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Duration of the menopausal transition is longer in women with young age at onset: the multi-ethnic Study of Women's Health Across the Nation

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Abstract

Objective—The menopausal transition (MT) is a critical period associated with physiologic changes that influence women's long-term health and longevity. However, information is limited

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regarding factors that influence age at onset of the MT and its duration (ie. Time from MT onset to the final menstrual period).

Methods—We analyzed data for 1145 women from 4 sites of the Study of Women's Health Across the Nation who participated in the menstrual calendar substudy, had the start of the MT identified, and had no missing covariate information. Participants included 4 racial/ethnic groups: African-American, White, Chinese, and Japanese. Women completed daily menstrual calendars from 1996–2006 and questions on hormone therapy use monthly. Baseline measures included education, economic strain, and menstrual cycle characteristics. Annual measures included height, weight, and smoking status. Cox proportional hazards models were used to analyze the data.

Results—The adjusted median duration of the MT ranged from 4.37 years among the oldest age-at-onset quartile to 8.57 years among the youngest age-at-onset quartile ($p<0.001$). Cigarette smoking was associated with an earlier onset ($p<0.001$) and a shorter duration ($p<0.001$). African-American women had a longer duration ($p=0.012$) compared to White women. Body mass index was associated with a later onset of the MT ($p=0.001$) but not its duration.

Conclusion—The duration of the MT was largely influenced by the age at which it began: earlier onset was associated with a longer transition. This finding provides a strong rationale for developing improved markers of the onset of the early MT.

Keywords

Menopause; Menopausal Transition; Race; Ethnicity; Smoking; Obesity

INTRODUCTION

The menopausal transition (MT), a critical period of physiologic change, is associated with transitory symptoms, such as hot flashes and depressive symptoms[1–3], and persistent changes in bone density and lipids[4–6]. Improving prediction of when the MT starts and who will have a shorter or longer transition would answer one of the questions midlife women most often ask clinicians and assist in decision making regarding symptom management and timing of screening and interventions to address bone loss, adverse changes in cardiovascular risk, and abnormal uterine bleeding and menopausal symptoms. Several studies have documented risk factors associated with age at the final menstrual period (FMP).[7–17] Only a few have elucidated factors that influence menstrual characteristics[18,19] or hormonal patterns[20–22] during the MT. Despite the importance of predicting when the MT will start and how long it will last, data addressing these questions are limited. In his landmark menstrual calendar study, Treloar estimated the median duration of the MT in white college-educated women to be 4.8 years[23]. Recent prospective studies have used interviews and questionnaires[15,24–26] to estimate both age-at-onset and duration of the MT. However, menstrual calendars remain the preferred method as questionnaires poorly identify the start of the MT[27].

Analyzing prospectively collected menstrual calendar data from the Study of Women's Health Across the Nation (SWAN), we examined the association of race/ethnicity, current smoking, body mass index (BMI), menstrual history, and socio-economic status with the timing of onset and duration of the early and late MT.

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METHODS

Study Population

This analysis included women from the four SWAN sites – Boston, southeastern Michigan, Los Angeles, and Oakland, CA – that had appropriate menstrual calendar data. The design of SWAN has been described previously.[28] Briefly, eligibility for enrollment into the cohort study included age 42–52 years, self-designation as a member of the targeted racial/ethnic groups, residence in the geographic area of one of the sites, the ability to speak English, Cantonese, or Japanese, an intact uterus and at least one ovary, not pregnant or lactating and at least one menstrual period and no use of reproductive hormones in the previous 3 months. Each site recruited White women and women from one specified minority group (African Americans in Boston and southeastern Michigan, Japanese in Los Angeles, and Chinese in Oakland). Institutional Review Boards at each study site approved the protocol, and all participants gave written informed consent.

Of the 1852 women enrolled in the SWAN menstrual calendar study at the four study sites, onset of the early menopausal transition was not observed in 705 women as 252 women were already in early transition at the time of enrollment and 453 women contributed fewer than 10 untreated menstrual cycles. These 705 women and the 2 women were missing information on education were excluded. Thus 1145 women (61.8%) were eligible for analysis.

Data Collection

Enrollment began in 1996 with approximately annual follow-up visits and a menstrual calendar component that continued through 2006, corresponding to the tenth follow-up visit. Each visit consisted of questionnaires that inquired about a broad range of topics, including information on menstrual experiences, socio-demographic characteristics, lifestyle, and medical history. Participants completed menstrual calendars daily to record any spotting or bleeding. On the last day of the month, women indicated if no bleeding occurred that month and answered questions about use of oral contraceptives, hormone therapy, or gynecological procedures. Women were asked to complete the menstrual calendar until two years after their final menstrual bleed or hysterectomy.

