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Ages at Menarche and Menopause and Reproductive Lifespan As Predictors of Exceptional Longevity in Women: The Women's Health Initiative

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Abstract

Objective—To investigate associations between reproductive factors and survival to age 90 years.

Methods—This was a prospective study of postmenopausal women from the Women's Health Initiative recruited from 1993-1998 and followed until the last outcomes evaluation on August 29, 2014. Participants included 16,251 women born on or before August 29, 1924 for whom survival to age 90 during follow-up was ascertained. Women were classified as having survived to age 90 (exceptional longevity) or died before age 90. Multivariable logistic regression models were used to evaluate associations of ages at menarche and menopause (natural or surgical) and reproductive lifespan with longevity, adjusting for demographic, lifestyle, and reproductive characteristics.

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Results—Participants were on average aged 74.7 years (range, 69-81 years) at baseline. Of 16,251 women, 8,892 (55%) survived to age 90. Women aged 12 years at menarche had modestly increased odds of longevity (odds ratio [OR], 1.09; 95% confidence interval [CI], 1.00-1.19). There was a significant trend toward increased longevity for later age at menopause (natural or surgical; $P_{\text{trend}}=0.01$), with ORs (95% CIs) of 1.19 (1.04-1.36) and 1.18 (1.02-1.36) for 50-54 and 55 compared with <40 years, respectively. Later age at natural menopause as a separate exposure was also significantly associated with increased longevity ($P_{\text{trend}}=0.02$). Longer reproductive lifespan was significantly associated with increased longevity ($P_{\text{trend}}=0.008$). The odds of longevity were 13% (OR, 1.13; 95% CI, 1.03-1.25) higher in women with >40 compared with <33 reproductive years.

Conclusions—Reproductive characteristics were associated with late-age survival in older women.

Keywords

Menopause; menarche; longevity; lifespan; aging

Introduction

The number of women aged 90 years or older in the United States has increased dramatically in the past century. Currently estimated at 1.3 million, this demographic is expected to quadruple by 2050.¹ Despite this rapid increase, exceptional longevity is still considered a rare phenomenon.² Factors predisposing to a long lifespan in women are not fully understood.

Although ages at menarche and menopause have been studied in relation to cardiovascular disease, diabetes, and mortality in previous reports,³⁻²⁶ their association with longevity has received little attention. Later ages at menarche and menopause have been associated with reduced all-cause and cardiovascular mortality risk in some^{4-6,9,13} but not all^{7,8,11} studies. Longer reproductive lifespan, defined as the time interval between menarche and menopause, has also been associated with decreased morbidity and mortality.²⁶⁻²⁸ These findings suggest that later age at menopause and longer reproductive lifespan may increase the likelihood of long-term survival. However, as prior studies were largely focused on mortality, no study to date has evaluated the association of reproductive factors with survival to a specific advanced age, such as 90 years.

We investigated the associations of ages at menarche and menopause and reproductive lifespan with survival to age 90 years in a large, ethnically diverse cohort of postmenopausal women from the Women's Health Initiative (WHI). We also determined whether associations varied by race/ethnicity, baseline smoking behavior, or use of hormone therapy (HT).

Methods

Study Population

The WHI is a large, prospective study investigating major determinants of chronic diseases in postmenopausal women. Details of the study have been previously described.^{29,30} Briefly,

a racially and ethnically diverse cohort of postmenopausal women aged 50 to 79 years old was recruited from 40 clinical centers across the United States between 1993 and 1998. A total of 68,133 women were randomized into one or more of three clinical trials (CT), including one of two HT trials, and 93,676 were enrolled in an observational study (OS). In 2005, 76.9% of 150,075 eligible women consented to further follow-up for an additional five years in the Extension Study (ES), and in 2010, 86.8% of 107,706 women consented for another five years of follow-up. All participants provided written informed consent, and Institutional Review Board approval was received by all participating institutions.

The present study was restricted to CT, OS, and ES participants born on or before August 29, 1924 who had potential to survive to age 90 years during follow-up ending August 29, 2014. Only those with complete information on ages at menarche and menopause whose survival status could be ascertained were included, resulting in a cohort of 16,251 women aged 69 to 81 years at baseline with up to 21 years of follow-up (Figure 1).

