Maturitas 75 (2013) 289–293

Contents lists available at SciVerse ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Assessing the utility of methods for menopausal transition classification in a population-based cohort: The CARDIA Study

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ARTICLE INFO

Article history:
Received 19 November 2012
Received in revised form 29 March 2013
Accepted 24 April 2013

Keywords:
Menopause
Perimenopause
Sensitivity
Specificity
Validity

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.

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.

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 4 [2–5] to 11 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 30s or as late as their 50s [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

Abbreviations: AUC, area under the curve; CARDIA, Coronary Artery Risk Development in Young Adults Study; LDL-c, low-density lipoprotein cholesterol; 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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http://dx.doi.org/10.1016/j.maturitas.2013.04.015

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 1060 cycles) intra-cycle length variability greater than 7 days was present in roughly 43% of women [13]. Similarly, Münster et al. found that among a sample of 1526 Danish women ages 15–44, 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 postmenopausal 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 5115 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, 2785 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, 2051 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 1164 women (2051-243-217-2-95-330 = 1164). 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 7 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]. These data 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