Review

Methods used in cross-cultural comparisons of vasomotor symptoms and their determinants

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Abbreviations:
BMI, body mass index;
E2, estradiol;
FSH, follicle stimulating hormone;
SHBG, sex hormone binding globulin;
HT, hormone therapy
HF, hot flush;
NS, night sweats;
QOL, quality of life;
VMS, vasomotor symptoms

Study Abbreviations:
AJMWHS, Australian/Japanese Midlife Women's Health Study;
DAMeS, Decisions At Menopause Study;
FMEG, Four Major Ethnic Groups;
HWHS, Hilo Women's Health Survey;
MAHWIS, Mid-Aged Health in Women from the Indian Subcontinent;
POAS, Penn Ovarian Aging Study;
SWAN, Study of Women's Health Across the Nation;
WHiMNS, Women's Health in Midlife National Study;
WISHeS, Women's International Study of Health and Sexuality;

ABSTRACT

Methodological differences among cross-cultural studies of vasomotor symptoms limit attempts at comparison or systematic review. We reviewed only cross-cultural studies of menopausal symptoms that explicitly examined symptoms in general populations of women in different countries or different ethnic groups in the same country. This resulted in the inclusion of nine studies: *Australian/Japanese Midlife Women's Health Study (AJMWHS), Decisions At Menopause Study (DAMeS), Four Major Ethnic Groups (FMEG), Hilo Women's Health Survey (HWHS), Mid-Aged Health in Women from the Indian Subcontinent (MAHWIS), Penn Ovarian Aging Study (POAS), Study of Women's Health Across the Nation (SWAN),Women's Health in Midlife National Study (WHiMNS),* and *Women's International Study of Health and Sexuality (WISHeS).*

Vasomotor symptoms generally include hot flushes and night sweats although other associated symptoms exist. Prevalence rates vary between and within populations, and data on frequency and bothersomeness/severity should be collected. Significant cultural differences in vasomotor symptoms were observed in 8/9 studies, and symptoms were influenced by the following determinants: menopausal status, hormones (and variance), age (or actually, the square of age, age^2), education, BMI, depression, anxiety, poor physical health, perceived stress, lifestyle factors (hormone therapy use, smoking and exposure to passive smoke), and acculturation (in immigrant populations). These studies highlight the methodological challenges involved in conducting multi-population studies, particularly when languages differ, but also highlight the importance of performing multivariate and factor analyses. Recommendations are made to improve methodological rigor and facilitate comparisons in future cross-cultural menopause studies.

Keywords:
Menopause
Cross-cultural
Methodology
Symptom reporting
Vasomotor symptoms
Hot flushes

Contents

1. Introduction

Vasomotor symptoms (VMS) are considered hallmark symptoms of menopause in most cultures. Cross-cultural differences in the prevalence and experience of VMS have been well-documented [1-3], but rigorous comparisons are hampered by methodological differences [2]. In order to increase the understanding of cultural variation in, and influences on, VMS and to improve methodological rigor in future research, this review examines nine studies that explicitly compare symptoms across different cultural (country/ethnic) groups using similar methodology: *Australian/ Japanese Midlife Women's Health Study* (AJMWHS) [4], *Decisions At Menopause Study* (DAMeS [5-9]), *Hilo Women's Health Survey* (HWHS) [10-12], *Four Major Ethnic Groups* (FMEG) [13]; *Mid-Aged Health in Women from the Indian Subcontinent* (MAHWIS)[14, 15]), *Penn Ovarian Aging Study* (POAS) [16-19], *Study of Women's Health Across the Nation* (SWAN) [20-28], *Women's Health in Midlife National Study* (WHiMNS) [29]; and *Women's International Study of Health and Sexuality* (WISHeS) [30]. The objectives of this review are to: (1) assess whether VMS differ cross-culturally; (2) identify determinants of VMS; (3) make recommendations on methods for future cross-cultural studies.

2. Methods

This review includes only studies that compare VMS frequencies across ethnic groups within or between countries. The studies are described in detail in the overview to this series of review papers [31].

We reviewed methodological and study design characteristics, frequencies of VMS, and determinants of VMS identified in multivariate analyses in the studies.

Recommendations are made throughout this review to enable more rigorous cross-cultural comparisons in future research.

