ORIGINAL RESEARCH

Duration of Reproductive Life Span, Age at Menarche, and Age at Menopause Are Associated With Risk of Cardiovascular Disease in Women

Sylvia H. Ley, PhD, RD; Yanping Li, PhD; Deirdre K. Tobias, ScD; JoAnn E. Manson, MD, DrPH; Bernard Rosner, PhD; Frank B. Hu, MD, PhD; Kathryn M. Rexrode, MD, MPH

***Background*—**Although the timing of menarche and menopause may be associated with cardiovascular disease (CVD), the entire reproductive life span has not been considered comprehensively as risk for CVD. We investigate the associations of reproductive life span duration and ages at menarche and menopause, induced by natural means or surgical bilateral oophorectomy, with incident CVD in women.

***Methods and Results*—**Prospective cohort study of 73 814 Nurses' Health Study following participants without CVD, defined as incident coronary heart disease or stroke, from 1980 through 2012. Duration of reproductive life span was generated by subtracting age at menarche from age at menopause. A shorter reproductive life span was associated with a higher risk of incident CVD after multivariable adjustment (relative risk, 1.32 [95% confidence interval, 1.16–1.49] comparing duration <30 with ≥42 years; *P* trend<0.0001). Early age at menopause was associated with higher multivariable-adjusted CVD risk (1.32 [1.16–1.51] comparing age <40 with 50 to <55 years; *P* trend<0.0001), with excess risk for both natural and surgical menopause. Compared with women with menarche at 13 years, the multivariable-adjusted CVD risk for early menarche at ≤10 years was 1.22 (1.09–1.36). The association between reproductive life span and CVD remained significant in sensitivity analyses excluding women who experienced extreme early age at menarche or who used hormone therapy.

***Conclusions*—**A shorter duration of reproductive life span is associated with a higher risk of CVD, which is likely driven by the timing of menopause induced either naturally or surgically. Extremely early age at menarche is also associated with a higher risk of CVD. **(*J Am Heart Assoc*. 2017;6:e006713. DOI: 10.1161/JAHA.117.006713.)**

Key Words: age at menarche • cardiovascular disease • coronary heart disease • menopause • reproductive life span • stroke

Women of reproductive age are at a lower risk of cardiovascular disease (CVD) compared with men of similar ages and lifestyles,[1] but women who experience an early menopause are exposed to increased CVD risk.[2] On the other hand, the timing of menarche is associated with type 2 diabetes mellitus risk,[3,4] potentially influenced by childhood adiposity and disturbances in the endocrine system.[5,6] However, these reproductive events have not been investigated thoroughly with consideration for both ends of reproductive life span, which may have an implication for cardiovascular health trajectory later in life.

Although the mechanism explaining these reported associations is not entirely clear, ovarian hormones are suspected to be involved in the cardioprotective effects.[7] Women may

From the Departments of Nutrition (S.H.L., Y.L., F.B.H.), Epidemiology (J.E.M., F.B.H.), and Biostatistics (B.R.), Harvard T.H. Chan School of Public Health, Boston, MA; Channing Division of Network Medicine (S.H.L., B.R., F.B.H.) and Division of Preventive Medicine (D.K.T., J.E.M., K.M.R.), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; Division of Women's Health, Department of Medicine, Brigham and Women's Hospital, Boston, MA (K.M.R.).

Accompanying Tables S1 through S4 are available at http://jaha.ahajournals.org/content/6/11/e006713/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Kathryn M. Rexrode, MD, MPH, Brigham and Women's Hospital; Harvard Medical School; Division of Women's Health, Department of Medicine, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115. E-mail: krexrode@bwh.harvard.edu and Sylvia H. Ley, PhD, RD, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School; Department of Nutrition, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Boston, MA 02115. E-mail: sylvia.ley@channing.harvard.edu

Received July 19, 2017; accepted September 29, 2017.

Clinical Perspective

What Is New?

- In this prospective cohort study, a shorter duration of reproductive life span, extremely early age at menarche, and early age at menopause were associated with a higher risk of cardiovascular disease.
- The association remained significant in a sensitivity analysis among nonusers of hormone therapy, indicating that the observed association was not driven by the use of exogeneous hormones.

What Are the Clinical Implications?

- The associations of timing of menarche and menopause with cardiovascular disease suggest an underlying role of sex hormones in cardiovascular disease.

experience protective benefits of these hormones before menopause, given that CVD incidence rises sharply after menopause.[1,8] If the primary mechanism of the association is the number of years of exposure to ovarian hormones, then the duration of reproductive life span from menarche to menopause might serve as an improved marker of CVD risk in women.

The association between duration of reproductive life span and CVD risk and the contribution of potential confounding factors has not been investigated thoroughly in a large prospective study. A shorter duration of reproductive life span was associated with a higher Framingham Risk Score[9] and type 2 diabetes mellitus risk.[10] However, this study was limited by its cross-sectional design to investigate a long-term CVD event risk. Gynecological procedures, such as hysterectomy with bilateral oophorectomy, are associated with higher risk of CVD.[11,12] Therefore, the association between age at menopause and risk of CVD warrants further investigation among women who experienced natural or surgically induced menopause, and consideration for the potential impact of exogenous hormone therapy use is needed. Extremely early age at menarche has been associated with type 2 diabetes mellitus risk previously,[3,4] potentially mediated through childhood obesity contributing to early onset of puberty and alteration in ovarian hormones.[5,6] Although earlier age at menarche has been associated with CVD morbidity and mortality in a few studies,[13–15] the association has not been consistently observed by others.[16–18] We therefore investigated the association between overall duration of reproductive life span and CVD risk, in addition to studying the independent associations of age at menarche and age at menopause with risk of CVD, in women from a large cohort study with long-term follow-up and detailed characterization of reproductive and medical history and lifestyle risk factors for CVD.

Methods

Study Population

The NHS (Nurses' Health Study) is a prospective cohort study of 121 700 female registered nurses aged 30 to 55 years living across the United States at the baseline data collection in 1976. The participants have been followed biennially with questionnaires on medical history and lifestyle factors. In 1980, dietary and physical activity questionnaires were added. The follow-up rate was above 90%. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital and the Human Subjects Committee Review Board of Harvard T.H. Chan School of Public Health (Boston, MA), and the participants gave informed consent.

Women were eligible for the current analysis beginning in 1980 if they were menopausal, or at the time of reporting menopause during follow-up, except for age at menarche analysis where premenopausal women were included. Women with cancer (n=4959), CVD (n=2568), or death (n=361) before 1980 were excluded. We also excluded those with missing main exposure variables, such as age at menarche, or with reported ages at menarche greater than 18 years because such delays are outside the spectrum of normal onset and are likely to have a pathological cause (n=5227). We excluded women who were missing age at menopause (n=3185). Women entered the follow-up analysis at the time of the first report of menopause, and therefore women with incident cancer or CVD before the entry of follow-up were further excluded. Women who underwent hysterectomy with ovarian conservation before menopause were excluded because age at menopause cannot be accurately determined in these women. Women who did not report a reason for menopause were excluded because of inability to determine whether periods ceased because of hysterectomy or to actual menopause. After exclusions, 73 814 participants with reproductive life span exposure variables were followed through June 2012.

