JCI insight

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JCI Insight. 2019;4(5):e124865. https://doi.org/10.1172/jci.insight.124865.

Research Article | Aging | Metabolism

BACKGROUND. The relation between the menopause transition (MT) and changes in body composition or weight remains uncertain. We hypothesized that, independent of chronological aging, the MT would have a detrimental influence on body composition.

METHODS. Participants were from the longitudinal Study of Women's Health Across the Nation (SWAN) cohort. We assessed body composition by dual energy x-ray absorptiometry. Multivariable mixed effects regressions fitted piece-wise linear models to repeated measures of outcomes as a function of time before or after the final menstrual period (FMP). Covariates were age at FMP, race, study site, and hormone therapy.

RESULTS. Fat and lean mass increased prior to the MT. At the start of the MT, rate of fat gain doubled, and lean mass declined; gains and losses continued until 2 years after the FMP. After that, the trajectories of fat and lean mass decelerated to zero slope. Weight climbed linearly during premenopause without acceleration at the MT. Its trajectory became flat after the MT.

CONCLUSION. Accelerated gains in fat mass and losses of lean mass are MT-related phenomena. The rate of increase in the sum of fat mass and lean mass does not differ between premenopause and the MT; thus, there is no discernable change in rate of weight gain at the start of the MT.

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Changes in body composition and weight during the menopause transition

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FUNDING. NIH, Department of Health and Human Services (DHHS), through the National Institute on Aging, National Institute of Nursing Research, and NIH Office of Research on Women's Health (U01NR004061, U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, and U01AG012495).

Introduction

The health consequences of obesity are myriad; leading examples include cardiovascular, metabolic, and neoplastic diseases (1). In developed countries, the epidemic of obesity, as well as the magnitude of the health burden it exerts, continue to inspire research into its etiologies, ranging from genetics to gut microflora (2, 3).

The menopause transition (MT), with concomitant alterations in the hypothalamic-pituitary-ovarian axis, may be an underappreciated contributing factor to women's obesity risk (4, 5). While gains in percent body fat and weight are observed among midlife women, studies to date attributed these principally to chronological aging, rather than to the MT; however, it is essential to recognize that the studies from which these inferences are drawn are limited (6–9). In observational cohorts, disaggregating the effects of chronological aging and ovarian aging is challenging because they occur contemporaneously. In addition to maximizing the sample size and number of observed MTs, a key to untangling the aging vs. MT problem is quantifying ovarian aging as precisely as possible. One way to do this is to model the outcome of interest (in this case, body weight or composition) in relation to the number of years before or after the final menstrual period (FMP). If the characteristic is indeed MT related, the FMP-based approach can demonstrate abrupt changes in the outcome that begin before the date of the FMP or slow down after it, strongly supporting a relation between the MT and the trait under consideration (10–12).

Conflict of interest: The authors have declared that no conflict of interest exists.

Submitted: September 27, 2018
Accepted: January 25, 2019
Published: March 7, 2019

Reference information:
JCI Insight. 2019;4(5):e124865.
https://doi.org/10.1172/jci.insight.124865.

Table 1. Characteristics of the analysis sample, overall and by race/ethnicity from the Study of Women's Health Across the Nation (SWAN)

Participant Characteristics[A,B]	Analysis Sample (*n* = 1246)	White Women (*n* = 559, 45%)	Black Women (*n* = 356, 29%)	Chinese Women (*n* = 153, 12%)	Japanese Women (*n* = 178, 14%)
Age					
At body composition baseline (y)	46.66 (2.64)	46.58 (2.67)	46.50 (2.69)	46.66 (2.51)	47.25 (2.50)
At final menstrual period (FMP) (y)	52.17 (2.77)	52.17 (2.85)	52.02 (2.85)	52.03 (2.62)	52.62 (2.49)
Anthropometrics at baseline					
Weight (kg)	72.77 (19.34)	74.82 (17.86)	84.01 (19.28)	57.44 (9.62)	56.99 (8.98)
BMI (kg/m2)	27.62 (6.79)	27.77 (6.39)	31.53 (7.16)	23.15 (3.75)	23.19 (3.61)
Body composition at baseline					
Fat mass (kg)	26.75 (11.35)	28.20 (11.15)	32.30 (11.75)	18.74 (5.76)	18.97 (5.56)
Proportion fat mass, times 100	39.44 (6.93)	40.14 (6.99)	42.11 (6.74)	35.68 (5.45)	35.62 (5.00)
Lean mass (kg)	38.71 (7.26)	39.84 (6.71)	42.37 (7.35)	32.96 (4.74)	33.43 (4.01)
Proportion lean mass × 100	60.56 (6.93)	59.86 (6.99)	57.89 (6.74)	64.32 (5.45)	64.38 (5.00)

[A]Percentages shown with race/ethnicity-specific *n*'s are the percent of analysis sample contributed by each racial group. All characteristics were measured at baseline except for age at FMP. Values provided in the table are means (SD). [B]SWAN enrolled 3302 women at baseline at 7 sites; 5 sites enrolled women into the SWAN Body Composition Cohort (*n* = 2349). Characteristics of the 1103 women who were ineligible for the present analysis (mainly, because they did not have ≥ 2 body composition measures or a date of FMP) were similar to those of the analysis sample (data not shown).

The overarching goal of this analysis is to discern whether the MT influences body composition or body weight. To address this question, we use longitudinal data from the Study of Women's Health Across the Nation (SWAN) to quantify rates of change in body composition and body weight in relation to the date of the FMP. Specifically, we attempt to describe (if present): (a) the timing of onset and offset of accelerated increases or decreases in fat mass, proportion fat mass, lean mass, proportion lean mass, weight, and BMI in relation to the FMP date; (b) quantification of the rate and amount of each during the 8 years before through 10.5 years after the FMP, if accelerated gains or losses in these body composition and weight characteristics are found; and (c) whether racial origin, age at FMP, or hormone therapy (HT) use influence the rates of change.

Results

Sample characteristics. The analysis sample numbered 1246 participants, including 356 Black, 153 Chinese, 178 Japanese, and 559 White women. Mean baseline age was 47.1 years (SD, 2.6 years) and average age at FMP was 52.2 years (SD, 2.8 years). Table 1 summarizes salient characteristics of the analysis sample overall and by each racial/ethnic group. These characteristics, as well as demographic descriptors, were similar to those of body composition cohort members who did not have a quantifiable date of FMP (data not shown). The median number of visits per woman was 10 (IQR, 7–11), with a maximum number of on-study observations of 13. The modal number of visits per woman represented 77% of total possible visits.

Crude trajectories of body composition and fat (LOESS plots). The 4 body composition measures each exhibited an accelerated increase (fat mass and proportion fat mass) or a decrease (lean mass and proportion lean mass) starting approximately 2 years before the FMP. At approximately 1.5 years after the FMP, decelerations were evident in both fat and lean compartments. Weight and BMI change-points differed from those of body composition: accelerations took place about 1 year before FMP, and decelerations about 3 years after the FMP (Figure 1). We therefore hypothesized a 2-knot model for each outcome. We tested this premise by fitting piece-wise linear growth curves with 3 linear segments anchored to FMP date, for each of the 6 outcomes, using mixed effects linear models and formal testing of knot locations. Figure 2 and Tables 2–4 present the results from these models.

Model-predicted trajectories of body composition and mass, averaged across all SWAN women. Figure 2 shows the model-predicted trajectories of all 6 outcomes in an average SWAN participant. To obtain the average participant's profile, each covariate is set to its analysis sample mean to create a composite of all women in the study. Therefore, variation by race/ethnicity or age at FMP cannot be discerned in this composite model. Associations of trajectory parameters (i.e., slopes) with covariates (race/ethnicity and age at FMP) are presented subsequently (Tables 2–4).

