THE EVALUATION OF THE MENOPAUSE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE AND ASSOCIATION OF VASOMOTOR AND PSYCHOSOCIAL SYMPTOMS AMONG POSTMENOPAUSAL WOMEN IN THE UNITED STATES: A DISSERTATION

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ABSTRACT

KRISTEN BROOKE VAN DOLE: The Evaluation of the Menopause-Specific Quality of Life Questionnaire and Association of Vasomotor and Psychosocial Symptoms among Postmenopausal Women in the United States
Under the direction of Michele Jonsson Funk)

This dissertation provides an in-depth analysis of the evaluation of the Menopause-Specific Quality of Life (MENQOL) Questionnaire, a tool used by clinicians to understand women's symptomatology as they progress through the menopausal transition. While the MENQOL was rigorously developed through various methods, a factor analysis had never been conducted on the instrument. A factor analysis was conducted on this tool, using the existing version, and again with the existing version and additional vaginal health items. Results showed that the items in the instrument largely held to the domains under which they were intended. When the vaginal health items were added, a new domain of vaginal health items emerged.

There currently exists little literature which examines the explicit association between vasomotor and psychosocial symptoms among postmenopausal women. An additional aim of this dissertation was to examine this association using a longitudinal population-based study of postmenopausal women in the United States. Results showed that there was a small, statistically significant association between an increase in vasomotor symptoms and an increase in psychosocial symptoms.

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CHAPTER I

STATEMENT OF SPECIFIC AIMS

The quality of life among menopausal women has become an increasingly hot topic in recent medical and sociological research. Specifically, vasomotor and psychological symptoms remain at the forefront of common, bothersome symptoms which affect a woman's quality of life. As many as 95% of menopausal women may exhibit vasomotor symptoms, which may frequently disrupt work, sleep and other activities. Furthermore, psychological symptoms such as depression are common in as many as 60% of women going through the menopausal transition. The high prevalence of these two common and bothersome conditions make it important that more studies be conducted to explore the degree to which these symptoms are interrelated. Several instruments have been designed to evaluate the quality of life among menopausal women. However, many of these instruments are used in small clinic populations, and have not yet been evaluated for psychometric properties within a population-based sample.

The specific aims of this dissertation are:

1) Evaluate and Revise the Menopause-Specific Quality of Life (MENQOL) Questionnaire.

A. **Evaluate the efficiency of items in the original MENQOL instrument in a population-based sample.**

Rationale: The MENQOL instrument domains have never been evaluated in a population-based study. When used in a population-based sample, there may be symptoms that load differently than originally assigned when the MENQOL was developed. Some symptoms may not load well into any of the domains and other symptoms may load into different domains than their original assignment.

B. **Evaluate the contribution of six candidate items on vaginal health to the original MENQOL instrument.**

Rationale: The original MENQOL contained one vaginal symptom, "Vaginal dryness during intercourse", that was part of the "Sexual" domain. Six additional vaginal symptoms were appended to the end of the MENQOL in the Menopause Epidemiology (MEPI) Study to gather information on presence and amount of bother for these symptoms. Given that vaginal symptoms are physical in nature, but have sexual implications, these symptoms divided into both physical and sexual vaginal health domains.

The MENQOL instrument has been used as an outcome tool in clinic populations to demonstrate the impact of an intervention on quality of life. Yet, it had not been factor-analyzed in a population-based sample and many vaginal symptoms were not included. The objective of these analyses is to make the MENQOL more efficient through the use of factor analysis. We used these aims to help address the current limitations of the MENQOL and intended to make it as accurate, efficient and as meaningful as possible through the analyses described herein.

2) Evaluation of the Relationship between Vasomotor Symptoms and Psychosocial Symptoms over time. Is an increase in bothersome vasomotor symptoms over time associated with an increase in bothersome psychosocial symptoms over time?

Rationale: Other studies have looked at the relationship between vasomotor and psychological symptoms, yet no literature reports on the relationship between the two with respect to the degree of bother it causes the woman.

These aims were met via the use of the Menopause Epidemiology (MEPI) study. The MEPI Study was a population-based, cross-sectional study conducted in 2005 among a randomly selected group of 4,402 pre-, peri-, and post-menopausal women in the United States. These women were followed over time to 2007 and given another survey, providing longitudinal information. This study examined the prevalence and predictors of menopausal symptoms, and included several questions on the frequency, duration, severity, and degree of bother from hot flashes. Additionally, the MEPI questionnaires included the Menopause–Specific Quality of Life (MENQOL) Questionnaire, which provided the ability to conduct factor analysis on a population-based sample of women. The MEPI follow-up survey, conducted among the same women in 2007, enrolled 1,626 women aged 42-67 years who participated in the MEPI study to assess menopausal symptoms. I utilized the Menopause Epidemiology Study cohort and the follow-up to determine whether there was an association between bothersome hot flash and depressive symptoms, using the MENQOL, which contained both a vasomotor and psychosocial domain.

The contribution that this research could have on both healthcare providers and menopausal women is profound. The evaluation of the existing MENQOL instrument can allow researchers to remove items which were not be pertinent to a woman's quality of life, thus reducing the time and burden on the respondent filling out the instrument. Additionally, vaginal symptoms are also bothersome to menopausal women, so the potential inclusion of

these items to an existing QOL instrument may prove to be beneficial to a physician working with a menopausal woman to find the best treatment. Finally, the evaluation of both vasomotor and psychosocial symptoms leads to better understanding of the overlap of these conditions and may lead to better treatment practices and improved therapies for the future.

CHAPTER II

REVIEW OF THE LITERATURE

A. Introduction and Background

A woman transitioning through midlife may be experiencing many adjustments with family and work life and bothersome menopausal symptoms may only add to this burden and discomfort. During this transitory period, it is important to identify and counteract these bothersome symptoms where possible, through traditional medications or alternative medicine. Reducing the degree of bother from menopausal symptoms may greatly enhance the quality of life of the menopausal woman.

