Original Contribution

Factors Related to Age at Natural Menopause: Longitudinal Analyses From SWAN

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Early age at the natural final menstrual period (FMP) or menopause has been associated with numerous health outcomes and might be a marker of future ill health. However, potentially modifiable factors affecting age at menopause have not been examined longitudinally in large, diverse populations. The Study of Women's Health Across the Nation (SWAN) followed 3,302 initially premenopausal and early perimenopausal women from 7 US sites and 5 racial/ethnic groups, using annual data (1996–2007) and Cox proportional hazards models to assess the relation of time-invariant and time-varying sociodemographic, lifestyle, and health factors to age at natural FMP. Median age at the FMP was 52.54 years (*n* = 1,483 observed natural FMPs). Controlling for sociodemographic, lifestyle, and health factors, we found that racial/ethnic groups did not differ in age at the FMP. Higher educational level, prior oral contraceptive use, and higher weight at baseline, as well as being employed, not smoking, consuming alcohol, having less physical activity, and having better self-rated health over follow-up, were significantly associated with later age at the FMP. These results suggest that age at the natural FMP reflects a complex interrelation of health and socioeconomic factors, which could partially explain the relation of late age at FMP to reduced morbidity and mortality.

age; education; ethnicity; menopause; oral contraceptives; race; smoking; weight

Abbreviations: CI, confidence interval; FMP, final menstrual period; HR, hazard ratio; SWAN, Study of Women's Health Across the Nation.

The age at the final menstrual period (FMP), natural menopause, holds intrinsic public health interest because it is associated with numerous health outcomes and might be a marker of aging and health (1–3). Later age at FMP has been associated with longer survival; greater life expectancy (4); reduced rates of all-cause mortality (5), cardiovascular disease (4, 6–12), cardiovascular death (13, 14), atherosclerosis (15), stroke (16), angina after myocardial infarction (17), low bone density (18), osteoporosis (19), and fracture (20); but increased breast (21, 22), endometrial, and ovarian cancer risk (4, 23, 24).

Physiological changes marking the onset of perimenopause (i.e., declining estradiol levels, rising follicle-stimulating hormone levels, and menstrual cycle irregularity) begin in women's mid-40s (25, 26). The median age at onset of the late perimenopause (defined as no periods in the prior 3 months but having period(s) in the prior 12 months) is 47.5 years

(27–31), and age at FMP (followed by 12 months of amenorrhea) in white women from industrialized countries is 50–52 years, with slight evidence of increasing age at FMP in more recent cohorts (31–35). Age at FMP could vary by race/ethnicity (36–39) and demographic and lifestyle factors, particularly smoking (28, 29, 33, 35–37, 40–50). Age at FMP has been positively associated with maternal age at menopause (41, 51–55), but few longitudinal studies have investigated this. One twin study indicated genetic control of age at menopause (56), but potentially modifiable factors that might affect age at menopause, including weight, calorie and alcohol intake, and passive smoke exposure, have not been examined longitudinally in large, diverse populations, nor has the time-varying effect of such factors been assessed longitudinally.

We therefore examined these research hypotheses in the multiracial/multiethnic sample of midlife women in the Study

of Women's Health Across the Nation (SWAN) cohort: 1) Previously established risk factors for early age at FMP that do not change meaningfully over time (e.g., smoking) would be related to early age at FMP in longitudinal analyses, consistent with prior cross-sectional analyses; 2) higher weight and caloric intake would be associated with later age at FMP, whereas passive smoke exposure and higher alcohol intake would be related to earlier age at FMP; and 3) age at FMP would be correlated with maternal age at menopause.

MATERIALS AND METHODS

Study population

We screened 16,065 community-based women aged 40–55 years (screener response rate = 46.6%) during 1995–1997 for eligibility for a longitudinal cohort in 7 sites in the United States (57). Each site screened 1 minority sample (African Americans in Pittsburgh, Boston, the Detroit area, and Chicago; Japanese in Los Angeles; Chinese in the Oakland, California, area; and Hispanics in New Jersey) and 1 Caucasian sample. Women who spoke English or Spanish, Cantonese, or Japanese (at New Jersey, Oakland, and Los Angeles, respectively) were eligible. The institutional review boards at all sites approved the protocol; all cohort participants provided signed, written informed consent.

Eligibility criteria for the cohort included age 42–52 years, having an intact uterus and at least 1 ovary, no use in the prior 3 months of exogenous hormones affecting ovarian function, not pregnant or lactating, had a menstrual period in the previous 3 months, and self-identification with each site's designated racial/ethnic groups. We recruited 3,302 eligible participants (50.7% response rate among eligible women). The present analyses included data through annual visit 10 (1996–2007), with 68% overall retention. Excluding the New Jersey site, which did not collect data for visits 6–10, retention was 78% through visit 10 (ranging from 71% for African-American women to 88% for Japanese women). We censored New Jersey participants after visit 5.

Data collection

Annual visits included an in-person interview, self-administered questionnaires, and measurement of weight and height (with calibrated scales and a stadiometer). All questionnaires were translated into Cantonese, Japanese, and Spanish and back-translated; translation discrepancies were resolved by 2 translators.

Outcome

Our primary outcome was age at the natural FMP, determined from annual interviews indicating 12 months of amenorrhea since the last menstrual period for no other cause (e.g., hysterectomy, bilateral oophorectomy). For 159 women missing this date at the visit before the first visit at which 12 months of amenorrhea was established, we interpolated the FMP date on the basis of interview date and reported number of months of amenorrhea at the prior visit.

Independent variables

Time-independent variables included primary race/ethnicity (self-defined as black or African American, non-Hispanic Caucasian, Chinese, Japanese, or Hispanic) and educational attainment from the screening questionnaire. Time-varying demographic variables included annual self-reported employment, marital status, and difficulty paying for basics such as food, shelter, and heat.