Assessment of Reproductive Life Span

Age at menarche, defined as age at the first menstrual period, was asked on the 1976 questionnaire. Age at menarche self-reported in middle age was previously validated in a population-based birth cohort from the United Kingdom and correlated with that reported at the time of puberty (r=0.6).[19] Menopausal status was captured by asking biennially whether the participants' menstrual periods had ceased permanently and, if so, at what age and for what reason (ie, natural menopause or surgical menopause [hysterectomy with bilateral oophorectomy]). Self-reported menopause status and age at menopause were highly reproducible in a validation study in

a subsample of the NHS participants.[20] Among women reporting natural menopause, 82% of women reported their age at menopause to within 1 year on the 2 follow-up questionnaires. When medical records were obtained from a subset of women who reported surgical menopause (n=200), agreement between self-report and medical record was evident in all but 2 women.[20] Duration of reproductive life span was generated by subtracting age at menarche from age at menopause. Because these reproductive events occur within a narrow range of women's life span, we have grouped these events into categories. Reproductive life span variable was categorized into 5 groups of 3-year incremental differences. The median age of menarche or menopause was used as a referent group for ages at menarche and menopause analyses.

Assessment of Other Exposures

Information on other potential CVD risk factors, including medical, reproductive, lifestyle practices, and body weight, was collected through biennial questionnaires. Cigarette smoking, physical activity, family history of diabetes mellitus, comorbidity of hypertension, hypercholesterolemia, diabetes mellitus, hormone therapy use, parity, and age at first birth were assessed from these questionnaires. The validity of these assessments has been documented previously.[21–23] Body mass index (BMI) was calculated as updated weight (kg) throughout the follow-up period divided by the square of height (m) in 1976. Based on the previous validation study, self-reported weights have been correlated highly with measured weights (r=0.97).[24] Dietary information has been updated using validated semiquantitative Food Frequency Questionnaires in every 4 years. Alternate Healthy Eating Index score to evaluate the diet quality, which has been significantly associated with CVD in this cohort,[25] was generated excluding alcohol intake, to adjust for alcohol as an independent risk factor.

Ascertainment of CVD

CVD was defined as coronary heart disease (CHD; nonfatal or fatal myocardial infarction [MI]) and nonfatal or fatal stroke. We requested permission to review medical records from women who reported having a newly diagnosed nonfatal MI or stroke on a follow-up questionnaire. Study physicians blinded to the participants' exposure status reviewed the medical records. Nonfatal MI was confirmed if it met the criteria of the World Health Organization for symptoms plus either diagnostic electrocardiographic changes or elevated cardiac enzyme concentrations. To confirm nonfatal stroke, the study physicians reviewed the results of computed tomography or magnetic resonance imaging, and a stroke diagnosis was confirmed if the medical records showed a neurological deficit with sudden or rapid onset that persisted for 24 hours or longer. Strokes were classified according to the criteria of the National Survey of Stroke as attributed to ischemia (embolic or thrombotic), hemorrhage (subarachnoid hemorrhage or intracerebral hemorrhage), or unknown cause.[26] Cerebrovascular disease caused by infection, trauma, or malignancy or silent strokes were excluded. Nonfatal strokes for which confirmatory information was obtained by interview or letter but no medical records were available were designated as probable and were assigned to stroke of unspecified type given lack of primary data for review.

Deaths were reported by next of kin and the postal system, or through the National Death Index. We estimated that follow-up for the deaths was over 98% complete using all sources combined.[27] Fatal CHD (MI), defined by *International Classification of Diseases, Eighth Revision* codes 410 to 412 (410), was defined as fatal MI if this was confirmed by hospital records or autopsy, or if CHD was listed as the cause of death on the certificate, which was then counted as the underlying and only plausible cause, and evidence of previous CHD was available. Probable fatal CHD (MI) events include deaths where no medical records surrounding the death were available but CHD was the underlying cause on the death certificate or National Death Index search or a family member provided supporting information regarding the diagnosis. Fatal strokes were coded using the same criteria as for nonfatal cases, but autopsy evidence was also accepted as was a death certificate listing the cause of death as stroke. Because the exclusion of probable CVD events did not alter the main results, both confirmed and probable CHD and stroke cases were included in this analysis to maximize statistical power. Similarly, fatal and nonfatal CVD event results did not differ when analyzed individually, and therefore the combined event results were presented.

Statistical Analysis

For each participant, person-time was allocated according to the categories of reproductive life span calculated from the earliest questionnaire after menopause occurrence to the date of diagnosis of CVD, death, or the end of follow-up, whichever came first. Multivariable time dependent Cox proportional hazards models were used to estimate relative risk (RR) and 95% confidence interval (CI). The time scale for the left truncated survival model was age (months) in model 1. Model 2 was additionally adjusted for demographic, reproductive and medical history, lifestyle factors including ethnicity (European descent, Asian, Hispanic, and black), hormone therapy use (never, current, or past), oral contraceptive use (never, ever), parity (nulliparous, 1–2, or ≥3), family history of MI (excluded in stroke outcome analysis), family history of

stroke (excluded in CHD outcome analysis), smoking (never, past, or current 1–14, 15–24, or ≥25 cigarettes/day), moderate-to-vigorous exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, or ≥6 h/week), Alternate Healthy Eating Index score (<45, 45 to <60, or ≥60), aspirin use (yes, no), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), BMI (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), and menopause type (natural, surgical). Model 3 was further adjusted for comorbidities, including a history of diabetes mellitus, hypertension, and hypercholesterolemia. All covariates were time-varying variables, except for ethnicity, parity, family history of MI and stroke, and menopause type, which were time-invariant. For those covariates with missing values (≤3% missing for each variable), missing indicators were generated to treat as a separate category. Tests for trend were conducted by assigning a median value to each category and modeling this value as a continuous variable. Potential interactions with other established risk factors of CVD were tested by adding an interaction term of reproductive life span with comorbidity of hypertension, hypercholesterolemia, diabetes mellitus, BMI, or smoking with adjustment for other covariates included in model 2. Sensitivity analysis among nonusers of hormone therapy was conducted to test the associations without the influence of exogenous hormones. To evaluate the contribution of comorbidities on the associations between age at menarche and CVD, SAS macro %MEDIATE (publicly available at https://www.hsph.harvard.edu/donna-spiegelman/software/mediate/) was applied using 1-(βmediator model/βbase model)×100.[28]

For all statistical analyses, 2-sided $P<0.05$ was considered to be statistically significant. All data analyses were performed using SAS software (version 9.4 for UNIX; SAS Institute Inc, Cary, NC).