Both fat mass and proportion fat mass increase prior to the MT, by 1.0% and 0.4% per year, respectively ($P < 0.0001$ for each), and the increase accelerates over the MT to 1.7% and 1.0% per year, respectively ($P < 0.0001$ for each) (Figure 2). The mean annual increase in absolute fat mass in the average SWAN participant is 0.25 kg per year before the MT and 0.45 kg per year during the MT.

Prior to the MT, lean mass increases by 0.2% per year ($P = 0.0002$), which is 0.06 kg annually. However, since lean mass does not increase as fast as does fat mass, which grows at 0.25 kg per year, the proportion lean mass decreases even prior to the MT by 0.2% year ($P < 0.0001$). During the MT, lean mass decreases (by 0.2% per year; $P = 0.007$), as does proportion lean mass (by 0.6% per year, $P < 0.0001$). During the MT, mean absolute decline in lean mass is 0.06 kg per year. After the MT, annual change in all 4 body composition variables was not significantly different from zero ($P = 0.1$ or greater). Body weight and BMI also rise both prior to and during the MT, with annual rates of increase over the MT of 0.3% and 0.4%, respectively ($P < 0.0001$ for each). In the MT interval, average annual gain in weight is 0.25 kg and, in BMI, is 0.12 kg/m^2.

At the onset of MT, all 4 dual energy X-ray absorptiometry (DXA)-based measures demonstrated a statistically significant change in slope ($P < 0.001$ for slope change for each), indicating that there is a statistically significant change in trajectory in relation to the MT (Figure 2). In contrast, body weight and BMI slopes at the onset of MT did not differ statistically from slopes during premenopause ($P = 0.98$ for change in weight slope; $P = 0.5$ for change in BMI slope). The lack of a slope change between premenopause and the MT signifies that weight and BMI gains, manifest during premenopause, continue on an unaltered trajectory during the MT. For each of the body composition and weight outcomes, there was a statistically significant reduction in slope between the MT and postmenopause ($P = 0.02$ for change in lean mass slope; $P < 0.001$ for change in slope in all other 5 outcomes). Further, slopes in postmenopause were not statistically different from zero for all but BMI, demonstrating that, for body composition and weight, there is no further change after the MT in the average SWAN participant. BMI was the one exception; the postmenopausal rate of increase in BMI was lower than that during the MT but was still positive at 0.11% per year ($P = 0.04$ test of nonzero postmenopausal slope). On average, there was a small decrease in height over course of the study (data not shown), which accounts for the slight increase in BMI, despite stable weight, during postmenopause.

Race/ethnicity and age-at-FMP effects on change in fat mass and proportion fat mass. Table 2 summarizes the associations of age at FMP and race/ethnicity with changes in the fat mass outcomes. These are shown for each of the 3 time segments (premenopause, 8–2 years prior to FMP; MT, 2 years before to 1.5 years after FMP; and postmenopause,1.5–10.5 years after FMP), as well as for total change (8 years before to 10.5 years after the FMP). Results are expressed as point estimates and 95% CI; 95% CI that exclude 1 are statistically significant. White women who did not use HT and, at FMP, were 52.2 years old (analysis sample average) are the referent. To obtain the model-predicted fat mass and proportion fat mass slopes in non-White women and women with age-at-FMP other than 52.2 years, the effect size estimates from the Table 2 (for race/ethnicity and age-at-FMP, respectively) must be added to the slopes in the White referent women.

White women's fat mass climbed by close to 1% annually in premenopause. Onset of MT saw a 2.3-fold increase in the annual rate of increase in fat; a halt in fat gain accompanied the cessation of MT (Table 2). In White participants, proportion fat mass changed similarly, growing by 0.37% annually in premenopause, followed by a 2.7-fold increase in annual rate of change during the MT and stabilization (zero slope) in postmenopause. Fat mass trajectories of Black participants did not differ from those of White participants.

Unlike White women, Japanese participants' fat mass did not increase significantly during MT (Table 2). Japanese-specific slopes for change in fat and proportion fat mass during the MT, computed by adding Japanese-White difference (effect size) estimates to White slope estimates, were –0.14% per year (95% CI, –1.41% to +1.13%) and +0.29% per year (95% CI, –0.43% to +1.01%), respectively; neither slope was significantly different from zero (indicating no gain in fat mass or proportion during the MT).

Postmenopausal changes in fat mass and proportion fat mass were significantly different in Chinese women compared with White women (Table 2). Adding the Chinese-White difference (effect size) and White estimates for postmenopausal slope reveals that fat mass declined in Chinese women (–1.06% per year; 95% CI, –1.80% to –0.38%), as did proportion fat mass (–0.53% per year; 95% CI, –0.93% to –0.14%). In the average Chinese woman, total change in fat mass and proportion fat mass during the 15-year period around the MT was statistically not different from zero ($P = 0.9$ and 0.98, respectively).

Greater age at FMP attenuated the annual gains in fat mass and proportion fat mass in both premenopause (0.11% and 0.05% smaller annual gain for each year delay in FMP, respectively) and MT (0.23% and 0.12% smaller per year delay, respectively).