Time-varying lifestyle variables included annual self-reported active (58) and passive (59) smoke exposure and physical activity (60, 61), as well as diet (total calories and alcohol) from baseline and annual visits 5 and 9. Information on diet was obtained through the use of a modified Block Food Frequency Questionnaire (62–64), with added foods for the Hispanic, Chinese, and Japanese versions (65, 66).

Baseline time-invariant health-related variables included self-reported parity, prior oral contraceptive and other exogenous hormone use, and maternal age at menopause (reported at visit 4), as well as measured weight and height. Time-varying variables included self-assessed health (excellent, very good, good, or fair/poor); diabetes (use of diabetes medications or elevated fasting serum glucose); and changes in weight, serum estradiol level, and follicle-stimulating hormone level. Blood was drawn annually on days 2–5 of the menstrual cycle for women who were still cycling regularly and on any day for other women. SWAN's central laboratory at the University of Michigan assayed all annual blood samples for glucose, estradiol, and follicle-stimulating hormone (67, 68).

Data analyses

To test baseline racial/ethnic differences, we computed χ^2 statistics for categorical variables and Kruskal–Wallis tests for continuous variables. We censored a participant's data at the visit at which she reported initiating hormone therapy if no subsequent hormone therapy-free bleeding occurred, at the date of hysterectomy or bilateral oophorectomy, or at the last menstrual period at the end of data collection if it occurred before 12 months of amenorrhea, either because of attrition or because of ending data collection at visit 10. Time-varying covariate information was included in analyses if it occurred ≤3 months after the date of FMP or censoring, to maximize use of observed data while avoiding inclusion of predictors that could be influenced by the FMP. We omitted 49 participants whose last menstrual period at initial eligibility screening occurred more than 3 months before baseline. Of the remaining 3,253 participants, 1,483 had an observed date at natural FMP, and 1,770 were censored because of one of the following: being postmenopausal but missing FMP date ($n = 30$); hysterectomy or bilateral oophorectomy before having ≥12 consecutive months of untreated amenorrhea ($n = 192$); hormone therapy initiation without hormone therapy-free bleeding after a 6-month washout period, followed by ≥12 consecutive months of amenorrhea ($n = 590$); missing data or attrition before visit 10 and before ≥12 consecutive months of amenorrhea ($n = 652$); or end of data collection at visit 10 before ≥12 consecutive months of amenorrhea ($n = 306$).

Table 1. Baseline (1996–1997) Characteristics of SWAN Cohort by Race/Ethnicity, United States (*n* = 3,253)

Baseline Characteristic	African American (n = 916)			Caucasian (n = 1,533)			Chinese (n = 248)			Hispanic (n = 277)			Japanese (n = 279)			P Value[a]
	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	
Age, years			46.0 (44.0–48.2)			46.0 (44.0–48.3)			46.6 (44.3–48.1)			46.0 (44.3–48.0)			46.7 (44.4–48.7)	0.1154
Menopause status																0.0001
Premenopausal	454	50.2		788	52.7		152	62.0		150	58.4		173	62.7		
Early perimenopausal	450	49.8		706	47.3		93	38.0		107	41.6		103	37.3		
Educational level																<0.0001
High school or less	243	26.9		245	16.1		72	29.0		190	70.9		51	18.3		
Some college	368	40.7		466	30.6		54	21.8		51	19.0		97	34.8		
College degree	294	32.5		811	53.3		122	49.2		27	10.1		131	47.0		
Financial strain																<0.0001
Very hard	114	12.5		88	5.8		13	5.2		69	25.8		10	3.6		
Somewhat hard	307	33.7		399	26.2		57	23.0		152	56.7		74	26.6		
Not hard	490	53.8		1,039	68.1		178	71.8		47	17.5		194	69.8		
Employed	718	79.1		1,285	85.3		218	88.6		145	55.3		203	73.0		<0.0001
Prior oral contraceptive use	735	81.0		1,206	80.2		156	63.4		117	44.8		147	52.9		<0.0001
Prior hormone therapy use	78	8.6		222	14.9		23	9.4		22	8.6		26	9.4		<0.0001
Smoking																<0.0001
Never	483	53.9		780	51.1		233	94.0		183	67.0		178	64.3		
Past	197	22.0		495	32.4		11	4.4		46	16.9		63	22.7		
Current	216	24.1		253	16.6		4	1.6		44	16.1		36	13.0		
Passive smoking, person-hours/week																<0.0001
0	313	34.6		602	39.5		194	78.2		174	63.0		170	61.6		
1–4	236	26.1		480	31.5		38	15.3		32	11.6		62	22.5		
≥5	357	39.4		443	29.1		16	6.5		70	25.4		44	15.9		
Parity																<0.0001
0	82	9.0		369	24.2		33	13.3		18	6.7		46	16.5		
1	159	17.4		259	17.0		37	14.9		42	15.7		39	14.0		
2	269	29.4		487	31.9		128	51.6		81	30.3		120	43.0		
3	202	22.1		254	16.6		40	16.1		75	28.1		57	20.4		
≥4	203	22.2		157	10.3		10	4.0		51	19.1		17	6.1		
Marital status																<0.0001
Never married	195	21.5		180	12.0		22	8.9		13	5.0		20	7.2		
Currently married/partnered	430	47.3		1,076	71.5		199	80.9		196	74.8		225	80.9		
Previously married/partnered	284	31.2		248	16.5		25	10.2		53	20.2		33	11.9		
Current diabetes	74	8.1		50	3.3		3	1.2		19	7.0		0	0.0		<0.0001

