Practice of Epidemiology

Distinguishing 6 Population Subgroups by Timing and Characteristics of the Menopausal Transition

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Changes in women’s menstrual bleeding patterns precede the onset of menopause. In this paper, the authors identify population subgroups based on menstrual characteristics of the menopausal transition experience. Using the TREMIN data set (1943–1979), the authors apply a Bayesian change-point model with 8 parameters for each woman that summarize change in menstrual bleeding patterns during the menopausal transition. The authors then use estimates from this model to classify menstrual patterns into subgroups using a K-medoids algorithm. They identify 6 subgroups of women whose transition experience can be distinguished by age at onset, variability of the menstrual cycle, and duration of the early transition. These results suggest that for most women, mean and variance change points are well aligned with proposed bleeding markers of the menopausal transition, but for some women they are not clearly associated. Increasing understanding of population differences in the transition experience may lead to new insights into ovarian aging. Because of age inclusion criteria, most longitudinal studies of the menopausal transition probably include only a subset of the 6 subgroups of women identified in this paper, suggesting a potential bias in the understanding of both the menopausal transition and the linkage between the transition and chronic disease.

menopause; menstrual cycle; ovary; women’s health

Abbreviations: FMP, final menstrual period; SE, standard error.

The menopausal transition is recognized to be a critical period for women’s health, as it is associated with temporal symptoms such as hot flashes, sleep disturbances, and depression (1–4), as well as with accelerated change in several physiologic parameters such as bone density and lipid levels (5, 6), influencing women’s quality of life and likelihood of healthy aging. Women’s menstrual patterns change across the reproductive life span (7–9) and, in midlife, signal the approach of menopause (10, 11). The average length of menstrual cycles and their variability tends to decline with age until women approach menopause, at which time cycle length and cycle variability increase (7). How menstrual cycle patterns vary across the population and whether patterns differ systematically across population subgroups is little understood despite clinical awareness that women’s menstrual and menopausal experiences differ markedly. Recently, considerable research has focused on identifying bleeding markers that define the onset of the menopausal transition (10, 11), yet few studies (12, 13) have attempted to identify subgroups of women who experience distinct menstrual cycle patterns during the menopausal transition.

Longer mean cycle length, both during the prime of reproductive life and preceding menopause, has been associated with later age at menopause (14–16). Weinstein et al. (17) found that lower variability was associated with early menopause and that a decrease in serial irregularity of menstrual cycles in late reproductive life was a strong predictor for the onset of menopause. More recently, Gorrindo et al. (13) proposed that women’s lifetime menstrual patterns could be categorized into 5 subtypes: 1) an oscillating or erratic history with decreasing median cycle length over time and then increasing cycle lengths as menopause approaches (the most common pattern); 2) an oscillating or erratic history with a decreasing median cycle length over time up to age 50 years (the second most common pattern); 3) a stable but more variable history characterized by a flat trajectory over time...
and a muted menopausal transition experience (the third most common pattern); 4) a very stable and consistent history characterized by a flat trajectory over time, with no evidence of a definable menopausal transition (the fourth most common pattern); and 5) a highly erratic and variable history over time, typically driven by high early variability between ages 15 and 30 years (the least common pattern, representing few women). While it is informative, the Gorrindo et al. (13) classification system was based on a visual inspection of cycle lengths over time, although specific quantitative measures of cycle length features were subsequently used to classify subjects.

Researchers have employed a range of methods to quantitatively examine menstrual patterns across women’s reproductive life spans (7, 8, 16–18). Most of these approaches describe the average or modal pattern of change in menstrual function over time. Although this is useful in describing the broad pattern of change in menstrual characteristics in the population as women age, the population average experience has more limited application when prediction of women’s expected experience is of interest. Huang et al. (18) quantified women’s menstrual patterns across the latter half of reproductive life using a Bayesian change-point model with 8 parameters for each woman: mean cycle length at age 35 years, rate of change in mean cycle length before and after a latent change point and age at the change point, and equivalent patterns for variability. Our goal in this paper is to distinguish subgroups of women with distinct transition experiences defined by their menstrual patterns over time, based on the 8 parameters defined by Huang et al. (18). We use a K-medoids algorithm to construct subgroups of women based on the summary measures of the menstrual cycle patterns. We then relate these subgroups to age at menopause, age at menarche, and parity, as well as to standard bleeding markers of the menopausal transition.