Data Collection and Study Variables

At baseline, participants completed self-administered questionnaires assessing demographic characteristics, medical history, reproductive history, and lifestyle behaviors. Age at menarche was defined as age at first menstrual period and categorized into <12 (early menarche) or ≥12 (average or late menarche) years according to the literature.^{3,7} Age at natural menopause was defined as the age at which a woman last had any menstrual bleeding among those without a self-reported history of hysterectomy or bilateral oophorectomy before age at last menstrual bleeding. Women whose age at natural menopause was ≥60 years were considered to have experienced menopause at age 60 years. Age at surgical menopause was defined as age at bilateral oophorectomy among those who reported having this procedure performed before the age at last menstrual bleeding. A separate variable representing age at natural or surgical menopause combined was also created. Age at menopause was classified into the following categories according to the literature: <40, 40-44, 45-49, 50-54, or ≥55 years.^{14,15,19} Reproductive lifespan was defined as the difference between ages at menopause (natural or surgical) and menarche and categorized into quartiles (<33, 33-37, 38-40, or ≥40 years). Parity was defined as the number of term pregnancies. Information on past oral contraceptive (OC) use was also collected. HT use was defined according to self-reported use and participation in the HT trials as part of the CT.

Additional covariates collected at baseline included race/ethnicity, marital status, education, smoking, alcohol consumption, and self-rated health. Race/ethnicity was self-selected as American Indian/Alaskan Native, Asian/Pacific Islander, black/African-American, Hispanic/Latina, white, or other. Physical activity was summarized into metabolic equivalents (MET)/week based on the duration, frequency, and intensity of walking and other recreational activities.³¹ Trained clinic staff measured height and weight at baseline. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, and categorized according to standard cutpoints.³²

A history of major age-related diseases was defined as occurrence of one or more of the following diseases, each of which greatly increases a woman's risk of morbidity and mortality: coronary heart disease, cerebrovascular disease, cancer (excluding non-melanoma

skin cancer), diabetes, and hip fracture. Disease status was self-reported at baseline, and incident diseases were identified via periodic clinic visits and mailed questionnaires conducted biannually for CT participants through 2005, annually for OS participants, and then annually by mail for all ES participants. Incident diseases except for diabetes were adjudicated by physician medical record review.³³ Diabetes was defined as self-reported physician diagnosis of diabetes treated with oral medication or insulin.³⁴

Study Outcome

Women were classified as having survived to age 90 years (exceptional longevity) or died before age 90 years. Death was confirmed by trained physician adjudicators based on hospital records, autopsy or coroner's reports, or death certificates. Periodic linkage to the National Death Index was performed for all participants, including those lost to follow-up. Survival status was ascertained for 82% of participants born on or before August 29, 1924.

Statistical Analysis

Comparisons of baseline characteristics across categories of ages at menarche and menopause and survival were performed using χ^2 tests for categorical variables. Categories of age at menarche and survival were compared using two-sample t-tests or Wilcoxon rank-sum tests for normally distributed and non-normally distributed continuous variables, respectively. Analysis of variance or Kruskal-Wallis tests were used for comparisons of continuous variables across menopausal age categories.

Multivariable logistic regression models were used to determine reproductive characteristics associated with longevity, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). All multivariable models adjusted for potential confounders including baseline age, WHI study membership (CT or OS), race/ethnicity, education, marital status, smoking, alcohol consumption, physical activity, BMI, HT use, past OC use, and parity.^{7,9,10,14,19,25} Models for age at menarche were also adjusted for age at menopause (natural or surgical) and vice versa. Models for reproductive lifespan were adjusted for all of these factors except for age at menopause because of multicollinearity. Additional models were adjusted for a history of age-related diseases and self-rated health to determine whether these factors explain associations between reproductive characteristics and longevity. Tests for linear trend were performed by including reproductive variables as continuous predictors in the models. Interactions between reproductive characteristics and race/ethnicity, HT use, and smoking were assessed using likelihood ratio tests. To determine whether age at menopause was associated with longevity irrespective of type (i.e., natural vs. surgical), an interaction between age at menopause and a binary variable indicating whether menopause occurred due to natural or surgical reasons was also tested in the multivariable model. *P*-values were two-tailed and considered nominally statistically significant at $P < 0.05$. All analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

Results

At baseline, women were on average 74.7 (standard deviation [SD] 2.3) years old (Table 1). Average ages at menarche and menopause (natural or surgical) were 12.8 (SD 1.4; range

9-17) and 49.0 (SD 6.4; range 30-60) years, respectively. Women had a mean of 36.1 (SD 6.5; range 13-51) reproductive years. Reproductive lifespan was highly correlated with age at menopause ($r=0.98$; $p<0.001$) but weakly correlated with age at menarche ($r=-0.19$; $p<0.001$).

At baseline, women with later ages at menarche and menopause were more likely to be in very good health and have never smoked, and less likely to be obese or have a history of diabetes (Table 1). Women with later menarche were also less likely to be college graduates or have a history of CHD and more likely to have later age at menopause and higher parity. Women with later age at menopause were more likely to be married or living as married, be college graduates, report higher levels of physical activity, have a history of past OC use, and have higher parity.