Results

During 1 467 987 person-years of follow-up, we documented 5404 incident cases of CVD including 2933 cases of CHD and 2684 cases of stroke. The age-standardized characteristics of study participants at the midpoint of follow-up in 1996 are presented according to reproductive life span categories (Table 1). Because the current study investigated a life span variable with long-term disease follow-up, the midpoint was chosen to capture the study population characterization. Prevalence of hypercholesterolemia was slightly lower across the categories of increasing duration of reproductive life span, whereas BMI, diet quality, and physical activity levels were similar across the categories. The mean±SD duration of reproductive life span in this cohort was 36.2±5.2 years: 37.5±3.9 years for natural menopause (n=58 927) and 31.5±6.5 years surgical menopause (bilateral oophorectomy; n=14 887). Mean ages were menarche at 12.6±1.4 years (12.6±1.4 years natural and 12.5±1.4 years for surgical) and menopause at 48.8±5.1 years (50.1±3.7 years for natural and 44.0±6.3 years for surgical).

Assessing the Association Between Reproductive Life Span and CVD

Multiple regression models were constructed to assess whether reproductive life span was associated with the total CVD (Table 2). A shorter duration of reproductive life span was associated with higher risk of CVD (model 3; RR, 1.32 [95% CI, 1.16–1.49] comparing duration ≥42 with <30 years; P for trend<0.0001). Furthermore, a shorter duration of reproductive life span was associated with higher risk of both CHD and total stroke (model 3; both P for trend<0.0001). When subtypes of stroke, ischemic and hemorrhagic, were examined individually, the trend of associations was similar for both subtypes, although the point estimates were not statistically significant, likely attributed to smaller case sizes (Table S1). There was no statistically significant effect modification in the association between reproductive life span and CVD by conventional risk factors, including hypertension, hypercholesterolemia, diabetes mellitus, BMI, and smoking (full sample analysis; data not shown).

Given the substantial impact of type of menopause on reproductive life span, the association between reproductive life span and CVD was examined separately by type of menopause (Table S2). The significant association of shorter reproductive life span with CVD remained in both natural and surgical (bilateral oophorectomy) menopause strata (model 3; P for trend ≤0.01 for both). When a sensitivity analysis among women who were postmenopausal in 1980 was conducted (Table S3) to ensure equal follow-up time for all women, the significant association remained.

Assessing the Association Between Age at Menarche and CVD

Multiple regression models were constructed to assess the association between age at menarche and CVD (Table 3). Extremely early onset of menarche (≤10 years) was associated with higher risk of total CVD (model 3; RR, 1.22 [95% CI, 1.09–1.36] compared with age of menarche at 13 years; P for nonlinear trend=0.05). The trend of association of extremely early age at menarche with CHD and stroke remained although the associations were significant for stroke but not CHD (Table 3). Extremely late onset of menarche (≥17 years) was not associated with total CVD (model 3; 0.95 [0.71–1.26]), CHD (1.10 [0.76–1.59]), and stroke (0.77 [0.50–1.19]). For the association between extreme age at menarche

Table 1. Age-Standardized Characteristics of Study Participants in 1996 According to Reproductive Life Span in the Nurses' Health Study*

	Reproductive Life Span (Years)				
	<30	30 to 33	34 to 37	38 to 41	≥42
No. of participants, n	4904	6977	17 791	20 591	6409
Age, y†	62.1±6.9	62.6±6.9	62.7±7.0	63.0±6.9	63.5±6.1
White, %	96	97	97	97	97
Natural menopause, %	28	62	83	91	94
Hormone therapy use, %					
Never	16	28	36	40	45
Current	29	25	21	18	15
Past	55	48	43	41	39
Ever oral contraceptive use,%	43	46	47	46	44
Nulliparous, %	12	8	6	5	4
Hypertension, %	46	42	39	40	44
Hypercholesterolemia, %	60	54	54	52	52
Diabetes mellitus, %	9	7	6	7	8
Family history of MI, %	23	22	22	22	22
Family history of stroke, %	6	5	5	5	5
BMI, kg/m^2	26.5±5.4	26.1±5.1	26.1±5.1	26.6±5.2	27.4±5.5
BMI at age 18 y, kg/m^2	21.2±3.0	21.1±3.0	21.2±2.9	21.4±2.9	21.8±3.1
Smoking status, %					
Never	42	41	42	47	52
Past	44	43	44	43	40
Current	14	16	14	11	8
Moderate-to-vigorous exercise, h/week	1.7±3.0	1.6±2.9	1.7±2.9	1.8±2.9	1.7±2.8
Alternate Healthy Eating Index score	47.8±10.4	47.6±10.3	47.8±10.1	48.2±10.3	48.7±10.2
Aspirin use, %	45	44	45	45	44
Alcohol consumption, g/d	4.5±8.7	5.1±9.4	5.5±9.9	5.2±9.3	4.9±8.9

BMI indicates body mass index.
*Mean±SD or percentages and are standardized to the age distribution of the study population; Alternate Healthy Eating Index scored without inclusion of alcohol consumption scores.
†Value is not age adjusted.

and higher risk for CVD, the proportional contribution of type 2 diabetes mellitus to CVD risk was 14% (95% CI, 10–20%; $P \leq 0.0001$) and of hypertension was 9% (6–13%; $P \leq 0.0001$). The proportion of effect mediated by hypercholesterolemia was less than 1%.

Assessing the Association Between Age at Menopause and CVD

The association between age at menopause and CVD was separately assessed (Table 4). Early age at menopause (<40 years) was associated with higher risk of CVD (model 3; RR, 1.32 [95% CI, 1.16–1.51] compared with the age group 50 to <55; *P* for trend<0.0001). Early age at menopause was associated with higher risk of CHD as well as stroke (model 3; both *P* for trend≤0.0001). When model 3 was additionally adjusted for age at menarche, the associations of age at menopause with CVD, CHD, and stroke remained significant (all *P* for trend ≤0.009). In a sensitivity analysis restricted to women with incident menopause during the follow-up period, the trend of association remained the same, although significance was not reached likely because of a smaller sample size (Table S4).

Sensitivity Analyses: Reproductive Life Span and CVD

Sensitivity analyses among women who did not use hormone therapy were conducted to test whether the associations

Table 2. Relative Risk and 95% Confidence Intervals of CVD According to Reproductive Life Span in the Nurses' Health Study