MATERIALS AND METHODS

TREMIN Study

Our analysis is based on the TREMIN Study (7), which recruited an initial cohort of 2,350 college-age women attending the University of Minnesota between 1934 and 1939 and ended in 1979. Our analysis includes 95,246 observed menstrual segment records from 617 women in this cohort who were under age 25 years at enrollment, used hormones for less than 4 years continuously, had at least 1 observed segment, and were not censored before age 40 (May 5, 1943–December 23, 1978; TREMIN data tape TRUST998.FINAL, March 1993).

A bleeding segment, analogous to the term “menstrual cycle,” is a period of consecutive bleeding days and the subsequent bleeding-free days, with bleed-free intervals required to consist of at least 3 days in order for 2 bleeding episodes to be considered distinct episodes. Age at menopause is determined by the date of the final menstrual period (FMP), which is determined retrospectively after 12 months of amenorrhea is determined retrospectively after 12 months of amenorrhea. The 617 women included in our analysis each contributed 15–321 nonmissing segments to the analysis, with observed segment lengths varying from 4 days to 366 days (median, 27).

Bleeding markers of the menopausal transition

In 2001, participants in the Stages of Reproductive Aging Workshop proposed a staging system for defining the end of a woman’s reproductive life which includes early and late menopausal transition stages before the FMP signals the onset of menopause (10, 11). Entry into early transition is characterized by increasing levels of follicle-stimulating hormone and increasing variability in menstrual cycle length. Entry into the late transition is characterized by continued elevation of follicle-stimulating hormone levels and the occurrence of skipped cycles or amenorrhea. Various menstrual characteristics have been proposed as bleeding markers for the early and late transition stages. The ReStage Collaboration investigators empirically evaluated these proposed bleeding markers in 4 cohort studies of midlife women (11). We consider 5 of the bleeding markers evaluated in ReStage. Two of these markers define the onset of early menopausal transition, including:

1) irregularity: the occurrence of more than 2 menstrual cycles outside the 21- to 35-day range over 10 cycles (20); and
2) DIFF7P: a persistent difference of 7 or more days in consecutive menstrual cycles, the marker recommended by the ReStage Collaboration (11).

Three markers have been proposed for defining the onset of the late menopausal transition:

3) D90: the first segment of at least 90 days, the marker that is currently widely used (19);
4) D60: the first segment of at least 60 days (16), the marker recommended by the ReStage Collaboration (11); and
5) RR10: first running range (difference between the maximum and minimum lengths of 10 consecutive segments) of more than 42 days (20).

Statistical analyses

Bayesian change-point model. Considering segment lengths beginning at age 35 years, Huang et al. (18) developed a Bayesian change-point model using the same TREMIN data set to describe women’s menstrual patterns from age 35 years to the onset of menopause. Segments were assumed to follow a lognormal distribution with a linear change point for both the mean and variance for each subject:
Figure 1. Histograms of posterior means of 8 individual-level parameters from a Bayesian hierarchical regression model used to characterize individual menstruation patterns (n = 617), TREMIN Study, University of Minnesota, 1934–1939.