3. Results and Discussion

3.1 Study design and methodological considerations

3.1.1 Study design

Following an earlier publication [2], this review focuses on publications since 2004. Individual studies utilized similar instruments and methodology for comparison between subpopulations, but design characteristics and methods varied considerably among studies (**Table 1** and **Overview** [31]). Eight of 9 studies documented significant cultural (ethnic/country) differences in VMS (**Table 2**), but more rigorous comparisons across studies would be facilitated by greater standardization of methodology and study design.

Detailed discussion of and recommendations concerning methodological issues can be found in the Overview [31]. We must distinguish between occurrence, perception and reporting of VMS [20], as these are differently assessed by different methods and mediated by language. Most studies translated and administered language-specific versions of questionnaires, but some (FMEG, HWHS) did not. Linguistic variation in symptom terminology complicates estimates of symptom prevalence and highlights potentially more nuanced physiological experiences. Rates of hot flush prevalence in one Japanese population differed by more than 7-fold, depending on the term [32]. To avoid influence of menopausal stereotypes on reporting, VMS should be embedded in an everyday complaint list, as in DAMeS and HWHS.

To characterize relevant variation in the menopausal transition, we recommend an age range of 45-55. This could be expanded to 40-60 if a more extended profile is

desired, or shifted earlier in populations with earlier age at menopause or in longitudinal studies (when inclusion of more premenopausal women at baseline would be recommended). However data should be reported for ages 45-55 to enable cross-study comparisons. Most questionnaires use either a 2-week or 1-month recall period. A shorter recall period may be more accurate, but a 1-month recall period covers an average menstrual cycle. We need studies that ask both, to provide data on how these are related (e.g., are 1 month recall rates similar to or double 2-week recall rates?) and to assess how they may change by factors such as menopausal status. Longer or ambiguous recall periods should not be used, although it may be informative to ask women if they have *ever* experienced VMS.

3.1.2 Constituent vasomotor symptoms

Hot flushes (HFs) are the defining VMS, but associated symptoms vary considerably between studies, and include thermoregulatory, sexual and sleep-related symptoms. Many studies include night sweats (NSs), which are HFs that occur at night with significant perspiration. These may disturb sleep, and sleep troubles may be a proxy for them in symptom reports. The extent to which sleep and sexual symptoms (see Sexual review [33]) are associated with vasomotor symptoms is influenced by cultural and individual practices related to sleep [34] and sexual behavior. In DAMeS, sleep disturbances were associated with VMS in Spain but with general somatic symptoms in Morocco [9]. HFs and NSs have been shown to have different determinants [35], and thus should be queried separately to enable comparisons between studies.

WISHes examined age patterns of symptom prevalence in women aged 20-70yrs and found that in addition to HFs and NSs, vaginal dryness, sexual arousal difficulties,

sleeping difficulties, aches from head to shoulders, and poor memory also peaked at age 50, the average age of menopause [30]. In contrast, symptoms such as sweating, sexual desire changes, and psychological symptoms peaked earlier [30]. Thus difficulty sleeping, vaginal dryness and sexual arousal difficulties might share underlying etiology with VMS.

3.1.3 Factor analyses

Factor analysis identifies symptoms that can be classified together (often assumed to share underlying etiology, such as hormonal changes), based on statistical rather than a priori concepts, to which cross-cultural work is particularly susceptible. Factor analysis can determine whether VMS constitutes a unique symptom factor and whether other symptoms are associated with VMS.

In DAMeS, factor analysis of the 20 symptoms shared among sites resulted in up to 8 factors in different countries. When final factor analyses were constrained to permit only three factors, HFs factored with sexual symptoms in Spain and with somatic symptoms in Morocco, but were not included in the US or Lebanon final solutions [9]. When more factors were permitted, HFs often showed high factor loading scores, suggesting that for some populations a greater number of factors may be required to include this symptom (rated most bothersome in 3 of 4 sites), particularly when everyday complaint lists are used [36]. In WHiMNS, HFs were excluded a priori [29], and thus assumed to constitute a unique symptom factor.