Menopausal Stage

Women’s menstrual experience was assessed by their sequence of menstrual cycle lengths, calculated using bleeding definitions recommended by the World Health Organization[29] as adapted by the ReSTAGE Collaboration for midlife women[30]. A menstrual cycle consisted of a bleeding episode and a subsequent bleed free interval of at least three days. Onset of the early MT was defined from the calendar data using the STRAW+10[31] criteria : a persistent difference of at least 7 days in the length of consecutive menstrual cycles with persistence defined as recurrence within 10 cycles of the first variable length cycle. Onset of the late transition was defined as the first occurrence of a menstrual cycle length of at least 60 days. The FMP was defined as the bleeding episode followed by at least 12 months of amenorrhea.

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Covariates

Hormone therapy (HT) use, including menopausal HT, oral contraceptives, or chemotherapy, was ascertained each month on the menstrual calendar. For each menstrual cycle, measured weight was linearly interpolated between the last and next annual visits. BMI, weight in kilograms divided by height in meters squared, was categorized as normal (≤ 24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2). At each annual visit, women reported whether they smoked currently (≥ one cigarette per day). If a woman indicated she was a current smoker, all menstrual cycles during the prior year were classified as smoking. Smoking was categorized as current smoker (yes/no) as timing and duration of former smokers did not differ from nonsmokers.

At baseline, women indicated their usual menstrual cycle length and whether they had unpredictable menstrual cycles at ages 25 to 30 years; self-defined race/ethnicity (African-American, Japanese, Chinese, or White); highest educational level achieved (less than high school, high school or at least some college), presence of economic strain (how hard is it to pay for basics: very hard, somewhat hard, or not hard).

Statistical Analyses

Frequency distributions were calculated for covariates. We used Cox-Proportional Hazards[32] models to determine the association between potential risk factors and age at the onset of the MT, duration of the early MT stage (time from the onset of the early MT to the onset of the late MT), duration of the late MT stage (time from the onset of the late MT to FMP), and total duration of the MT (time from the onset of the early MT to FMP). Smoking status and BMI were defined by women's status at the onset of the MT when modelling age at start of the transition and the duration of the early and late transition and by her status at the onset of the late MT for when modelling duration of the late transition. Kaplan-Meier survival curves were generated to graph the timing and length of each transition stage, adjusting for confounding variables.

The proportional hazards assumption for each of the predictors was checked graphically with none violating this assumption. Women were censored at time of hysterectomy, bilateral oophorectomy, or chemotherapy, or if they started continuous HT use and had no subsequent untreated cycles. Pregnancy, periods of HT use and missing calendars were treated as gaps in the menstrual history, with the assumption that staging events did not occur during gaps based on our prior work showing this assumption had little impact on estimated timing of menopausal stages[33]. Statistical analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Baseline characteristics of the study population are provided in Table 1. In total 1145 of the 1852 women participating in the menstrual calendar substudy were eligible for this analysis. Eligible women were more likely to be Chinese or Japanese and, consequently, to be from Oakland or Los Angeles, to be of normal weight and nonsmokers, to have graduated from college, and to find it not hard to pay for basics compared to women ineligible for these

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analyses. Eligibility was not associated with prior hormone use at baseline. The eligible population was 48.0% white, 18.8% African American, 17.9% Japanese and 15.3% Chinese. Half of the women had at least a college education and about one-third found it somewhat or very hard to pay for basics, Forty percent were overweight or obese. Twelve percent had taken HT, but three-quarters had used oral contraceptive prior to enrolling in the study, Only 11.9% were current smokers.

The 1145 eligible women contributed a total of 4712 women-years of observation following the start of the early MT. The FMP was observed in 428 (37.4%) of the 1145 women, 44 (3.6%),were censored due to hysterectomy, 152 (13.3%) because of HT use or chemotherapy, while 521 were still bleeding at the time of their last observation.

Age at onset of the Menopausal Transition

For age-at-onset (Table 2, column 1), a hazard ratio (HR) of greater than one indicated a greater likelihood to transition, i.e, a younger age at the start of the MT, while a HR of less than one indicated an older age at MT onset. Women who were overweight (HR=0.77, 95% CI: 0.646 0.90) started the MT later than women who were normal weight, but the HR for obese women was not significant (HR=0.88, 95% CI: 0.74, 1.03, p=0.11). Current smokers were younger at the onset of the MT (HR=1.46, 95% CI: 1.21, 1.76) than non-smokers with an adjusted median age-at- onset of the MT of 46.05 years for current smokers compared to 47.27 years for non-smokers(Figure 1).