The function \((x)_+ = x \text{ if } x \geq 0\), and \((x)_+ = 0\) if \(x < 0\). The model used 8 parameters to characterize the individual menstruation patterns of each woman, including mean segment length at age 35 years \((\alpha_i^a)\), mean slope of segment length before the change point \((\beta_i^b)\), mean slope of segment length after the change point \((\gamma_i^b)\), mean change-point age \((\theta_i^b)\), log variance of segment length at age 35 years \((\alpha_i^v)\), slope of log variance before the variability change point \((\beta_i^v)\), slope of log variance after the variability change point \((\gamma_i^v)\), and variability change-point age \((\theta_i^v)\). These 8 subject-level parameters for woman \(i\) were denoted as

\[
\Phi_i = (\alpha_i^a, \beta_i^b, \gamma_i^b, \theta_i^b, \alpha_i^v, \beta_i^v, \gamma_i^v, \theta_i^v)' .
\]

Further, Huang et al. (18) used a multivariate prior \(\Phi_i \sim \text{N}(\Lambda, \Omega)\) to link the individual models, as well as a non-informative hyper-prior \(p(\Lambda, \Omega) = \text{Inv-Wishart}(\Omega; 1, I)\).

In the absence of covariates, the prior parameters \(\Lambda\) and \(\Omega\) give the population mean and covariance matrix, respectively, for the 8 individual-level parameters. Missing segment lengths and missing FMPs were imputed under a missing-at-random assumption. Posterior means from the individual-level parameter values are displayed in Figure 1.

**K-medoids algorithm.** We use the K-medoids method (21) to cluster women into different subgroups according to their 8 characteristic summary measures. Medoids are defined as the elements at the center of a \(p\)-dimensional cluster, where a fixed number of clusters are constructed so that the average distance between the elements within a cluster and the medoids is minimized. The algorithm searches across possible medoids and partitions of other elements to their nearest medoid. In order to accelerate the computation, we apply random sampling and the expectation-maximization algorithm to identify medoids and clusters. The algorithm is as follows:

**Step 1.** Calculate the Mahalanobis distance matrix for 617 women:

\[
\{ D(i,j) = \sqrt{((\hat{\Phi}_i - \hat{\Phi}_j)^T \Omega^{-1}(\hat{\Phi}_i - \hat{\Phi}_j))} : \\
i = 1, \ldots, 617, \ j = 1, \ldots, 617 \}
\]

where \(\hat{\Phi}_i = E(\Phi_i|y)\) is the posterior mean of the 8 summary characteristic measures of subject \(i\) and \(\Omega = E(\Omega|y)\)
is the population-level covariance matrix for these 8 parameters.

Step 2. Sample K subjects randomly from 617 women as temporary medoids: \( \{m_1, \ldots, m_K\} \).

Step 3. E-step: assign subjects to the closest clusters by minimizing the total distance to cluster centers (medoids):

\[
C(i) = \arg \min_{1 \leq k \leq K} D(i, m_k).
\]

Step 4. M-step: for a given assignment C, find the center in the cluster minimizing the total distance to other subjects in that cluster. This center is the new medoid:

\[
i^*_k = \arg \min_{i \in C(i) = k} \sum_{i' \in C(i') = k} D(i, i').
\]

Step 5. Iterate steps 3 and 4 until the assignments do not change.

Step 6. Iterate from step 2 to step 5 until the combination of medoids does not change.

We use silhouettes (22) to choose the optimal number of clusters. We define the silhouette measure as follows. For any subject \( i \) assigned to cluster A, \( a(i) \) is the average distance of subject \( i \) from all other subjects in A. For any cluster C other than A, \( d(i, C) \) is the average distance of subject \( i \) from all subjects in C. We then calculate \( d(i, C) \) for all clusters \( C \neq A \) and select the smallest of those: \( b(i) = \min_{C \neq A} d(i, C) \), which is the average distance of subject \( i \) from all subjects in the closest neighbor cluster. The silhouette measure is then

\[
s(i) = \frac{b(i) - a(i)}{\max\{a(i), b(i)\}}.
\]

For a given number of clusters \( K \), the average silhouette for all subjects is

\[
\bar{s}(K) = \frac{1}{n} \sum_{i=1}^{n} s(i)/n.
\]

We then calculate the average silhouette across a variety of values of \( K \). The one with the highest average silhouette is the appropriate number of clusters for our data.

