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Assessing the Utility of Methods for Menopausal Transition Classification in a Population-Based Cohort: The CARDIA Study

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Abstract

Objectives—Perimenopause significantly impacts women's health, but is under-researched due to challenges in assessing perimenopause status. Using CARDIA data, we compared the validity of six approaches for classifying perimenopause status in order to better understand the performance of classification techniques which can be applied to general cohort data. Specifically, we examined the validity of a self-reported question concerning changes in menstrual cycle length and two full prediction models using all available data concerning menstrual cycles as potential indicators of perimenopause. The validity of these three novel methods of perimenopause classification were compared to three previously established classification methods.

Methods—For each method, women were classified as pre- or peri-menopausal at Year 15 of follow-up (ages 32–46). Year 15 perimenopause status was then used to predict Year 20 post-menopausal status (yes/no) to estimate measures of validity and area under the curve.

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Competing Interests
The authors declare no conflict of interest.

Ethical Approval
The CARDIA Study has received IRB approval each exam year, for each of the four study sites. Signed informed consent was received for each participant prior to commencement of data collection.

Results—The validity of the methods varied greatly, with four having an area under the curve greater than 0.8.

Conclusions—When designing studies, researchers should collect the data required to construct a prediction model for classifying perimenopause status that includes age, smoking status, vasomotor symptoms, and cycle irregularities as predictors. The inclusion of additional data regarding menstrual cycles can be used to construct a full prediction model which may offer improved validity. Valid classification methods that use readily available data are needed to improve the scientific accuracy of research regarding perimenopause, promote research on this topic, and inform clinical practices.

Keywords

menopause; perimenopause; sensitivity; specificity; validity

1. INTRODUCTION

Menopause is defined as the complete cessation of menstruation for 12 consecutive months, while perimenopause (often referred to as the menopausal transition) is the time period during which women transition from premenopause (the reproductive years) into menopause.[1] The median length of perimenopause has been estimated to be anywhere from four [2–5] to eleven years [6,7], which includes the year following the final cycle. During perimenopause, women's menstrual cycles become less consistent in terms of cycle length, cycle duration, and quantity of menstrual flow, and many women report a number of other vasomotor or somatic symptoms resulting from hormonal changes (such as hot flashes, vaginal dryness, and depression). Women are most likely to exhibit signs of perimenopause sometime in their 40s, although some women exhibit signs as early as their 30's or as late as their 50's.[8]

Researchers and clinicians are interested in perimenopause as certain characteristics of this transition (i.e., age at onset, duration, etc.) may be associated with important health conditions, such as abdominal obesity, decreased bone density, and high cholesterol.[9–11] Unfortunately, no gold standard exists for identifying women who are currently experiencing peimenopause. Thus, research on the associations between perimenopause and various health outcomes is hindered by the lack of an easily implemented surrogate measure of perimenopause onset and an ambiguous reference for identifying changes in menstrual cycles. In general terms, perimenopause is the departure from the "normal" cycles of reproductive years. However, what constitutes normal is entirely dependent on an individual woman, with a substantial amount of within- and between-person variability.[12–14] For instance, among a sample of 141 women (with data on 1,060 cycles) intra-cycle length variability greater than seven days was present in roughly 43% of women.[13] Similarly, Münster et al. found that among a sample of 1,526 Danish women ages 15 to 44, cycle length variation greater than 14 days was present in 29%.[14]Moreover, the menopausal transition progresses inconsistently as regular cycles can occur after periods of irregularity leading to misclassification of women's perimenopause status.[15] In short, without extraordinarily detailed tracking of women's cycles, departures from normal are difficult to define.

These difficulties have led to the development of a number of methods (algorithms) used to distinguish pre-, peri-, and post-menopausal women. These methods were created with the idea that any significant predictors of menopause are in fact indicators of antecedent perimenopause as well. Classification methods vary by the number of indicators used to classify women and many require frequent repeated measures, which limits their application.

We explored the utility of six different methods for classifying perimenopause status using data from the Coronary Artery Risk Development in Young Adults Study (CARDIA) at Year 15 and 20 follow-up examinations. Our objective was to assess and compare the validity of each method based on how well they predicted observed menopause. Three of the six methods examined have been used in prior research, while three are methods developed using CARDIA data (two of which are predictive models) and may be applied in other research settings.