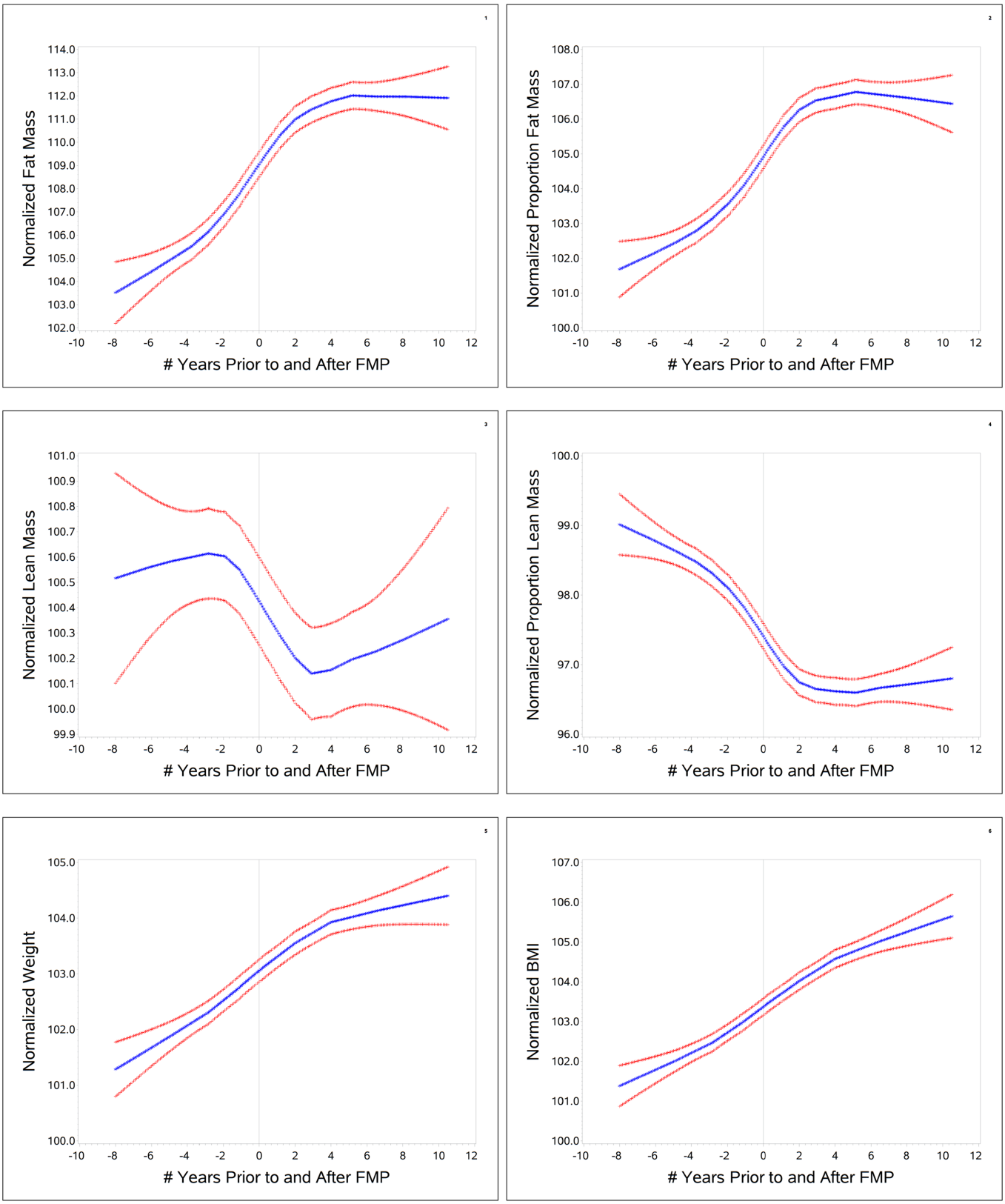

Figure 1. LOESS plots of baseline-normalized values of each outcome (fat mass, proportion fat mass, lean mass, proportion lean, weight, and BMI) in relation to time prior to and after the final menstrual period (FMP-time) from the Study of Women's Health Across the Nation (SWAN). Blue curves illustrate mean values. Cross-sectional, 95% CI are indicated by the red curves. Number of observations in each plot ranges from 11837–11901; plots truncated at 8 years prior to and 10.5 years after FMP – the 5th and 95th percentiles, respectively – of the distribution of FMP-time. LOESS plots are a cross-section at each time point, thus are influenced by the composition of the study sample at each time and by between-women differences; they are not equivalent to longitudinal, repeated measures models. LOESS plots are used to develop a hypothesis about the functional form of the

relation between the exposure (FMP-time) and the outcomes (body composition or weight measures). Apparent slopes should not be overinterpreted; the tails are particularly susceptible to influence by sparser data. The presence of knots (changes in slope direction) and slope of each putative segment must be formally tested, as described in the Methods.

Race/ethnicity and age-at-FMP effects on change in lean mass and proportion lean mass. Among White women, lean mass increased during premenopause (0.19% per year), declined during the MT (–0.21% annually), and stabilized in postmenopause (no change) (Table 3). Neither non-White race/ethnicity nor age at FMP had an independent effect on lean mass slopes in the 3 phases; thus, the trajectories of change in lean mass were similar among the 4 racial/ethnics represented.

In the White referent, proportion lean mass declined during both premenopause (–0.17% per year) and MT (–0.68% per year), and it did not change in postmenopause (zero slope); total decline over 15 years was 2.71%. Estimates of change in proportion lean mass did not differ in Black women compared with those of White women. In contrast, Japanese women's proportion lean mass did not decline during the MT. Japanese transmenopausal slope was –0.03% (95% CI, –0.45% to 0.38%). Unlike the White referent, proportion lean mass increased during postmenopause in Chinese women (0.36%; 95% CI, 0.11% to 0.61%), and the predicted 15-year change was significantly different from that in White women; Chinese women saw no total decrease in proportion lean mass over 15 years ($P = 0.3$).

Greater age at FMP diminished the amount of MT-related loss in proportion lean mass (a 0.07% smaller annual loss for each year's delay in FMP) and the predicted total 15-year decline in proportion lean mass (0.24% smaller loss for each year delay in FMP).

Race/ethnicity and age at FMP effects on change in weight and BMI. On average, in White women, weight increased by 0.50% per year in premenopause, increased by 0.45% per year in the MT, and stabilized (zero slope) in postmenopause (Table 4). In the White referent, results for BMI mirrored those for weight, with increases of 0.54% per year during premenopause and 0.57% per year in the MT, and with no increase in postmenopause. Black participants' rates of change in weight and BMI in each segment did not differ from those of White participants'.

In contrast, Japanese women had significantly smaller increases than did White women in weight ($P = 0.004$) and BMI ($P = 0.003$) during the MT. The Japanese-specific transmenopausal slopes for weight (–0.40%; 95% CI, –0.92% to 0.13%) and BMI (0.33%; 95% CI, –0.86% to 0.21%) did not differ from zero, signifying that, unlike White women, Japanese women did not gain weight in the MT. Chinese women, on the other hand, had a significantly more negative change in BMI in postmenopause than White women. As a result, Chinese women had a significantly smaller total increase in BMI over the 15-year period spanning the MT than did White women (4.87% smaller gain). Over the 15-year period, Chinese women's average weight did not change significantly (–0.38%; 95% CI,–3.59% to 2.82%), nor did their BMI (0.60%; 95% CI, –2.63% to 3.82%).

Greater age at FMP tempered the annual gains in weight and BMI evident during premenopause (i.e., diminished by 0.04% per additional year delay in FMP for both weight and BMI) and the MT (lessened by 0.07% per additional year delay in FMP for weight and 0.06% for BMI).

Influence of HT on change in outcomes. There were 11,213 observations in this analysis; women were taking HT at the time of 404 of these observations. All HT use took place after the FMP occurred (data not shown). Use of HT did not independently predict change in fat mass ($P = 0.3$), proportion fat mass ($P = 0.5$), lean mass ($P = 0.3$), or proportion lean mass ($P = 0.7$), nor was HT use associated with change in body weight ($P = 0.3$) or BMI ($P = 0.2$) (data not shown).

Discussion

Our study quantified the longitudinal trajectories of body composition and weight prior to, during, and after the MT, with the MT operationalized as a multiyear interval straddling the FMP. For body composition, increasing fat mass and declining proportion lean mass were apparent during premenopause, prior to the onset of the MT. Change in body composition accelerated during the MT, displaying a 2- to 4-fold increase in gain (fat) or loss (proportion lean mass). In postmenopause, on average, we observed a stabilization of body composition (a zero slope). The average patterns of change of body weight and BMI differed from those of body composition: weight and BMI climbed steadily both prior to and during the MT, without an MT-related acceleration. Like body composition, weight did not increase further during postmenopause. For all outcomes, White and Black women's results were similar. In contrast, trajectories in Japanese