Table continues

Table 1.   Continued

Baseline Characteristic	African American (n = 916)			Caucasian (n = 1,533)			Chinese (n = 248)			Hispanic (n = 277)			Japanese (n = 279)			P Value[a]
	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	No.	%	Median (IQR)	
Body mass index, kg/m^2			30.2 (26.1–36.3)			26.0 (22.9–31.3)			22.4 (20.8–24.7)			28.3 (25.4–32.2)			22.1 (20.4–24.6)	<0.0001
<25	169	18.8		655	43.2		189	76.8		65	23.6		219	79.1		
25–29.9	268	29.9		393	25.9		46	18.7		108	39.1		45	16.3		
≥30	460	51.3		470	31.0		11	4.5		103	37.3		13	4.7		
Total calories			1,818 (1,344–2,409)			1,704 (1,375–2,157)			1,659 (1,353–2,161)			1,547 (1,275–1,949)			1,798 (1,342–2,140)	<0.0001
Dietary fiber, g			10.7 (7.8–14.7)			11.3 (8.4–14.9)			13.6 (10.6–18.0)			11.5 (8.4–14.7)			11.3 (8.7–14.8)	<0.0001
Physical activity score (excluding work)			7.3 (6.1–8.4)			8.1 (6.9–9.3)			7.3 (5.9–8.4)			6.6 (5.8–7.6)			7.8 (6.8–9.0)	<0.0001
Maternal age at menopause, years																<0.0001
Unknown type or age	283	36.6		365	26.8		95	40.4		54	32.0		103	38.6		
Medical,[b] <40	52	6.7		105	7.7		3	1.3		5	3.0		9	3.4		
Medical, 40–44	42	5.4		84	6.2		2	0.9		5	3.0		10	3.8		
Medical, 45–49	39	5.1		90	6.6		10	4.3		4	2.4		10	3.8		
Medical, 50–54	21	2.7		43	3.2		3	1.3		2	1.2		5	1.9		
Medical, ≥55	15	1.9		26	1.9		3	1.3		3	1.8		1	0.4		
Natural, <45	25	3.2		61	4.5		9	3.8		6	3.6		5	1.9		
Natural, 45–49	73	9.4		134	9.9		21	8.9		18	10.7		28	10.5		
Natural, 50–54	142	18.4		337	24.8		60	25.5		48	28.4		69	25.8		
Natural, ≥55	81	10.5		116	8.5		29	12.3		24	14.2		27	10.1		
Follicle-stimulating hormone, mIU/mL			16.4 (11.2–27.8)			15.3 (10.7–25.3)			16.4 (11.2–27.5)			15.6 (10.1–28.4)			14.5 (10.6–23.8)	0.2746
Estradiol, pg/mL			55.0 (34.2–89.3)			56.5 (34.3–89.2)			49.0 (27.7–81.3)			59.3 (27.6–98.8)			51.9 (31.0–84.9)	0.0247
Number of alcohol servings per week																<0.0001
None	479	56.9		581	39.1		191	78.9		133	50.8		147	57.9		
<1	25	3.0		40	2.7		4	1.7		15	5.7		7	2.8		
1–7	226	26.8		499	33.6		37	15.3		102	38.9		65	25.6		
>7	112	13.3		365	24.6		10	4.1		12	4.6		35	13.8		
Self-reported health																<0.0001
Excellent	140	15.4		438	29.1		42	17.1		13	5.0		54	19.4		
Very good	299	32.9		638	42.4		73	29.7		59	22.5		102	36.7		
Good	322	35.5		330	21.9		78	31.7		120	45.8		72	25.9		
Fair/poor	147	16.2		100	6.6		53	21.5		70	26.7		50	18.0		

Abbreviations: IQR, interquartile range; SWAN, Study of Women's Health Across the Nation.

[a] Kruskal–Wallis for continuous variables, χ^2 for categorical variables.

[b] Medical includes menopause induced surgically or by medications.

Table 2. Unadjusted and Adjusted Hazard Ratios (95% Confidence Intervals) for Age at Natural Final Menstrual Period From Cox Proportional Hazards Modeling Accounting for Left-Truncation, All 7 SWAN Sites, United States, Baseline Through Follow-up Visit 10 (1996–2007)

Characteristic	Unadjusted (n = 3,253)			Adjusted[a] (n = 2,878)		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Race/ethnicity			0.0009			0.624
African American	1.24	1.10, 1.40		1.05	0.09, 1.21	
Caucasian	1.00	Referent		1.00	Referent	
Chinese	1.24	1.04, 1.48		1.14	0.85, 1.53	
Hispanic	1.38	1.08, 1.76		0.81	0.51, 1.28	
Japanese	1.04	0.87, 1.24		0.90	0.67, 1.20	
Financial strain			<0.0001			
Very hard	1.57	1.30, 1.89				
Somewhat hard	1.22	1.09, 1.36				
Not at all hard	1.00	Referent				
Baseline smoking[b]			0.132			0.236
Never	1.00	Referent		1.00	Referent	
Past	0.98	0.86, 1.10		1.03	0.90, 1.19	
Current	1.26	0.98, 1.62		1.26	0.97, 1.65	
Time-varying smoking[b]	1.49	1.16, 1.91	0.0017	1.53	1.18, 2.00	0.002
Maternal type/age at FMP, years[c]			<0.0001			
Unknown	1.05	0.91, 1.21				
Medical[d]						
Age <40	0.90	0.69, 1.15				
Age 40–44	0.96	0.74, 1.25				
Age 45–49	0.72	0.55, 0.93				
Age 50–54	0.87	0.62, 1.21				
Age ≥55	0.45	0.28, 0.73				
Natural						
Age <45	1.36	1.02, 1.81				
Age 45–49	1.30	1.07, 1.58				
Age 50–54	1.00	Referent				
Age ≥55	0.83	0.68, 1.01				
Marital status[b]						
Baseline			0.115			
Never	1.20	1.00, 1.43				
Previously married/ partnered	1.02	0.87, 1.20				
Currently married/ partnered	1.00	Referent				
Time-varying married/ partnered	1.01	0.87, 1.16	0.934			
Ever diabetes	1.24	1.02, 1.50	0.0297			
Self-reported health, baseline	1.17	1.11, 1.24	<0.0001	1.11	1.04, 1.19	0.002
Educational level			<0.0001			0.003
High school or less	1.00	Referent		1.00	Referent	
Some college	0.83	0.72, 0.95		0.88	0.75, 1.03	
College degree	0.67	0.59, 0.76		0.77	0.66, 0.90	
Baseline ever-use of oral contraceptives	0.82	0.73, 0.92	0.0007	0.85	0.75, 0.97	0.015
Exogenous hormone therapy[b]						
Ever use (baseline)	0.83	0.69, 0.98	0.031			
Time-varying	0.93	0.78, 1.10	0.378			

