never-HRT users, only current smokers with early age at menopause showed significantly increased risk of mortality; mortality risk was not increased for never and former smokers,

Table 4
Age at menopause and risk of cause-specific mortality among women in the REGARDS study, 2003–2013.

	Mortality					
	No. of deaths	Event rate/1000 person-years (95% CI)	Circulatory disease HR (95% CI)[a]	No. of deaths	Event rate/1000 person-years (95% CI)	Coronary heart disease HR (95% CI)[a]
Overall[b]						
< 45 years	23	0.75 (0.47–1.08)	0.76 (0.42–1.40)	166	5.39 (4.60–6.24)	1.50 (1.17–1.93)
≥ 45 years	38	0.76 (0.53–1.01)	Referent	172	3.42 (2.93–3.95)	Referent
Race						
Black						
< 45 years	12	0.86 (0.45–1.41)	n/a	89	6.39 (5.13–7.79)	1.42 (1.01–1.99)
≥ 45 years	19	0.94 (0.57–1.41)	Referent	99	4.91 (3.99–5.92)	Referent
White						
< 45 years	11	0.65 (0.33–1.09)	n/a	77	4.57 (3.61–5.64)	1.76 (1.20–2.57)
≥ 45 years	19	0.63 (0.38–0.94)	Referent	73	2.42 (1.90–3.01)	Referent

	Mortality					
	No. of deaths	Event rate/1000 person-years (95% CI)	Stroke HR (95% CI)[a]	No. of deaths	Event rate/1000 person-years (95% CI)	All other causes HR (95% CI)[a]
Overall[b]						
< 45 years	39	1.27 (0.90–1.69)	1.16 (0.71–1.87)	404	13.13 (11.88–14.46)	1.08 (0.93–1.25)
≥ 45 years	54	1.07 (0.81–1.38)	Referent	628	12.48 (11.52–13.48)	Referent
Race						
Black						
< 45 years	19	1.36 (0.82–2.04)	n/a	189	13.57 (11.71–15.57)	n/a
≥ 45 years	23	1.14 (0.72–1.65)	Referent	263	13.04 (11.51–14.66)	Referent
White						
< 45 years	20	1.19 (0.72–1.76)	n/a	215	12.76 (11.11–14.52)	n/a
≥ 45 years	31	1.03 (0.70–1.42)	Referent	365	12.11 (10.90–13.38)	Referent

[a] Adjusted for demographic characteristics, education, medical conditions, behavioral characteristics & type of menopause.
[b] Models for former and current smokers are also adjusted for pack-years of smoking.

black and white women.

CHD mortality risk after early age at menopause was significantly increased overall modified by HRT use. CHD mortality risk was also increased in black and white women. No statistically significant associations were observed for mortality from circulatory disease, stroke, and all other causes, possibly due to assessment of broad mortality causes.

4.1. Mechanisms linking menopause to health outcomes

Prior to menopause, endogenous estrogens help to maintain a state of vasodilation. However, with the loss of endogenous estrogens and with age, increases in hypertension and associated cardiovascular risks are observed in postmenopausal women (Barton and Meyer, 2009; Barton et al., 2007). Menopause is associated with elevated plasma fibrinogen, antithrombin III, factor VII coagulant activity, total serum cholesterol, and triglycerides as well as a subsequent increase in the waist-hip ratio (van der Graaf et al., 1997). Both early menopause and a longer period post menopause have been related to increased blood pressure among women (Izumi et al., 2007), which is associated with an increased risk of cardiovascular disease (Archer, 2009). The relationship between early and premature (< age 40 years) menopause and health outcomes, including CVD and mortality, may be promoted by the cardiovascular effects of altered hormonal status including the withdrawal of endogenous estrogens (Rocca et al., 2009; Shuster et al., 2010).