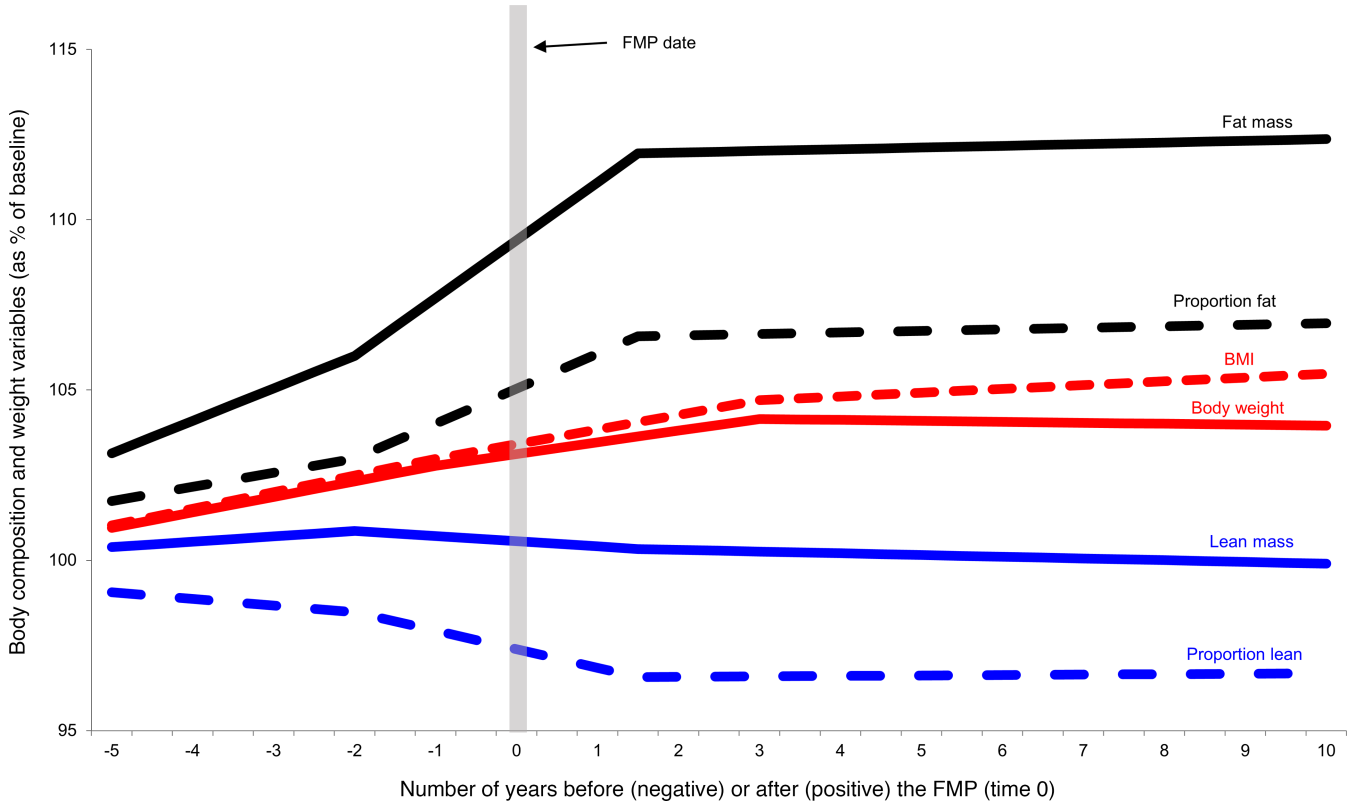

Figure 2. Model-predicted trajectories of body composition and body weight outcomes relative to the time prior to or after the FMP, SWAN. Values shown are for an average study participant (i.e., with each model covariate set at its analysis sample mean). Covariates were age at FMP, race, SWAN study site, and HT use.

and Chinese women were distinct from those of the White referent sample: accelerated gains in fat mass and declines in lean mass did not characterize the MT. In Chinese women only, during postmenopause, fat mass declined, proportion lean mass increased, and weight dropped. A later age at FMP mitigated body composition changes and weight gains. Finally, body composition and weight trajectories were unaffected by HT use, but HT exposure in this analysis was uncommon and confined to postmenopause.

Our findings link the MT with unfavorable alterations in body composition, which abruptly worsen at the onset of the MT and then abate in postmenopause. During the MT, the mean rate of increase in fat mass in the average woman nearly doubles from 1%–1.7% per year, leading to a 6% total gain in fat mass over the 3.5 year–long MT (an average absolute gain of 1.6 kg). At the onset of the MT, women begin to lose, rather than gain, lean mass (annual slope fell from approximately +0.2% in premenopause to –0.2% during MT). The total loss of lean mass during the MT averages 0.5% (a mean absolute decrease of 0.2 kg). In concert, in the average SWAN participant, the accelerated increase in fat mass and decrease in lean mass results in a 3.6% cumulative rise in proportion fat mass and 1.9% cumulative decline in proportion lean mass over the course of the 3.5 year–long MT.

Jointly examining the rates of change in fat and lean mass during premenopause and the MT sheds light on why there is no measurable change in body weight trajectory accompanying the MT. The rate of increase in the sum of fat mass and lean mass is 0.32 kg per year in premenopause and 0.40 kg per year during the MT. This is not a discernable change in rate, especially if bone loss during the MT (which is not incorporated in the estimation of lean mass used here) further lowers the MT slope estimate. Framed alternately, the difference in slopes between premenopause and the MT for the sum of fat mass and lean mass is only 80 grams per year, while the difference in the slope of fat mass between premenopause and the MT is 199 grams per year and the corresponding difference for lean mass is –119 grams per year. Thus, although there are MT-related effects on body composition, we observe no acceleration in weight gain at the time of the MT.

Aging, rather than the MT, is the oft-cited reason for women's mid-life rise in both fat mass and weight (6–9). However, close examination of existing evidence suggests that it is inadequate to either support or

Table 2. The influence of race/ethnicity and age at the final menstrual period (FMP) on annualized rates of change in fat mass and proportion fat mass in the Study of Women's Health Across the Nation: Results of mixed effects linear regression[A]

		Annualized rates of change (percentage per year) during each interval prior to and after the FMP, with 95% CI[B,C,D]			15-year change: −5 years before to +10 years after FMP	Race/ethnicity-specific 15-year change
		Premenopause 8 years to 2 years before FMP	Menopause transition 2 years before to 1.5 years after FMP	Postmenopause 1.5 years to 10.5 years after FMP		
Fat mass	Race/ethnicity					
	White (referent)	**0.93% (0.58%, 1.28%)**	**2.11% (1.65%, 2.57%)**	0.10% (−0.18%, 0.38%)	**11.03% (8.60%, 13.46%)**	**11.03% (8.60%, 13.46%)**
	Japanese	−0.15% (−1.20%, 0.91%)	**−2.25% (−3.64%, −0.86%)**	0.37% (−0.48%, 1.22%)	−5.20% (−12.67%, 2.27%)	5.82% (−0.96%, 12.60%)
	Chinese	0.21% (−0.82%, 1.23%)	−0.65% (−2.02%, 0.71%)	**−1.16% (−1.96%, −0.37%)**	**−11.54% (−18.58%, −4.50%)**	−0.51% (−7.08%, 6.06%)
	Black	0.07% (−0.54%, 0.68%)	−0.07% (−0.90%, 0.76%)	0.16% (−0.33%, 0.65%)	1.28% (−3.01%, 5.58%)	**12.31% (8.52%, 16.10%)**
	Age-at-FMP (per y)	**−0.11% (−0.20%, −0.02%)**	**−0.23% (−0.34%, −0.12%)**	0.005% (−0.06%, 0.07%)	**−1.10% (−1.70%, −0.49%)**	N/A
Fat mass proportion[C]	Race/ethnicity					
	White (referent)	**0.37% (0.16%, 0.58%)**	**1.30% (1.04%, 1.56%)**	0.04% (−0.11%, 0.19%)	**5.99% (4.73%, 7.25%)**	**5.99% (4.73%, 7.25%)**
	Japanese	−0.01% (−0.63%, 0.62%)	**−1.01% (−1.79%, −0.22%)**	0.24% (−0.21%, 0.70%)	−1.50% (−5.38%, 2.39%)	**4.49% (0.97%, 8.01%)**
	Chinese	0.29% (−0.31%, 0.90%)	−0.58% (−1.36%, 0.19%)	**−0.57% (−0.99%, −0.15%)**	**−6.03% (−9.65%, −2.40%)**	−0.04% (−3.42%, 3.34%)
	Black	0.03% (−0.33%, 0.39%)	−0.21% (−0.68%, 0.26%)	0.16% (−0.10%, 0.42%)	0.69% (−1.53%, 2.91%)	**6.68% (4.71%, 8.64%)**
	Age-at-FMP (per y)	**−0.05% (−0.10%, −0.003%)**	**−0.12% (−0.19%, −0.06%)**	0.01% (−0.03%, 0.05%)	**−0.51% (−0.82%, −0.19%)**	N/A