Quality of life of menopausal women has been the subject of controversial literature for a number of years and various instruments have been developed in an effort to define and quantify these symptoms (1). *Menopause* is defined as the day that is one year (365 days) after the last menstrual period. The time after this point is termed *post-menopause*. The *menopausal transition* is defined by the period of time prior to menopause when there is a gradual loss of estrogen after decreasing periods of ovulation. Symptoms that may accompany menopause include hot flashes, night sweats, depression and other mood disorders, vaginal atrophy, female sexual dysfunction, changes in skin (tone, appearance and elasticity) and weight gain. These symptoms may impact work, family life, and social settings. The objectives of this dissertation are to evaluate 1) the psychometric properties of the Menopause-Specific Quality of Life Questionnaire and 2) the association between bothersome hot flashes and depression.

The Menopause-Specific Quality of Life Questionnaire

The Menopause-Specific Quality of Life Questionnaire (MENQOL) was developed in 1996 as an instrument to measure menopausal symptoms and their associated degree of bother (2). Item formulation was based on existing literature, items on existing questionnaires on menopause-related quality of life, and the clinical experience of the investigators. Additional items were based on focus group discussion with eight women. This resulted in 106 symptoms generated by input from researchers and post-menopausal women.

To begin item reduction, 88 women were recruited from clinics via mailed questionnaires, newspaper articles and advertisements, and word-of-mouth. Eligible women were between the ages of 42 and 67 years, were two to seven years postmenopause, had not used hormone therapy in the previous six months and had an intact uterus. The participants were asked to rate whether or not they had experienced the symptom in the past month. If the answer was yes, then they were asked to rate the degree to which that symptom was bothersome on a 7-point Likert scale. The scale ranged from 0 (not at all bothered) to 6 (extremely bothered).

Development and Psychometric Properties of the MENQOL

The development of the MENQOL included designing the individual symptoms, and defining and scoring four domains based on these items. The authors of the MENQOL calculated *importance scores* for each item by multiplying the frequency that the symptom was reported and the mean bothersome score for that item for each of the 88 postmenopausal women that had taken the initial questionnaire. Each question was assigned to a domain which most closely represented a specific construct based on the authors' clinical experience. Four domains were created: vasomotor, psychosocial, physical and sexual. Items were ranked by importance scores and were removed if the

importance scores were too low (no threshold was given in the paper). Exceptions to this general rule were items that frequently appeared in the participants' responses but were not necessarily bothersome; these items remained in the questionnaire. There were several items in the sleep disturbances and joint and muscle aches that were redundant, so the item with the highest importance score was selected to avoid redundancy. The top three items in each domain, based on the importance scores remained in the questionnaire. The rest of the items were ranked by importance score from high to low and were added to the appropriate domains, resulting in the MENQOL contained 29 items.

Several different properties of the MENQOL were measured to determine validity and reliability. Face validity of the test was determined by asking a separate set of postmenopausal women if they felt the questionnaire assessed the intended concepts. Content validity to determine the importance of the items was assessed using ten experts in the field of menopause and quality of life. In order to determine construct validity, each domain was validated against an existing questionnaire which measured similar items. The vasomotor, physical, and psychosocial domains were validated using the somatic, psychosomatic and psychosocial subscales of the Neugarten and Kraines' Menopausal Symptom checklist (2). Discriminant validity was good in each of these cases, indicating that those who were not experiencing the problem would not be likely to select it ($p<0.001$). The psychosocial domain of the MENQOL was also validated against the General Well-Being Schedule (3). The sexual domain of the MENQOL was validated against Channon and Balinger's Vaginal Symptoms Score, also with good discriminant validity (2).

Test-retest reliability was measured via intraclass correlation coefficients and Pearson correlations. Intraclass correlation coefficients showed good stability over time for all domains except the Vasomotor domain, which the authors argue is an artifact of

the changing hot flashes frequency and degree of bother over time. Pearson correlation coefficients constructed against the other validated measures of menopausal symptoms were very high (all above 0.80). Internal consistency, measured by Cronbach's alpha, was also very high for each of the four domains.

The final Menopause-Specific Quality of Life Questionnaire contained four domains and 29 items, each on a Likert scale (Appendix A1).

Scoring of the MENQOL

The systematic scoring for each of the four MENQOL domains is identical. The seven-point Likert scale used during the administration of the MENQOL is converted for scoring and data analysis. For each of the 29 items, this seven-point Likert scale is converted to an eight point scale, ranging from 1 to 8. A "one" is equivalent to a woman responding "no", indicating she has not experienced this symptom in the past month. A "two" indicates that the woman experienced the symptom, but it was not at all bothersome. Scores "three" through "eight" indicate increasing levels of bother experienced from the symptom, and correspond to the "1" though "6" check boxes on the MENQOL. Once each item has been manipulated into a 1 – 8 score, each domain is scored by averaging the manipulated values. Hence, the average for each domain is constrained between 1 (not at all a problem; respondent selected "no" for each item in the domain) to 8 (respondent reported experiencing each symptom in the domain at the highest degree of bother) (Appendix A2).

Usage of the MENQOL

Traditionally, the MENQOL has been used in clinic-based populations among postmenopausal women with an intact uterus and naïve to hormone therapy (4-11). The

limitations of using the tool in these populations have been small sample sizes and lack of generalizability to a broader general population of post-menopausal women.

When used in clinical trials to compare the efficacy of a drug to either a comparator medication or placebo, the MENQOL has shown that estrogen and estrogen-like compounds are effective in reducing bothersome hot flashes (4, 5, 9, 12). The MENQOL has also been used in hospital-based cross-sectional studies using a small, convenience sample (13, 14). The use of the MENQOL in non-population-based studies has provided researchers with a large volume of information about quality of life of menopausal women, yet studies in population-based samples would further our knowledge of this topic.

Limitations of the MENQOL

The MENQOL has traditionally been limited by its lack of use in population-based studies. Though there is evidence that this is changing, given the increased use in other countries such as China and Chile, this instrument has yet to be used in a population-based sample of the United States (15, 16). Literature has supported the hypothesis that women of European descent differ from those in Asian and Hispanic cultures; thus, the generalizability of studies conducted outside the United States has little bearing on the understanding of quality of life among women in the United States (17). Additionally, authors of the MENQOL constructed the domains based on importance score and not by factor analysis. This method has been critiqued by other authors and is considered inferior when compared to the development of other instruments measuring menopausal quality of life (1).

It is an additional limitation that the finalized items in the MENQOL have been pre-selected by the instrument developers and that researchers do not have access to

the fully enumerated set of potential items, many of which did not make it into the final instrument, and all of which could have been used in factor analysis.