Duration of the Menopausal Transition

For duration models (Table 2, columns 2 and 3), a HR greater than one represented faster progression through the stage and thus a shorter duration than the referent group. A HR less than one represented slower progression and thus a longer duration than the referent group. Age at the onset of the early MT was strongly associated with duration of the early MT and total MT. Women in the youngest age-at-onset quartile had a longer early MT (HR=0.37, 95% CI: 0.30, 0.46, p<.001) and longer total MT (HR=0.30, 95% CI: 0.22,0.40, p<0.001), while women who were in the oldest age-at-onset quartile had a shorter duration of the early MT (HR=1.32, 95% CI: 1.10, 1.60, p<.001) and total MT (HR=1.80, 95% CI: 1.40, 2.31, p<.001) compared to women in quartile 3. Results were similar for the duration of the late MT. Compared to women in age-at-onset quartile 3, women in the youngest quartile at onset of the late MT had a longer late MT stage (HR=0.51, 95%CI: 0.39, 0.68, p<0.001) while those in the oldest quartile had a shorter late MT stage (HR=1.29, 95%CI: 1.00, 1.72, p=0.05).

Adjusted for race/ethnicity, BMI, short menstrual cycles at baseline, unpredictable menstrual cycles during ages 25–30 years, current smoking status, and baseline education, for the early MT stage, the adjusted median duration was 5.14 years, 3.27 years, 2.18 years, and 1.68 years for the first, second, third and fourth age-at-onset quartiles, p<0.001 (Figure 2a). For the late MT stage and the total MT, the adjusted median durations were 3.42 years, 2.55 years, 2.47 years, and 2.15 years and 8.57 years, 6.84 years, 5.08 years, and 4.37 for the first, second, third and fourth age-at-onset quartiles, respectively, p<0.001 (Figures 2b and 2c).

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African American women had longer total MTs (HR=0.68, 95% CI: 0.50, 0.92, p=0.012) than White women. Current smokers had a shorter duration of the early MT and a shorter duration of the total MT (HR= 1.66, 95% CI: 1.33, 2.08 p<0.001; HR= 1.87, 95% CI: 1.37, 2.54), p<0.001, respectively). BMI was not associated with the duration of the MT or its stages. Women whose usual menstrual cycles at the start of the study were short (≤25 days) had a shorter late and total MT (HR= 1.29, 95% CI: 1.02, 1.61, p=0.030; HR= 1.39, 95% CI: 1.12, 1.74 p=0.003). Women who had unpredictable menstrual cycles at age 25 to 30 had a longer early MT (HR=0.76, 95% CI: 0.60, 0.95, p=0.148). Women who were high school graduates or had less education had a shorter early MT (HR= 1.25, 95% CI: 1.04, 1.51 p=0.021) than women who had more education.

It is possible that the onset of the early and/or late transitions may have been more likely to have occurred prior to enrollment in women who were older at enrollment than in women who were younger at enrollment, thus biasing the results. We therefore re-ran the analysis including only those women who were age 45 years or less at enrollment. Although the smaller sample size reduced the statistical power, the HR for age at onset of each transition stage were consistent with younger age at the start of the stage remaining associated with longer duration of the transition (data not shown).

DISCUSSION

This multi-racial/ethnic cohort study used prospectively collected menstrual calendars from over 1000 participants to assess factors associated with the age at which the MT begins and its duration. Age-at-onset was the strongest predictor of MT duration: the length of each MT stage was shorter in women who were older at the onset of the MT. Smoking was associated with an earlier onset and shorter duration of MT while greater BMI was associated with a later onset of the MT but not with its duration. African-Americans experienced longer duration than whites.

These results are consistent with both the landmark TREMIN menstrual calendar study in which women who were younger at the onset of the MT had a longer MT[19] and the questionnaire-based Massachusetts Women's Health Study (MWHS) in which older age at onset of the MT was associated with shorter perimenopause[24]. Notably, longer duration of hot flashes have also been associated with younger age at onset in SWAN[34]. These data provide valuable information for women and clinicians regarding factors that alter the expected duration of the transition which may assist in decision making regarding symptom management and choice of interventions to address abnormal bleeding as well as screening for bone loss and adverse changes in cardiovascular risk. An earlier onset of the MT would suggest a longer duration of possible intervention for perimenopausal health concerns whereas a late onset could permit the option of observation for an expected briefer duration of symptoms or abnormal bleeding. A woman who is aware that her menopausal symptoms are likely to be prolonged may be more likely to seek more effective forms of treatment for her symptoms, rather than passively await their decrease over time. Also, a frequent clinical question that women ask is when they may safely stop using contraception. A woman who has an early onset of her menopausal transition might inappropriately assume that she is no

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longer fertile before that it truly the case. Knowing that her transition may be prolonged will help her avoid an unexpected pregnancy.

Smoking affected both the timing and duration of the MT. Others have reported that smokers have an earlier age at FMP[7–11,17]. In the MWHS, smokers had an earlier age at MT onset and a shorter overall MT duration[24]. In the Penn-Ovarian Aging Study (POAS), smokers had an earlier onset of each stage.[25] We found smokers to have a younger age-at-onset as well as a shorter early MT, leading to a shorter duration of the MT. These findings provide further evidence of the cytotoxic effect of smoking on the ovaries leading to accelerated ovarian aging[35].