Reproductive Life Span (Years)						
	<30	30 to 33	34 to 37	38 to 41	≥42	*P* Trend
Total CVD						
Cases/person-years	569/143 756	725/192 323	1660/454 887	1862/512 534	588/164 488	
Model 1*	1.39 (1.23–1.56)	1.19 (1.06–1.32)	1.07 (0.97–1.17)	1.01 (0.92–1.11)	1	<0.0001
Model 2†	1.30 (1.15–1.48)	1.12 (1.00–1.25)	1.03 (0.93–1.13)	1.00 (0.91–1.10)	1	<0.0001
Model 3‡	1.32 (1.16–1.49)	1.15 (1.02–1.28)	1.06 (0.96–1.16)	1.02 (0.93–1.12)	1	<0.0001
Total CHD						
Cases/person-years	304/143 941	406/192 541	926/455 405	994/513 131	303/164 689	
Model 1*	1.37 (1.17–1.61)	1.24 (1.06–1.44)	1.12 (0.98–1.28)	1.03 (0.91–1.17)	1	<0.0001
Model 2†	1.37 (1.15–1.63)	1.20 (1.03–1.40)	1.09 (0.96–1.25)	1.03 (0.90–1.17)	1	<0.0001
Model 3‡	1.39 (1.17–1.65)	1.24 (1.06–1.45)	1.13 (0.99–1.29)	1.05 (0.93–1.20)	1	<0.0001
Total stroke						
Cases/person-years	289/143 933	353/192 568	808/455 435	938/513 095	296/164 660	
Model 1*	1.44 (1.22–1.69)	1.18 (1.01–1.37)	1.05 (0.92–1.20)	1.02 (0.89–1.16)	1	<0.0001
Model 2†	1.26 (1.05–1.51)	1.07 (0.91–1.26)	0.99 (0.87–1.14)	1.00 (0.88–1.14)	1	0.007
Model 3‡	1.27 (1.06–1.52)	1.09 (0.93–1.28)	1.01 (0.89–1.16)	1.02 (0.89–1.16)	1	0.005

CHD indicates coronary heart disease; CVD, cardiovascular disease.

*Model 1 age adjusted.

†Model 2 additionally adjusted for ethnicity (European descent, Asian, Hispanic, or black), hormone therapy use (never, current, or past), oral contraceptive use (never, ever), parity (nulliparous, 1–2, or ≥3), family history of myocardial infarction (excluded in stroke outcome analysis), family history of stroke (excluded in CHD outcome analysis), smoking (never, past, current 1–14, 15–24, or ≥25 cigarettes/day), moderate-to-vigorous exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, and ≥6 h/week), Alternate Healthy Eating Index score (<45, 45 to <60, or ≥60), aspirin use (yes, no), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), body mass index (BMI; <18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), and menopause type (natural, surgical).

‡Model 3 additionally adjusted for a history of diabetes mellitus, hypertension, and hypercholesterolemia.

remained without the influence of the exogenous hormone use. The associations of reproductive life span, age at menarche, and menopause with CVD were similar among women who never used menopausal hormone therapy (Table 5). Shorter duration of reproductive life span remained associated with higher risk of CVD with adjustment for model 3 (RR, 1.41 [95% CI, 1.14–1.75] comparing duration ≥42 with <30 years in never users; *P* for trend=0.002; Table 5).

Because extremely early age at menarche (≤10 years) was associated with higher risk of CVD, sensitivity analyses were performed excluding these women at the extreme. The association between reproductive life span and CVD remained and was slightly more pronounced (model 3; 1.42 [1.24–1.62] comparing duration ≥42 with <30 years among age at menarche >10 years; *P* for trend<0.0001).

Discussion

A shorter duration of reproductive life span, particularly an earlier age at menopause, was associated with a higher risk of total CVD, as well as a higher risk of CHD and stroke, individually. A modest association was found between extremely early age at menarche (≤10 years) and higher risk of CVD. The significant association between reproductive life span and CVD remained when stratified by natural or surgical menopausal status. Furthermore, the association between reproductive life span and CVD remained significant in sensitivity analyses excluding women who experienced extremely early age at menarche or who used hormone therapy.

Our findings are generally consistent with past studies. In a cross-sectional, population-based study, a longer duration of reproductive life span was associated with a lower 10-year CVD risk assessed by the Framingham Risk Score in postmenopausal women.[9] In recent meta-analyses, early age at natural menopause was associated with a higher risk of CVD mortality.[29,30] Previously, in this NHS cohort, a significant association was reported between bilateral oophorectomy and increased CVD mortality in women aged younger than 50 years, and especially in nonusers of hormone therapy.[31] Here, we expand this previous finding by providing evidence that women who experienced a shorter reproductive life span, driven by earlier age at menopause induced by either natural or surgical means, are at a higher risk of CVD. In

DOI: 10.1161/JAHA.117.006713

Table 3. Relative Risk and 95% Confidence Intervals of CVD According to Age at Menarche in the Nurses' Health Study

Age at Menarche (y)									
	≤10	11	12	13	14	15	≥16	*P* Trend (Linear)	*P* Trend (Nonlinear)
Total CVD									
Cases/person-years	414/87 915	997/260 188	1565/424 631	1837/424 631	795/202 167	252/72 604	250/56 524		
Model 1*	1.45 (1.30–1.61)	1.08 (1.00–1.16)	1.01 (0.94–1.08)	1	1.01 (0.93–1.10)	0.86 (0.75–0.98)	1.05 (0.92–1.19)	<0.0001	0.0001
Model 2†	1.28 (1.15–1.43)	1.02 (0.95–1.10)	0.99 (0.92–1.05)	1	1.03 (0.95–1.12)	0.86 (0.75–0.98)	1.02 (0.89–1.16)	0.007	0.02
Model 3‡	1.22 (1.09–1.36)	1.00 (0.92–1.08)	0.97 (0.91–1.04)	1	1.04 (0.96–1.13)	0.87 (0.76–0.99)	1.03 (0.91–1.18)	0.10	0.05
Total CHD									
Cases/person-years	222/88 041	545/260 510	850/425 112	967/498 884	406/202 445	133/72 683	131/56 599		
Model 1*	1.45 (1.25–1.68)	1.11 (1.00–1.24)	1.04 (0.95–1.14)	1	0.99 (0.88–1.11)	0.87 (0.73–1.04)	1.05 (0.87–1.26)	<0.0001	0.004
Model 2†	1.23 (1.06–1.43)	1.03 (0.93–1.15)	1.01 (0.92–1.11)	1	1.02 (0.90–1.14)	0.87 (0.72–1.04)	1.02 (0.85–1.23)	0.04	0.18
Model 3‡	1.16 (1.00–1.34)	1.00 (0.90–1.12)	1.00 (0.91–1.09)	1	1.03 (0.91–1.15)	0.88 (0.73–1.05)	1.05 (0.87–1.26)	0.28	0.31
Total stroke									
Cases/person-years	204/88 043	479/260 496	781/425 122	943/254 046	419/202 399	180/72 675	128/56 601		
Model 1*	1.41 (1.21–1.64)	1.01 (0.91–1.13)	0.98 (0.89–1.08)	1	1.03 (0.92–1.16)	0.86 (0.72–1.03)	1.03 (0.86–1.24)	0.03	0.02
Model 2†	1.31 (1.12–1.52)	0.98 (0.88–1.10)	0.97 (0.88–1.06)	1	1.05 (0.93–1.18)	0.86 (0.72–1.04)	1.00 (0.83–1.21)	0.16	0.11
Model 3‡	1.25 (1.07–1.46)	0.96 (0.86–1.07)	0.95 (0.86–1.05)	1	1.06 (0.94–1.18)	0.87 (0.72–1.04)	1.02 (0.84–1.22)	0.44	0.16

CHD indicates coronary heart disease; CVD, cardiovascular disease.