To examine the association between characteristics of women’s reproductive lives and menstrual pattern categories, we conduct analysis of variance using pairwise comparisons to study differences between categories or groups of categories.

RESULTS

Change points and bleeding markers of the menopausal transition

The variance change point \( \theta^v_i \) corresponds to an early transition marker, since an increase in variability is typically the first change in menstrual cycle patterns experienced by a woman during the menopausal transition. The mean change point \( \theta^m_i \) corresponds to a late transition marker, with increases in mean menstrual cycle length typically occurring later than increases in variability. In the TREMIN

### Table 1. Transition Markers Used in an Analysis of Menstrual Characteristics of the Menopausal Transition (n = 617), TREMIN Study, University of Minnesota, 1935–1979

<table>
<thead>
<tr>
<th>Marker</th>
<th>Stage of Menopause</th>
<th>Mean Age, years (SE)</th>
<th>No. of Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregularity</td>
<td>Early</td>
<td>44.76 (4.51)</td>
<td>502</td>
</tr>
<tr>
<td>DIFF7P</td>
<td>Early</td>
<td>40.98 (4.24)</td>
<td>572</td>
</tr>
<tr>
<td>D90</td>
<td>Late</td>
<td>48.80 (3.45)</td>
<td>359</td>
</tr>
<tr>
<td>D60</td>
<td>Late</td>
<td>46.96 (4.25)</td>
<td>443</td>
</tr>
<tr>
<td>RR10</td>
<td>Late</td>
<td>47.18 (3.96)</td>
<td>440</td>
</tr>
</tbody>
</table>

| Abbreviation: SE, standard error. |
| Irregularity, occurrence of more than 2 out of 10 menstrual cycles outside the 21- to 35-day range; DIFF7P, persistent difference of 7 or more days in consecutive menstrual cycles; D60, first segment of at least 60 days; D90, first segment of at least 90 days; RR10, first running range (difference between the maximum and minimum lengths of 10 consecutive segments) of more than 42 days. |

### Table 2. Correlations of Age at Mean Change Points and Age at Variance Change Points With Markers of the Menstrual Transition, TREMIN Study, University of Minnesota, 1935–1979

<table>
<thead>
<tr>
<th>Marker</th>
<th>Irregularity</th>
<th>DIFF7P</th>
<th>D90</th>
<th>D60</th>
<th>RR10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change points</td>
<td>0.48</td>
<td>0.28</td>
<td>0.86</td>
<td>0.61</td>
<td>0.69</td>
</tr>
<tr>
<td>Variance change points</td>
<td>0.39</td>
<td>0.17</td>
<td>0.68</td>
<td>0.47</td>
<td>0.55</td>
</tr>
</tbody>
</table>

| Abbreviation: SE, standard error. |
| Irregularity, occurrence of more than 2 out of 10 menstrual cycles outside the 21- to 35-day range; DIFF7P, persistent difference of 7 or more days in consecutive menstrual cycles; D60, first segment of at least 60 days; D90, first segment of at least 90 days; RR10, first running range (difference between the maximum and minimum lengths of 10 consecutive segments) of more than 42 days. |

### Table 3. Average Silhouette Associated With Different Numbers of Clusters in Determination of the Optimal Number of Clusters for the K-Medoids Algorithm, TREMIN Study, University of Minnesota, 1935–1979