[A]Proportion fat mass, fat mass divided by total mass. [B]Model-predicted slopes (percentage of baseline level gained per year) for the referent individual (White, not taking hormone therapy, age at FMP = 52.2 years) and the associations of slopes with race/ethnicity and age at FMP. In addition to age at FMP, race/ethnicity, and hormone therapy use (time varying), the model also adjusts for SWAN study site and includes random effects for the intercept and the 3 slopes. Random effect SDs for the 3 slopes were 2.65%, 4.13%, and 2.27% per year for fat mass, and 1.00%, 1.19%, and 0.68% per year for proportion fat mass. [C]Bold font indicates that confidence intervals do not include zero. [D]SD of the unmodeled residual error is 8.33% for fat mass and 5.50% for proportion fat mass.

refute the hypothesis that the MT influences body composition or weight (13–23). Most directly comparable to ours are studies that gauged the impact of the MT on body composition or weight by examining these characteristics in relation to FMP time (17, 19, 23). Using bioelectrical impedance, Sowers and colleagues did not detect an effect of FMP time on either fat mass or lean mass in a sample of 130 women at the Michigan SWAN site (19). Rather, they reported a linear increase in fat mass and a small, linear decrease in lean mass over time. To investigate the relation between FMP time and weight, Davies et al., combined data from 1 study of 191 women assessed every 5 years and another that examined 75 women every 6 months (17). No effect of FMP time on weight was apparent; instead, the authors described a linear increase in weight with time. Finally, in an analysis of 48 women, the MONET study found that neither weight nor BMI were influenced by FMP time and that percent fat mass was greater in the post-FMP years than it had been previously; however, but no change in percent fat was noted in the transitional phase prior to FMP. Although each of these studies concluded that the MT did not influence body composition or weight, small samples, correspondingly few observed FMP dates, and — in one instance — long intervals between assessments constrained their ability to discover a nonlinear trajectory of body composition or weight with FMP time. More frequently, investigators examined the relation between advancing menstrual pattern–based MT stage (i.e., pre-, peri-, or postmenopause) and changes in body composition or weight; all MT-stage–based studies concluded that menopause exerted no effect on these parameters (13–16, 18, 20–22). Five of these studies, including 2 from the initial years of SWAN, found that weight increased over time but was unrelated to evolving MT stage (13–16, 18). Limitations included few conversions from earlier to later MT stages and, in some cases, long spans between assessments (13–16, 18).

Table 3. The influence of race/ethnicity and age at the final menstrual period (FMP) on annualized rates of change in lean mass and proportion lean in the Study of Women's Health Across the Nation: Results of mixed effects linear regression[A]

		Annualized rates of change (% per year) during each interval prior to and after the FMP, with 95% CI[B,C,D]			15-year change: −5 years before to +10 years after FMP	Race/ethnicity-specific 15-year change
		Premenopause 8 years to 2 years before FMP	Menopause transition 2 years before to +1.5 years after FMP	Postmenopause +1.5 years to +10.5 years after FMP		
Lean mass	Race/ethnicity					
	White (referent)	**0.19% (0.07%, 0.31%)**	**−0.21% (−0.37%, −0.04%)**	0.00% (−0.10%, 0.10%)	−0.17% (−1.05%, 0.72%)	−0.17% (−1.05%, 0.72%)
	Japanese	−0.11% (−0.46%, 0.24%)	−0.44% (−0.94%, 0.05%)	−0.07% (−0.38%, 0.23%)	−2.51% (−5.22%, 0.19%)	**−2.68% (−5.13%, −0.23%)**
	Chinese	−0.06% (−0.40%, 0.27%)	0.27% (−0.21%, 0.76%)	0.00% (−0.28%, 0.28%)	0.80% (−1.74%, 3.34%)	0.63% (−1.74%, 3.01%)
	Black	−0.03% (−0.23%, 0.17%)	0.29% (−0.004%, 0.58%)	−0.14% (−0.31%, 0.03%)	−0.26% (−1.82%, 1.29%)	−0.43% (−1.81%, 0.94%)
	Age-at-FMP (per y)	−0.02% (−0.05%, 0.01%)	0.0005% (−0.04%, 0.04%)	−0.02% (−0.05%, 0.001%)	**−0.25% (−0.47%, −0.03%)**	N/A
Lean mass proportion	Race/ethnicity					
	White (referent)	**−0.17% (−0.30%, −0.05%)**	**−0.68% (−0.83%, −0.52%)**	0.02% (−0.07%, 0.11%)	**−2.71% (−3.47%, −1.94%)**	**−2.71% (−3.47%, −1.94%)**
	Japanese	−0.05% (−0.42%, 0.32%)	**0.64% (0.18%, 1.09%)**	−0.12% (−0.41%, 0.16%)	1.03% (−1.34%, 3.39%)	−1.68% (−3.82%, 0.46%)
	Chinese	−0.12% (−0.47%, 0.24%)	0.36% (−0.09%, 0.81%)	**0.34% (0.08%, 0.61%)**	**3.83% (1.63%, 6.04%)**	1.13% (−0.93%, 3.19%)
	Black	0.003% (−0.21%, 0.22%)	−0.008% (−0.28%, 0.26%)	−0.12% (−0.28%, 0.04%)	−1.05% (−2.40%, 0.30%)	**−3.76% (−4.95%, −256%)**
	Age-at-FMP (per y)	0.02% (−0.01%, 0.05%)	**0.07% (0.03%, 0.11%)**	−0.01% (−0.03%, 0.02%)	**0.24% (0.05%, 0.43%)**	N/A

[A]Proportion lean, lean mass divided by total mass. [B]Model-predicted slopes (percentage of baseline level gained per year) for the referent individual (White, not taking hormone therapy, age at FMP = 52.2 years), and the association of slopes with race/ethnicity and age at FMP. In addition to age at FMP, race/ethnicity, and hormone therapy use (time varying), the model also adjusts for SWAN study site and includes random effects for the intercept and the 3 slopes. Random effect SD for the 3 slopes were 0.65%, 1.26%, and 0.70% per year for lean mass and 0.87%, 1.21%, and 0.69% per year for proportion lean mass. [C]Bold font indicates that confidence intervals do not include zero. [D]SD of the unmodeled residual error is 3.74% for lean mass and 3.25% for proportion lean mass.

Dissimilar to prior reports, the current analysis supports a strong, adverse influence of the MT on body composition that is manifest during the MT and then halts. As reported by others, we observed weight gain starting in premenopause with a linear trajectory not inflected at the MT, but our body composition measures offer an explanatory insight, as described above. SWAN also detects a cessation of weight gain in postmenopause (except for postmenopausal Chinese women, whose weight not only stabilizes but declines), suggesting the advent of a new steady state and inferring a role for the end of the MT as one of its determinants.