In DAMeS, HFs and NSs did not load onto the same factor as anxiety and depression in any country. Similarly in SWAN, two consistent symptom factors emerged from analyses across ethnic groups: vasomotor and psychological/psychosomatic [22]. In HWHS, factor analyses identified 3 factors,

with one factor containing HFs, NSs, loss of sexual desire, trouble sleeping and vaginal dryness [11]. Cross-sectional results may differ from longitudinal studies, as POAS found that psychological factors were associated with, and even predicted, VMS [18].

We recommend that factor analyses should be performed on the whole sample as well as each subgroup separately as in DAMeS; and all symptoms with high prevalence should be included in final solutions (the number of factors should not be limited a priori, so that symptoms associated with HFs can be assessed).

3.1.4 VMS Measures

4.1.4.1. Subjective

Self-reported symptoms often include measures of frequency, severity, and/or bothersomeness. Of these, frequencies may be the most comparable across cultures because populations may vary in the degree to which they are bothered by symptoms or rate their severity. HF frequencies range from 21 to 84%, but methodological differences between studies render comparisons difficult (**Table 3)**.

Although HF frequency generally accounts for the majority (60-75%) of variability in treatment outcome, additional information is gained from severity [37]. If a single endpoint is desired, a combined Frequency x Severity score could be used [36, 37]. The terms severity and bothersomeness are often used interchangeably. While severe symptoms are likely to be bothersome, this may not always be the case. For example, severe HFs at home or in cold environments may be less bothersome than less severe HFs in public (where removing clothes is not possible) or in warmer environments.

Not all women who experience VMS are bothered [24], but bothersomeness may be important to quality of life (QOL). In DAMeS, there appeared to be a correlation between frequency and bothersomeness of HFs, as well as other emotional and somatic symptoms [7]. In SWAN, negative affect, symptom sensitivity, sleep problems and number of visits reporting HFs were associated with HF bother, even after adjusting for HF frequency [24]. Women with frequent but not bothersome HFs had lower negative affect and were more likely to be married. Women with infrequent but bothersome HFs were more likely to be in poorer health, have lower education, and to be African-American vs. Caucasian, and less likely to be Japanese [24]. Since perception of severity or bothersomeness may exhibit significant cultural differences, collection of such data in addition to frequency is recommended.

3.1.4.2. Objective

While most studies of menopausal symptoms rely on subjective report, recent studies have used skin conductance as an 'objective' measure of thermoregulatory instability associated with HFs [10, 38]. However, skin conductance relies on sweating, and HFs are heat dissipation events that involve vasodilation but not always sweating. Thus measurements do not exhibit one-to-one correspondence with self-reports [39], suggesting that information on severity or bothersomeness may be important, particularly in terms of QOL. Ambulatory HF monitors have been developed [40, 41], and are recommended for use in future cross-cultural studies.

In a 24-hour ambulatory study and a 3-hour laboratory study in HWHS, Japanese-Americans (JAs) and European-Americans (EAs) showed no significant differences between reported or objectively demonstrated HFs. In contrast, 2-week recall of bothersome symptoms was significantly lower in JAs, possibly due to

reporting bias because JAs also reported fewer symptoms of other conditions [10]. Lower recall of bothersome HFs by JAs [12] might also result from physiological differences in HFs, as JAs experienced fewer HFs as flushing with an associated change in pulse compared to EAs [10].

Subjective and objective measures of HFs may provide insight into the range of differences between occurrence, perception and bothersomeness [20]. Thus, future research should collect data on symptom frequency (subjective and objective) and severity and/or bothersomeness (as measure of interference with daily life activities and QOL).

3.2 Determinants of vasomotor symptoms

To answer the question of whether cultural differences in VMS derive from confounding variables that exhibit cultural variation, and to identify determinants of menopausal symptoms (**Table 4**), multivariate analyses are essential. Many factors appear significant in bivariate analyses, but are no longer significant in multivariate models.

WISHeS reported regression coefficients, permitting estimation of symptom prevalence at age 50 in subpopulations with various determinants [30]. For example, the estimated prevalence of HFs = 36.8 + 3.9*(# mental morbidity items) + 2.1*(# physical morbidity items) + 5.8*(early surgical menopause: yes=1, no=0). Thus for 50-year old women with no morbidity and not surgically menopausal, 36.8% would be expected to have HFs. For 50-year old women with early surgical menopause, 2 chronic physical diseases, and 3 mental morbidity items, the prevalence of HFs would be 56.7%. Similar regression analyses in non-western populations with additional

determinants may lead to more complex and culturally-diverse models of VMS variability and midlife symptoms in general.