Of 16,251 women who met the inclusion criteria for this study, 8,892 (55%) survived to age 90. Average age at death was 83.7 (SD 3.9) years, and the most common causes of death were cardiovascular disease, cerebrovascular disease, and cancer. At baseline, women who lived to 90 years were more likely to report higher levels of physical activity and be older, college graduates, current drinkers, and in excellent or very good health (Table 2). Women achieving longevity were also less likely to be current smokers, be obese, or have a history of age-related diseases.

The odds of longevity were modestly higher in women with menarche at ≥ 12 years (adjusted OR, 1.09; 95% CI, 1.00-1.19) than <12 years (Table 3). There was a significant linear trend toward increased longevity for later age at natural or surgical menopause ($P_{\text{trend}}=0.01$), with adjusted ORs (95% CIs) of 1.19 (1.04-1.36) and 1.18 (1.02-1.36) for 50-54 and ≥ 55 compared with <40 years, respectively. There was no significant interaction between age at menopause and natural vs. surgical menopause in the multivariable model (data not shown). In a separate model, later age at natural menopause was significantly associated with increased longevity ($P_{\text{trend}}=0.02$).

There was a significant association of reproductive lifespan with longevity ($P_{\text{trend}}=0.008$). Compared with women with <33 reproductive years, the odds of longevity were elevated across all other quartiles of reproductive lifespan. When defining reproductive lifespan as the difference between ages at natural menopause and menarche, findings were similar ($P_{\text{trend}}=0.01$; adjusted OR 1.09 [95% CI 0.99-1.20]; OR 1.17 [95% CI 1.06-1.29]; and OR 1.12 [95% CI 1.02-1.24] for 33-37, 38-40, and >40 compared with <33 years).

Findings for age at menarche were no longer significant after adjustment for a history of age-related diseases (and specifically, CHD) and self-rated health. Findings for age at menopause (natural or surgical) were no longer significant after adjustment for self-rated health, but persisted after adjustment for age-related diseases. Findings for reproductive lifespan were similar after additional adjustment for these factors. No interactions between reproductive factors and race/ethnicity, smoking, or HT use were observed (data not shown).

Discussion

In this large, prospective study in a racially and ethnically diverse cohort of postmenopausal women with up to 21 years of follow-up, survival to age 90 years was significantly higher in women with later menarche and menopause. Additionally, longer reproductive lifespan was significantly associated with survival to age 90 years. Findings were independent of demographic characteristics, lifestyle behaviors, BMI, reproductive factors, past OC use, and HT use.

Some studies have observed decreased risk of all-cause and cardiovascular mortality at older menarcheal ages.^{3-6,22} In a meta-analysis, each one-year increase in age at menarche was associated with a 3% lower risk of all-cause mortality.³ Another study observed that the association of later menarche with lower mortality was attenuated in women older than 80 years, suggesting that age at menarche may become less important over time as a risk factor for survival.⁵ Concordantly, we observed a modest increase in survival to age 90 years associated with an average or later age at menarche.

We found that later age at menopause overall, age at natural menopause as a separate exposure, and longer reproductive lifespan were associated with increased odds of longevity. Age at natural menopause has been associated with mortality in some^{10,14,16} but not all²⁵ studies. The association of age at surgical menopause with mortality has also been inconsistent across studies.^{16,17,19,20,24,25} A prior study among white women observed reduced mortality with increased (i.e., 40) reproductive years.²⁸

Inconsistent associations of age at menopause with mortality may be due to varying definitions of age at menopause, an important consideration when interpreting associations of this reproductive factor with health outcomes. Previous studies used varying methods to determine age at natural or surgical menopause, making direct comparisons with our results difficult.^{14,17-20} For example, some studies determined age at menopause by asking whether menstruation stopped due to natural or surgical reasons, without querying history of hysterectomy or bilateral oophorectomy;^{17,20} thus, misclassification may have biased findings. Our definition of age at menopause was comprehensive by taking into account age at final menstrual period, hysterectomy, and bilateral oophorectomy. However, few studies have examined age at menopause as a variable including both natural and surgical menopause.^{19,24} A study in >12,000 Dutch women observed a 2% reduction in mortality risk for every one-year increase in age at menopause occurring naturally or surgically, and life expectancy was two years longer among women aged at 55 compared with <40 years at menopause.¹⁹ It is also possible that the association of later age at menopause with longevity may be partly explained by lower odds of survival due to comorbidities and adverse health status among women who experienced premature menopause, irrespective of the cause.³⁵

Several mechanisms may explain the association of reproductive characteristics with longevity. Early menarche has been associated with increased risk of adult obesity, diabetes, and CVD.^{9,12,36,37} Later age at menopause and longer reproductive lifespan have been associated with decreased CVD risk, suggesting that prolonged endogenous ovarian hormone exposure may be cardioprotective^{23,27,38}, or conversely, that factors such as

smoking that may damage the ovary causing earlier menopause also damage the cardiovascular system.^{39,40} Although our findings persisted after adjustment for BMI and diabetes, age at menarche was no longer significant after adjustment for CHD and self-rated health, and age at menopause was no longer significant after adjustment for self-rated health. We did observe that women with later age at menarche were less likely to have a history of CHD and those with later age at menopause were more likely to be in excellent health at baseline, suggesting a possible explanation for our findings.