Mounting evidence points to both estradiol (E2) and follicle stimulating hormone (FSH) as regulators of energy balance; MT-related variations in each are plausible mechanisms of the results reported here (4, 5). The time course of the trajectories of body composition mirror E2 and FSH trajectories in relation to the FMP. There is an accelerated drop in E2 and a similar rapid increase in FSH bracketing the FMP, beginning about 2 years prior to and ceasing about 2 years after the FMP (24–27). E2 affects numerous energy homeostasis pathways; major examples include CNS control of food intake and energy expenditure, regulation of adipose tissue lipid storage and metabolism, and insulin sensitivity (4). Murine and rodent experimental manipulations (e.g., estrogen receptor–KO and –knock in models and ovariectomy with and without hormone supplementation) provide evidence that an overarching mechanism for fat gain in the absence of estrogen is reduction of resting metabolic rate, decline in spontaneous physical activity, and greater caloric intake (28). Small cross-sectional and longitudinal observational studies find that resting energy expenditure (REE) is less in postmenopause than in premenopause (29, 30). In premenopausal women,

Table 4. The influence of race/ethnicity and age at the final menstrual period (FMP) on annualized rates of change of in body weight and body mass index in the Study of Women's Health Across the Nation: Results of mixed effects linear regression

		Annualized rates of change (percentage per year) during each interval prior to and after the FMP, with 95% CI[A,B,C]			15-year change: 5 years before to 10 years after FMP	Race/ethnicity-specific 15-year change
		Premenopause 8 years to 1 year before FMP	Menopause transition 1 year before to 3.0 years after FMP	Postmenopause 3.0 years to 10.5 years after FMP		
Body weight	Race/ethnicity					
	White (referent)	**0.50% (0.37%, 0.63%)**	**0.45% (0.26%, 0.64%)**	0.01% (−0.15%, 0.16%)	**3.85% (2.67%, 5.03%)**	**3.85% (2.67%, 5.03%)**
	Japanese	−0.26% (−0.66%, 0.13%)	**−0.85% (−1.42%, −0.27%)**	0.21% (−0.27%, 0.70%)	−2.94% (−6.61%, 0.73%)	0.91% (−2.41%, 4.23%)
	Chinese	0.02% (−0.36%, 0.40%)	−0.35% (−0.92%, 0.22%)	−0.41% (−0.86%, 0.04%)	**−4.24% (−7.68%, −0.80%)**	−0.38% (−3.59%, 2.82%)
	Black	−0.04% (−0.26%, 0.18%)	0.20% (−0.13%, 0.53%)	−0.05% (−0.32%, 0.22%)	0.31% (−1.72%, 2.34%)	**4.16% (2.36%, 5.96%)**
	Age-at-FMP (per y)	**−0.04% (−0.08%, −0.01%)**	**−0.07% (−0.11%, −0.02%)**	−0.02% (−0.06%, 0.01%)	**−0.62% (−0.91%, −0.33%)**	N/A
BMI	Race/ethnicity					
	White (referent)	**0.54% (0.41%, 0.66%)**	**0.57% (0.38%, 0.76%)**	0.15% (−0.01%, 0.31%)	**5.46% (4.27%, 6.65%)**	**5.46% (4.27%, 6.65%)**
	Japanese	−0.27% (−0.67%, 0.12%)	**−0.90% (−1.48%, −0.31%)**	0.23% (−0.26%, 0.72%)	−3.04% (−6.76%, 0.68%)	2.42% (−0.94%, 5.97%)
	Chinese	0.05% (−0.34%, 0.43%)	−0.47% (−1.05%, 0.11%)	**−0.45% (−0.90%, −0.0001%)**	**−4.87% (−8.33%, −1.41%)**	0.60% (−2.63%, 3.82%)
	Black	−0.06% (−0.28%, 0.16%)	0.16% (−0.18%, 0.50%)	−0.05% (−0.32%, 0.22%)	0.06% (−1.99%, 2.11%)	**5.52% (3.70%, 7.34%)**
	Age-at-FMP (per y)	**−0.04% (−0.07%, −0.01%)**	**−0.06% (−0.11%, −0.01%)**	−0.01% (−0.05%, 0.03%)	**−0.48% (−0.77%, −0.19%)**	N/A

[A]Model-predicted slopes (percentage of baseline level gained per year) for the referent individual (White, not taking hormone therapy, age at FMP = 52.2 years) and the association of slopes with race/ethnicity and age at FMP. In addition to age at FMP, race/ethnicity, and hormone therapy use (time varying), the model also adjusts for SWAN study site and includes random effects for the intercept and the 3 slopes. Random effect SD for the 3 slopes were1.08%, 1.76%, and 1.20% per year for body weight and 1.07%, 1.79%, and 1.19% per year for BMI. [B]Bold font indicates that confidence intervals do not include zero. [C]SD of the unmodeled residual error is 3.65% for weight and 3.71% for BMI.

pharmacological suppression of sex hormones by sustained administration of a gonadotropin releasing hormone agonist (GnRH-a) lowers REE; adding back transdermal E2 offsets the GnRH-a–induced decline in REE (31). This same paradigm of pharmacological hormone suppression with and without the addition of transdermal E2 results in a loss of lean mass (assessed by DXA) only in the women who do not receive the E2 treatment (32). Murine studies with a potentially novel FSH-blocking antibody demonstrate that, in ovarian-intact animals with unaltered serum E2 levels, FSH antibody reduces body fat but does not change body weight, similar to our human data (33). The FSH antibody exerts several beneficial effects on energy balance, such as inducing the beiging of adipocytes (conversion of white adipocytes to beige adipocytes, which are more metabolically active), a greater rate of thermogenesis, and activation of brown (energy consuming) adipocytes (33).

In our study, lean mass declined at the onset of the MT. DXA lean mass measurement consists of total body water, muscle mass, and organ mass (as noted in Methods, we excluded bone mass from the lean mass computation). Therefore, decreasing lean mass could be due to diminution of any of these components. As reviewed by Stachenfeld, estrogen influences several physiological mechanisms that maintain water and salt balance (34). Thus, an MT-related shift in fluid regulation could contribute to our observed reduction in lean mass. There have been some investigations of the relation between menopause and muscle, but these have compared pre- vs. postmenopausal women or made inferences based on age rather than MT stage (35, 36). Nonetheless, these studies suggest plausible means by which the MT may diminish muscle mass, such as upregulation of skeletal muscle catabolism or lessened muscle response to anabolic stimuli (e.g., resistance training) (35). Declines in estrogen could underlie detrimental MT effects on muscle; the neuromuscular system is replete with α and β estrogen receptors, and when taken in early postmenopause, HT