3.2.1. Culture (country/ethnicity)

The 9 studies reviewed here used country (3/9), ethnicity (5/9) and both (1/9) as proxies for cultural group, and ranged from only western countries with similar health profiles (mean BMI ≥ 25, clinically overweight) (WISHeS) to more culturally diverse populations such as Western/Asian (AJWMHS, MAHWIS) and US/European/Middle Eastern (DAMeS). Seven of the eight studies conducting multivariate analyses on VMS reported significant differences in VMS by culture group (only WISHeS, with significance $P<0.001$, did not). Yet the significance of difference decreased in some studies when confounding variables were controlled for (POAS) but not in others (SWAN, WHiMNS).

3.2.2. Menopausal status and hormonal

After adjusting for other risk factors, menopausal status showed the most consistent association with HFs. Data on menopausal status should be collected and reported following STRAW stages [42, 43], and data on surgical menopause and hormone therapy (HT) use should be collected and reported separately. Comparison of VMS frequency is complicated by varying rates of HT use, ranging from 0% among surgically menopausal women in Morocco to 42% among postmenopausal women in the US (DAMES) [7].

Hormone data may clarify menopausal status, and be correlated with VMS. In the POAS, the standard deviation in estradiol (E2), but not E2 levels were significantly associated with symptoms, highlighting the importance of repeated measures and

measures of variability over the menopausal transition [18]. In the SWAN, serum sex steroid, FSH and SHBG levels varied by ethnicity, but were highly confounded by ethnic disparities in body size [25].

3.2.3. Demographic

Truly menopausal symptoms, the increased prevalence of which is due to underlying changes of menopause, should exhibit an inverted U-shaped curve with age (or an inverse relationship with age^2), achieving maximum prevalence around the average age of menopause (50 yrs), while symptoms of aging should exhibit a positive linear relationship with *age*. In WISHeS, all of the symptoms that peaked at 50 had significant regression coefficients for early reproductive surgery, no significant coefficients for age, negative coefficients for age^2 (ie, inverted parabola), and significant positive coefficients for mental and physical morbidity [30] Thus controlling for age or menopausal status in a linear fashion is inadequate, and future studies of midlife symptoms should include a quadratic age term in models.

When examined, demographic factors such as socioeconomic status and education showed inconclusive or non-significant patterning across studies. Education showed a negative relationship with VMS in 2 studies, a positive relationship in one study, and was not significant in two studies.

3.2.4. Anthropometric

High BMI may increase the risk of HFs due to increased insulating effects of excess body fat [26, 27], which may increase core body temperature. BMI exhibited positive relationships with VMS in 2/5 studies, and a strong positive relationship with total symptom number in FMEG.

3.2.5. Mental/physical health

Measures of mental and physical morbidity should be included in any cross-cultural study of menopausal symptoms, as these often vary by culture group and contribute significantly to prevalence (and bothersome) rates (see Psychological symptom review [44] and Somatic symptom review [45]). Both depression and anxiety were positively related to VMS in 3/3 studies. Women with depression were more likely to report HFs (POAS and WHiMNS), and an Australian longitudinal study showed that depression often preceded HFs [46]. In POAS, anxiety scores at previous assessment significantly predicted HFs, with those reporting high anxiety being nearly 5 times more likely to experience HFs [19]. Physical morbidity and perceived stress were positively related to VMS in 3/4 and 2/2 studies, respectively.

32.6. Lifestyle

Lifestyle variables included in the studies reviewed here are not exhaustive, and lack of significant relationships may reflect inadequate variation or statistical power. However, smoking and passive smoke exposure were identified as significant determinants of VMS. Dietary factors such as soy isoflavones were not [21], possibly due to relatively low intake levels compared to Asian intakes [2, 47]. Religion was not significant in studies reviewed here, but religious differences have been observed in other studies [38]. Hormone therapy is included in Table 4 as a lifestyle variable because, although HT use influences endogenous hormone concentrations, it also reflects access to medical care and medicalization of menopause.