Reproductive events, such as menarche, menopause, and pregnancy, may simply be indicators of underlying health status. For example, hypertension of pregnancy and gestational diabetes, which typically resolve after delivery, may be harbingers of later type 2 diabetes and cardiovascular disease that were unmasked by pregnancy.^{41,42} In-utero exposures and childhood exposures (e.g., obesity) can also play a role in reproductive health status.^{43,44} Genetic factors have been associated with age at menarche, ages at natural and surgical menopause, and longevity⁴⁵⁻⁴⁸, suggesting that a common set of genetic factors may explain the link between these reproductive factors and longevity. For example, a genome-wide association study of age at natural menopause identified genetic variants involved in DNA replication and repair pathways, which are pathways central to aging.⁴⁶ Specifically, the DNA repair gene exonuclease 1 (*EXO1*) was significantly associated with age at menopause and has been previously associated with increased life expectancy among female centenarians.⁴⁹

This study had several limitations. Women who participated in the WHI may have been healthier at baseline than the general population of postmenopausal women. Furthermore, women who enrolled for additional follow-up were more likely to be white, educated, and healthier at baseline than those who withdrew, thus our findings may be biased by selective attrition. This may explain the large number of exceptional survivors in our cohort. Ages at menarche and menopause were reliant on self-reported recall of past events that could not be verified with medical records, which could result in misclassification. However, a previous study showed recall of age at menarche to be highly reproducible.⁵⁰ Age at menopause has been shown to be reproducible but more variable with increasing years since menopause.⁵¹ However, any misclassification of age at menopause is likely to be non-differential, given that survivors and non-survivors had similar average baseline age. The WHI cohort was recruited using extensive community-based outreach, and principally using mass mailings, which does not represent a national probability sample. Although information was available on a large array of covariates, we did not have information on family history of longevity, and we did not examine occupation, stress, or dietary variables, which may also predict longevity.

Strengths of this study include the prospective design with 21 years of follow-up, high retention of study participants over time, adjudicated outcome ascertainment, and large, multi-ethnic sample of postmenopausal women who reached nonagenarian status. The large sample size gave us excellent power to detect even small associations with precision. This study included a cohort of women with a narrow age range, thus limiting potential bias due to birth cohort effects.

Conclusions

Average or later age at menarche, later age at menopause, and longer reproductive lifespan were associated with higher likelihood of survival to age 90 years among postmenopausal women. Further studies are needed to elucidate lifestyle, genetic, and environmental factors associated with ages at menarche and menopause and reproductive lifespan to determine potential mechanisms explaining the link between characteristics of reproductive lifespan and longevity. With secular trends showing decreasing age at menarche, increasing age at menopause, and a concurrent rise in longevity,^{2,52,53} additional studies in younger birth cohorts will be needed in the future to precisely define the relationship between the timing of reproductive events and a woman's length of life.

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Figure 1.
Derivation of Final Analytic Sample

Table 1

Baseline Characteristics of Postmenopausal Women by Ages at Menarche and Menopause^a