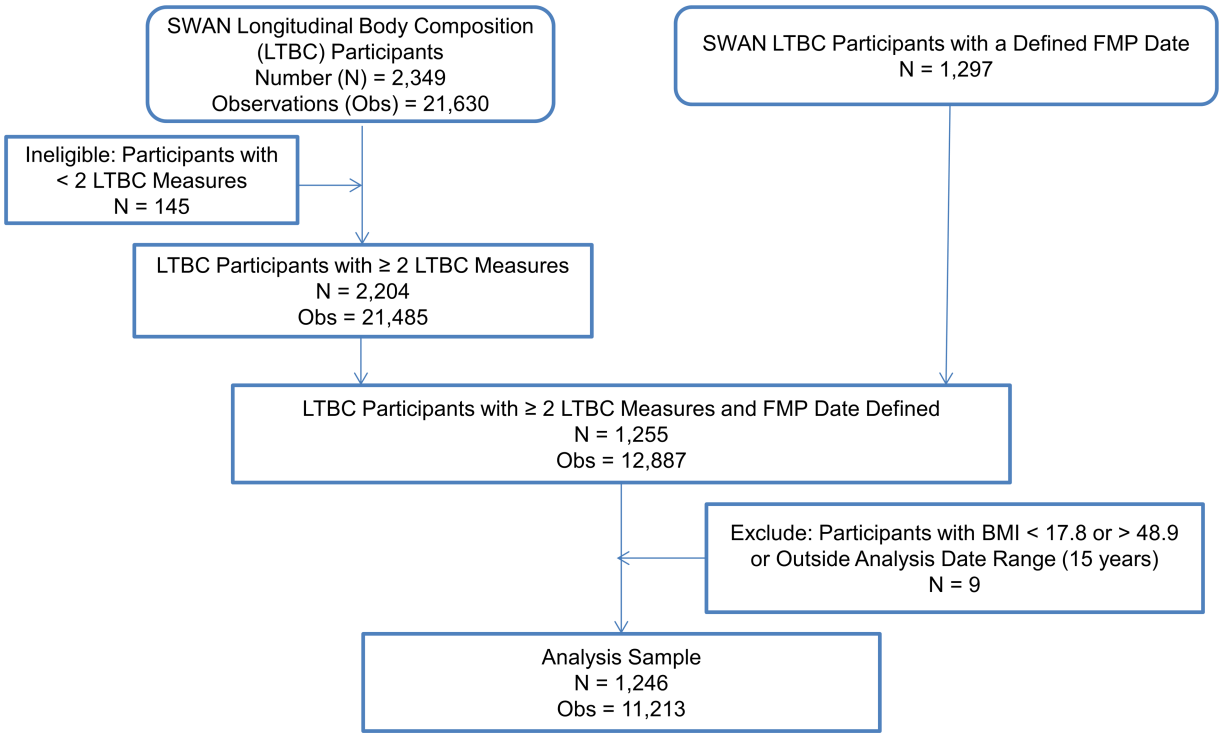

Figure 3. Derivation of the analysis sample for analysis of body composition and weight in relation to the FMP. Participants are from the Study of Women's Health Across the Nation (SWAN).

may preserve the muscle transcriptome and benefit muscle strength (36). Progesterone can increase protein synthesis in women; therefore, persistently low progesterone levels could contribute to a decline in lean mass (37). In men, androgens regulate lean mass, but androgen levels do not decline across the MT and are, therefore, unlikely to account for the a decrease in lean mass (38, 39). The menopause may also negatively influence muscle by indirect pathways — for example, by downregulating the anabolic IGF-1 pathway or by leading to a more preinflammatory milleu (40, 41).

We observed racial/ethnic variation in MT-associated changes in body composition and weight. While increases in fat mass and decreases in lean mass were similar in Black and White women, findings in the 2 Asian groups were distinctive. Our findings do not align with the few existing reports in Asian samples. On average, we found that Japanese SWAN participants, like White participants, lost lean mass during the MT, but unlike White participants, their fat mass and weight did not change during the MT. This is in contrast to a cross-sectional survey of Japanese women aged 20–70 years that found postmenopause was associated not only with lower lean mass, but also with greater body fat (42). In our study, during the postmenopausal interval, Chinese SWAN participants lost fat mass and body weight and gained lean mass proportion, which is in opposition to a prior single-site, cross-sectional SWAN analysis that reported lower lean mass and higher percent body fat in late peri- or postmenopausal Chinese participants (43). That our findings in SWAN's Asian subgroups differ from those of earlier, cross-sectional approaches is likely attributable to the current study's methodologically stronger, longitudinal design.

We did not witness an effect of HT on body composition or weight measures, but HT use was infrequent and only occurred during postmenopause. The absence of HT use during the MT is an unavoidable consequence of SWAN's research design; we cannot determine the date of the FMP in women who are taking HT because it may obscure the natural bleeding patterns used to determine FMP date. Thus, whether the use of HT lessens or prevents worsening of body composition during the transition from pre- to postmenopause, analogous to the GnRH-a with E2 add-back model, cannot be inferred from our analysis (32).

A limitation of this study is that we were unable to consider the effect of the MT on regional body composition and visceral fat at this time. Owing to the complexity of the current analysis, we did not directly examine the relation between trajectories of sex steroids or gonadotropins and body composition and weight outcomes. Subsequent investigations will remedy these limitations. Factors such as clothing worn

and time of day may affect both accuracy and precision of anthropometric measures; standard SWAN protocols mitigated against these potential influences. SWAN did not conduct DXA precision estimate studies; the Supplemental Material, Sections A–D (supplemental material available online with this article; https://doi.org/10.1172/jci.insight.124865DS1), presents a detailed description of measurement and analysis protocols, hardware, software, coefficients of variation, and calibrations. The SWAN site that enrolled Hispanic women did not assess body composition using Hologic DXA; thus, we are unable to include this racial/ethnic group. Ours is a community-based, but not a population-based, sample; therefore, results may not be generalizable to US Black, Chinese, Japanese, and White women. Study strengths are several. First, we analyzed DXA-quantified body composition and measured weight in proximity, providing insight about how they are related. We also benefitted by using time to and from FMP to capture the effect of the transition from pre- to postmenopause on body composition and weight; an FMP time-referenced analysis is a more discriminating assessment of progress through the transition that is an analysis based on clinical MT stages (12). Lastly, the diversity of SWAN's participants afforded a window on unique racial/ethnic patterns of body composition and weight change, which will spur subsequent interventions into the mechanisms and meanings of this variation.

In summary, the MT is accompanied by accelerated gains in fat mass and simultaneous losses in lean mass; their joint rates of change result in no detectable acceleration in weight or BMI at the onset of the MT. That an MT-related acceleration in weight or BMI is not observed, despite the high-velocity increase in fat mass, is concordant with the growing appreciation that, while BMI is a well-established, strong composite indicator of cardiometabolic risk, it is a less strong index of adiposity and particular aspects of adiposity such as the location of fat (44, 45). As a result, BMI is a less useful indicator of cardiometabolic risk in older women (46). BMI is body weight normalized to the square of height. However, inputs to weight include fat mass and lean mass, each of which may vary differentially and may variably contribute to specific aspects of cardiometabolic (and other health) risks (44). This description of how the MT affects individual compartments of body composition lays the groundwork for investigating how MT-related body composition changes may affect the health of postmenopausal women and how relative weight and body composition may make distinctive contributions to a range of physiological outcomes.

Methods

Study sample. SWAN is a multisite, community-based, longitudinal cohort study (47). Baseline eligibility criteria included the following: aged between 42 and 52 years, intact uterus and ≥1 intact ovary, no use of HT, ≥1 menses in the 3 months prior to screening, and self-identification with 1 of 5 eligible ethnic/racial groups. The 7 SWAN clinical sites (Boston, Massachusetts, USA; Chicago, Illinois, USA; Detroit, Michigan, USA; Pittsburgh, Pennsylvania, USA; Los Angeles, California, USA; Newark, New Jersey, USA: and Oakland, California, USA) enrolled 3302 participants. All sites enrolled White women. Boston, Chicago, Detroit, and Pittsburgh enrolled Black women and the remaining 3 sites enrolled Japanese, Hispanic, and Chinese women, respectively. The baseline visit (visit 00) occurred in 1996–1997, and the final study visit included in this analysis (visit 13) occurred during 2011–2013. The Chicago and Newark sites did not assess body composition using Hologic DXA instruments; thus, 2413 participants from the remaining 5 sites were eligible for the SWAN Bone Density and Body Composition Cohort. Of these, 2349 (97%) joined the body composition study. Figure 3 illustrates the current analysis sample derivation. This analysis includes data from each woman's baseline through follow-up visit 13, with the exception of follow-up visit 11, which was omitted because the requisite hormone-use data was not collected; thus, the maximum number of visits per woman was 13. Participants who had ≥2 body composition scans were eligible (n = 2204). Additionally, participants had to have a known FMP date (n = 1255). We excluded those with extreme baseline values of BMI (<17 or >49) and observations that occurred >8 years before or >10.5 years after the FMP (the lower and upper 5% of the distribution of time prior to and after the FMP [FMP time]).