Table continues

Table 2.   Continued

Characteristic	Unadjusted (n = 3,253)			Adjusted[a] (n = 2,878)		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
Alcohol, no. of servings/week[b,e]						
Baseline	0.94	0.89, 0.996	0.0357	0.97	0.92, 1.04	0.395
Change since baseline	0.88	0.81, 0.95	0.0018	0.90	0.83, 0.98	0.017
Current employment[b]						
Baseline	0.92	0.80, 1.06	0.264	0.99	0.85, 1.17	0.941
Time-varying	0.82	0.73, 0.92	0.0009	0.87	0.77, 0.98	0.026
Baseline height, 75th vs. 25th percentile	0.91	0.84, 0.98	0.0134			
Parity			0.688			
0	1.00	Referent				
1	1.04	0.88, 1.25				
2	0.99	0.85, 1.15				
3	1.01	0.85, 1.19				
≥4	1.11	0.93, 1.33				
Physical activity score[b]						
Baseline	0.99	0.95, 1.02	0.348	1.03	0.99, 1.07	0.153
Change since baseline	1.05	1.001, 1.10	0.0434	1.07	1.02, 1.12	0.007
Passive smoking, person-hours/week[b]						
Baseline			0.0154			
0	1.00	Referent				
1–4	0.86	0.74, 0.99				
≥5	1.09	0.92, 1.29				
Time-varying			0.470			
0	1.00	Referent				
1–4	0.99	0.85, 1.15				
≥5	1.10	0.92, 1.31				
Log total calories, 75th vs. 25th percentile[b]						
Baseline	0.94	0.30, 2.96	0.913			
Change since baseline	0.99	0.95, 1.03	0.610			
Baseline weight, 75th vs. 25th percentile[f]	1.00	0.93, 1.07	0.967	0.92	0.84, 0.996	0.039
Change in weight, 75th vs. 25th percentile[f]	1.02	0.97, 1.07	0.431			

Abbreviations: CI, confidence interval; FMP, final menstrual period; SWAN, Study of Women's Health Across the Nation.

[a] Adjusted for all other variables with hazard ratios entered in this column.
[b] Baseline and time-varying values of the predictor are both included as predictors.
[c] Measured at first annual follow-up; sample size = 2,805 for unadjusted analyses.
[d] Medical includes menopause induced surgically or by medications.
[e] 0 = none, 1 = infrequent (<2), 2 = moderate (2–7), 3 = heavy (>7).
[f] Baseline height, baseline weight, and change in weight all are included as predictors.

To identify predictors of age at natural FMP, we used Cox proportional hazards modeling (69). We used age, rather than time since baseline, as the time scale (70). In our final model, we did not adjust for estradiol or follicle-stimulating hormone because they probably constitute the underlying biological process that determines concurrent menopause status and the path-way to age at FMP. For time-invariant covariates, we applied the Kaplan–Meier approach to generate survival graphs and median age at FMP. Variables were retained in Cox models at $P \leq 0.05$, applying backward elimination. Race/ethnicity was included as a predictor, and study site was included as a stratifying factor to account for nonproportional hazards by site (71).

We assessed the validity of the proportional hazards assumption for each predictor by testing the significance of its interaction with age (71) and determining whether its inclusion improved model fit, indicated by the Akaike Information Criterion statistic (72). The data were subject to left truncation or late entry, because participants had "survived" (as not yet postmenopausal) to at least age at screening minus 90 days. To account for this, participants were excluded from all risk sets at ages younger than this age (71).

For time-varying covariates, to distinguish cross-sectional (between-woman) from longitudinal (within-woman) effects, we included both the baseline value and change since baseline (for continuous predictors) or follow-up (for categorical predictors) value as separate predictors in the multivariate model. Variables indicating change since baseline were treated as linearly related to the log hazard; thus, positive coefficients are presented as hazard ratios >1 for increase over time (e.g., increase in weight since baseline). Because the coefficients for baseline and follow-up diabetes were not different, we combined these into a single time-varying predictor, "ever had diabetes," to increase statistical power. For covariates with intermittent missing values, we compared unadjusted hazard ratios using 2 approaches: carrying the last value forward and omitting observations with missing covariate data. All results were very similar (data not shown). Within-woman correlation was high for all time-varying covariates except anxiety, life events, and depressive symptoms scores; thus, we carried the last value forward for all missing covariate data except for these variables, although these 3 variables were not preserved in the final model.