2. MATERIALS AND METHODS

2.1 Overview of CARDIA

The CARDIA cohort has been described in detail in previous publications.[16] Briefly, CARDIA was first undertaken to examine the evolution and determinants of cardiovascular risk factor trends in young adults. This prospective longitudinal cohort study began in 1985 with a group of 5,115 black and white men and women age 18–30 years from four participating sites (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). Exams were conducted at baseline (1985–1986), and 2, 5, 7, 10, 15, and 20 years after baseline with 72% of the surviving cohort examined at Year 20. At baseline, 2,785 women participated in CARDIA. This analysis uses data from Years 15 and 20 (gathered in 2000 and 2005 respectively) when information regarding women's menstrual cycles were available.

2.2 Data

For this analysis, self-reported data regarding women's menstrual cycles in the 12 months prior to survey completion were used. Year 15 menopause was assessed based on women's responses to a survey question [*Have you gone through menopause or the change of life: no, yes, not sure*]. Surgical menopause at Year 20 was defined as self-reported surgical menopause [*Given that you have gone through menopause, how did your periods stop: naturally, surgically, other*] or reported bilateral oophorectomy based on follow-up questions regarding surgical procedures. Cycle regularity was established from survey responses [*During the past 12 months, have your menstrual cycles been regular at least half the time (excluding times when you were on birth control pills, pregnant, or nursing)?: no, yes, not sure*].

At Year 15, 2,051 women participated in the CARDIA study. We excluded 243 women who were pregnant, always on birth control, or nursing as they could not provide reliable details regarding recent menstrual cycles at the time of Year 15 CARDIA data collection. To ensure our analysis included only incident cases of menopause at Year 20 we excluded 217 women who reported that they had already experienced menopause at Year 15. We excluded two women who reported that they had a bilateral oophorectomy at Year 15 based on follow-up questions regarding surgical procedures. We excluded 95 women who had surgical menopause at Year 20 to limit prediction to natural menopause. An additional 330 women were excluded due to missing data. Our final sample size included 1,164 women (2,051-243-217-2-95-330 = 1,164). Of the final sample, 55% were Caucasian and the average age was 40 at Year 15.

2.3 Perimenopause Classification Methods

We performed a literature review to identify previously reported and commonly used methods for classifying perimenopausal status. Several methods could not be replicated using CARDIA data because of data requirements, including: the need for repeated measures of reproductive hormones (e.g., follicle-stimulating hormone), specific information on the number of cycles skipped (as opposed to loosely defined periods of amenorrhea), changes in the quantity of menstrual flow over time, and precise definitions of variability in cycle length and duration (e.g., changes in cycle length greater than seven days from normal as opposed to general self-reported cycle variability).[1,17–19] In total, seven existing methods for identifying perimenopausal women were reviewed three of which could be replicated: 1) a method including data regarding age, smoking, vasomotor symptoms, and cycle irregularity developed by Brambilla based on data from the Massachusetts Women's Health Study (MWHS); 2) a modification of one of Brambilla's methods used by the Study of Women's Health Across the Nation (SWAN) including data regarding changes in cycle length and amenorrhea; 3) a method with age as the sole predictor.[20–22] See Table 1 for details.

Of note, Brambilla et al. examined a number of perimenopause classification methods, one of which is commonly referred to as the MWHS method.[20] This method, when applied to CARDIA data, is identical to SWAN. Thus, we chose to evaluate another classification method that Brambilla et al. examined, which we refer to as the MWHS method in the context of this paper.

In addition to examining the validity of the three existing perimenopause classification methods discussed above, we developed three novel methods based on Year 15 CARDIA data pertaining to menstrual cycles and symptoms of perimenopause (see Table 1 for details). First, we examined the validity of a single self-reported survey question, which inquires about changes in menstrual cycle length (MCL), as a proxy of perimenopause status. Notably, this question is one component of the data used for the SWAN classification method. Second, we explored the use of a full prediction model comprised of all other available data relevant to perimenopause as established in the literature.[23] The factors were used to improve the accuracy of the prediction model. Third, we explored the use of the full prediction model with the addition of the MCL question as an independent predictor.

2.4 Analytical Approach

These six perimenopause classification methods were used to classify women as either pre- or peri-menopausal using Year 15 data. The validity of these classification methods was assessed by examining their ability to predict self-reported Year 20 natural menopause (as measured by sensitivity, specificity, area under the curve, and positive and negative predictive values). In the absence of a true gold standard for perimenopause, we assumed that women who were post-menopausal at Year 20 were perimenopausal at Year 15.