Induced early menopause may be due to surgical or medical interventions including bilateral oophorectomy, chemotherapy or radiation (Shuster et al., 2010). For example, some women undergo bilateral oophorectomy for ovarian cancer prophylaxis or for benign gynecological conditions (Melton III et al., 1991; Rocca et al., 2018; Shuster et al., 2008). Treatment for cancers such as breast or gynecologic may require medical interventions such as chemotherapy or irradiation that induce early menopause (Rosenberg and Partridge, 2013; Shuster et al., 2010). Women with certain health conditions including autoimmune diseases (e.g., rheumatoid arthritis, thyroid disorders or premature ovarian failure) may also experience induced early menopause. Early menopause whether induced or natural has been associated with long-term health outcomes including increased risk of mortality, although less is known regarding potential long-term health effects differentiated by the specific type of menopause (Shuster et al., 2010). However, among women with premature menopause, an increased prevalence of atherosclerosis is thought to be associated with elevated incidence of CVD morbidity and mortality, with cardiovascular risks further increased for women experiencing premature menopause following bilateral oophorectomy (Archer, 2009; Mack et al., 2004).

4.2. Previous studies

Previous studies of the relationship between age at menopause and all-cause and cause-specific mortality are inconsistent. While some studies reported an association between early age at menopause and higher risk of mortality (Jacobsen et al., 1997; Jansen et al., 2002; Muka et al., 2016; Ossewaarde et al., 2005; Snowdon et al., 1989), one found lower mortality risk (Jacobsen et al., 2003), and several others did not observe an association (Cooper and Sandler, 1998; Jacobsen et al., 2004; Lapidus et al., 1985; Mondul et al., 2005; Snowdon et al., 1989). Our findings are similar to a 2016 meta-analysis of 32 studies (n = 310,329 women) that observed increased all-cause mortality risk among women with menopause at age < 45 compared with ≥45 years (relative risk [RR] = 1.12, 95% CI: 1.03–1.21) (Muka et al., 2016). Our study did not observe statistically significant associations for early age at menopause and mortality from stroke, circulatory disease, or all other causes of death. However, increased CVD mortality risk and fatal CHD risk for women with menopause at age < 45 compared with ≥45 (RR = 1.19, 95% CI: 1.08–1.31 and RR = 1.11, 95% CI: 1.03–1.20, respectively), and decreased risk of CHD mortality for women with menopause between ages 50–54 vs. < 50 years (RR = 0.87, 95% CI: 0.80–0.96) was reported in a recent meta-analysis (Muka et al., 2016).

4.3. HRT use and age at menopause and mortality

The effect of post-menopausal HRT (estrogen with or without progestin) compared with placebo on clinical outcomes such as CHD, MI, stroke, and death due to other causes was evaluated in women aged 50–79 years in the Women's Health Initiative (Rossouw et al., 2002). The trial was stopped early due to adverse events and increased risk of several major outcomes in the HRT group including CHD (HR = 1.29, 95% CI: 1.02–1.63) and stroke (HR = 1.41, 95% CI: 1.07–1.85) (Rossouw et al., 2002). Increased all-cause mortality risk was reported in the BWHS for women never using postmenopausal hormones with natural menopause at ages < 40 (mortality rate ratio [MRR] = 1.97, 95% CI: 1.30–2.99) and 40–44 (MRR = 1.50, 95% CI: 1.08–2.06) compared to ages 50–54; however, no associations were found for ever-postmenopausal hormone use (Li et al., 2013). Our study observed a statistically significant interaction between use of HRT and age at menopause, although the role of prescription guidelines with regard to HRT and type of menopause should also be considered. Among HRT users with early age at menopause, increased mortality risk was reported overall, among former smokers, and white women after adjustment for covariates. Risk of mortality was also increased among current smokers with early age at menopause who never used HRT.