Several studies have reported that BMI is not related to age at FMP[8,9,12,13,36]. In the SWAN cross-sectional survey, BMI was not associated with age at FMP,[9] but a longitudinal analysis of the SWAN cohort observed a later age at FMP among higher weight women[17]. Our findings suggest that BMI does influence onset of the MT. Premenopausal women can be misclassified as in the MT because of the increased frequencies of menstrual irregularity in women who are obese[37]; however, obesity has been associated with an earlier entry into the perimenopause in one other study[26] and with earlier entry into the late reproductive stage but not later stages in another[25]. We found that BMI was associated with older age at onset of the MT, but not with duration of the MT after adjusting for age at MT onset.

Women with longer average cycle length during their reproductive years have a later age at menopause[14,16], while women with shorter cycles have an earlier age at menopause[15]. We found that short cycles at baseline were associated with a shorter duration of the late and total MT. Shorter cycles may simply mark the onset of early transition; however, they may also suggest more frequent recruitment of follicles and possible accelerated depletion of the primordial reserve. In contrast, we found reporting unpredictable menstrual cycles at ages 25 to 30 years was associated with a longer early MT stage. Irregular menstrual cycles between ages 20 to 35 years have been associated with a later age at FMP[7].

Although race/ethnicity and age at menopause have been inconsistently associated,[7,9,17] we found African-American women had a longer duration of the MT as compared to White women. While it did not reach statistical significance, we found African-American women tended to have an earlier age-at-onset of the MT. Two other studies have reported an earlier age-at-MT-onset among African-Americans.[25, 26] This study provides additional evidence that low socio-economic position may adversely affect menstrual function.[38,39] In SWAN, women with less education had an earlier age at FMP.[9,17] We found that less education was associated with a shorter early MT. Although it is difficult to link plausibly educational level directly to ovarian function, it is a proxy for socio-economic status (which was previously found in SWAN to account for racial/ethnic differences in age at FMP[17]) and thus for increased chronic stress and poorer nutrition. Oxidative stress[40] and diet[41] have been associated with reduced ovarian function, but a direct association with MT duration remains speculative.

This study had some limitations. Left truncation, which occurred in SWAN because participants were excluded if they had had their FMP, no period for three months or

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hysterectomy, may have biased our results by selectively excluding women with earlier or shorter transitions. However, when we conducted sensitivity analyses including only women enrolled before age 45 years our results were similar. Similarly, left censoring, i.e. when the MT started before the enrollment, was another potential source of bias. Women with polycystic ovarian syndrome (PCOS) who experience irregular cycles were more likely to be excluded, which may have influenced findings related to BMI[42]. Selection bias also may have been present as eligibility rates for this analysis differed by race/ethnicity, body size, and socio-economic status.

Despite these limitations, this large multi-racial/ethnic prospective study is the first of which we are aware to evaluate duration of each MT stage as defined by the STRAW + 10 criteria. Notably, earlier age-at-onset of the MT was associated with a longer transition, important information for guiding women regarding their likely menopausal experience. This finding provides a strong rationale for developing improved markers of the onset of the early transition, including evaluation of an inexpensive, validated, reliable anti-Mullerian hormone assay and an improved questionnaire for assessing bleeding markers of the early transition.[31] Both tools would prove useful for forecasting duration of MT stages and permitting better management of common symptoms such as hot flashes, irregular bleeding, and sleep disturbances, all of which impair quality of life and are amenable to a variety of effective treatments[2]. Similarly improved identification of MT onset with knowledge of the likely duration of each stage would assist decision-making regarding timing of screening and interventions to address bone loss and change in cardiovascular risk during the late MT.[4,5]

CONCLUSIONS

This large multi-racial/ethnic prospective study is among the first to evaluate duration of the MT stages as defined by the STRAW + 10 criteria, using daily menstrual calendars, and provided data on factors associated with duration of MT stages. Our results provide further evidence of the cytotoxic effects of smoking on the reproductive system and its consequences for reproductive aging. High BMI appeared to delay MT onset, but had little influence on the duration of the transition beyond its influence on age when the transition starts. Most notably, duration of the MT was largely influenced by the age at which it began, a key finding for women and their clinicians regarding factors that may alter the expected duration of the transition and assist in decision making regarding symptom management and choice of interventions to address abnormal bleeding as well as screening for bone loss and adverse changes in cardiovascular risk.