Women were categorized as premenopausal or perimenopausal based on predicted probabilities outputted from logistic regression. Using a range of cut-points, a series of receiver operator characteristic (ROC) curves were generated for each of the six perimenopause classification methods. Optimal probability cut-points for each method were derived using the Youden Index [24]:

$$J=max_c\{SE_c+SP_c-1\}$$

The cut-point (J) that yielded the maximum Youden Index was the optimal cut-point (c) as it maximized the model's differentiating ability with equal weight given to sensitivity and specificity. Using the ROC curve corresponding to the optimal cut-point, sensitivity, specificity, and area under the curve (AUC) were calculated for each model. AUC was used to statistically test for differences in validity (using SAS software, ROCCONTRAST statement). Confidence intervals for estimates of validity were calculated using bootstrapping (1,000 samples with replacement) to assess internal validity. For those classification methods that included age as a predictor, age was modeled as a linear term (departures from linearity were examined but were not statistically significant).

3. RESULTS

Of the final sample (N=1,164), there were 106 cases of incident natural menopause at Year 20 (9% of the sample); these women were assumed to have been perimenopausal at Year 15. The average age of those at Year 20 who had experienced menopause was 48, in comparison to the average age of 44 for those who were either premenopausal or perimenopausal.

As shown in Table 2, the validity of the different methods varied considerably with AUC ranging from 0.665 to 0.893. When examining area under the curve (AUC), the MCL question performed comparably to the SWAN method. Age alone preformed better than the MCL question and the SWAN method. The MWHS method preformed better than the SWAN, MCL and age methods. As expected, in the MWHS model, smoking, age, and cycle length irregularity were the only statistically significant independent predictors of Year 20 menopause (the vasomotor symptoms term was marginally significant).

The final full prediction model contained only those variables with *P*-values less than 0.1 as a conservative assessment of significance: irregularities in cycle length (yes/no), vasomotor symptoms (yes/no), smoking status (never, former, current), age (continuous), feeling blue (yes/no), the absence of reported symptoms of perimenopause (yes/no), frequent mood changes (yes/no), body mass index (continuous), and vaginal dryness (yes/no). Notably, the addition of the MCL question to the full prediction model resulted in a statistically significant increase in the validity of the model based on comparison of AUC. With the addition of the MCL question, body mass index, vaginal dryness, and absence of perimenopausal symptoms were no longer significant predictors of menopause. Based on AUC, the full prediction models performed better than all others. Those classification methods that included age preformed better than those that did not (SWAN and the MCL).

4. DISCUSSION

When applied to CARDIA data, the six classification methods examined displayed a great degree of variability in terms of validity. Notably, three approaches based on self-reported data alone (and no biological samples) achieved an AUC greater than 0.85. The full prediction models, which performed best in terms of validity, were almost entirely comprised of simple yes or no questions concerning menstruation and symptoms of perimenopause. If possible, researchers should consider collecting these data when designing research studies related to women’s health. Full prediction models benefit from using all available data, and avoid the specific data needs of conventional classification methods. In the absence of data regarding cycle changes and perimenopause symptoms, researchers may consider using age alone to classify women’s perimenopause status. Overall, age alone is a parsimonious option and applicable to all data, but affords only moderate validity.

The MWHS model provides a balance between the two options presented above. Using self-reported questions regarding cycle length irregularity and vasomotor symptoms (while accounting for age and smoking status), the MWHS model has a similar degree of validity as the full prediction models, but is much more parsimonious. Overall, the MWHS model yields a moderate degree of validity while remaining relatively simple.

Despite the reasonable validity of the methods discussed above, the low positive predictive value (PPV) exhibited by all six methods examined is concerning. For all six methods examined, the discordance between Year 15 perimenopause status and Year 20 menopause status was mainly due to false positives (women who were classified as perimenopausal at Year 15 and did not report being in menopause at Year 20) as reflected by the low PPVs. The low PPV is largely a function of somewhat low menopause prevalence (9%), and would increase if the methods were applied to older populations. However, application to samples with a high prevalence of menopause will result in a diminished negative predictive value. These predictive values highlight the limitations of these six methods and the need for continued efforts to develop easily implemented, highly valid perimenopause status classification methods.