Attitudes toward menopause and medicalization of menopause vary cross-culturally [3], and may influence rates of VMS reporting. Westernization,

acculturation and medicalization are not always highly correlated and future research is required to parse the variance in VMS attributed to these factors. In DAMeS, the highest HF rates were reported in the site (Morocco) that is least medicalized, and where the traditional vocabulary does not even have a word for menopause [7]. In the SWAN, Chinese- and Japanese-American women who were least acculturated tended to report more negative attitudes toward the menopause [28], yet had lower rates of vasomotor symptoms compared to African-, Caucasian- and Hispanic-Americans. In contrast, in MAHWIS, UK Asian women who were less acculturated reported more VMS [14]. In MAHWIS, although UK Asian and Delhi women reported poorer health and higher physical and emotional symptoms than the UK Caucasian, the 2 UK groups reported significantly higher rates of HFs and night sweats than the Delhi group [15], suggesting that westernization might correlate with higher rates of VMS.

3.2.7. Environmental variables

Ethnic and cultural differences in VMS frequency may derive not only from individual physiological and lifestyle differences but also environmental differences such as ambient temperature [48, 49], which may be influenced by indoor heating and air conditioning.

4. Conclusions

Among menopausal symptoms, VMS are of great clinical importance, as they impact quality of life and often lead women to seek treatment. Evaluation of how VMS rates vary between cultural (country and ethnic) groups, and which factors influence them, has been complicated by methodological and reporting differences. Culture group was not significant in regression analyses of HFs in WISHeS, nor in

AJMWHS. In POAS ethnic differences decreased significantly when many confounding variables were controlled for in adjusted models [16], suggesting that in same country multi-ethnic studies much of the variability may be attributed to confounding variables that correlate with ethnicity. In contrast, SWAN found significant ethnic differences even after adjusting for many covariates [21]. In studies such as DAMeS and MAHWIS with greater cultural differences between populations (e.g., western, Middle Eastern, Asian), country differences remained significant, even in multivariate models, suggesting that indeed there may be true cultural differences, or at least that the relevant local biological factors have not yet been identified [50].

Cross-cultural differences in VMS are likely confounded by differences in important determinants such as hormonal, health, and lifestyle factors. Of the determinants examined by at least 3 studies (ie, denominator of 3 or greater in Summary column of Table 4), age, menopausal status and mental/physical health factors were significant in a majority of the studies. Few studies found significant relationships with the following: demographic variables such as education and employment status; lifestyle variables such as smoking, activity level and diet; and BMI. However, inadequate variation in variables such as BMI and activity level, and lack of statistical power, might explain these results. Additionally, in some studies the most appropriate variable may not have been examined: exposure to passive smoke might be more important than smoking (as in SWAN), and age^2 might be better than age (WISHeS).

Recommendations on study design and analysis are presented in **Table 5**. With the exception of hormonal data and objective measures of hot flushes, all of these recommendations can be easily followed in any study, thereby strengthening the field of menopausal research and facilitating cross-cultural comparisons. In choosing which

data to collect, researchers must evaluate issues and constraints such as: subject and researcher burden; invasiveness (eg, daily diaries may be more burdensome for some than wearing a HF monitor or having blood drawn); cost; questionnaire administration (ranging from postal questionnaires not requiring interviewer contact to those requiring blood samples, dietary assessments and objective HF measurements). For variables such as socioeconomic status and activity level, relative assessments (e.g., financial comfort, or ability to meet basic needs in local context) may be more useful than absolute numbers.

Non-vasomotor symptoms, such as psychological symptoms (eg, anxiety and depression), may influence VMS or be influenced by them (eg, night sweats may affect sleep). Thus even if the primary interest is VMS, collection of data on other symptoms is important. Future research should build on the foundational studies reviewed here and methodological recommendations proposed in this review and the Overview [31] , to identify local cultural and biological determinants that will explain more of the observed cross-cultural variability in vasomotor symptoms and experience.

List of Tables

Contributors and their role

Paper conception, review, data extraction, drafting of manuscript and preparation of tables were done by MKM. Critical review and editing was done MKM, DA, LLS, and CMO.

Competing interests

None of the authors have a conflict of interest or competing interests.

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