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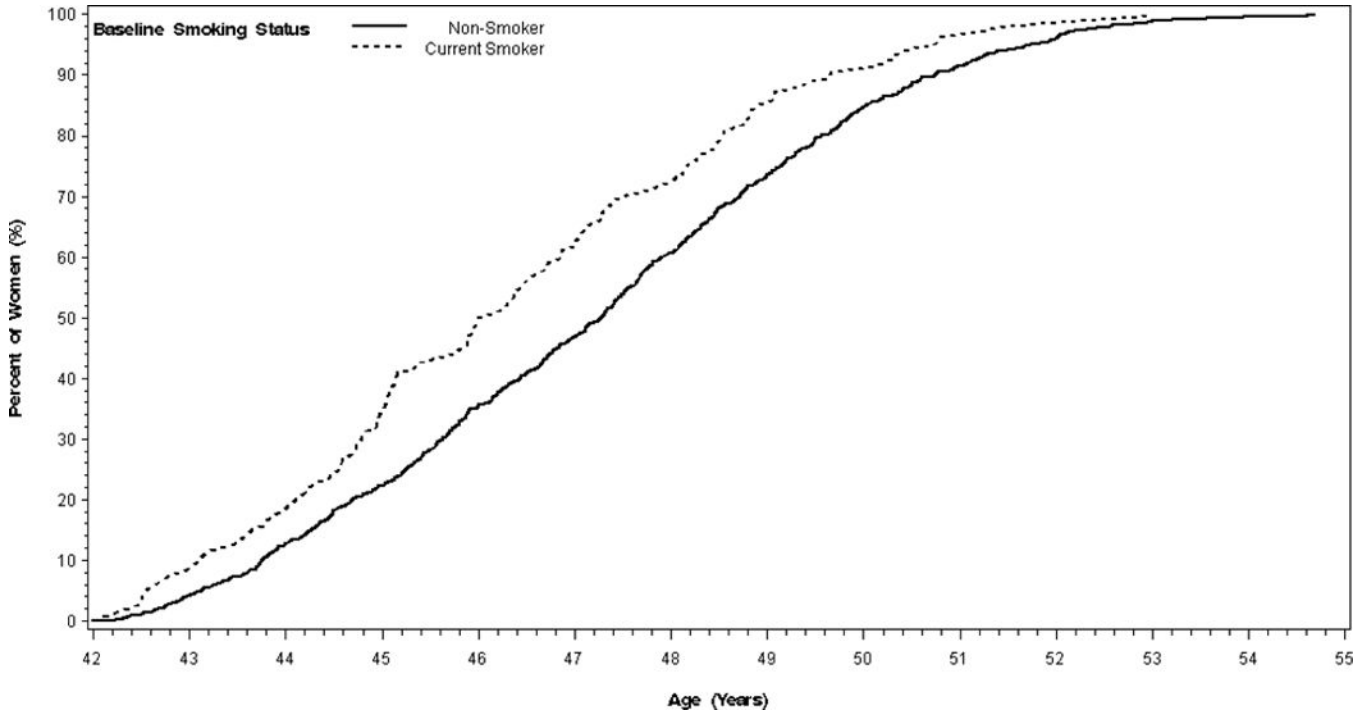

Figure 1.

Adjusted distribution of age at onset of the menopausal transition by baseline smoking status, Study of Women's Health Across the Nation (SWAN). Distributions adjusted for race/ethnicity, BMI, short menstrual cycles at baseline, unpredictable menstrual cycles during age 25–30, and baseline education. Current smokers had an earlier age at the onset of the menopausal transition than non-smokers ($p<0.001$).

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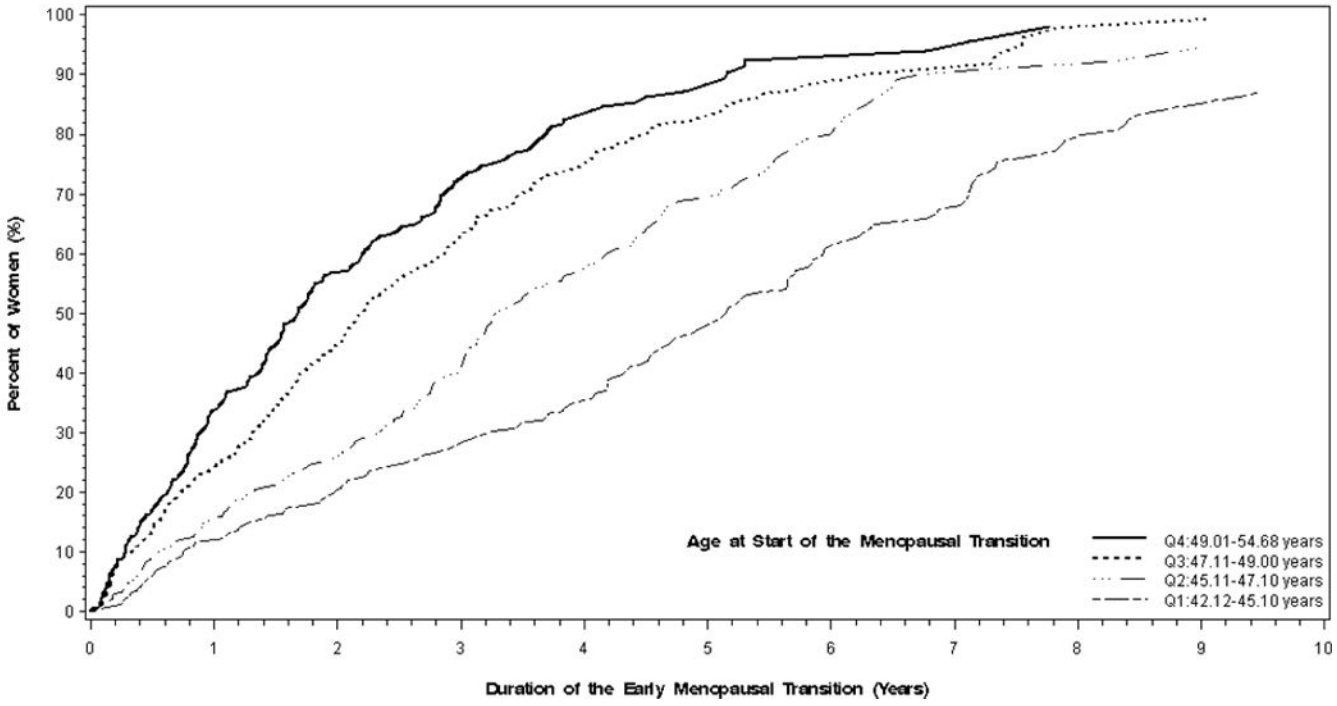
A