Baseline current smokers were overrepresented in the 49 excluded women, perhaps because of earlier FMPs and higher early attrition. The reasons for the disproportionate exclusion of New Jersey (including Hispanic) participants could have been similar, plus greater error in self-reported date of last menstrual period at screening, consistent with their higher proportion of "don't know" responses. In sensitivity analyses, we omitted an additional 411 women whose baseline data collection occurred on or after their reported last menstrual period (i.e., women with no time-varying covariates measured before FMP/censoring), yielding additional losses of smokers, Hispanics, and New Jersey participants and a slight increase in the median age at FMP (52.79 years). The resulting Cox model, however, was very similar, except baseline weight was no longer retained in the model (P = 0.065), probably because of reduced power with the reduced sample size.

RESULTS

Baseline sample characteristics

The median baseline age was 46.3 years (Table 1). About half of the women were premenopausal, with a significantly higher proportion among the Chinese and Japanese participants. Most women had at least some college education, did not report difficulty paying for basics, were employed, and reported oral contraceptive use but not other exogenous hormone use before baseline—all with significant racial/ethnic differences. Less than half of the women had ever smoked;

the highest proportion of current smokers and the greatest passive smoke exposure were among African-American women, again with significant racial/ethnic variation.

Parity was significantly higher in African-American and Hispanic women and was lowest in Chinese women. A significantly greater proportion of Chinese and Japanese women were currently married or partnered, and a higher proportion of African-American women were previously or never married.

More African-American women and fewer Hispanic, Chinese, and Japanese women had diabetes or were obese. Calorie and fiber intake, physical activity score, and maternal age at menopause also differed significantly by race/ethnicity. No significant racial/ethnic differences were observed in serum follicle-stimulating hormone, but Chinese and Japanese women had significantly lower estradiol levels. Caucasians had the highest alcohol intake and best self-rated health.

Unadjusted results

Factors significantly related to reaching the FMP (i.e., earlier FMP) in unadjusted analyses were (in descending strength of association) reporting it was very or somewhat difficult to pay for basics; smoking during follow-up; maternal natural menopause under age 49 years; not being Caucasian or Japanese; ever having diabetes; never having been married; having poorer baseline self-rated health; and reporting more physical activity during follow-up (Table 2). Women had significantly later FMPs if they had a mother who had medically induced menopause at ≥55 years or at 45–49 years; had some college or had graduated college; had previous oral contraceptive or hormone therapy use; had higher alcohol consumption; were employed during follow-up; or were taller. No significant associations were observed for parity, baseline physical activity, passive smoke exposure during follow-up, calorie intake, baseline weight, or change in weight.

Adjusted results

In multivariable analyses, racial/ethnic differences were no longer statistically significant (Table 2). Earlier age at FMP was related most strongly to smoking during follow-up (not at baseline) (hazard ratio (HR) = 1.53, 95% confidence interval (CI): 1.18, 2.00). The following variables were less strongly but significantly related to earlier age at FMP: reporting poorer health at baseline (HR = 1.11, 95% CI: 1.04, 1.19) and more physical activity during follow-up (HR = 1.07, 95% CI: 1.02, 1.12). The following were significantly related to later age at FMP: having graduated college (HR = 0.77, 95% CI: 0.66, 0.90), having used oral contraceptives before baseline (HR = 0.85, 95% CI: 0.75, 0.97), being employed during follow-up (HR = 0.87, 95% CI: 0.77, 0.98), having higher alcohol consumption during follow-up (HR = 0.90, 95% CI: 0.83, 0.98), and having higher baseline weight (interquartile range HR = 0.92, 95% CI: 0.84, 0.996). Financial strain, maternal age at menopause, marital status, ever having diabetes, hormone therapy use, parity, height, passive smoke exposure, weight change, and calorie intake were not statistically significantly associated with age at FMP and thus

Table 3.   Median Age (Years) at Final Menstrual Period Accounting for Left-Truncation, Unadjusted and Adjusted for Baseline Covariates and Time-Invariant Predictors in Multivariate Cox Proportional Hazards Model, SWAN, United States, Baseline through Follow-up Visit 10 (1996–2007)

	Unadjusted	P Value	Adjusted[a]	P Value
Baseline smoking		<0.0001		<0.0001
Never[b]	52.73		52.76	
Past	52.88		52.83	
Current	51.35		51.43	
Baseline self-reported health		<0.0001		0.0014
Excellent[b]	53.05		52.96	
Very good	52.88		52.99	
Good	52.00		52.36	
Fair/poor	51.98		52.31	
Educational level		<0.0001		0.0021
High school or less	51.53		52.15	
Some college	52.32		52.54	
College degree or higher[b]	53.07		53.06	
Baseline weight		0.178		0.0027
1st quartile[b]	52.45		52.41	
2nd quartile	52.66		53.14	
3rd quartile	52.37		52.67	
4th quartile	52.70		53.07	
Prior oral contraceptive use		0.0007		0.006
No	52.07		51.82	
Yes[b]	52.72		52.59	
Baseline alcohol servings/week		0.857		0.245
None	52.53		52.54	
Light	52.77		52.79	
Moderate	52.59		52.52	
Heavy	52.62		52.54	
Baseline diabetes[c]		0.0947		
No[b]	52.62			
Yes	48.65			
Baseline physical activity		0.616		0.820
1st quartile[b]	52.35		51.33	
2nd quartile	52.62		52.54	
3rd quartile	52.80		52.22	
4th quartile	52.82		52.42	

Table continues

Table 3.   Continued

	Unadjusted	P Value	Adjusted[a]	P Value
Race/ethnicity		0.0009		0.653
African American	52.17		52.59	
Caucasian[b]	52.88		52.85	
Chinese	52.41		52.86	
Hispanic	50.86		53.10	
Japanese	53.14		53.24	
Financial strain		<0.0001		
Very hard	51.51			
Somewhat hard	52.04			
Not at all hard	52.90			
Baseline employment		0.0017		0.260
No	51.58		51.53	
Yes[b]	52.75		52.44	
Baseline hormone therapy (ever)		0.0234		
No	52.48			
Yes	53.18			
Baseline marital status		0.0677		
Never married	51.94			
Previously married/partnered	52.55			
Currently married/partnered	52.68			
Parity[d]		0.688		
0	52.35			
1	52.48			
2	52.54			
3	52.76			
≥4	52.32			

Abbreviation: SWAN, Study of Women's Health Across the Nation.
[a] Adjusted for all variables in table except no. of children, as well as for site and baseline day of cycle.
[b] Reference group for covariate adjustment (i.e., apply their covariate distribution to all groups).
[c] P value omitted because hazards were not proportional.
[d] Adjusted for all variables in table, as well as for site and baseline day of cycle.