Outcomes. This analysis considers 6 outcomes: 4 DXA-acquired body composition measures, measured weight, and BMI. Body composition outcomes are fat mass (kilograms), lean mass (kilograms), proportion fat mass (fat mass/[fat mass + lean mass]), and proportion lean mass (lean mass/[lean mass + fat mass]). Body composition variables omit the head from the calculation. The lean mass estimate used here is exclusive of bone mass (to avoid contamination by unremovable metal artifacts). We measured body composition at each SWAN visit using Hologic instruments (Hologic Inc.). Three sites began SWAN with

Hologic QDR 4500A models; 2 of these transitioned to Discovery models during follow-up. Two sites began with QDR 2000 models and upgraded to QDR 4500A models during follow-up. Sites that changed densitometers scanned volunteers on their old and new machines for cross-calibration. The Supplemental Material, Setions B and C presents a detailed description of hardware, software, coefficients of variation, and calibrations. DXA procedures require exclusion of the left arm when the participant is too large to allow both upper extremities to rest on the scan bed while maintaining sufficient separation to define soft tissue regions. Employing data from women who had both arms measured, we used right arm values to impute left arm values, accounting for hand dominance (if unknown, assumed right-handedness). For right-handed participants, the imputation equations were left arm fat = 0.985 × right arm fat and left arm lean = ([0.932 + 0.00122] × [BMI – 30]). For left-handed participants, raw right arm and left arm values were similar; therefore, we substituted their right arm values for left. Using calibrated scales and stadiometers, we measured height (to the nearest 0.01 m) and weight (to the nearest 0.1 kg) at each visit. The SWAN protocol asked participants to come for visits in the morning in the fasting state. For physical measures, they wore hospital gowns and removed shoes. We calculated BMI as weight in kg/(height in m)^2.

Primary predictor. The primary exposure was the number of months before or after the FMP at the time of the body composition, weight, or height measurement (FMP time). We computed FMP time using month and year of the FMP and month and year of each DXA or anthropometry. SWAN defined FMP date as the last menstrual bleeding date immediately prior to the first visit when the participant was postmenopausal. The FMP date can only be identified after the woman has completed 12 months of amenorrhea.

Other predictors. Age at FMP (in years), self-defined race/ethnicity (Black, Chinese, Japanese, White), self-reported menstrual bleeding patterns (used to compute FMP date), and systemic HT use (yes/no, time varying; i.e., use assessed at each visit and exposure coded accordingly) were obtained from standardized interviews conducted at each visit. For each of these predictors, except for HT use, information was available for each participant at every visit. For HT, 56 values were missing, which represents 0.5% of the total possible observations. Observations missing HT were excluded from the longitudinal models.

Statistics. To analyze change in the 4 body composition outcomes and 2 weight outcomes in relation to FMP date, we used a 3-step approach: (a) nonparametric, LOESS-based selection of the functional form of each outcome's trajectory in relation to FMP time, (b) piece-wise linear regression (testing a range of alternate knot locations) to determine the best knot placement for the parametric outcome trajectories; and (c) piece-wise linear regression with fixed knots to estimate each outcome's rate of decline or increase during each phase of the trajectory (48).

In step 1, we used the LOESS method on repeated annualized measurements of each of the 6 outcomes; each participant's values were normalized to her baseline. Baseline normalization allows comparison of slopes (rates of increase or decrease) among outcomes because the units of slope are percent change per year. Additionally, the initial normalized level is 1 (100%) for all women, eliminating between-women differences prior to the observation period.

Step 1 LOESS plots suggested piece-wise linear trajectories with 3 segments and 2 changes in slope, or knots, for all outcomes (Figure 1). In steps 2 and 3, we used mixed effects linear regression to fit piece-wise linear growth curves to repeated measurements of baseline-normalized values of each of the 6 outcomes (in separate models) as functions of FMP time, using linear splines with 2 fixed knots. See below for knot selection and for formal testing of whether the slopes in each of the postulated 3 segments were different from zero and different from each other. To account for within-woman correlation between repeated observations, we included random effects for the intercept and 3 slopes (allowing intercept and slope to vary from woman to woman).

In step 2, we tested model adequacy and appropriateness of knot locations by running null models with only random effects and no fixed effects. We evaluated knot selection by examining the change in the explained proportion of within-woman variance (pseudo R^2) when each of the 2 knots were varied (in 6-month intervals) around the candidate knot locations suggested by the LOESS plots. For each of the 4 DXA outcomes, unexplained variance was minimized by knot locations at FMP minus 2 years and FMP plus 1.5 years. Knot locations at FMP minus 1 year and FMP plus 3 years minimized unexplained variance for weight and BMI. Thus, all outcome trajectories were modeled as being composed of 3 linear segments with knots anchored to the FMP date. For DXA measures, the 3 segments were: years –8 to –2 relative to the FMP (premenopause); years –2 to +1.5 relative to the FMP (MT); and years +1.5 to +10.5 after the FMP (postmenopause). Weight and BMI segments were: –8 to –1 years relative to FMP (premenopause); –1 to +3 years relative to FMP (MT); and +3 to +10.5 years relative to FMP (postmenopause).

In step 3, we added age at FMP and race/ethnicity to the mixed effects models as fixed effects on the intercept and 3 slopes to assess how each influenced the rate of increase or decrease in the outcome during each segment (premenopause, MT, and postmenopause) of the piece-wise linear trajectory. The model also adjusted for SWAN study site (as a fixed effect on intercept and each of 3 slopes) and time-varying HT use (as fixed effect on intercept). We ran analyses in SAS version 9.2 and used 2-sided α of 0.05 for statistical significance.

Study approval. Each site obtained IRB approval and participants provided written informed consent. Names and locations of IRBs follow. UCLA: The Office of the Human Research Protection Program (OHRPP); Kaiser: IRB for the Protection of Human Subjects Northern California Kaiser Permanente; Michigan: IRB-University of Michigan Health Sciences and Behavioral Sciences (HSBS); Pittsburgh: University of Pittsburgh IRB; Massachusetts General Hospital: Partners Human Research Committee.

Author contributions

Participant recruitment and enrollment was contributed by GAG, BS, MHH, CK-G, and JSF; data management and cleaning were contributed by GAG, BS, MHH, WH, KR, SJ, and ASK; analytic design was contributed by GAG and ASK; statistical analysis was contributed by GAG, MHH, WH, and ASK; primary manuscript drafting was contributed by GAG and ASK; critical review and revision of manuscript were contributed by all authors.

Acknowledgments

SWAN has grant support from the NIH, DHHS, through the National Institute on Aging (NIA), the National Institute of Nursing Research (NINR), and the NIH Office of Research on Women's Health (ORWH) (grants U01NR004061, U01AG012505, U01AG012535, U01AG012531, U01AG012539, U01AG012546, U01AG012553, U01AG012554, and U01AG012495). The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the NIA, NINR, ORWH or the NIH. We thank the study staff at each site and all the women who participated in SWAN. Clinical Centers: University of Michigan, Ann Arbor, Siobán Harlow and MaryFran Sowers; Massachusetts General Hospital, Joel Finkelstein and Robert Neer; Rush University, Howard Kravitz and Lynda Powell; University of California, Davis/Kaiser, Ellen Gold; UCLA, Gail Greendale; Albert Einstein College of Medicine, Carol Derby, Rachel Wildman, and Nanette Santoro; University of Medicine and Dentistry, Gerson Weiss; and the University of Pittsburgh, Karen Matthews. NIH Program Office: National Institute on Aging, Chhanda Dutta, Winifred Rossi, Sherry Sherman, and Marcia Ory; National Institute of Nursing Research, Program Officers. Central Laboratory: University of Michigan, Daniel McConnell (Central Ligand Assay Satellite Services). Coordinating Center: University of Pittsburgh, Maria Mori Brooks and Kim Sutton-Tyrrell; New England Research Institutes, Sonja McKinlay. Steering Committee:Susan Johnson, current chair, and Chris Gallagher, former chair.

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