The results from this study indicate that HRT use among women who experienced menopause at < 45 years of age may increase the risk of mortality. Our findings add to the body of literature and suggest the need for further research on the implications of HRT use with regard to mortality. Similar to previous findings described above, a significantly increased risk for stroke among women using estrogen and estrogen plus progestin therapy compared with placebo was reported in a recent review (Gartlehner et al., 2017). Another review reported a low risk of stroke for oral estrogen use among women who began HRT before age 65, although this study did not observe increased risk of CVD among women with HRT use prior to 60, or increased CVD mortality (National Collaborating Centre for Women's and Children's Health (UK), 2015). While current U.S. guidelines do not recommend routine use of HRT for primary or secondary prevention of heart disease based on the existing evidence, the use of HRT to alleviate symptoms may be considered for some women depending on their cardiovascular health profile and risk of associated events as well as timing of menopause (2013; Food and Drug Administration, 2019; Gartlehner et al., 2017). Prevention of bone loss and fracture as well as treatment for vasomotor symptoms and the genitourinary syndrome of menopause have been reported as benefits of hormone therapy by the 2017 Hormone Therapy Position Statement of The North American Menopause Society (NAMS) (The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017). Regardless of the indication and potential benefits, the various risks in relation to age, timing of menopause onset at hormone therapy initiation, and hormone therapy type must be considered, and individualized treatment should occur with regular reassessment of the risks and benefits over time (The NAMS 2017 Hormone Therapy Position Statement Advisory Panel, 2017).

4.4. Race and age at menopause and mortality

Racial differences in the relationship between age at menopause and mortality are important given the diverse racial distribution of the U.S. population. Risk of mortality was significantly increased for women in the BWHS experiencing natural menopause between ages 40–44 compared with 50–54 after adjustment for covariates (MRR = 1.33, 95% CI: 1.04–1.70) (Li et al., 2013). While our study similarly found increased all-cause mortality risk for black women with early age at menopause after adjustment for menopause type, the association and interaction

were not statistically significant although the literature is inconsistent with regard to age at menopause among black women. It is possible the analysis was underpowered to detect a significant difference between the groups. Our findings did show an increase in all-cause mortality for white women, albeit not significantly different from the association in black women.

4.5. Smoking and age at menopause and mortality

Smoking is associated with early age at menopause (Bromberger et al., 1997; Cooper et al., 1999; Gold et al., 2001; Hardy et al., 2000; Hayatbakhsh et al., 2012; Sun et al., 2012) with one study reporting an association between age at menopause and all-cause mortality modified by smoking (Bellavia et al., 2016). Our study observed increased risk of all-cause mortality for current smokers that was not significantly different from nonsmokers. However, only two studies have explored the relationship between age at menopause and mortality by smoking status (Bellavia et al., 2016; Li et al., 2013). Compared to women with menopause between ages 50–54, the BWHS reported increased all-cause mortality risk among ever smokers with natural menopause between ages 40–44 (MRR = 1.54, 95% CI: 1.14–2.04), but not never smokers (MRR = 0.91, 95%: 0.51–1.50) (Li et al., 2013). Among current smokers in the Swedish Mammography Cohort with menopause at ages 40 and 60, the median difference in age at death was 2.6 years (95% CI: 0.8–4.5); there was no relationship with never smokers (Bellavia et al., 2016). After including an interaction term for smoking by age at menopause, median age at death ranged from 81 to 82.7 for current smokers with menopause between ages 40–44 and 55–60, respectively, and remained constant among never-smokers for both menopause groups (86.5 to 87 years) (Bellavia et al., 2016).

A potential trend was observed for the effects of smoking on all-cause mortality among those with early menopause after adjustment. When stratified by HRT use, all-cause mortality risk increased for never-HRT/current smokers and ever-HRT/former smokers with early age at menopause compared to ≥45 year old non-smoking counterparts. Previous studies have suggested smoking may reduce the effects of oral estrogens (Ruan and Mueck, 2015) or may reflect smoking cessation caused by health problems and associated higher risk of mortality.

4.6. Limitations

Among women included in our study, the mean age at menopause was lower than reported in other U.S. studies (American Congress of Obstetricians and Gynecologists, 2011; Gold et al., 2001; Mondul et al., 2005). Possible explanations may be inclusion of women from the Southern U.S. in our study, a group for which menopause was previously reported to occur earlier compared with women from the Northeastern, Midwestern, and Western regions (McKnight et al., 2011), and a region that was not included in the Study of Women's Health Across the Nation (SWAN) study (Gold et al., 2001). There could also be a real difference in age at menopause or our findings could be affected by exclusion of women not meeting the study eligibility criteria due to implausible or unknown age at menopause.