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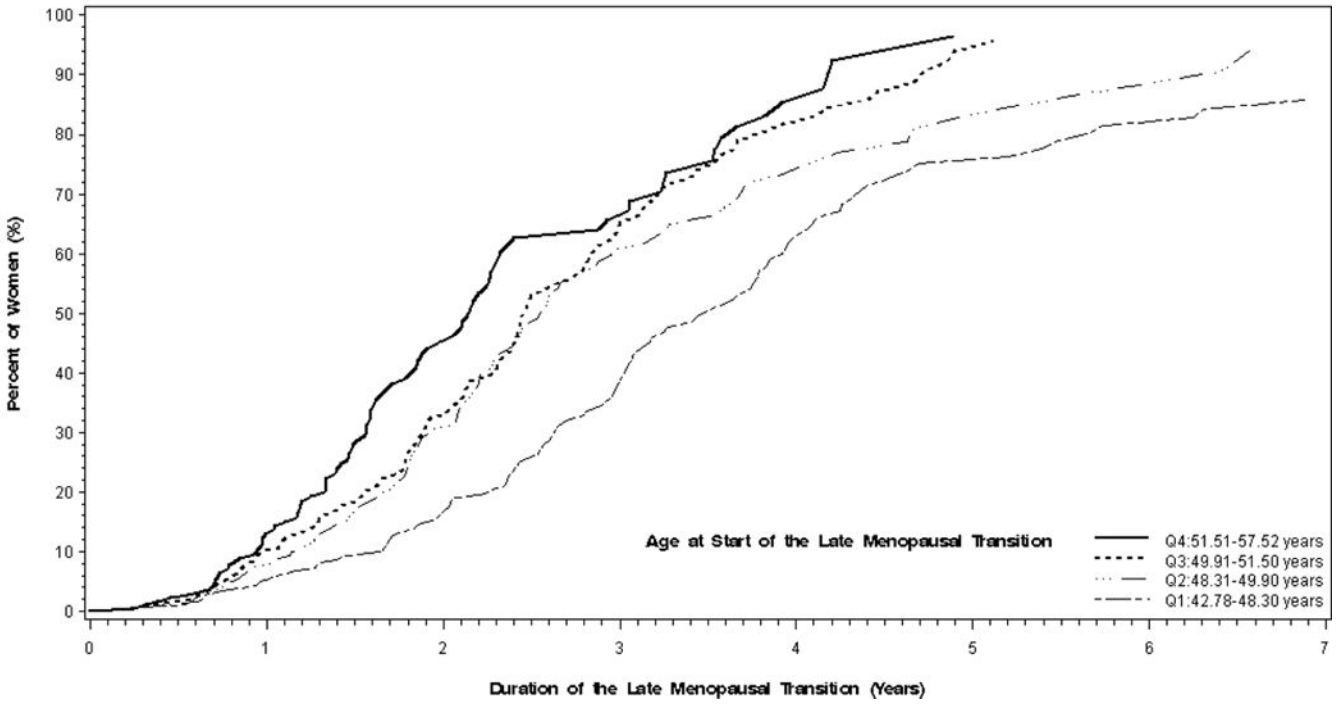