*Model 1 age adjusted.

†Model 2 additionally adjusted for ethnicity (European descent, Asian, Hispanic, or black), hormone therapy use (never, current, or past), oral contraceptive use (never, ever), parity (nulliparous, 1–2, or ≥3), family history of myocardial infarction (excluded in stroke outcome analysis), family history of stroke (excluded in CHD outcome analysis), smoking (never, past, or current 1–14, 15–24, or ≥25 cigarettes/day), moderate-to-vigorous exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, or ≥6 h/week), Alternate Healthy Eating Index score (<45, 45 to <60, or ≥60), aspirin use (yes, no), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), body mass index (BMI; <18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), and BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2).

‡Model 3 additionally adjusted for a history of diabetes mellitus, hypertension, and hypercholesterolemia.

Table 4. Relative Risk and 95% Confidence Intervals of CVD According to Age at Menopause in the Nurses' Health Study

Age at Menopause (y)						
	<40	40 to 44	45 to 49	50 to 54	≥55	*P* Trend
Total CVD						
Cases/person-years	327/85 147	534/138 950	1701/457 950	2446/676 988	396/109 052	
Model 1*	1.45 (1.29–1.62)	1.30 (1.18–1.42)	1.13 (1.06–1.20)	1	0.99 (0.89–1.10)	<0.0001
Model 2†	1.36 (1.19–1.54)	1.23 (1.11–1.36)	1.08 (1.01–1.15)	1	1.04 (0.94–1.16)	<0.0001
Model 3‡	1.32 (1.16–1.51)	1.23 (1.11–1.36)	1.08 (1.01–1.15)	1	1.04 (0.93–1.16)	<0.0001
Total CHD						
Cases/person-years	177/85 239	282/139 151	977/458 326	1306/677 808	191/109 183	
Model 1*	1.41 (1.20–1.65)	1.24 (1.09–1.42)	1.20 (1.10–1.30)	1	0.92 (0.79–1.07)	<0.0001
Model 2†	1.41 (1.18–1.68)	1.22 (1.06–1.40)	1.14 (1.05–1.24)	1	0.96 (0.83–1.12)	<0.0001
Model 3‡	1.37 (1.14–1.63)	1.22 (1.06–1.40)	1.14 (1.05–1.24)	1	0.96 (0.83–1.12)	<0.0001
Total stroke						
Cases/person-years	163/85 259	277/139 111	793/458 434	1239/677 727	212/109 161	
Model 1*	1.46 (1.24–1.72)	1.36 (1.19–1.55)	1.06 (0.97–1.16)	1	1.04 (0.90–1.20)	<0.0001
Model 2†	1.28 (1.06–1.53)	1.24 (1.08–1.43)	1.00 (0.91–1.09)	1	1.09 (0.94–1.26)	0.006
Model 3‡	1.25 (1.04–1.51)	1.23 (1.07–1.42)	1.00 (0.91–1.09)	1	1.09 (0.94–1.26)	0.009

CHD indicates coronary heart disease; CVD, cardiovascular disease.

*Model 1 age adjusted.

†Model 2 additionally adjusted for ethnicity (European descent, Asian, Hispanic, or black), hormone therapy use (never, current, or past), oral contraceptive use (never, ever), parity (nulliparous, 1–2, or ≥3), family history of myocardial infarction (excluded in stroke outcome analysis), family history of stroke (excluded in CHD outcome analysis), smoking (never, past, or current 1–14, 15–24, or ≥25 cigarettes/day), moderate-to-vigorous exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, or ≥6 h/week), Alternate Healthy Eating Index score (<45, 45 to <60, or ≥60), aspirin use (yes, no), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), body mass index (BMI; (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), and menopause type (natural, surgical).

‡Model 3 additionally adjusted for a history of diabetes mellitus, hypertension, and hypercholesterolemia.

a sensitivity analysis among women who did not use hormone therapy in the current article, the association between reproductive life span and CVD remained significant. Although the initial results support the hypothesis that duration of reproductive life span might serve as an improved marker of CVD risk in women, additional comprehensive analyses indicate that this association is mainly driven by early age at menopause and that extremely early age at menarche is another independent risk factor for CVD.

Although earlier age at menarche has been associated with CVD morbidity and mortality in a few studies,[13–15] the association has not been consistently found by others.[16–18] In a prospective study following 867 women, each year of later age at menarche was associated with a 24% decreased risk of ischemic heart disease.[13] Although reproductive risk factors were well documented, other CVD risk factors, such as adiposity and comorbidities, were not captured in detail.[13] A U-shaped relation between age at menarche and CHD was observed in the Million Women Study, which found significantly increased risk among women in extreme age at menarche categories (≤10 and ≥17 years).[15] In this cohort study with long-term follow-up and detailed characterization of CVD risk factors including reproductive events, lifestyle, and comorbidities, we observed a higher CVD risk for those with extremely early age at menarche (≤10 years), but we did not observe higher risk at extremely late menarche. It is possible that we were underpowered in this category given that only <0.1% of study population had menarche at 18 years or older. However, women with such a late onset of menarche may have an underlying pathological cause for delayed menarche which may also lead to different cardiometabolic risk trajectories. Furthermore, women with extremely early age at menarche may have experienced hormonal disturbances, such as higher exposure to estradiol, potentially mediated through childhood obesity.[5] In sensitivity analyses excluding these women, the association between reproductive life span and CVD became more pronounced.

Similar overall results of age at menopause and CVD for women with surgical and natural menopause support the hypothesis that the alteration in sex hormones with menopause might be, at least partially, responsible for the association between reproductive life span and CVD. Changes in endogenous estrogens in the menopausal transition may affect lipid levels and subsequent cardiovascular risk.[32] The menopausal transition is accompanied by detrimental changes in lipids. In the Healthy Women Study, those who

DOI: 10.1161/JAHA.117.006713

Table 5. Relative Risk and 95% Confidence Intervals of Total CVD According to Reproductive Life Span Factors Among the Nurses' Health Study Participants Who Never Used Hormone Therapy

Reproductive Life Span (y)						
	<30	30 to 33	34 to 37	38 to 41	≥42	*P* Trend
Cases/person-years	147/26 304	263/62 343	733/186 061	916/228 432	296/76 234	
Model 1*	1.66 (1.36–2.03)	1.27 (1.08–1.51)	1.11 (0.97–1.27)	1.05 (0.92–1.20)	1	<0.0001
Model 2†	1.40 (1.13–1.73)	1.14 (0.96–1.35)	1.05 (0.92–1.21)	1.04 (0.91–1.19)	1	0.003
Model 3‡	1.41 (1.14–1.75)	1.17 (0.99–1.40)	1.08 (0.94–1.24)	1.06 (0.93–1.21)	1	0.002