	Age at menarche, y			Age at menopause, y					P value
	Total sample	<12	12	<40	40-44	45-49	50-54	55	
Age, mean (SD), y	74.7 (2.3)	74.6 (2.3)	74.7 (2.3)	74.6 (2.3)	74.7 (2.3)	74.7 (2.3)	74.7 (2.2)	74.7 (2.3)	0.17
Race/ethnicity	(n=16191)	(n=2696)	(n=13495)	(n=1247)	(n=2103)	(n=3432)	(n=6312)	(n=3097)	
White	14468 (89.4)	2400 (89.0)	12068 (89.4)	1016 (81.5)	1802 (85.7)	3113 (90.7)	5735 (90.9)	2802 (90.5)	<0.001
Black	856 (5.3)	155 (5.8)	701 (5.2)	145 (11.6)	155 (7.4)	157 (4.6)	259 (4.1)	140 (4.5)	
Hispanic	222 (1.4)	46 (1.7)	176 (1.3)	23 (1.8)	47 (2.2)	36 (1.1)	73 (1.2)	43 (1.4)	
Other	645 (4.0)	95 (3.5)	550 (4.1)	63 (5.1)	99 (4.7)	126 (3.7)	245 (3.9)	112 (3.6)	
Educational level	(n=16155)	(n=2694)	(n=13461)	(n=1242)	(n=2095)	(n=3418)	(n=6305)	(n=3095)	
Less than high school	1085 (6.7)	171 (6.4)	914 (6.8)	145 (11.7)	180 (8.6)	216 (6.3)	370 (5.9)	174 (5.6)	<0.001
High school	2807 (17.4)	420 (15.6)	2387 (17.7)	249 (20.1)	419 (20.0)	599 (17.5)	1082 (17.2)	458 (14.8)	
Some college	6425 (39.8)	1012 (37.6)	5413 (40.2)	509 (41.0)	860 (41.1)	1388 (40.6)	2465 (39.1)	1203 (38.9)	
College graduate	5838 (36.1)	1091 (40.5)	4747 (35.3)	339 (27.3)	636 (30.4)	1215 (35.6)	2388 (37.9)	1260 (40.7)	
Marital status	(n=16183)	(n=2693)	(n=13490)	(n=1248)	(n=2093)	(n=3426)	(n=6314)	(n=3102)	
Married/living as married	7474 (46.2)	1216 (45.2)	6258 (46.4)	532 (42.6)	942 (45.0)	1507 (44.0)	2970 (47.0)	1523 (49.1)	<0.001
Widowed	6372 (39.4)	1064 (39.5)	5308 (39.4)	538 (43.1)	848 (40.5)	1380 (40.3)	2470 (39.1)	1136 (36.6)	
Divorced/separated	1552 (9.6)	282 (10.5)	1270 (9.4)	126 (10.1)	193 (9.2)	354 (10.3)	567 (9.0)	312 (10.1)	
Never married	785 (4.9)	131 (4.9)	654 (4.9)	52 (4.2)	110 (5.3)	185 (5.4)	307 (4.9)	131 (4.2)	
Smoking behavior	(n=15968)	(n=2657)	(n=13311)	(n=1226)	(n=2066)	(n=3381)	(n=6224)	(n=3071)	
Never smoked	8919 (55.9)	1386 (52.2)	7533 (56.6)	678 (55.3)	1136 (55.0)	1858 (55.0)	3480 (55.9)	1767 (57.5)	0.04
Past smoker	6415 (40.2)	1147 (43.2)	5268 (39.6)	484 (39.5)	832 (40.3)	1382 (40.9)	2517 (40.4)	1200 (39.1)	
Current smoker	634 (4.0)	124 (4.7)	510 (3.8)	64 (5.2)	98 (4.7)	141 (4.2)	227 (3.7)	104 (3.4)	
Alcohol intake	(n=16126)	(n=2680)	(n=13446)	(n=1240)	(n=2092)	(n=3416)	(n=6288)	(n=3090)	
Nondrinker	2162 (13.4)	325 (12.1)	1837 (13.7)	220 (17.7)	298 (14.2)	463 (13.6)	826 (13.1)	355 (11.5)	<0.001
Past drinker	3256 (20.2)	563 (21.0)	2693 (20.0)	294 (23.7)	474 (22.7)	672 (19.7)	1203 (19.1)	613 (19.8)	
Current drinker	10708 (66.4)	1792 (66.9)	8916 (66.3)	726 (58.6)	1320 (63.1)	2281 (66.8)	4259 (67.7)	2122 (68.7)	
Recreational physical activity, mean (SD), MET-hours/week	12.1 (13.1)	11.9 (13.2)	12.2 (13.1)	11.8 (14.1)	11.1 (12.2)	11.5 (12.2)	12.5 (13.4)	12.9 (13.3)	<0.001
Body mass index kg/m ²	(n=16074)	(n=2676)	(n=13398)	(n=1244)	(n=2083)	(n=3399)	(n=6262)	(n=3086)	