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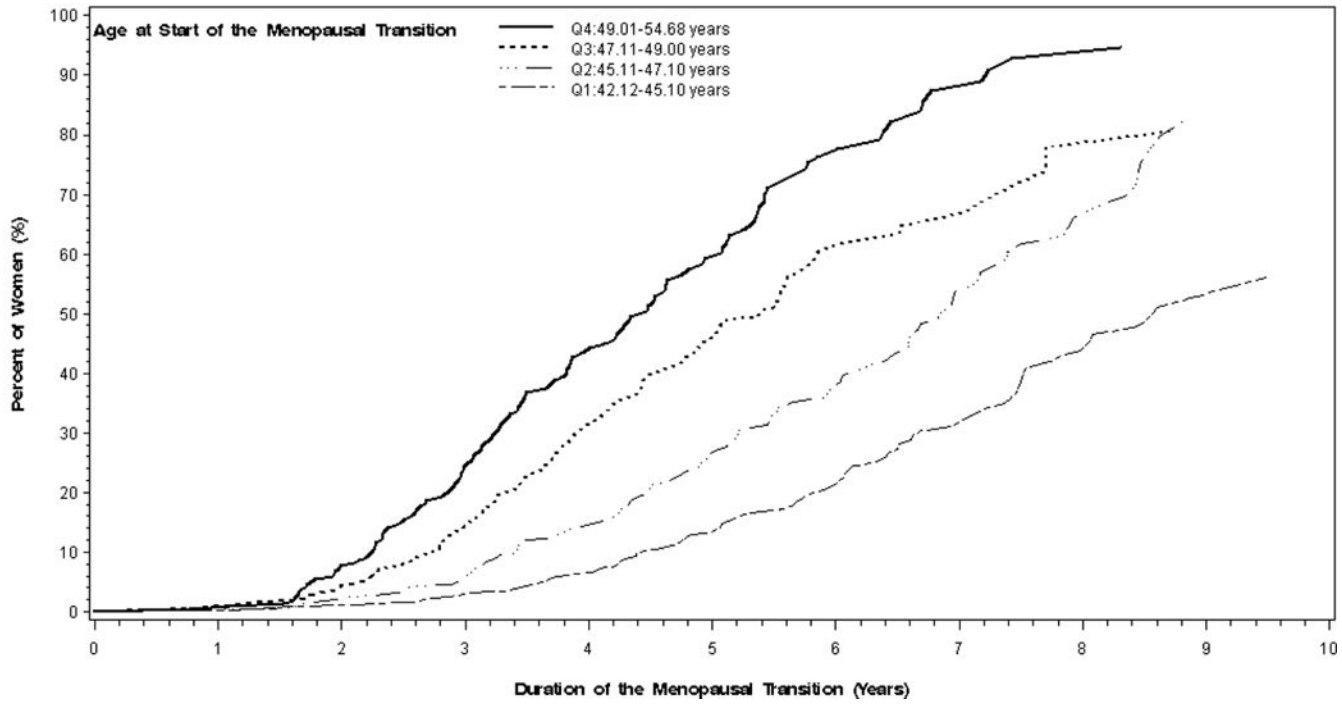

Figure 2.

A–C. Adjusted distributions of duration of the early menopausal transition (A), late menopausal transition (B), and total menopausal transition (C) by quartiles of age at onset of the stage, Study of Women's Health Across the Nation (SWAN). Distributions adjusted for race/ethnicity, BMI, short menstrual cycles at baseline, unpredictable menstrual cycles during age 25–30, current smoking status, and baseline education. Women in the youngest quartile had longer duration of the early menopausal transition ($p<0.001$), late menopausal transition ($p<0.001$), and total menopausal transition ($p<0.001$) than women in the older quartiles.

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Table 1

Baseline demographics of women in the Study of Women's Health Across the Nation (SWAN) who enrolled in the menstrual calendar substudy at four sites, by eligibility status, n= 1852

	Eligible for this analysis n=1145 n(%)	Not eligible for this analysis n=707 n (%)	P value[a]
Ethnicity			
African-American	215 (18.8)	253 (35.8)	<0.01
Chinese	175 (15.3)	69 (9.8)	
Japanese	205 (17.9)	70 (9.9)	
White	550 (48.0)	315(44.6)	
Education[b]			
Less than High School	39 (3.4)	45 (6.5)	<0.01
High School Grad	169 (14.8)	128 (18.6)	
Some College/Vocation	360 (31.4)	244 (35.4)	
College Graduate	287 (25.1)	126(18.3)	
Post College	290 (25.3)	147 (21.3)	
How Hard Is It To Pay For Basics[c]			
Very Hard	69 (6.1)	78 (11.2)	<0.01
Somewhat Hard	283 (25.1)	222 (31.8)	
Not Hard	777 (68.8)	398 (57.0)	
Body Mass Index, kg/m[d]			
Normal/Underweight	671 (59.4)	313 (45.4)	<0.01
Overweight	230 (20.3)	164 (23.8)	
Obese	229 (20.3)	213 (30.9)	
Baseline Smoking Status[e]			
Never	732 (65.1)	370 (53.2)	<0.01
Past	258 (23.0)	186(26.7)	
Current	134 (11.9)	140 (20.1)	
Ever Taken Hormones Prior to Study[f]	135 (12.0)	80 (11.5)	0.71
Ever Taken Oral Contraceptives Pill Prior to Study[g]	848 (74.8)	531 (76.0)	0.57
Study Site			
Michigan	235 (20.5)	258 (36.5)	<0.01
Boston	245 (21.4)	180 (25.5)	
Oakland	304 (26.6)	146 (20.7)	
Los Angeles	361 (31.5)	123 (17.4)	