<table>
<thead>
<tr>
<th>No. of Clusters (A)</th>
<th>Silhouette (s(k))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.1431</td>
</tr>
<tr>
<td>3</td>
<td>0.1404</td>
</tr>
<tr>
<td>4</td>
<td>0.1265</td>
</tr>
<tr>
<td>5</td>
<td>0.1304</td>
</tr>
<tr>
<td>6</td>
<td>0.1434</td>
</tr>
<tr>
<td>7</td>
<td>0.1363</td>
</tr>
<tr>
<td>8</td>
<td>0.1351</td>
</tr>
<tr>
<td>9</td>
<td>0.1182</td>
</tr>
<tr>
<td>10</td>
<td>0.1287</td>
</tr>
</tbody>
</table>
data, the population mean age at the change point for segment length variability was 42.21 years (95% confidence interval: 41.84, 42.58), and the population mean age at the change point for segment length means was 46.20 years (95% confidence interval: 45.87, 46.54). The variability of log-segment length was stable before the change point and increased by 79% per year after the change point. Mean segment length declined on average about 1% per year before the change point and increased about 15% per year afterwards. (See Huang et al. (18) for details.)

Characteristics of the markers are summarized in Table 1. Mean ages at bleeding markers of the early menopausal transition were 40.98 years (standard error (SE), 4.24) for DIFF7P and 44.76 years (SE, 4.51) for irregularity. For the late transition markers, the mean ages were 48.80 years (SE, 3.45) for D90 and 46.96 years (SE, 4.25) for D60. Table 2 summarizes the correlations between markers and change points. As expected, D90 has higher correlations with the change points than D60, while the earlier markers have lower correlations, particularly for DIFF7P. All markers are more strongly correlated with mean change points than with variance change points, even though mean change points are conceptually consistent with late transition and variance change points are conceptually consistent with early transition.

**Classification of women’s menstrual patterns**

Using the K-medoids algorithm described above, we classify women into 6 categories based on the silhouette optimality criteria (see Table 3). Figure 2 illustrates the observed segment lengths as well as the predicted means and variances by age of the medoid subject if FMP is observed or, if FMP is censored, of the subject with an observed FMP who has the smallest distance to the corresponding medoid subject. Figure 3 presents the average menstrual profile across subjects in each category. Table 4 gives the posterior means of the individual-level change-point parameters for the women who are the medoids of each category.

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**Figure 2.** Profiles of menstrual medoids, by age. The graphs show the posterior mean of the mean segment length (central solid line) and its associated 95% credible interval (dotted lines surrounding central solid line) and the posterior means for the upper and lower 2.5th percentiles of the segment distribution (upper and lower solid lines) and their associated 95% credible intervals (upper and lower pairs of dotted lines). The 6 panels represent the medoid identification numbers shown in Table 4.
Category 1 has 74 (12.0%) subjects, and category 2 has 80 (13.0%) subjects. They represent subjects with both early variance and early mean change points and a short duration of early transition of approximately 2 years. The medoid variance change points occur around age 40.5 years, and the medoid mean change points occur around age 42.7 years. The biggest difference between these two subgroups is that category 1 has a generally stable pattern before change points and a rapid increase in both mean and variability of segment lengths thereafter, while category 2 has generally stable variability before and after the change points. Category 2 represents women with large variability across time with minimally apparent change points (little change in bleeding patterns) compared with other categories.

Categories 3 and 4 have similarly early variance change points to categories 1 and 2 but later mean change points and, therefore, longer durations of early transition. Category 3, the largest category, has 187 (30.3%) subjects, and category 4 has 76 (12.3%) subjects. For category 3, the medoid variance change point is at age 41.45 years and the medoid mean change point is at age 44.83 years, as compared with 39.84 years and 45.69 years for category 4. Category 4 has larger variability at age 35 years and larger decreases before variance change points, while category 3 has smaller variability at age 35 years, as well as a more stable pattern before variance change points. Category 4 also has an exceptionally large difference of nearly 6 years, between the early (variance) and late (mean) change points, as compared with 2–3.5 years in other subgroups, and thus a total transition of almost 11 years.

Category 5, with 113 (18.3%) women, and category 6, with 87 (14.1%) women, have substantially later variance change points than the other 4 subgroups, but the duration of early transition is similar in length to that of categories 1 and 2. Their medoid variance change points occur at about age 46.5 years, and their medoid mean change points occur at about age 48.5 years. Category 6 has smaller variability at age 35 years and larger increases after the variance change points.