The Need and Significance for Further Evaluation of the MENQOL

The MENQOL is an informative tool that is designed to detect and discriminate between four domains representing different constructs of quality of life. This instrument has been used in various situations, typically pertaining to use in clinical trials. The Food and Drug Administration recently has exerted more control over surveys and questionnaires which could be treated as patient-reported outcomes (18). The enactment of this guidance occurred after the development of the MENQOL. The authors have determined that there are four constructs under which all 29 questions should fall; however, this was not determined by factor analysis, and is a limitation of the instrument's development. It was conceivable that more or fewer domains would be sufficient to explain the various constructs of quality of life among postmenopausal women.

The MENQOL has demonstrated the stability of some psychometric properties, but not all. Items that were selected in the early 1990s may not necessarily be of utmost importance to postmenopausal women's quality of life today. For instance, vaginal health is arguably a very important part of a woman's quality of life, yet it is captured only in one question relating to vaginal dryness during intercourse. For postmenopausal women who do not regularly engage in intercourse, the validity of this item is lost. Hence, it may be of use to evaluate whether or not the addition of such questions could help explain and evaluate quality of life among women eligible for the MENQOL.

The Epidemiology of Vasomotor Symptoms and Depression

The Epidemiology of Vasomotor Symptoms

Vasomotor symptoms including hot flashes, night sweats and sweating are among one of the most commonly reported symptoms among menopausal women. Hot flashes are a sudden sensation of warmth generally felt in the upper extremities and chest and are a common and bothersome symptom among peri- and postmenopausal women. Symptoms that may indicate a hot flash (or hot flush) include changes in the temperature of the finger, hand, calf and forearm, in addition to common symptoms found in the cheek, forehead and chest (19). Additionally, it has been noted that elevated core body temperature serves as a trigger for an upcoming hot flash (20). Vasodilation occurs following a hot flash, which may elicit shivering (21). Hot flashes have been found to follow a circadian rhythmic pattern, with most bothersome hot flashes occurring in the evening.

The etiology of hot flashes is not well known, other than the hypothesis that they occur due to reduced estrogen associated with the menopausal transition. Typically, hot flashes are a symptom caused by the decrease in estrogen, are hypothesized to manifest in a sharp peak soon after the last time of ovulation for a woman, and tend to decrease after a period of one to three years (22). Serotonin synthesis maintains the thermoregulatory system in the hypothalamus. A decrease in estrogen alters this thermoregulatory ratio between hyperthermic and hypothermic serotonin receptors, creating an unstable environment that is vulnerable to increased core temperatures and hot flashes (9).

The prevalence of hot flashes among menopausal women varies from study to study; a longitudinal study in Australia showed hot flash prevalence at approximately 27%; and a population-based study of US women yielded a prevalence of hot flashes of 75% among post-menopausal women 41-53 years old (19, 23-25). This prevalence may

be as high as 95% for women in menopause transition (ages 52-56 years) (26). These symptoms may be more prevalent among African American women, but such results are not substantiated by literature (27, 28). There are several risk factors/predictors of hot flashes: having a mother who experienced hot flashes, higher body mass index (BMI), tobacco use, tubal sterilization, age, residence at higher altitude, stress, and depression have all been shown to be associated with menopausal hot flashes (29-36).

Treatment of hot flashes has typically been with hormone therapy (37). However, after the Women's Health Initiative released results contradicting the previously reported cardiovascular benefits of Hormone Therapy (HT), the use of HT declined (38). Yet, there is evidence that shows that the timing of initiation of HT is important, and that women may still reap benefits from using hormones on a short term basis (39). In addition, complementary and alternative medicines are also used for the relief of hot flashes. Due to the thermoregulatory system being regulated by serotonin, several classes of antidepressants have been used to treat hot flashes, with moderate success (4, 6, 9, 12). Nearly three quarters of women would like to be able to take a nonhormonal agent that could reduce their bothersome hot flashes by 50% or more (40).

There is little disagreement that hot flashes occur naturally with the menopausal transition, but objective characterization for purposes of research has proved difficult. Some studies have measured the dichotomous existence of hot flashes (yes vs. no), as self-reported over the past month by study participants (41). Others have used a continuous outcome based on the number of hot flashes experienced in the past 2 weeks, known as a hot flash frequency score (28). Although the frequency score is more thorough than a dichotomous measure, both outcomes ignore hot flash severity. Another way of categorizing hot flashes would be to take into account the severity of each hot flash. This categorization has been used as an outcome in many studies and

seems to be a more effective way of measuring the impact on a woman's daily functioning (42).

Perhaps the most efficient and useful way of measuring hot flashes and the impact on quality of life is to measure the amount that a woman is bothered by hot flashes or night sweats. The Menopause-Specific Quality of Life Questionnaire measures the existence of, and degree of bother from, hot flashes, night sweats and sweating, along with many other common symptoms.

Epidemiology of Depression

Depression is marked by a loss of interest or pleasure in doing things, constant depressed mood, loss of appetite, sleeplessness, feelings of guilt or low self-esteem, poor concentration, and low energy (43). It has been noted that depression has a significant effect on quality of life, and that worldwide, it is the fourth leading contributor to the global burden of disease (43). Clinical diagnosis is typically made using the Structured Clinical Interview for DSM-IV validated scale to be administered by a clinician (44). Other tools have been produced to be administered in an interview of survey setting, such as the Edinburgh Depression Scale, and the Center for Epidemiological Studies- Depression Scale (45-50).

The prevalence of depressive symptoms during the menopausal transition is somewhere between 40 and 60 percent (26, 51). Women with a history of clinical depression or postpartum depression are at a higher risk for experiencing depressive symptoms during the transition into menopause (52-55). In general, depression is associated with reduced quality of life (56). Well-conducted studies have shown that depression, specifically in the years surrounding menopause, has a significant impact on physical and mental well-being (57- 58). Other literature has claimed that the menopausal transition has no effect on a decline in cognitive functioning (59). Several

medications have been successful in alleviating depression, such as bupropion, venlafaxine, sertraline, escitalopram and allopregnanalone (60-67). Some of these medications are also used, though not indicated for, the treatment of vasomotor symptoms. Also, regular exercise programs have been noted to help reduce depression among post-menopausal women (68).