	Total sample	Age at menarche, y		P value	Age at menopause, y					P value
		<12	12		<40	40-44	45-49	50-54	55	
Underweight (<18.5)	245 (1.5)	32 (1.2)	213 (1.6)	<0.001	14 (1.1)	26 (1.3)	56 (1.7)	96 (1.5)	53 (1.7)	<0.001
Normal weight (18.5-24.9)	6238 (38.8)	838 (31.3)	5400 (40.3)		420 (33.8)	747 (35.9)	1309 (38.5)	2501 (39.9)	1261 (40.9)	
Overweight (25.0-29.9)	5910 (36.8)	994 (37.1)	4916 (36.7)		479 (38.5)	759 (36.4)	1288 (37.9)	2309 (36.9)	1075 (34.8)	
Obese (≥ 30)	3681 (22.9)	812 (30.3)	2869 (21.4)		331 (26.6)	551 (26.5)	746 (22.0)	1356 (21.7)	697 (22.6)	
History of major age-related diseases ^b	(n=16251)	(n=2708)	(n=13543)		(n=1251)	(n=2107)	(n=3443)	(n=6335)	(n=3115)	
Coronary heart disease	2325 (14.3)	430 (15.9)	1895 (14.0)	0.01	199 (15.9)	333 (15.8)	499 (14.5)	868 (13.7)	426 (13.7)	0.05
Stroke	1772 (10.9)	292 (10.8)	1480 (10.9)	0.82	148 (11.8)	227 (10.8)	370 (10.8)	693 (10.9)	334 (10.7)	0.85
Cancer (excluding non-melanoma skin cancer)	4861 (29.9)	821 (30.3)	4040 (29.8)	0.61	360 (28.8)	648 (30.8)	991 (28.8)	1878 (29.6)	984 (31.6)	0.09
Diabetes	2266 (13.9)	442 (16.3)	1824 (13.5)	<0.001	206 (16.5)	321 (15.2)	475 (13.8)	835 (13.2)	429 (13.8)	0.01
Hip fracture	1430 (8.8)	244 (9.0)	1186 (8.8)	0.67	107 (8.6)	182 (8.6)	317 (9.2)	532 (8.4)	292 (9.4)	0.49
1 disease	9335 (57.4)	1617 (59.7)	7718 (57.0)	0.009	738 (59.0)	1236 (58.7)	1956 (56.8)	3583 (56.6)	1822 (58.5)	0.16
Self-rated health	(n=16138)	(n=2684)	(n=13454)		(n=1240)	(n=2090)	(n=3418)	(n=6293)	(n=3097)	
Excellent	2059 (12.8)	340 (12.7)	1719 (12.8)	0.02	115 (9.3)	236 (11.3)	431 (12.6)	815 (13.0)	462 (14.9)	<0.001
Very good	6327 (39.2)	1004 (37.4)	5323 (39.6)		420 (33.9)	784 (37.5)	1317 (38.5)	2567 (40.8)	1239 (40.0)	
Good	5971 (37.0)	1003 (37.4)	4968 (36.9)		499 (40.2)	807 (38.6)	1298 (38.0)	2275 (36.2)	1092 (35.3)	
Fair/poor	1781 (11.0)	337 (12.6)	1444 (10.7)		206 (16.6)	263 (12.6)	372 (10.9)	636 (10.1)	304 (9.8)	
Self-reported HT use	(n=16038)	(n=2673)	(n=13365)		(n=1235)	(n=2082)	(n=3393)	(n=6250)	(n=3078)	
Never	6522 (40.7)	1033 (38.7)	5489 (41.1)	0.07	410 (33.2)	780 (37.5)	1398 (41.2)	2776 (44.4)	1158 (37.6)	<0.001
Past	5202 (32.4)	896 (33.5)	4306 (32.2)		401 (32.5)	695 (33.4)	1143 (33.7)	2001 (32.0)	962 (31.3)	
Current	4314 (26.9)	744 (27.8)	3570 (26.7)		424 (34.3)	607 (29.2)	852 (25.1)	1473 (23.6)	958 (31.1)	
Past oral contraceptive use	(n=16251)	(n=2708)	(n=13543)		(n=1251)	(n=2107)	(n=3443)	(n=6335)	(n=3115)	
Age at menarche, mean (SD), y	2049 (12.6)	349 (12.9)	1700 (12.6)	0.63	32 (2.6)	149 (7.1)	418 (12.1)	940 (14.8)	510 (16.4)	<0.001
Age at menopause, mean (SD), y	12.8 (1.4)				12.7 (1.5)	12.8 (1.5)	12.9 (1.4)	12.8 (1.4)	12.9 (1.5)	<0.001
Age at menopause, mean (SD), y	49.0 (6.4)	48.5 (6.8)	49.0 (6.3)	<0.001						
Age at natural menopause, mean (SD), y	49.2 (6.2)	48.8 (6.6)	49.3 (6.2)	0.004						
Age at surgical menopause, mean (SD), y	45.5 (7.8)	45.3 (8.2)	45.6 (7.7)	0.86						
Reproductive lifespan, mean (SD), y	36.1 (6.5)	37.8 (6.8)	35.8 (6.4)	<0.001						
Parity	(n=16174)	(n=2697)	(n=13477)		22.2 (3.2)	28.8 (2.0)	33.9 (2.0)	38.5 (2.0)	44.3 (2.7)	<0.001
Nulliparous	2165 (13.4)	395 (14.7)	1770 (13.1)	0.03	(n=1246)	(n=2094)	(n=3430)	(n=6298)	(n=3106)	
	1502 (9.3)	273 (10.1)	1229 (9.1)		254 (20.4)	332 (15.9)	481 (14.0)	765 (12.2)	333 (10.7)	<0.001
					146 (11.7)	228 (10.9)	332 (9.7)	536 (8.5)	260 (8.4)	