Figure 3. Cluster average menstrual pattern profiles, by age. The graphs show the cluster mean of the posterior mean of the mean segment length (central solid line) and its associated 95% credible interval (dotted lines surrounding central solid line) and the cluster means of the posterior means for the upper and lower 2.5th percentiles of the segment distribution (upper and lower solid lines) and their associated 95% credible intervals (upper and lower pairs of dotted lines). The 6 panels represent the medoid identification numbers shown in Table 4.
Note that the silhouette measure for 2 clusters is nearly as large (0.1431) as the 6-cluster solution (0.1434). The 2 clusters are defined by early and late change points, respectively, and can be approximated by combining categories 1 and 2 with part of categories 3 and 4 into a single “early change point” category and the remainder into a “late change point” category. We have retained the full 6 categories for the analysis based on the silhouette optimality criteria and the fact that the 6 categories present a richer understanding of the menstrual cycle during perimenopause by highlighting differences in the lengths of transitions and patterns of bleeding.

### Associations between menstrual categories and women’s reproductive pattern characteristics

Examining differences in age at menopause in Table 4 suggests that age at FMP differs significantly between the population subgroups defined by these 6 categories ($F_{5,611} = 89.05; P < 0.001$ for test of differences between means). Women with the oldest change points tend to have an older age at FMP than women with younger change points, with women in categories 5 and 6 having a mean age at FMP of 52.66 years (SE, 0.14) and women in categories 1–4 having a mean age at FMP of 49.82 years (SE, 0.12) ($P < 0.001$). Among women with younger change points, there is no significant difference in age at FMP among categories 2–4 ($F_{2,340} = 0.99; P = 0.37$). Category 1, with its more rapid increases in mean segment length and segment variability after change points than category 2, the other category with early change points, has a significantly younger age at FMP: 47.05 years (SE, 0.24) versus 50.17 years (SE, 0.26) ($P < 0.001$).

There is some evidence that ages at menarche (see Table 4) also differ significantly between the population subgroups defined by these 6 categories ($F_{5,611} = 2.87; P = 0.014$ for test of differences between means). Women in categories 4 and 6 tend to have older ages at menarche (mean age at menarche of 12.09 years (SE, 0.08) vs. 11.78 years (SE, 0.07) in categories 1–3 and 5; $P = 0.003$). Categories 4 and 6 share the characteristic of having larger variability at age 35 years.

We observe no differences in parity across categories ($F_{5,611} = 0.62; P = 0.68$ for test of differences between means).

### Menstrual categories and transition markers

The colors in Figure 4 illustrate how the correlation between change points and markers differs in the menstrual pattern subcategories. These figures suggest that for most subjects, there are strong linear associations between change points and markers, while some subjects’ change points have no clear relation with markers. Most of these latter subjects are in categories 4 (turquoise) and 6 (blue), with a few in category 2 (red). Both category 4 and category 6 have larger early variability. Thus, their bleeding markers of the menopausal transition, which were defined on the basis of population-average as opposed to subject-specific characteristics, may occur early, while their actual change points may occur much later. Subjects in category 2 tend...
to have less obvious change points, that is, less apparent transitions. These findings suggest that woman-specific change points tend to capture menstrual patterns over a longer life span and may better distinguish the onset of the menopausal transition among women with highly variable cycles.

**DISCUSSION**

In this paper, we use 8 summary measures of individual women’s menstrual patterns (18) to classify women into 6 subgroups whose transition experience can be distinguished by age at onset, variability of cycles, and duration of the early and late stages of the menopausal transition using a K-medoids algorithm. Four subgroups begin the menopausal transition near age 40 years, on average, while 2 subgroups representing one-third of the population begin the transition much later, at age 46.5 years, on average. The average duration of the transition for the 2 late-onset transition subgroups and 1 early-onset transition subgroup is 6 years, while for the other 3 early-onset transition subgroups, the average duration is 9–11 years.