Four theories have been posited that may explain the increased incidence of depression during the menopausal transition (69). The first, known as the *symptom hypothesis*, posits that increased vasomotor symptoms lead to depression. The second, *biochemical hypothesis,* argues that vasomotor symptoms are purely a mediator, and that the driving factor causing menopause-associated depression is merely the decreasing estrogen. The third hypothesis, *the psychoanalytic view,* maintains that depression is increased because the menopausal transition poses a threat to one's self-concept and role in life. The fourth, *social circumstances perspective,* states that an increase in depression during the menopause is purely coincidental and may not be attributed to anything specifically menopause-related.

While both hot flashes and depression are common symptoms during the menopausal transition, the actual mechanism by which the two may be related is unclear. Several studies have hypothesized various pathways, leading to a circumstance that is much like a "chicken or egg" situation. The longitudinal studies that could substantiate the temporal relationship are costly and inefficient and have not been done. However, it has been theorized that the changing levels of estrogen surrounding the menopausal transition may lead to increased vasomotor symptoms (hot flashes), which in turn, may increase the risk for depressive symptoms (27). Other studies have found no association between vasomotor symptoms and depression, but are limited by small sample sizes (35). Additionally, one study hypothesized that having low self-esteem made coping with bothersome hot flashes more difficult (70).

The Need and Significance for an Association Study

Literature has identified that hot flashes and depression are both common symptoms in menopause (20). There was a need to examine the association between these two conditions, especially since anti-depressants are currently being used to treat both depressive symptoms and hot flashes (71), yet are not as effective as hormone therapy for treatment of hot flashes. Hence, it was important to recognize that if there was an association, and if a treatment was effective for both symptoms it could lead to an increase in quality of life for a subset of women transitioning through menopause.

Literature that assesses the specific overlap and association between the two was sparse and contradictory. A study using factor analysis on menopausal symptoms found that two distinct domains emerged: Vasomotor and Psychosocial domains (27). This study showed that the Vasomotor domain was more strongly associated with perimenopausal women and the Psychosocial domain was more strongly associated with postmenopausal women. In contrast, other studies which conducted factor analysis showed that some domains of health-related quality of life are affected by the menopausal transition, but the psychosocial symptom domain was not one of them (72-73).

Menopausal symptoms, such as hot flashes and depression, that are both highly prevalent are necessarily (though not sufficiently) associated. Studies have suggested that prior psychological issues, health related behaviors, socioeconomic status and a woman's attitude toward menopause may be potential effect measure modifiers or confounders (10, 24, 73). This study controlled for many potential confounders and consider potential effect modifiers, as had not been previously done, in an attempt to evaluate the association more rigorously. This is especially important given that depression and hot flashes are two of the most common menopausal symptoms (41, 74).

It was hypothesized that vasomotor and psychological symptoms were linked via the conceptual mechanism shown in Figure 1. All women in this study were postmenopausal, and were considered "at risk" for hot flashes and depression. To our knowledge, the specific link between the vasomotor and psychological domains had never been examined using the MENQOL Questionnaire, despite the fact that it is a well known, validated instrument. We hypothesized that, over time, there was a distinct and direct relationship between increased vasomotor symptoms and subsequent psychological symptoms.

Summary

The Menopause-Specific Quality of Life instrument is a valuable tool that was used to evaluate the existence and severity (via bothersome score) of menopausal symptoms. While this instrument was created with the experience of many experts in the field, some symptoms, such as vaginal health, were potentially not captured well with this tool and other symptoms in the instrument were either ambiguous or redundant. Evaluating the efficiency of items in this tool through factor analysis was one objective of this dissertation. The results of this factor analysis, which had previously never been conducted on the MENQOL, adds great amount of knowledge to the field.

The MENQOL instrument also provided a useful way of evaluating the association between vasomotor symptoms and depression because various components of psychological health and vasomotor symptoms are included. Longitudinal analysis using the Menopause Epidemiology (MEPI) Study allowed me to explore the temporal relationship between these symptoms. Understanding in more detail the impact that menopausal symptoms have on quality of life, and the association between specific symptoms, now provides researchers and physicians with a better picture of the impact of menopausal symptoms on daily life and may help guide treatment.

CHAPTER III

METHODS

A. OVERVIEW OF METHODS

We evaluated the appropriateness of the Menopause-Specific Quality of Life Questionnaire (MENQOL) in a population-based sample of women aged 40-65 years in the United States. To do so, we explored this instrument using factor analytic methods. Factor analysis, the standard by which many patient-reported instruments are constructed, had never been conducted on the MENQOL. This resulted in a gap in the literature that was easily filled by this study. The factor structure relating to each MENQOL item was challenged and developmental theories behind this covariate structure was tested. We explored both the factor and covariate structure of the original MENQOL instrument and appended items relating to vaginal health. This research added extensive knowledge to existing literature with respect to items that were appended or removed from the original instrument.

We also evaluated the relationship between vasomotor symptoms and psychological symptoms over time. This was done using data from both the initial and follow-up Menopause Epidemiology Study. Data on women were collected at two time points, in 2005 and 2007. Longitudinal linear models were constructed to relate changing vasomotor scores from the MENQOL to changing psychosocial domain scores. Covariates that modified or confounded this relationship were explored.

B. STUDY DESIGN

The Menopause Epidemiology Study

The Menopause Epidemiology (MEPI) Study is a population-based, cross-sectional study designed to evaluate the prevalence and characteristics of menopausal symptoms among women 40-65 years old. Participants were recruited from the KnowledgePanel[SM] held by Knowledge Networks. The KnowledgePanel[SM] is based on random digit dialing (RDD) and probability sampling. Those recruited by the KnowledgePanel[SM] who currently do not have Internet access were provided access free of charge. Hence, this was not a convenience sample of Internet users and has been shown to be representative of the United States population (Table 1).

The survey was self-administered and participants were allowed to pause and continue the survey at their convenience. Data was collected electronically as the participant advanced through the Internet-based survey. Data collection took place nationally between April 1, 2005 and April 20, 2005.

The MEPI study investigators invited 6,201 women to participate, who were randomly selected from the approximate 11,400 women aged 40 to 65 years old in the KnowledgePanel[SM]; 1,278 women did not reply to the emailed invitation, 293 did not consent to the study, and 228 were ineligible (did not have a period in the previous 12 months due to: a pregnancy in the last year, intra-uterine device, chemotherapy, strenuous exercise, anorexia, or other medical condition). This left 4,402 women in the MEPI Study population (Figure 2).