Median age at natural FMP

The median age at FMP was 52.54 years. After adjustment for baseline covariates using Cox models (69), the median age at FMP was significantly higher in women who (in descending order of significance) did not smoke, reported better health at baseline, had more education, had higher baseline weight, or had used oral contraceptives previously (Table 3, Figures 1–4).

were not retained in the final multivariable model after adjustment for other variables.
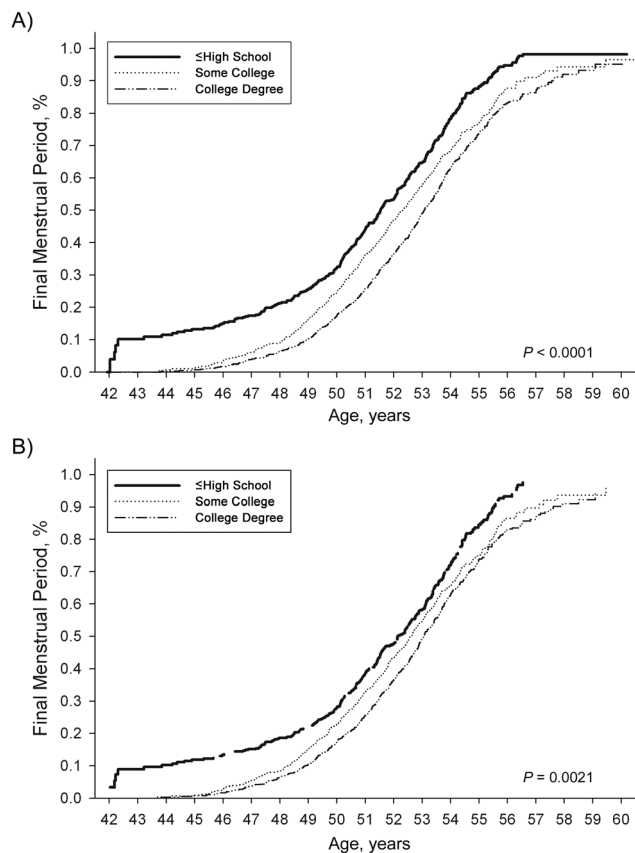
A)

B)
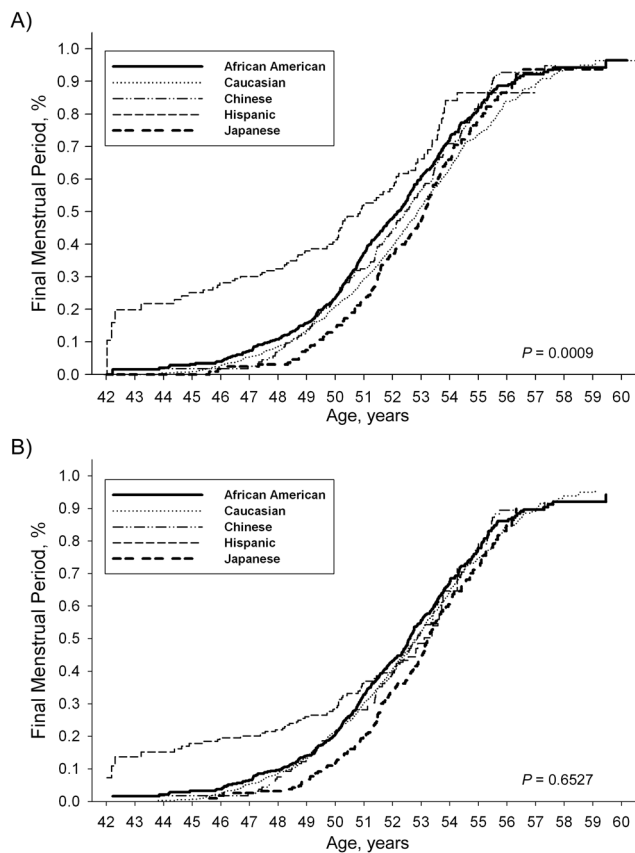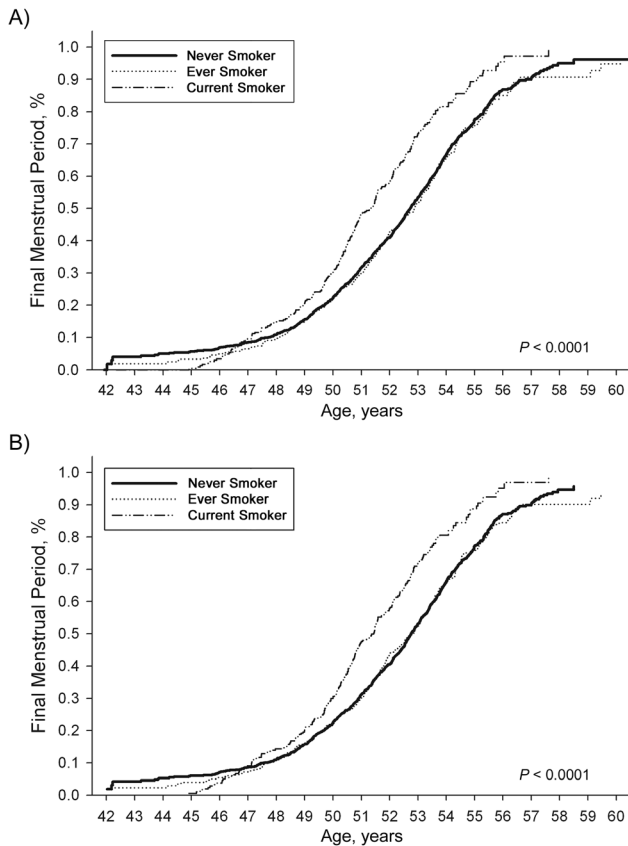