Age at Menarche (y)								
	≤10	11	12	13	14	15	≥16	*P* Trend
Cases/person-years	181/32 863	436/101 344	670/163 856	805/194 942	332/79 795	103/28 157	108/24 249	
Model 1*	1.46 (1.24–1.71)	1.06 (0.95–1.20)	1.00 (0.90–1.10)	1	0.95 (0.84–1.08)	0.84 (0.68–1.03)	0.98 (0.80–1.20)	0.0002
Model 2†	1.27 (1.08–1.49)	1.01 (0.89–1.13)	0.97 (0.87–1.07)	1	0.99 (0.87–1.12)	0.82 (0.67–1.01)	0.96 (0.78–1.17)	0.02
Model 3‡	1.22 (1.03–1.44)	0.98 (0.87–1.10)	0.96 (0.86–1.06)	1	0.99 (0.87–1.13)	0.84 (0.68–1.03)	0.97 (0.79–1.19)	0.12

Age at Menopause (y)						
	<40	40 to 44	45 to 49	50 to 54	≥55	*P* Trend
Cases/person-years	71/11 982	162/35 648	715/176 230	1223/305 832	184/49 682	
Model 1*	1.76 (1.38–2.24)	1.38 (1.17–1.63)	1.15 (1.04–1.26)	1	0.89 (0.76–1.04)	<0.0001
Model 2†	1.43 (1.09–1.86)	1.20 (1.02–1.43)	1.06 (0.96–1.16)	1	0.95 (0.81–1.11)	0.001
Model 3‡	1.36 (1.04–1.77)	1.22 (1.03–1.44)	1.06 (0.96–1.16)	1	0.95 (0.81–1.11)	0.002

CVD indicates cardiovascular disease.

P for interaction of hormone therapy use with reproductive life span, age at menarche, or age at menopause is >0.05. *P* for nonlinear trends between age at menarche and CVD are 0.03 (model 1), 0.30 (model 2), and 0.38 (model 3).

*Model 1 age adjusted.

†Model 2 additionally adjusted for ethnicity (European descent, Asian, Hispanic, or black), oral contraceptive use (never, ever), parity (nulliparous, 1–2, or ≥3), family history of myocardial infarction (excluded in stroke outcome analysis), family history of stroke (excluded in CHD outcome analysis), smoking (never, past, or current 1–14, 15–24, or ≥25 cigarettes/day), moderate-to-vigorous exercise (0, 0.01–1.0, 1.1–3.4, 3.5–5.9, or ≥6 h/week), Alternate Healthy Eating Index score (<45, 45 to <60, or ≥60), aspirin use (yes, no), alcohol intake (0, 0.1–4.9, 5.0–14.9, or ≥15.0 g/day), body mass index (BMI; <18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5–22.4, 22.5–24.9, 25.0–27.4, 27.5–29.9, 30.0–34.9, or ≥35.0 kg/m^2), and menopause type (natural, surgical).

‡Model 3 additionally adjusted for a history of diabetes mellitus, hypertension, and hypercholesterolemia.

experienced a natural menopause and did not use hormone therapy had lower high-density lipoprotein cholesterol and higher low-density lipoprotein cholesterol concentrations at 2.5-year follow-up compared with those who did.[32] In the SWAN (Study of Women Across the Nation) study, postmenopausal women had more small high-density lipoprotein particles compared with premenopausal women,[33] suggesting that the protective effect of high-density lipoprotein cholesterol might be altered in postmenopausal women because of changes in the lipoprotein subclass profile. A potential mechanism explaining these lipoprotein profile changes is that large high-density lipoprotein particles are converted to smaller particles by increased hepatic lipase,[34] and estrogen inhibits hepatic lipase. Therefore, decreased estrogen concentrations over the menopause transition may lead to alteration in the lipoprotein profiles, which may subsequently contribute to atherosclerosis.

The current study has strengths, such as long-term follow-up from a large number of women with detailed reproductive, medical, and lifestyle information and careful end point follow-up, but it also has limitations. The study participants were female nurses of primarily European ancestry; thus, the observed associations may not be generalizable to other populations. However, the absence of detectable ethnic differences in the influence of menopause on lipids and lipoproteins has been reported in the SWAN study.[35] Although we have adjusted our models for multiple lifestyle risk factors of CVD, we cannot entirely exclude that these associations are confounded by unmeasured lifestyle practices. Although we collected information on age at menopause closer to the event in this long-term prospective cohort of women aged 30 to 55 years at baseline, age at menarche was retrospectively assessed by recall; therefore, potential misclassification exists. However, reported age at menarche has been associated with other end points in the current study cohort, including type 2 diabetes mellitus[3] and breast cancer,[36] with consistent magnitude and direction of the association as in the literature.

In conclusion, a shorter duration of reproductive life span is associated with a higher risk of CVD. This association appears to be driven primarily by earlier age at menopause, whether by natural or surgical means. Furthermore, the association between reproductive life span and CVD remained significant in a sensitivity analysis among nonusers of hormone therapy, indicating that the observed association was not driven by the use of exogeneous hormones. A modest association between extremely early age at menarche (≤10 years) and higher risk of CVD was observed and may be of a concern given the decline in the average age at menarche in the United States.[37] The association of reproductive life span and CVD supports an underlying role of sex hormones in CVD.

Sources of Funding

This study was supported by research grants (UM1 CA186107, UM1 CA87969, R01 HL034594, and R01 HL088521) from the NIH. None of the authors had a conflict of interest to disclose. The sponsor had no role in the design and conduct of the study; collection, analysis, and interpretation of the data; writing of the article; or submission of the article for publication.

Acknowledgments

We thank the participants and staff of the Nurses' Health Study for their valuable contributions.

Disclosures

None.