This study has important limitations. First, this research relies on an imperfect gold standard (Year 20 self-reported menopause) to assess the validity of various methods for classifying women as either pre- or peri-menopausal. However, McKinley et al. estimated that at the age of 45 roughly 9% of women will experience natural menopause.[2] In our sample with an average age of 45 at Year 20, 9% of the sample reported that they had experienced menopause indicating that self-reported menopause in the CARDIA sample follows observed patterns established in other cohort studies. Second, a key assumption of this analysis is that those women who were truly perimenopausal at Year 15 will be post-menopausal by Year 20. While previous research has shown that the median duration of perimenopause is roughly four years [2–5], other research has indicated it could be as long as six to eleven years.[6,7] Women who progress through perimenopause more slowly will inflate the number of false positives and reduce estimates of validity. However, as we assessed *prevalent* perimenopause at Year 15, many women may have begun to experience symptoms of perimenopause years prior to Year 15, extending the duration of perimenopause captured in this research beyond five years. Notably, based on recently available data for Year 25 of follow-up we replicated the analysis using Year 25 menopause status as the gold standard instead of Year 20, thus extending the duration of perimenopause captured in the analysis beyond the reported normal ranges. Importantly, the substantive findings remained unchanged. Further, comparisons of the validity *across* classification methods remain sound as they are all impacted by this phenomenon (i.e. the duration of perimenopause exceeding the range captured in this research). Third, given that the average age of the sample was 40 at Year 15, the cases of perimenopause at Year 15 and menopause at Year 20 used in the analysis represent early cases and may not be fully representative of the menopausal transition. However, it is important to note that the ages for the perimenopause and menopause cases included in this analysis overlap with the reported normal age ranges for these events, and early transitions to perimenopause are often of primary substantive importance for research and clinical care. Fourth, as the full prediction models were developed based on and applied to CARDIA data, the results may be skewed in favor of the full prediction models. Models perform particularly well in the datasets in which they were developed. The bootstrap estimates of interval validity only partially correct for this bias. Further, it is possible that some of the variables used to predict menopause (e.g. smoking and BMI) are also associated with the duration of the menopausal transition. This could affect the accurate identification of perimenopausal women. Notably, research regarding factors associated with the duration of the menopausal transition is limited (due to difficulties in identifying women during this important phase). Fifth, it should be noted that the SWAN classification method distinguishes between early and late perimenopause. When replicating the SWAN method for the purposes of this research, the early and late stages of perimenopause were collapsed as we were interested in assessing perimenopause (yes/no) at a given time point and maintaining consistency in terms of statistical modeling (each classification method was assessed using perimenopause as a dichotomous variable). Lastly, this research should be replicated in other research settings in order to examine the validity of these methods when applied to different populations. Notably, misclassification for many outcomes of interest may be non-differential and estimates of association will on average be biased toward the null. However, differential misclassification may occur. Researchers should carefully consider the potential implications of differential misclassification to study conclusion before adopting classification methods.

We note that four of the seven conventional methods that we reviewed from the scientific literature could not be replicated with CARDIA data (criteria resulting from the Stages of Reproductive Aging Workshop, the Seattle Midlife Women's Health Study, the Harvard Study of Moods and Cycles, and the Women's Ischemia Syndrome Evaluation). However, classification methods requiring particularly detailed information regarding women's cycles lack applicability to a diverse range of datasets. Many studies (particularly those that do not focus on women's health) do not have access to such detailed menstrual cycle data, but contain rich data that may help shed light on important associations between perimenopause and various health outcomes.

This research highlights the need for classification methods which are easily applied to a wide range of datasets without compromising validity. High quality research regarding perimenopause could be used to inform improved clinical practices. For instance, accurately identifying perimenopausal women may allow for early implementation of increased monitoring and/or interventions regarding lipids and central weight gain which may result in improved long-term outcomes. Thus, the development of a valid and easily applied perimenopause classification method is of importance to researchers, clinicians, and patients. Without the use of a valid measure for perimenopause status, estimates of association may be biased or remain undetected, and possible prevention tools may remain undeveloped.

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Abbreviations

AUC	area under the curve
CARDIA	Coronary Artery Risk Development in Young Adults Study
MCL	menstrual cycle length
MWHS	Massachusetts Women's Health Study
NPV	negative predictive value
PPV	positive predictive value
ROC	receiver operator characteristic
SWAN	Study of Women's Health Across the Nation

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Table 1

Application of Methods for Classifying Perimenopause Status to CARDIA Data, 2000–2005