	Total sample	Age at menarche, y		P value	Age at menopause, y					P value
		<12	12		<40	40-44	45-49	50-54	55	
2	3907 (24.2)	665 (24.7)	3242 (24.1)		311 (25.0)	474 (22.6)	825 (24.1)	1525 (24.2)	772 (24.9)	
3	3747 (23.2)	602 (22.3)	3145 (23.3)		231 (18.5)	462 (22.1)	806 (23.5)	1495 (23.7)	753 (24.2)	
4	2436 (15.1)	396 (14.7)	2040 (15.1)		150 (12.0)	281 (13.4)	500 (14.6)	997 (15.8)	508 (16.4)	
5	2417 (14.9)	366 (13.6)	2051 (15.2)		154 (12.4)	317 (15.1)	486 (14.2)	980 (15.6)	480 (15.5)	

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation

^aData are presented as No. (%) unless otherwise indicated

^bIncludes baseline self-reported and incident adjudicated diseases

Table 2Baseline Characteristics of Postmenopausal Women in Relation to Survival to Age 90 Years^a

Characteristic	Survived to age 90 (n=8892)	Died before age 90 (n=7359)	P value
Age, mean (SD), y	75.1 (2.2)	74.2 (2.3)	<0.001
Race/ethnicity	(n=8859)	(n=7332)	
White	7936 (89.6)	6532 (89.1)	
Black	430 (4.9)	426 (5.8)	0.008
Hispanic	115 (1.3)	107 (1.5)	
Other	378 (4.3)	267 (3.6)	
Educational level	(n=8849)	(n=7306)	
Less than high school	528 (6.0)	557 (7.6)	
High school	1482 (16.8)	1325 (18.1)	<0.001
Some college	3503 (39.6)	2922 (40.0)	
College graduate	3336 (37.7)	2502 (34.3)	
Marital status	(n=8860)	(n=7323)	
Married/living as married	4267 (48.2)	3207 (43.8)	<0.001
Widowed	3417 (38.6)	2955 (40.4)	
Divorced/separated	759 (8.6)	793 (10.8)	
Never married	417 (4.7)	368 (5.0)	
Smoking behavior	(n=8762)	(n=7206)	
Never smoked	5276 (60.2)	3643 (50.6)	
Past smoker	3317 (37.9)	3098 (43.0)	<0.001
Current smoker	169 (1.9)	465 (6.5)	
Alcohol intake	(n=8832)	(n=7294)	
Nondrinker	1184 (13.4)	978 (13.4)	
Past drinker	1560 (17.7)	1696 (23.3)	<0.001
Current drinker	6088 (68.9)	4620 (63.3)	
Recreational physical activity, mean (SD), MET-hours/week	12.9 (13.4)	11.2 (12.6)	<0.001
Body mass index, kg/m ²	(n=8797)	(n=7277)	
Underweight (<18.5)	104 (1.2)	141 (1.9)	
Normal weight (18.5-24.9)	3518 (40.0)	2720 (37.4)	<0.001
Overweight (25.0-29.9)	3348 (38.1)	2562 (35.2)	
Obese (≥ 30)	1827 (20.8)	1854 (25.5)	
History of major age-related diseases ^b	(n=8892)	(n=7359)	
Coronary heart disease	719 (8.1)	1606 (21.8)	<0.001
Stroke	542 (6.1)	1230 (16.7)	<0.001
Cancer (excluding non-melanoma skin cancer)	2021 (22.7)	2840 (38.6)	<0.001
Diabetes	1078 (12.1)	1188 (16.1)	<0.001
Hip fracture	704 (7.9)	726 (9.9)	<0.001
>1 disease	4022 (45.2)	5313 (72.2)	<0.001
Self-rated health	(n=8838)	(n=7300)	
Excellent	1339 (15.2)	720 (9.9)	

Characteristic	Survived to age 90 (n=8892)	Died before age 90 (n=7359)	P value
Very good	3786 (42.8)	2541 (34.8)	<0.001
Good	3063 (34.7)	2908 (39.8)	
Fair/poor	650 (7.4)	1131 (15.5)	
	(n=8773)	(n=7265)	
Ever HT use ^c	5646 (64.4)	4546 (62.6)	0.02
	(n=8892)	(n=7359)	
Past oral contraceptive use	1115 (12.5)	934 (12.7)	0.77
	(n=8892)	(n=7359)	
Age at menarche, y			0.005
<12	1415 (15.9)	1293 (17.6)	
12	7477 (84.1)	6066 (82.4)	
	(n=8892)	(n=7359)	
Age at menopause, y			<0.001
<40	609 (6.9)	642 (8.7)	
40-44	1099 (12.4)	1008 (13.7)	
45-49	1878 (21.1)	1565 (21.3)	
50-54	3554 (40.0)	2781 (37.8)	
55	1752 (19.7)	1363 (18.5)	
	(n=8336)	(n=6900)	
Age at natural menopause, y			<0.001
<40	494 (5.9)	515 (7.5)	
40-44	995 (11.9)	915 (13.3)	
45-49	1721 (20.7)	1447 (21.0)	
50-54	3450 (41.4)	2709 (39.3)	
55	1676 (20.1)	1314 (19.0)	
	(n=556)	(n=459)	
Age at surgical menopause, y			0.06
<40	115 (20.7)	127 (27.7)	
40-44	104 (18.7)	93 (20.3)	
45-49	157 (28.2)	118 (25.7)	
50-54	104 (18.7)	72 (15.7)	
55	76 (13.7)	49 (10.7)	
	(n=8892)	(n=7359)	
Reproductive lifespan, y			<0.001
<33	2127 (23.9)	2014 (27.4)	
33-37	2499 (28.1)	2015 (27.4)	
38-40	2068 (23.3)	1601 (21.8)	
>40	2198 (24.7)	1729 (23.5)	
	(n=8849)	(n=7325)	
Parity			<0.001
Nulliparous	1160 (13.1)	1005 (13.7)	
1	764 (8.6)	738 (10.1)	
2	2234 (25.3)	1673 (22.8)	
3	2111 (23.9)	1636 (22.3)	
4	1347 (15.2)	1089 (14.9)	
5	1233 (13.9)	1184 (16.2)	