Figure 1.   Estimated distribution of age at final menstrual period, unadjusted and adjusted racial/ethnic differences, in the SWAN cohort, 1996–2007. For African Americans, unadjusted median age = 52.17 years and adjusted median age = 52.59 years; for Caucasians, unadjusted median age = 52.88 years and adjusted median age = 52.85 years; for Chinese, unadjusted median age = 52.41 years and adjusted median age = 52.86 years; for Hispanics, unadjusted median age = 50.86 years and adjusted median age = 53.10 years; and for Japanese, unadjusted median age = 53.14 years and adjusted median age = 53.24 years. SWAN, Study of Women's Health Across the Nation.

A)

B)

Figure 2.   Estimated distribution of age at final menstrual period, unadjusted and adjusted differences by educational level, in the SWAN cohort, 1996–2007. For ≤high school, unadjusted median age = 51.53 and adjusted median age = 52.13 years; for some college, unadjusted median age = 52.32 years and adjusted median age = 52.62 years; and for ≥college degree, unadjusted median age = 53.07 years and adjusted median age = 53.05 years. SWAN, Study of Women's Health Across the Nation.

DISCUSSION

In our longitudinal study of 3,302 initially premenopausal and early perimenopausal women from 5 racial/ethnic groups followed up for 10 years, multivariable Cox models identified later age at natural FMP as significantly associated with greater educational attainment, prior oral contraceptive use, employment during follow-up, absence of smoking during follow-up, higher baseline weight, greater alcohol consumption during follow-up, better self-rated health, and lower physical activity. However, we found no significant racial/ethnic difference in age at natural menopause once socioeconomic, lifestyle, and health variables were controlled. Findings from previous studies are inconsistent with regard to racial/ethnic differences in age at FMP (36, 37, 40, 73–77). However, our large, well-controlled and analyzed data set provides evidence that social determinants are key factors related to age

at menopause, a finding strengthened by other associations found that were consistent with previously published results.

Consistent with prior studies, our results showed that lower educational attainment (29, 30, 36, 41, 43, 50, 76) was significantly associated with an earlier menopause. A birth cohort study indicated that early life socioeconomic status was more strongly associated with age at FMP than adult status (77), although the former association was greatly attenuated when adjusted for childhood cognitive ability and having been breast-fed (52), factors not measured in our study.

Prior studies have consistently shown that current smoking (28, 29, 33, 35–37, 41, 43–48, 78, 79) and nonuse of oral contraceptives (30, 36, 41, 43, 80) are associated with an earlier FMP, as was observed in our study. Previous studies and ours have indicated that former smokers have an age at FMP similar to that of nonsmokers, which seems inconsistent with the polycyclic aromatic hydrocarbons in cigarette smoke being nonreversibly toxic to ovarian follicles (81, 82).

A)

B)

Figure 3. Estimated distribution of age at final menstrual period, unadjusted and adjusted differences by baseline smoking status, in the SWAN cohort, 1996–2007. For never smokers, unadjusted median age = 52.73 years and adjusted median age = 52.76 years; for ever smokers, unadjusted median age = 52.88 years and adjusted median age = 52.83 years; and for current smokers, unadjusted median age = 51.35 years and adjusted median age = 51.43 years. SWAN, Study of Women's Health Across the Nation.

A)

B)
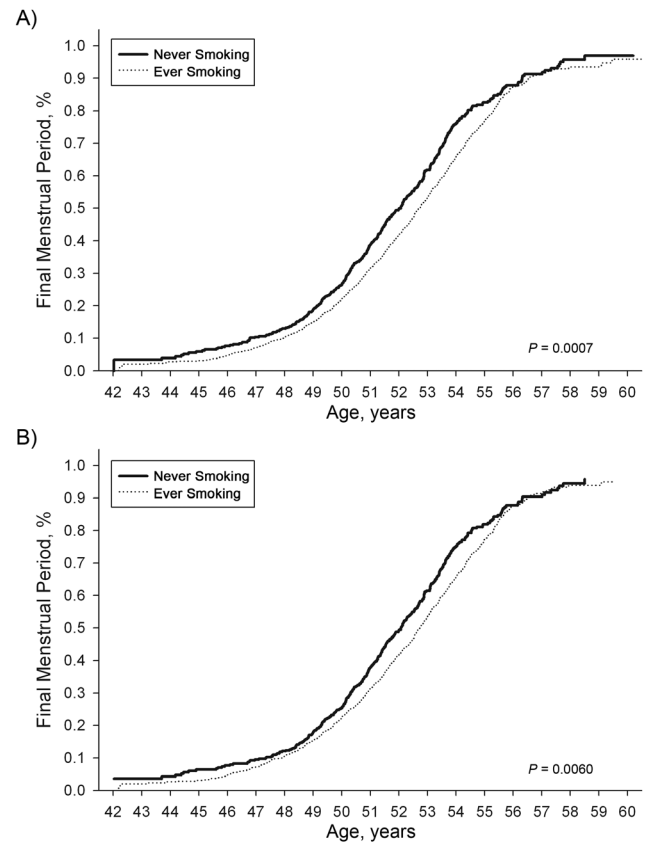
Figure 4. Estimated distribution of age at final menstrual period, unadjusted and adjusted differences by oral contraceptive use, in the SWAN cohort, 1996–2007. For never users, unadjusted median age = 52.07 years and adjusted median age = 52.08 years; for ever users, unadjusted median = 52.72 years and adjusted median age = 52.75 years. SWAN, Study of Women's Health Across the Nation.