Menopausal status was identified as pre-menopausal (n=1,267, no irregular periods in the previous 12 months, peri-menopausal (n=432, irregular periods less than 12 months), or post-menopausal (n=2,703, cessation of menses for 12 months or longer). Data for this study was restricted to postmenopausal women only.

The Menopause Epidemiology Follow-up Study

Following the data collection from the Menopause Epidemiology Study, a follow-up study was conducted two years later in the same manner with women who had been participants in the first study. Retention was approximately 60% between the two phases. For the longitudinal analyses to be explored among this population, all eligible postmenopausal women who completed both the initial and follow up questionnaires were analyzed (n=1,506). Statistics comparing the two MEPI populations are shown in Table 1. KnowledgePanel^{SM} panel members were enrolled on the panel for 3 years total, after which they were released from the Panel. Thus, some of the loss of follow-up between the two phases of the study is likely to have occurred at random due to participants' completion of panel participation.

C. METHODS

C.1 Aim #1 Methods

Factor Analytic Methods

Factor analysis is a method of examining the degree to which various items in a questionnaire cluster together, or *factor*. A *factor* is a representation of a specific construct. Factor analysis seeks to look at the degree of covariance among questionnaire items that may in turn be expressed via a smaller number of constructs (factors). The covariance structure between the items can be used to determine how many factors can be extracted from a set of questionnaire items, as tightly correlated items may often represent the same construct.

Factor analysis may be *exploratory* or *confirmatory* in nature. Exploratory Factor Analysis (EFA) seeks to eliminate items which do not factor well into any one given construct and is typically used during instrument development. That is, once an EFA is

conducted, items which appear to not factor well and are not correlated with other items may be eliminated from future versions of the instrument (75).

Confirmatory Factor Analysis (CFA) is a theory-testing method used once an instrument has already been developed and tested in a population to determine whether the properties and factors in a pre-established theory hold in an external population. It is assumed that each variable within an instrument has a known factor with which it should cluster.

Eigenvalues and Factor Extraction

There are two commonly used methods to determine how many factors are needed in a factor analysis: The Eigenvalue Rule, and scree plots. Eigenvalues in factor analysis are values that represent the amount of variability explained by the factor. In the Eigenvalue Rule, the number of factors to extract from a model is sometimes based on the number of factors with eigenvalues greater than 1.0. However, this method, while frequently used, can be too liberal and lead to too many factor being extracted (76). Scree plots are a graphical representation of each factor and are another method of factor extraction (77). The factor extraction theory which uses scree plots implies that the total number of factors to be extracted is based on the function of the chart in which an elbow appears (Figure 3). This elbow shows a sharp distinction between the number of factors that should be kept, and the number of factors which do not add enough to the explanation of variance.

Parallel Analysis

When the number of factors to extract is difficult to determine via standards such as the Eigenvalue Rule or Scree plots, Parallel Analysis is sometimes used. Whereas the Eigenvalue Rule works best on very large samples as the size reaches infinity, parallel analysis overcomes this limitation and is easily used in smaller samples (77).

Parallel analysis takes the same sample size and constructs a number of correlation matrices among random variables and compares them to the variables in the dataset. Factors associated with the actual eigenvalues that exceed those associated with the randomly generated eigenvalues are kept. For this analysis, parallel analysis was run using 100 iterations to determine the most appropriate number of factors to extract.

Orthogonality and Factor Rotation

The rotation of factors in factor analytic methods serves to provide the researcher with more interpretable factors. Rotation will often alter factor loadings and change the percentage of variance explained by each eigenvalue. Several types of rotation exist, and can be chosen based on the orthogonality of the factors. Orthogonality is determined by the degree of independence between factors. Perhaps the most conservative approach to factor rotation would be to assume complete independence between factors and to choose a *varimax* rotation. While other methods of factor rotation will create a factor correlation matrix, varimax will not, because of the assumption that each factor's correlation with any other factor is precisely 0. A varimax rotation will provide high loadings on the relevant construct and low loadings on other factors, resulting in fewer cross-loadings and factors which are more interpretable.

However, it is often difficult to assume complete independence of factors, which makes *promax* rotation an efficient alternative. *Promax* rotation is an oblique rotation which measures interfactor correlations before outputting a factor structure. Examining these interfactor correlation coefficients can help to determine whether or not an oblique rotation is needed. For instance, correlation coefficients in the order of 0.15 tell us that we are not gaining much with an oblique rotation (and that the factors are not tightly correlated) and we can be safe with an orthogonal rotation.

Item Reduction

Factor loadings were determined by the standardized regression coefficients. Items were considered candidates for exclusion if the associated factor loading was less than 0.40 (78). Items were also deleted if they loaded on more than one factor, indicating ambiguity.

Aim #1a. Evaluation of Menopause Specific Quality of Life (MENQOL) Questionnaire.

To evaluate the appropriateness of the MENQOL in a population-based sample, both exploratory and confirmatory factor analysis were used. The authors who developed the MENQOL previously determined that four domains (Vasomotor, Psychosocial, Physical, and Sexual) were sufficient to explain the constructs bound by the 29 MENQOL items. The a priori hypothesis was that the items would filter into the domains as shown in Table 2.

Data Analysis

Data analysis for this aim was conducted using the 2,703 postmenopausal women from the initial Menopause Epidemiology Study. These women were randomly split into two equal groups based on a uniform distribution. Doing this avoided overfitting a model to the data. Factor analysis was performed on one group, tested on the other group, and finally reported for the group as a whole.

Factor analysis was conducted in a exploratory nature, and factors were extracted using scree plots, the Eigenvalue Rule, and Parallel Analysis. This approach used an oblique rotation for factor extraction, as complete independence between domains could not be assumed. Reliability coefficients were calculated for each domain; those domains with coefficients exceeding 0.70 were considered to have good reliability (79).

It was expected that the sexual and vasomotor domains would cluster well, based on the small number of items within each domain. Items that did not correspond to the domains under which they were created were explored in further detail and potentially dropped according to the aforementioned criteria. The goal for this analysis was to examine how well each item in the MENQOL holds to its theorized domain in a population-based study of postmenopausal women.