Abbreviations: HT, hormone therapy; MET, metabolic equivalent; SD, standard deviation;

^aData are presented as No. (%) unless otherwise indicated

^bIncludes baseline self-reported and incident adjudicated diseases

^cIncludes HT use based on self-report and due to participation in HT trials

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Table 3

Associations of Reproductive Characteristics with Survival to Age 90 among Postmenopausal Women

	No./total (%) survived to 90	Age-adjusted OR (95% CI)	P value for trend	Multivariable-adjusted OR (95% CI)	P value for trend
Age at menarche ^a , y					
<12	1415/2708 (52.3)	1 [Reference]		1 [Reference]	
12	7477/13543 (55.2)	1.11 (1.02-1.21)	0.61	1.09 (1.00-1.19)	0.77
Age at menopause ^a , y					
<40	609/1251 (48.7)	1 [Reference]		1 [Reference]	
40-44	1099/2107 (52.2)	1.13 (0.98-1.31)		1.09 (0.94-1.27)	
45-49	1878/3443 (54.6)	1.24 (1.09-1.41)	<0.001	1.13 (0.98-1.30)	0.01
50-54	3554/6335 (56.1)	1.32 (1.17-1.50)		1.19 (1.04-1.36)	
55	1752/3115 (56.2)	1.34 (1.17-1.53)		1.18 (1.02-1.36)	
Age at natural menopause ^a , y					
<40	494/1009 (49.0)	1 [Reference]		1 [Reference]	
40-44	995/1910 (52.1)	1.12 (0.96-1.31)		1.06 (0.90-1.25)	
45-49	1721/3168 (54.3)	1.22 (1.05-1.41)	<0.001	1.11 (0.95-1.29)	0.02
50-54	3450/6159 (56.0)	1.31 (1.14-1.50)		1.18 (1.02-1.36)	
55	1676/2990 (56.1)	1.32 (1.14-1.53)		1.16 (0.99-1.36)	
Age at surgical menopause ^a , y					
<40	115/242 (47.5)	1 [Reference]		1 [Reference]	
40-44	104/197 (52.8)	1.23 (0.83-1.82)		1.35 (0.88-2.08)	
45-49	157/275 (57.1)	1.46 (1.02-2.09)	0.02	1.33 (0.90-1.98)	0.11
50-54	104/176 (59.1)	1.59 (1.06-2.38)		1.50 (0.96-2.34)	
55	76/125 (60.8)	1.50 (0.96-2.36)		1.43 (0.86-2.38)	
Reproductive lifespan ^b , y					
<33	2127/4141 (51.4)	1 [Reference]		1 [Reference]	
33-37	2499/4514 (55.4)	1.17 (1.07-1.27)		1.11 (1.01-1.21)	
38-40	2068/3669 (56.4)	1.22 (1.12-1.34)	<0.001	1.17 (1.06-1.29)	0.008
>40	2198/3927 (56.0)	1.21 (1.11-1.33)		1.13 (1.03-1.25)	

Abbreviations: CI, confidence interval; OR, odds ratio; y, years

^a Multivariable model adjusts for baseline age, study membership (clinical trial or observational study), demographics (race/ethnicity, educational level, baseline marital status), lifestyle behaviors (baseline smoking behavior, baseline alcohol intake, baseline physical activity), baseline body mass index, and reproductive factors (ever using hormone therapy, past oral contraceptive use, age at menopause, age at menarche, and parity)

^b Multivariable model adjusts for baseline age, study membership (clinical trial or observational study), demographics (race/ethnicity, educational level, baseline marital status), lifestyle behaviors (baseline smoking behavior, baseline alcohol intake, baseline physical activity), baseline body mass index, and reproductive factors (ever using hormone therapy, past oral contraceptive use, age at menarche, and parity)