Few studies have examined the relation of passive smoke exposure to age at FMP, although one early study showed that nonsmoking women whose spouses smoked had a similar age at FMP to that of smokers (83); we found no relation of time-varying passive smoke exposure.

Previous studies have reported that greater height was associated with later age at FMP (84–86), but we did not observe any such association in multivariable longitudinal models. However, although our multivariable model indicated that higher baseline weight was associated with later age at FMP, previous studies have been inconsistent, with some showing both increased body mass index and waist-to-hip ratio associated with later age at FMP (28, 35, 42, 49, 78, 85–88), but many showing no significant association (29, 30, 36, 37, 89, 90), although most did not adjust for weight change. Inconsistent results could be due to differences in design (cross-sectional or retrospective vs. longitudinal) or analysis (inadequate or differing control of confounding and using survival analyses vs. comparing unadjusted mean ages at

FMP). Also, our estimated association with baseline weight was small; thus, varying results across studies could be due to variations in samples or covariates included in the model.

We found that greater physical activity was modestly associated with earlier age at the FMP. Prior studies have been inconsistent, with one finding no relation (37) and one showing a later age at FMP associated with leisure-time physical activity (91). The inconsistency in results might be due at least partially to the weakness of the association, if it exists at all. We also found no significant relation of calorie intake to age at FMP. The literature is inconsistent with regard to the relation of dietary patterns to age at menopause, with some showing an earlier menopause among vegetarians (92), but one study showing a later age at natural menopause associated with higher green and yellow vegetable intake (93), and another study showing high intakes of fat, cholesterol, and coffee associated with earlier menopause (94). A large, longitudinal study found that high intakes of carbohydrates, vegetables, fiber, and cereal were related to earlier menopause, whereas higher intakes of fat, protein, and meat were associated with later menopause (95). A large, prospective

study reported that higher calorie, fruit, and protein intakes were associated with later age at menopause but that vegetable, fat, soy, and fiber intakes were not related (91).

A few small or cross-sectional studies (51, 53–55) and one longitudinal study (52) have shown significant associations between mothers' and daughters' ages at menopause. Our analyses resulted in maternal age at menopause not being retained in adjusted models. However, this variable must be interpreted cautiously because mothers' age at menopause was reported by daughters.

Our study had several significant strengths. We provided longitudinal results on prospectively measured age at natural FMP from a large cohort of community-based midlife women from 5 racial/ethnic groups followed up for 10 years with high retention rates. Standard annual clinic visits provided relatively precise estimates of age at FMP. We also adjusted for multiple factors simultaneously in the Cox models, censoring at initiation of hormone therapy use or at hysterectomy or oophorectomy, thus providing hazard ratios for age at the natural FMP for the relations of all factors examined, using all available data over 10 years of follow-up.

The study also had limitations. First, the cohort included only women who had menstruated recently at baseline so that we could observe menstrually defined menopause, but this excluded women who at screening had had at least 3 months of amenorrhea (1.8%–2%) or hysterectomy or bilateral oophorectomy (8%–11%). Also, the age range for the cohort was restricted to 42–52 years. This left-truncation likely resulted in an overestimation of median age at FMP (96, 97) because women who experienced their FMP before age 42 years were not included in the cohort. However, the bias was likely to be small, inasmuch as the distribution of age at FMP from the cross-sectional screener shifted upward only slightly; for example, at age 52 years, 50.24% were postmenopausal in the full sample, versus 49.28% in the sample omitting 40–41-year-olds. Moreover, analyses accounted for left-truncation for entry at ages 42 years and higher. Second, over 10 years of follow-up, we tended to lose women who were less healthy, smokers, less educated, or Hispanic, which potentially could lead to overestimation of the median age at menopause because these factors are associated with an earlier FMP, although we adjusted for all of these factors in multivariable analyses. Third, we did not have exact dates of the FMP for all women, and age at maternal menopause was based on recall. This could have resulted in some inaccuracy or imprecision in estimating age at FMP, although was likely not differential and thus should not have produced markedly biased results. Fourth, self-reported race/ethnicity might have been misclassified, but this was unlikely to be differential with regard to age at menopause and thus might have resulted in underestimation of differences. Finally, censoring women who initiated hormone therapy use and had no bleeding after stopping use (17.9% of cohort) could have resulted in underestimation of the age at FMP because these women tended to have higher socioeconomic status and better health. However, we included their data up to hormone therapy initiation and included those who had bleeding after ceasing use, which should have reduced potential bias.

In conclusion, we found no significant racial/ethnic differences in age at natural FMP in our large cohort, representing 5 racial/ethnic groups, after controlling for several sociodemographic, lifestyle, and health factors. Our results suggest that the age at natural FMP reflects a complex interplay of host and environmental factors, many of which are related to social determinants and better health, which could partially explain the relation of late age at FMP to reduced morbidity and mortality for many health outcomes. Because the age at natural FMP is an important indicator of future morbidity, life expectancy, and mortality and affects women's reproductive capability, these results have clinical and public health implications for early identification of women who are at high risk for future morbidity and advising women about family planning as they approach midlife.

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