Aim #1b Potential Revision of the Menopause-Specific Quality of Life (MENQOL) Questionnaire.

Vaginal symptoms are also very common among women transitioning through menopause (25). These symptoms have implications which affect a woman's quality of life. Prevalence estimates for vaginal symptoms range from ten to fifty percent (24, 80-87). Common symptoms include vaginal itching, irritation, dryness, and dyspareunia, but many women may not be symptomatic (88).

Given the high prevalence of bothersome vaginal symptoms during the menopausal transition, there is great potential for these symptoms to affect a woman's quality of life. The Menopause Epidemiology Study explored this possibility by adding six items to the existing MENQOL questionnaire relating to vaginal health, shown in Table 3. Each item was asked in the same manner as the original MENQOL instrument; respondents first were asked to indicate whether they had experienced the problem in the past month (yes/no); if so, respondents rated the degree of bother on a scale from 0 to 6. These values were then rescaled on a 1 to 8 scale, with 1 indicating 'symptom not experienced', 2 indicating 'symptom experienced but was not bothersome' and 3 through 8 indicated the 'symptom was experienced' with increasing levels of bother (Appendix A-2).

These items were explored using an exploratory factor analysis because these items have never been examined in conjunction with the MENQOL before. They had the

propensity to factor in several different ways, some of which are shown in Table 4. Similarly to Aim #1a, this analysis was also conducted on a split sample.

The number of factors extracted from this analysis was assessed in several ways. First, SAS default settings allowed for an initial look at the factoring structure without restraints. Next, the number of factors extracted was restricted by using scree plots and traditional eigenvalue thresholds to examine if the vaginal symptoms factored into one (or several) of the existing domains. Third, parallel analysis was used to determine the appropriate number of factors to extract. Varimax rotation was used to reduce the propensity for items to cross-load on multiple factors.

The results from the first aim helped determine if items were kept or removed from the existing MENQOL. The second part of this aim was to restructure the original MENQOL, incorporating vaginal symptoms into the questionnaire where appropriate, and deleting items which did not load well.

C.2 Aim #2 METHODS

Aim #2. Evaluation of the Relationship between Vasomotor Symptoms and Psychosocial Symptoms over time.

A longitudinal analysis was conducted to explore the relationship between change in vasomotor symptoms and a change in psychosocial symptoms. Using the MENQOL instrument the two domains of focus were the vasomotor symptom domain and the psychosocial domain, controlling for a variety of related covariates. To do this, we employed a change-score method for outcome of psychosocial symptoms, while controlling for baseline psychosocial score as an independent variable. This method allowed us to examine the association between a change in vasomotor symptoms (either an increase or a decrease) with change in psychosocial domain scores from the MENQOL.

The overall function that this analysis followed was:

ΔPsychosocial Domain =

Δ VMS[1] Domain + Baseline Psychosocial score + Baseline VMS score + Covariates

This formula deviates slightly from what has been taught in traditional longitudinal epidemiology studies in that this analysis was not restricted to those without psychosocial symptoms in baseline. Instead, baseline psychosocial score was controlled for, which will allow us to see if there is a relationship with respect to not only an increasing psychosocial score, but a decreasing one as well. Restricting to a population without any psychosocial symptoms at baseline would have only allowed us to see how the change in VMS domain score was associated with an increase in psychosocial score.

The main analysis for this aim was conducted using a linear regression, as maintaining the continuous nature of the outcome provided the most statistical power. However, the relationship was also explored using a dichotomous outcome variable using a cutoff of a 1.5 unit change to verify the results of the linear model.

Outcome Assessment

Psychosocial symptoms were defined using the MENQOL scoring algorithm. The psychosocial outcome was explored using scoring that was both continuous and dichotomous. Continuous scoring for the psychosocial domain change score was constructed by subtracting the baseline psychosocial domain score from the follow up psychosocial domain score and ranged from -7 to 7.

For the dichotomous outcome scoring, a cutpoint was placed to divide women who had a positive change greater than or equal to positive 1.5 units on the change score for psychosocial symptoms. This resulted in an approximate ten percent cutpoint

[1]VMS = Vasomotor Score

and made logistic regression an appropriate decision. Because literature had not yet established a longitudinal study in which the MENQOL has been assessed over time, this cutpoint seemed the most appropriate way to dichotomize this outcome.

Exposure Assessment

*V*asomotor symptoms were evaluated using the MENQOL scoring system for both the initial and the follow up study. This continuous outcome was constructed by subtracting the baseline vasomotor domain score from the follow up vasomotor domain score and had a range spanning -7 to positive 7.

Effect Measure Modification

Covariates from the baseline survey were used to assess potential effect measure modification. The relationship between change in vasomotor domain score and change in psychosocial domain score were assessed within each level of each covariate to explore potential modifiers via stratification. To assess any potential interaction, *a priori* p-values were set at 0.10 for interaction terms in linear regression with the covariate*exposure terms.

For the logistic modeling, effect measure modification was assessed between the covariates and the exposure using the Breslow-Day test of homogeneity. An *a* priori *p*-value was set at 0.20 to determine if the covariate is an effect measure modifier for inclusion into the initial model (89).

Confounding

Covariates that were determined to be effect measure modifiers remained in the model with their associated interaction terms for the logistic regression model. Other covariates which did not meet the criteria for effect measure modification were then assessed for confounding. Confounding was determined in three ways- via the relationship between covariate and exposure, covariate and outcome, and via a directed acyclic graph (Figure 4) (90). The directed acyclic graph showed that all covariates lie

on unblocked back-door paths; thus, all covariates contained within the figure were evaluated for potential confounding and included in the full model.

Table 5 depicts the potential confounders for this analysis and their respective distributions. Potential confounders were broadly lumped into the following constructs: demographics (age, race, income, marital status, and BMI), behavioral (physical activity and tobacco use), healthcare-related (hormone therapy, depression medication use) and reproductive (parity, hysterectomy, years since menopause), in addition to baseline VMS score, and baseline psychosocial score (Appendix A3). Age, Body Mass Index, and years since menopause were assessed in the baseline survey continuously. These variables were evaluated for normality via historgrams and remained continuous for this analysis. All other covariates were categorical in nature.

The following covariates from the baseline survey were eliminated for the following reasons: history of depression, and healthcare seeking for depression (high correlation with baseline psychosocial score), breast cancer (small n), healthcare seeking for hot flashes (high correlations with baseline hormone therapy use), and female sexual dysfunction (no relation to the exposure).