Method	Description of Method	Application to CARDIA Data
Literature Based Methods		
SWAN[21]	Creates 3 classifications for perimenopause: • Premenopausal: had a cycle in past 3 months and no change in cycle length • Early Perimenopausal: had a cycle in past 3 months and changes in cycle length • Late Perimenopausal: had a period in past 12 months but not in the last 3 months	• Early and late stages of perimenopause were collapsed (amenorrhea in past 3 months or cycle length irregularities in past 12 months) • All others were premenopausal • Logistic regression: Dichotomized Year 15 perimenopause status as the predictor and Year 20 cumulative incident menopause as the outcome
Age[22]	• Age alone may be a meaningful indicator of perimenopause	• Logistic regression: Year 15 age (continuous) as the predictor and Year 20 cumulative incident menopause as the outcome
MWHS[20,a]	• Logistic regression: age, smoking status, vasomotor symptoms, and cycle irregularities were significant predictors of subsequent menopause after 5 years follow-up	• Logistic regression: Year 15 age, smoking status (never, former, current), vasomotor symptoms (yes/no), and cycle length irregularity (yes/no) as predictors and Year 20 cumulative incident menopause status as the outcome
Novel CARDIA Methods		
MCL[a]	• Survey question regarding menstrual cycle length: During the past 12 months have your periods become: farther apart, closer together, occurred at more variable intervals, stopped completely, or stayed the same?	• First four categories were considered perimenopausal and last category represented women who were pre-menopausal • Logistic regression: Dichotomized Year 15 perimenopause status as the predictor and Year 20 cumulative incident menopause as the outcome
Full Prediction	• Full prediction models (comprised of all available and relevant data) may classify perimenopause status to a reasonable degree. • Non-significant terms are dropped one at a time, until all predictors have p-values ≤ 0.1.	• Logistic regression: Year 15 cycle length (days), cycle duration (days), irregularities in cycle length (yes/no), irregularities in cycle duration (yes/no), quantity menstrual flow (light, moderate, heavy, variable), smoking status (never, former, current), age (continuous), body mass index (continuous), physical activity (composite continuous score), vasomotor symptoms (yes/no), feeling blue (yes/no), irritability (yes/no), forgetfulness (yes/no), frequent mood changes (yes/no), vaginal dryness (yes/no), leaking urine (yes/no), joint pains (yes/no), headaches (yes/no), the absence of perimenopause symptoms (yes/no), race (Caucasian/African-American), years of education (continuous), follicle-stimulating hormone (FSH) and Year 20 cumulative incident menopause status as the outcome
Full Prediction + MCL	• The final full prediction model (reduced to terms with *P*-value ≤ 0.1)	• The MCL question was added to the full prediction model

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; MCL, menstrual cycle length; MHWS, Massachusetts Women's Health Study; SWAN, Study of Women's Health Across the Nation.

[a]Women who reported that their cycle had stopped were *not* menopausal yet.

Table 2

Validity of Methods: Classifying Perimenopause Status at Year 15 to Predict Observed Menopause Status at Year 20, CARDIA Cohort, 2000–2005

	Sensitivity		Specificity				
Method	Estimate	95 % CI	Estimate	95%	PPV [a]	NPV [b]	AUC [c]
SWAN	44.7	34.8, 54.5	88.9	86.9, 90.9	29.1	94.0	0.665
MCL	65.7	56.3, 75.5	70.2	67.4, 73.1	18.6	95.2	0.672
Age	77.4	69.4, 85.3	74.4	71.8, 77.2	23.9	96.9	0.830
MWHS	84.2	77.1, 90.7	75.0	73.6, 78.9	25.5	97.9	0.879
Full Prediction Model	75.2	67.9, 85.4	83.1	81.0, 85.6	31.3	97.0	0.885
Full Prediction Model + MCL	81.6	74.7, 89.8	81.0	78.5, 83.4	30.5	97.7	0.893

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults Study; CI, confidence interval; MCL, menstrual cycle length; MHWS, Massachusetts Women's Health Study; NPV, negative predictive value; PPV, positive predictive value; SWAN, Study of Women's Health Across the Nation.

[a] Positive predictive value (PPV: the percentage of women who were identified as perimenopausal at Year 15 and were menopausal at Year 20)

[b] Negative predictive value (NPV: the percentage of women who were identified as premenopausal at Year 15 and were not menopausal at Year 20)

[c] Differences in area under the curve (AUC) were tested using the SAS ROCCONTRAST statement (P-value ≤ 0.1):

- SWAN AUC is statistically different from all other methods except for the MCL
- MCL AUC is statistically different from all other methods except for the SWAN method
- Age AUC is statistically different from all other methods.
- MWHS AUC is statistically different from all other methods except for the Full Prediction Model
- Full Prediction Model AUC is statistically different from all other methods except for the MWHS Model
- Full Prediction Model + MCL AUC is statistically different from all other methods