While the previous classification (13) was based on visual examination and simple statistics from 2-year sliding windows, our approach is more deeply rooted in statistical modeling and features of menstrual patterns during women’s late reproductive lives. Our findings suggest that ages at transition (change points) are a key feature with respect to classification, while features such as early mean and variance of segment lengths and rates of change before and after change points provide a more nuanced understanding.

While Gorrindo et al. (13) found no significant associations between their subtypes and age at menopause, we find that age at menopause is strongly associated with age at transition (change points), and, as might be expected, women with an older transition age tend to have an older age at menopause. Given age restrictions in enrollment criteria, most studies of the menopausal transition—including the Massachusetts Women’s Health Study (23), the Melbourne Women’s Midlife Health Project (24), and the Study of Women’s Health Across the Nation (25)—have included predominately women from categories 5 and 6; using follicle-stimulating hormone change points, the average deviation of the transition in the Study of Women’s Health Across the Nation is 6 years (26).

While Gorrindo et al. (13) suggested that women with stable menstrual patterns tended to have later menarche than women with erratic patterns, our findings suggest that the key factor here is variability in late reproductive age (variance...
of segment lengths at age 35 years), and women with larger variability at this time tend to have had a later age at menarche. Gorrindo et al. (13) found that women with stable menstruation patterns had fewer births than women with erratic patterns, but our findings suggest no significant association between number of births and the menstrual patterns of midlife women.

To assess whether change points can serve as transition markers, we studied their associations with previously defined transition markers. Our results suggest that for most women, mean and variance change points are well aligned with proposed bleeding markers of the menopausal transition, but women with highly variable cycles may have bleeding markers triggered long before the true onset of the menopausal transition. Other authors have addressed the issue of misclassification of transition status by introducing a more rigorous threshold for meeting marker criteria before age 45 years (27) or by proposing woman-specific criteria for bleeding markers (28). Further research is needed on the transition experience of women with highly variable cycles, including women with oligomenorrhea or polycystic ovarian syndrome, and on how to identify onset of the transition in these women (29, 30).

This study has some limitations. Data were derived from a Caucasian cohort established in the 1930s, members of which experienced menopause in the 1960s and 1970s. Secular changes in nutrition, body size, and use of exogenous hormones and lack of ethnic heterogeneity may limit the generalizability of our findings. We also had no data on biomarkers of aging. An alternative approach to our analysis would be to assume that the prior distribution underlying the components of the growth curve is a mixture of normals and to model the mixing probabilities as a function of covariates such as age and FMP or age and menarche. The hints of slight multimodality and skewness in the posterior means of the model components in Figure 1 suggest that such an approach could be successful in theory. However, given the complexity and time required to fit the single-component model, we chose to pursue a 2-stage approach, which trades the advantages of statistical efficiency and model coherence for flexibility and freedom from parametric assumptions.

In conclusion, we have shown that woman-specific mean and variance change points, which are identified using data throughout women’s late reproductive lives, contain comprehensive information about the timing and duration of the menopausal transition. We have further shown that women can be quantitatively classified into subgroups with distinct transition experiences based on relatively few parameters. These findings may facilitate development of staging criteria based on women’s menstrual histories for those subpopulations of women who are misclassified by currently recommended markers. Increasing understanding of population differences in the transition experience and identification of subgroups of women who experience distinct patterns in timing and variability of the menopausal transition may lead to new insights into the link between ovarian aging and subsequent risk of chronic diseases. Because of age-based inclusion criteria, most of the extant longitudinal studies of the menopausal transition have probably included only 2, or at most 4, of the 6 subgroups of women identified in this paper, suggesting a potential bias in our understanding of both the transition and the linkage between the transition and chronic disease.

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