Modeling Strategies

The relationship between vasomotor change score and psychosocial change score was primarily evaluated using a linear regression model, controlling for potential effect modifiers and confounders. To confirm the results of the linear regression model, a logistic regression model was also used. The outcome of change in psychosocial domain score for this logistic model was coded using a cutoff value of +1.500 units or greater, versus 1.499 or less. In each model, a backward elimination approach was used, with a user-selected elimination based on highest p-value.

To examine the potential for confounding, covariates which alter the crude estimate between change in vasomotor domain score and change in psychosocial

domain score by more than ten percent will be considered confounders, and remain in the model (91). Traditionally, this process is iterated until only important covariates remain in the model. However, recent papers argue that if nonsignificant covariates do not alter the precision of the main effect, it is suitable to retain them in the model (92).

Assessment of Missingness and Loss to Follow-up

For this analysis, formal assessment of missingness was not necessary. The computer-automated nature of the MEPI provides hard prompts to the respondents when an item is requested to be skipped. These hard prompts, while a second attempt to skip was successful, generally resulted in the respondent choosing an appropriate response. There were few covariates with any missing data, and those with missing data were less than five percent. Hence, a strict analysis of missing data (multiple imputation) was not needed here. Missing values remained missing and were not imputed.

To evaluate the potential impact loss to follow-up, an analysis of baseline demographics and characteristics was conducted to examine those women who were postmenopausal at baseline and did not complete the follow-up study. There was a similar distribution of all characteristics found (Appendix A4). Hence, there was no reason to believe that our sample behaved any differently than the women who could have been eligible for participation in the follow-up study.

Outliers

Five respondents were excluded from this analysis based on the value of their BMI being an extreme outlier. Having a BMI less than 15 with extreme height and/or weight values, such as women reporting height greater than 7 feet with an associated weight of 130 pounds were determined to be improbable and were excluded. Likewise,

women reporting a very short stature such as height less than 4 feet tall and an associated weight of over 250 were also excluded. There were no other outliers found in this dataset among covariates.

Sensitivity Analyses

There were several sensitivity analyses that were conducted in this study to explore the relationship of vasomotor symptoms on psychosocial symptoms. Despite the fact that hormone therapy and depression medication were not found to be effect modifiers, we also ran this model among those on and off hormone therapy and those one and off depression medication. Additionally, I ran a fifth model on those not taking hormone therapy or depression medications. All of these populations had similar demographic distributions as the study population (Appendix A5).

The outcome of psychosocial symptoms encompasses more than just depression. To get a better understanding of how a change in vasomotor domain score effects the single item "Feeling Down, Depressed, or Blue" from the MENQOL, I additionally examined a model just on that one item (Appendix A6).

D. POWER AND SAMPLE SIZE

Categorical Outcome

Statistical power for this aim was estimated using PS Power and Sample Size Calculator, version 2.1.3, 1997 (93). The power for main effects in the MEPI population was estimated using an alpha level at 0.05, with a fixed sample size of 1,506. Assuming 0.23 probability of increase in hot flash among those with no change or decrease in psychosocial domain score with 313 participants with increasing vasomotor score, and a ratio of increasing psychosocial domain score vs no change or decrease at 8.91, there is greater than 90 percent power to detect an odds ratio of 1.30. We may maintain

greater than 80 percent power detecting an odds ratio as small as 1.20. Table 6 shows alternate power calculations with a fixed sample size, using various expected effect sizes.

Continuous Outcome

By measuring the change in psychosocial score domain continuously, we can calculate statistical power by estimating the difference in the change in mean domain scores, using a categorically scored change in vasomotor domain score. Using an alpha level of 0.05, and a fixed ratio of those in increased vasomotor scores as compared to no change or decrease in vasomotor scores of 0.65 (with 899 with increased vasomotor score), and a standard deviation of 1.3 for the distribution of the continuous change in psychosocial domain score, we have over 99% power to detect a 0.5 unit change in psychosocial domain score. Table 7 shows alternate power calculations for various unit changes in psychosocial domain score

CHAPTER IV

RESULTS

A. Paper 1: The Evaluation and Revision of the Menopause-Specific Quality of Life Questionnaire: A Factor Analytic Approach.

Potential Journals for Submission: *Menopause, Maturitas*

B. Paper 2 : The Longitudinal Association Between Vasomotor Symptoms and Psychosocial Outcomes among Postmenopausal Women in the United States: a Population-Based Study.

Potential Journals for Submission: *Menopause, Climacteric, Maturitas*

Paper 1: The Evaluation and Revision of the Menopause-Specific Quality of Life Questionnaire: A Factor-Analytic Approach

Running title: Revision of the MENQOL

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ABSTRACT

Objective*:* Despite being used in multiple studies, the Menopause-Specific Quality of Life Questionnaire (MENQOL) has not been assessed with factor analysis, a common method of item reduction in quality of life tools. We also assessed the benefit of adding six candidate vaginal health items to the existing instrument.

Design: The Menopause Epidemiology Study is a cross-sectional population-based study of women 40-65 years old in the United States chosen from a source population selected by random digit dialing and probability sampling. We focused on 2,703 postmenopausal women for our analyses. Prior to analysis, and to prevent model overfitting, we split our sample into two equal groups using a uniform random sample. Using parallel analysis for factor extraction, we performed confirmatory and exploratory factor analysis on the MENQOL to examine the current factor structure and to evaluate the candidacy of six new items appended to the current MENQOL. Reliability coefficients were calculated for each of the new domains.

Results**:** With few exceptions, the items from the original MENQOL factored into the domains under which they were originally placed. Five items were suggested for removal based on crossloading across domains (Difficulty Sleeping, Poor Memory, Accomplishing Less than I Used to, Changes in Appearance Texture or Tone of my Skin, and Feeling Tired). Reliability coefficients for the four original domains were acceptable: Vasomotor, 0.86; Psychosocial, 0.84; Physical, 0.86; and Sexual, 0.78. When six vaginal health items were added to the MENQOL, one was a candidate for exclusion based on poor factor loading (Vaginal Bleeding on Sex). The other five items went into two domains, one into sexual (Vaginal Pain on Sex) and the other four into a new domain. Reliability statistics for this five factor model were also acceptable: Vasomotor, 0.86; Psychosocial, 0.84; Physical, 0.86; Sexual, 0.77; and Vaginal Health 0.67.