[a] Calculated excluding missing

[b] Missing 17 from non eligible

[c] Missing 16 from eligible and 9 from non-eligible

[d] Missing 15 from eligible and 17 from non-eligible

[e] Missing 21 from eligible and 11 from non-eligible

[f] Missing 16 from eligible and 9 from non-eligible

[g] Missing 11 from eligible and 8 from non-eligible

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Table 2

Adjusted hazard ratios for predictors of age at onset of the menopausal transition (MT) and duration of the MT, Study of Women's Health Across the Nation Menstrual Calendars (four sites, n=1145).

	Age at Start of MT[a]		**Duration of Early[b]**		**Duration of Late[c]**		**Duration of MT[b]**	
	HR[d]	**95%CI**	**HR[e]**	**95%CI**	**HR[e]**	**95%CI**	**HR[e]**	**95%CI**
Age at the onset of early menopausal transition stage[f]								
Quartile 4 (49.01–54.68 years)	n/a		**1.32**	**1.10, 1.60**	n/a		**1.80**	**1.40, 2.31**
Quartile 3 (47.11–49.00 years)	n/a		1.00	referent	n/a		1.00	referent
Quartile 2 (45.11–47.10 years)	n/a		**0.63**	**0.52, 0.77**	n/a		**0.60**	**0.45, 0.77**
Quartile 1 (42.12–45.10 years)	n/a		**0.37**	**0.30, 0.46**	n/a		**0.30**	**0.22, 0.40**
Age at the onset of late menopausal transition stage[f]								
Quartile 4 (51.06–57.52 years)	n/a		n/a		**1.29**	**1.00, 1.72**	n/a	
Quartile 3 (49.91–51.05 years)	n/a		n/a		1.00	referent	n/a	
Quartile 2 (48.31–49.90 years)	n/a		n/a		0.82	0.62, 1.08	n/a	
Quartile 1 (42.78–48.30 years)	n/a		n/a		**0.51**	**0.39, 0.68**	n/a	
Race/Ethnicity								
African-American	1.18	0.99, 1.40	0.85	0.69, 1.04	0.75	0.55, 1.03	**0.68**	**0.50, 0.92**
Chinese	1.09	0.93, 1.30	1.11	0.89, 1.37	0.84	0.62, 1.13	0.99	0.74, 1.33
Japanese	0.89	0.75, 1.05	1.15	0.95, 1.40	1.09	0.83, 1.42	1.15	0.89, 1.49
White	1.00	Referent	1.00	referent	1.00	referent	1.00	referent
Body mass index, kg/m^2								
Normal (≤24.9)	1.00	Referent	1.00	referent	1.00	referent	1.00	referent
Overweight (25.0–29.9)	**0.77**	**0.66, 0.90**	1.06	0.88, 1.27	0.80	0.62, 1.03	0.83	0.64, 1.07
Obese(≥ 30.0)	0.88	0.74, 1.03	1.14	0.94, 1.37	0.85	0.64, 1.12	0.98	0.76, 1.27
Usual menstrual cycle length at start of study is ≤ 25 days	0.94	0.82, 1.08	1.15	0.98, 1.36	**1.29**	**1.02, 1.61**	**1.39**	**1.12, 1.74**
Unpredictable menstrual cycles at age 25 to 30 years	1.13	0.94, 1.36	**0.76**	**0.60, 0.95**	1.05	0.77, 1.43	0.81	0.60, 1.09
Current smoker	**1.46**	**1.21, 1.76**	**1.66**	**1.33, 2.08**	1.04	0.75, 1.46	**1.87**	**1.37, 2.54**
High school graduate or less education	0.94	0.80, 1.10	**1.25**	**1.04, 1.51**	0.91	0.70, 1.17	1.13	0.88, 1.46

[a]Model includes 1145 women and includes race/ethnicity, BMI, usual menstrual cycle length ≤ 25 days, current smoker, and High School education or less.

[b]Model includes 1145 women and includes race/ethnicity, BMI, usual menstrual cycle length ≤ 25 days, current smoker, High School education or less and age at the start of early menopausal transition stage

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[c]Model includes 792 women and includes race/ethnicity, BMI, usual menstrual cycle length ≤ 25 days, current smoker, High School education or less and age at the start of the late menopausal transition stage

[d]Hazard Ratio >1 corresponds to younger age at onset of the transition and < 1 corresponds to older age as compared to referent group.

[e]Hazard Ratio >1 corresponds to shorter duration and < 1 corresponds to longer duration than referent group.

[f]p-value for trend <0.01.