A total of 7.1 years of follow-up was available which may be too short of a time frame to observe deaths from some of the outcomes assessed and may partially explain the lack of associations. There is a lack of detailed information on conditions besides hysterectomy that could contribute to menopause. In women with hysterectomy, there is the potential for misclassification when categorizing age of menopause solely by the age at cessation of menses. Data on use of contraception medication containing estrogen or progestin and length of HRT use were not available. Therefore, we were unable to evaluate whether early menopause might be a proxy for duration of time on HRT; however, in analyses stratified by HRT use, an association between menopause at age < 45 years and all-cause mortality was reported among women ever using HRT at baseline and not among never-HRT users. Additionally, the literature related to the long-term risks and benefits of HRT is inconsistent with some risks and benefits noted in recent guidelines, as previously described (Gartlehner et al., 2017; National Collaborating Centre for Women's and Children's Health (UK), 2015).

Although increased mortality risk was observed for black women with early menopause, small numbers limited statistical significance. In cause-specific mortality analyses, we were unable to stratify by smoking status and race due to the low number of events, except for CHD mortality which was stratified by race. Results of this study may not be representative of the general population. Self-report of age at menopause may increase the potential for recall bias or misclassification. However, dichotomization limits that impact.

5. Conclusions

We observed increased risk of all-cause mortality among ever-HRT users with early age at menopause in a geographically and bi-racially diverse cohort of women. While current U.S. guidelines do not recommend routine use of HRT for primary or secondary prevention of heart disease, four indications are FDA-approved including alleviation of vasomotor symptoms (e.g., hot flashes and night sweats) and significant genitourinary symptoms after consideration of their cardiovascular health profile, risk of associated adverse events, and the timing of menopause. Further studies are needed to better elucidate the relationship between early age at menopause and mortality and to study the role of underlying etiologies of early age at menopause. In particular, examination of the burden of menopausal symptoms and adverse effects are of interest given the large population at risk, the potential morbidity and costs associated with treatment and management, as well as lost productivity compared to potential benefits of HRT. Understanding these associations is critical for clinical applications to risk assessment and to reduce long-term public health consequences of early age at menopause.

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Declaration of Competing Interest

None.

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Appendix A

Table A
Baseline characteristics of women in the REGARDS study included vs. excluded in the analysis, 2003–2007.

Characteristic	Included vs. excluded participants	
	Included (n = 11,287) n (%), mean ± SD	Excluded (n = 1278) n (%), mean ± SD
Age	64.8 ± 8.8	65.8 ± 9.4
Race, black	4884 (43.27)	675 (52.8)**
Death	1524 (13.5)	224 (17.5)**
Time to death, years	5.3 ± 2.5	5.1 ± 2.6
Stroke belt region (vs. non-belt)	6483 (57.4)	710 (55.6)
Education		
Less than high school	1405 (12.5)	182 (14.4)
High school graduate	3169 (28.1)	332 (26.2)
Some college	3194 (28.3)	383 (30.2)
College graduate and above	3519 (31.2)	370 (29.2)
Smoking status		
Never	5965 (52.9)	616 (49.9)
Former	3687 (32.7)	426 (34.5)
Current	1635 (89.4)	193 (15.6)
Pack-years smoked	9.7 ± 18.5	9.9 ± 18.9
BMI		
Underweight/normal	2902 (25.8)	320 (25.6)
Overweight	3579 (31.9)	396 (31.7)
Obese	4748 (42.3)	535 (42.8)
Moderate/heavy alcohol consumption (vs. none)	3429 (30.4)	284 (26.0)*
Menopause induced by surgery/other condition (vs. natural)	5154 (45.7)	423 (42.5)
Ever use of hormone replacement therapy	6675 (59.3)	715 (56.5)
Current use of estrogen medication	1414 (12.5)	135 (10.6)*
Current use of progestin medication	300 (2.7)	30 (2.4)
History of cardiovascular disease	1470 (13.0)	133 (13.1)
History of stroke	626 (5.6)	83 (6.7)
Diabetes	2308 (20.5)	204 (27.2)**
Hypertension	6799 (60.2)	772 (61.7)

Abbreviations: vs., versus; BMI, body mass index.
* $p < 0.05$.
** $p < 0.0001$.

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