References

1. Isles CG, Hole DJ, Hawthorne VM, Lever AF. Relation between coronary risk and coronary mortality in women of the Renfrew and Paisley survey: comparison with men. *Lancet*. 1992;339:702–706.
2. Atsma F, Bartelink MEL, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause*. 2006;13:265–279.
3. He C, Zhang C, Hunter DJ, Hankinson SE, Buck Louis GM, Hediger ML, Hu FB. Age at menarche and risk of type 2 diabetes: results from 2 large prospective cohort studies. *Am J Epidemiol*. 2010;171:334–344.
4. Elks CE, Ong KK, Scott RA, van der Schouw YT, Brand JS, Wark PA, Amiano P, Balkau B, Barricarte A, Boeing H, Fonseca-Nunes A, Franks PW, Grioni S, Halkjaer J, Kaaks R, Key TJ, Khaw KT, Mattiello A, Nilsson PM, Overvad K, Palli D, Quirós JR, Rinaldi S, Rolandsson O, Romieu I, Sacerdote C, Sánchez MJ, Spijkerman AMW, Tjonneland A, Tormo MJ, Tumino R, van der A DL, Forouhi NG, Sharp SJ, Langenberg C, Riboli E, Wareham NJ; InterAct Consortium. Age at menarche and type 2 diabetes risk: The EPIC-InterAct study. *Diabetes Care*. 2013;36:3526–3534.
5. Zhai L, Liu J, Zhao J, Liu J, Bai Y, Jia L, Yao X. Association of obesity with onset of puberty and sex hormones in Chinese girls: a 4-year longitudinal study. *PLoS One*. 2015;10:e0134656.
6. Pinkney J, Streeter A, Hosking J, Mohammod M, Jeffery A, Wilkin T. Adiposity, chronic inflammation, and the prepubertal decline of sex hormone binding globulin in children: evidence for associations with the timing of puberty (Earlybird 58). *J Clin Endocrinol Metab*. 2014;99:3224–3232.
7. Tikkanen MJ, Vihma V, Jauhiainen M, Höckerstedt A, Helisten H, Kaamanen M. Lipoprotein-associated estrogens. *Cardiovasc Res*. 2002;56:184–188.
8. Vitale C, Fini M, Speziale G, Chierchia S. Gender differences in the cardiovascular effects of sex hormones. *Fundam Clin Pharmacol*. 2010;24:675–685.
9. Kim SH, Sim MY, Park SB. Association between duration of reproductive lifespan and Framingham Risk Score in postmenopausal women. *Maturitas*. 2015;82:431–435.
10. Brand JS, van der Schouw YT, Onland-Moret NC, Sharp SJ, Ong KK, Khaw KT, Ardanaz E, Amiano P, Boeing H, Chirlaque MD, Clavel-Chapelon F, Crowe FL, de Lauzon-Guillain B, Duell EJ, Fagherazzi G, Franks PW, Grioni S, Groop LC, Kaaks R, Key TJ, Nilsson PM, Overvad K, Palli D, Panico S, Quirós JR, Rolandsson O, Sacerdote C, Sánchez MJ, Slimani N, Teucher B, Tjonneland A, Tumino R, van der A DL, Feskens EJM, Langenberg C, Forouhi NG, Riboli E, Wareham NJ; InterAct Consortium. Age at menopause, reproductive life span, and type 2 diabetes risk: results from the EPIC-InterAct study. *Diabetes Care*. 2013;36:1012–1019.
11. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, Shoupe D, Berek JS, Hankinson S, Manson JE. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the Nurses' Health Study. *Obstet Gynecol*. 2009;113:1027–1037.
12. Howard BV, Kuller L, Langer R, Manson JE, Allen C, Assaf A, Cochrane BB, Larson JC, Lasser N, Rainford M, Van Horn L, Stefanick ML, Trevisan M. Risk of

cardiovascular disease by hysterectomy status, with and without oophorectomy: the Women's Health Initiative Observational Study. *Circulation*. 2005;111:1462–1470.

13. Cooper GS, Ephross SA, Weinberg CR, Baird DD, Whelan EA, Sandler DP. Menstrual and reproductive risk factors for ischemic heart disease. *Epidemiology*. 1999;10:255–259.
14. Jacobsen BK, Oda K, Knutsen SF, Fraser GE. Age at menarche, total mortality and mortality from ischaemic heart disease and stroke: the Adventist Health Study, 1976–88. *Int J Epidemiol*. 2009;38:245–252.
15. Canoy D, Beral V, Balkwill A, Wright FL, Kroll ME, Reeves GK, Green J, Cairns BJ. Age at menarche and risks of coronary heart and other vascular diseases in a large UK cohort. *Circulation*. 2015;131:237–244.
16. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. A prospective study of age at menarche, parity, age at first birth, and coronary heart disease in women. *Am J Epidemiol*. 1987;126:861–870.
17. Charalampopoulos D, McLoughlin A, Elks CE, Ong KK. Age at menarche and risks of all-cause and cardiovascular death: a systematic review and meta-analysis. *Am J Epidemiol*. 2014;180:29–40.
18. Cui R, Iso H, Toyoshima H, Date C, Yamamoto A, Kikuchi S, Kondo T, Watanabe Y, Koizumi A, Inaba Y, Tamakoshi A. Relationships of age at menarche and menopause, and reproductive year with mortality from cardiovascular disease in Japanese postmenopausal women: the JACC study. *J Epidemiol*. 2006;16:177–184.
19. Cairns BJ, Liu B, Clennell S, Cooper R, Reeves GK, Beral V, Kuh D. Lifetime body size and reproductive factors: comparisons of data recorded prospectively with self reports in middle age. *BMC Med Res Methodol*. 2011;11:1–13.
20. Colditz GA, Stampfer MJ, Willett WC, Stason WB, Rosner B, Hennekens CH, Speizer FE. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol*. 1987;126:319–325.
21. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894–900.
22. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51–65.
23. Willett W. *Nutritional Epidemiology*. 2nd ed. New York, NY: Oxford University Press; 1998.
24. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*. 1990;1:466–473.
25. Chiuve SE, Fung TT, Rimm EB, Hu FB, McCullough ML, Wang M, Stampfer MJ, Willett WC. Alternative dietary indices both strongly predict risk of chronic disease. *J Nutr*. 2012;142:1009–1018.
26. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke*. 1981;12:I13–I44.
27. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. *Am J Epidemiol*. 1984;119:837–839.
28. Lin DY, Fleming TR, De Gruttola V. Estimating the proportion of treatment effect explained by a surrogate marker. *Stat Med*. 1997;16:1515–1527.
29. Gong D, Sun J, Zhou Y, Zou C, Fan Y. Early age at natural menopause and risk of cardiovascular and all-cause mortality: a meta-analysis of prospective observational studies. *Int J Cardiol*. 2016;203:115–119.
30. Muka T, Oliver-Williams C, Kunutsor S, Laven JS, Fauser BC, Chowdhury R, Kavousi M, Franco OH. Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes, intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol*. 2016;1:767–776.
31. Parker WH, Feskanich D, Broder MS, Chang E, Shoupe D, Farquhar CM, Berek JS, Manson JE. Long-term mortality associated with oophorectomy compared with ovarian conservation in the Nurses' Health Study. *Obstet Gynecol*. 2013;121:709–716.
32. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. *N Engl J Med*. 1989;321:641–646.
33. Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA, Sutton-Tyrrell K. Lipids, menopause, and early atherosclerosis in Study of Women's Health Across the Nation Heart women. *Menopause*. 2011;18:376–384.
34. Berg GA, Siseles N, González AI, Ortiz OC, Tempone A, Wikinski RW. Higher values of hepatic lipase activity in postmenopause: relationship with atherogenic intermediate density and low density lipoproteins. *Menopause*. 2001;8:51–57.
35. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, Sutton-Tyrrell K. Are changes in cardiovascular disease risk factors in midlife women due to chronological aging or to the menopausal transition? *J Am Coll Cardiol*. 2009;54:2366–2373.
36. Colditz GA. Epidemiology of breast cancer: findings from the Nurses' Health Study. *Cancer*. 1993;71:1480–1489.
37. Anderson SE, Must A. Interpreting the continued decline in the average age at menarche: results from two nationally representative surveys of U.S. girls studied 10 years apart. *J Pediatr*. 2005;147:753–760.

SUPPLEMENTAL MATERIAL

Table S1. Relative risk and 95% confidence intervals of ischemic and hemorrhagic stroke according to reproductive lifespan in the Nurses' Health Study

	Reproductive lifespan (years)					
	<30	30-33	34-37	38-41	≥42	p-trend
Ischemic stroke						
Cases/person-years	*124/144040*	*144/192701*	*388/455685*	*446/513373*	*135/164763*	
Age adjusted	1.33 (1.04-1.71)	1.05 (0.83-1.33)	1.11 (0.91-1.35)	1.06 (0.88-1.29)	1	0.04
Multivariate-adjusted*	1.21 (0.93-1.59)	1.01 (0.79-1.29)	1.09 (0.89-1.33)	1.08 (0.89-1.30)	1	0.32
Hemorrhagic stroke						
Cases/person-years	*28/144127*	*37/192808*	*61/456004*	*65/513740*	*22/164864*	
Age adjusted	1.56 (1.88-2.75)	1.43 (0.84-2.44)	0.96 (0.59-1.58)	0.92 (0.56-1.49)	1	0.01
Multivariate-adjusted*	1.37 (0.73-2.56)	1.27 (0.73-2.21)	0.88 (0.53-1.45)	0.88 (0.54-1.43)	1	0.09

*additionally adjusted for ethnicity (European descent, Asian, Hispanic, African American), hormone therapy use (never, current, past), oral contraceptive use (never, ever), parity (nulliparous, 1-2, ≥3), family history of stroke, smoking (never, past, current 1-14, 15-24, or ≥25 cigarettes/d), moderate to vigorous exercise (0, 0.01-1.0, 1.1-3.4, 3.5-5.9, ≥6 h/wk), Alternate Healthy Eating Index score (<45, 45-<60, ≥60), Aspirin use (yes, no), alcohol intake (0, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), BMI (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), menopause type (natural, surgical), a history of diabetes, hypertension, hypercholesterolemia

Table S2. Relative risk and 95% confidence intervals of total CVD according to reproductive lifespan in the Nurses' Health Study stratified by menopause type

Reproductive lifespan (years)						
	<30	30-33	34-37	38-41	≥42	p-trend
Natural menopause						
Cases/person-years	*186/38977*	*473/118277*	*1388/375762*	*1697/466701*	*558/154726*	
Age adjusted	1.42 (1.20-1.68)	1.21 (1.07-1.37)	1.06 (0.96-1.17)	1.00 (0.91-1.10)	1	<0.0001
Multivariate-adjusted*	1.33 (1.13-1.58)	1.16 (1.02-1.31)	1.05 (0.95-1.16)	1.01 (0.92-1.11)	1	0.0001
Surgical menopause						
Cases/person-years	*383/104779*	*252/74047*	*272/79125*	*165/45833*	*30/9761*	
Age adjusted	1.61 (1.11-2.34)	1.31 (0.90-1.91)	1.22 (0.84-1.78)	1.21 (0.82-1.79)	1	<0.0001
Multivariate-adjusted*	1.38 (0.95-2.01)	1.18 (0.81-2.01)	1.15 (0.78-1.68)	1.16 (0.78-1.71)	1	0.001

*additionally adjusted for ethnicity (European descent, Asian, Hispanic, African American), hormone therapy use (never, current, past), oral contraceptive use (never, ever), parity (nulliparous, 1-2, ≥3), family history of MI, family history of stroke, [smoking (never, past, current 1-14, 15-24, or ≥25 cigarettes/d)], moderate to vigorous exercise (0, 0.01-1.0, 1.1-3.4, 3.5-5.9, ≥6 h/wk), Alternate Healthy Eating Index score (<45, 45-<60, ≥60), Aspirin use (yes, no), alcohol intake (0, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), BMI (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), [menopause type (natural, surgical)], a history of diabetes, hypertension, hypercholesterolemia

p for interaction is >0.05 between menopause type and reproductive lifespan or between smoking and reproductive lifespan.

Table S3. Sensitivity analysis of relative risk and 95% confidence intervals of total CVD according to reproductive lifespan in the Nurses' Health Study participants who were in postmenopausal status in 1980

Reproductive lifespan (years)						
	<30	30-33	34-37	38-41	≥42	p-trend
Cases/person-years	*598/13188*	*624/127811*	*1275/240172*	*1169/206681*	*202/34592*	
Age adjusted	1.33 (1.13-1.68)	1.15 (0.98-1.36)	1.11 (0.95-1.29)	1.06 (0.91-1.23)	1	<0.0001
Multivariate-adjusted*	1.33 (1.12-1.59)	1.17 (0.99-1.38)	1.13 (0.97-1.32)	1.08 (0.93-1.26)	1	0.0003

*additionally adjusted for ethnicity (European descent, Asian, Hispanic, African American), hormone therapy use (never, current, past), oral contraceptive use (never, ever), parity (nulliparous, 1-2, ≥3), family history of MI, family history of stroke, [smoking (never, past, current 1-14, 15-24, or ≥25 cigarettes/d)], moderate to vigorous exercise (0, 0.01-1.0, 1.1-3.4, 3.5-5.9, ≥6 h/wk), Alternate Healthy Eating Index score (<45, 45-<60, ≥60), Aspirin use (yes, no), alcohol intake (0, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), BMI (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), menopause type (natural, surgical), a history of diabetes, hypertension, hypercholesterolemia

Table S4. Sensitivity analysis of relative risk and 95% confidence intervals of total CVD according to age at menopause in the Nurses' Health Study participants who were in premenopausal in 1980

Age at menopause (years)						
	<40	40-44	45-49	50-54	≥55	p-trend
Cases/person-years	*8/5902*	*75/41089*	*465/212575*	*1022/410844*	*288/91190*	
Age adjusted	1.71 (0.84-3.50)	1.40 (1.09-1.79)	1.13 (1.00-1.27)	1	1.01 (0.88-1.17)	0.004
Multivariate-adjusted*	1.67 (0.81-3.44)	1.28 (0.99-1.65)	1.06 (0.94-1.19)	1	1.05 (0.91-1.21)	0.12

*adjusted for ethnicity (European descent, Asian, Hispanic, African American), hormone therapy use (never, current, past), oral contraceptive use (never, ever), parity (nulliparous, 1-2, ≥3), family history of MI (excluded in stroke outcome analysis), family history of stroke (excluded in CHD outcome analysis), smoking (never, past, current 1-14, 15-24, or ≥25 cigarettes/d), moderate to vigorous exercise (0, 0.01-1.0, 1.1-3.4, 3.5-5.9, ≥6 h/wk), Alternate Healthy Eating Index score (<45, 45-<60, ≥60), Aspirin use (yes, no), alcohol intake (0, 0.1-4.9, 5.0-14.9, ≥15.0 g/d), BMI (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), BMI at age 18 years (<18.5, 18.5-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-34.9, ≥35.0 kg/m^2), menopause type (natural, surgical), a history of diabetes, hypertension, hypercholesterolemia