Conclusions: Results from factor analysis indicate that the MENQOL would be strengthened by elimination of five original items and the addition of five vaginal health items.

INTRODUCTION

Menopause-related symptoms such as hot flashes, night sweats, weight gain, and decreased sexual functioning all have negative impacts on quality of life, and affect daily activities such as sleep, work, and leisure activities (94). Health-related quality of life among menopausal women has long been a controversial topic in published literature. Several instruments have been developed in an attempt to quantify these symptoms (1).

The Menopause-Specific Quality of Life (MENQOL) instrument was developed in 1996 and has been used in various clinic and ethnic populations (4-11). A 29-item questionnaire, the MENQOL aims to capture health-related QOL in areas centered around vasomotor, physical, psychosocial and sexual functioning (2). One of the strengths of the MENQOL is its ability to not only gauge the frequency of these menopausal symptoms, but also to capture the degree of disruption in the woman's life in the previous 30 days due to the menopausal symptoms. Additionally, the MENQOL scoring is standardized among domains, because of the discordant number of items within each domain, creating the ability to draw comparisons between the different factors and their impact on a woman's quality of life.

However, one of the limitations of the MENQOL that has been cited in literature is the lack of factor analytic methods performed on the instrument, a common method of item reduction of quality of life tools (95). Additionally, the MENQOL in its current form does not capture many symptoms related to vaginal health, despite recent literature indicating that such symptoms may be strongly related to health-related quality of life (95). Vaginal symptoms such as vaginal itching, irritation, dryness, and dyspareunia are very common among women transitioning through menopause, with prevalence

estimates ranging from ten to fifty percent (24, 25, 80-88). These symptoms may also negatively impact quality of life (94).

While widely used and accepted as a quality of life instrument among postmenopausal women, this is the first study that performed a factor analysis on the MENQOL instrument using a population-based study of postmenopausal women in the United States. Furthermore, this study assesses the value of augmenting the existing instrument with vaginal health items using exploratory factor analysis. Proposed vaginal health Items assess dryness, irritation, itching, difficulty urinating, and pain during sexual activity. These items are not currently captured in the existing MENQOL instrument and were therefore evaluated for potential inclusion. The overall objective of this study was to evaluate the items in the MENQOL and suggest revisions to the tool based on factor analysis.

METHODS

Study population

This study population included the postmenopausal women from the Menopause Epidemiology (MEPI) Study, which is a population-based, cross-sectional study of women in the United States aged 40-65 conducted in April 2005 (94, 96). The source population for our study was the Knowledge Networks (KN) panel, which was selected by random digit dialing and probability sampling. Individuals who did not have access to the Internet were provided with free Web-TV and Internet service upon enrollment into the panel. Because of this enrollment process, the KN panel is a reasonably representative sample of the US population and is not a convenience sample of Internet users (97).

When participant selection for the study began, there were approximately 11,000 women aged 40-65 years on the Knowledge Networks panel. Just over six thousand (n=6,201) women were randomly selected from this group and invited to participate in

the MEPI study. There were 4,923 (79%) women who replied and 4,630 (75%) who consented to the study. Exclusion criteria included missing periods in the last 12 months due to pregnancy, breastfeeding, intra-uterine device, chemotherapy, strenuous exercise, anorexia, or other medical condition that resulted in lack of a menstrual period other than menopause. After exclusion criteria were applied, 4,402 women remained in the full MEPI study. Postmenopausal status was defined by self-report of not having a period in the past 12 months (n=2,703) and included both naturally and surgically menopausal women. Our analyses focus on these 2,703 postmenopausal women. As part of our study, these women were administered the most current 29-item MENQOL at the time of the study period in 2005 (2).

Factor analysis is used to examine the degree of covariance among questionnaire items that may in turn be expressed via a smaller number of constructs (factors). The covariance structure between the items can be used to determine how many factors can be extracted from a set of questionnaire items in light of the fact that tightly correlated items may often represent the same construct. Factor analysis may be *confirmatory* or *exploratory* in nature. Confirmatory Factor Analysis (CFA) is a theory-testing method used once an instrument has already been developed and tested in a population to determine whether the properties and factors in a pre-established theory hold in an external population. Exploratory Factor Analysis (EFA) seeks to eliminate items which do not factor well into any one given construct and is typically used during instrument development. That is, once an EFA is conducted, items which appear to not factor well and are not correlated with other items may be eliminated from future versions of the instrument (75).

This study was conducted in two phases; first using confirmatory factor analytic techniques on the existing instrument and the second using exploratory factor analysis to evaluate the candidacy of six additional vaginal health items.

Phase I – Confirmatory Factor Analysis

Prior to performing the analysis, we randomly split the sample into two equal groups to prevent model overfitting. By splitting the sample randomly and performing the factor analysis on each half and comparing results, we were able to confirm that the extraction and item reduction was valid. To determine the number of factors to extract, two methods were used: scree plots and parallel analysis. Scree plots were constructed and evaluated for a clear break in the amount of variability explained by the factor. Additionally, we used the Eigenvalue Rule as a guide to retain the number of factors with associated eigenvalues greater than 1.0. However, this method, while used frequently, is not conservative and can lead to the suggestion of too many factors (76). In such cases, parallel analysis may provide a more accurate representation of the appropriate number of factors to extract (77).

Factor analysis was conducted among each half of the sample using an oblique factor rotation and promax solution allowing non-independence in the correlation between the factors. Items with loading less than 0.40 were considered weak and were removed from subsequent factor analyses. Items that cross-loaded across more than one factor were considered candidates for exclusion from further factor analyses. The two samples were compared for agreement and then the factor analysis was conducted on the full sample. Once the final factor structure was determined, reliability coefficients were calculated for each factor for all women in the study population.

Phase II – Exploratory Factor Analysis

To begin this phase of the study, we began with the restricted version of the MENQOL as found in Phase I. To evaluate the candidacy of six vaginal health items, we asked the study population about recent (within the last 30 days) vaginal itching, irritation, pain, difficulty or burning during urination, vaginal pain associated with sexual activity, vaginal bleeding associated with sexual activity, or vaginal discharge. These

items were asked in the same manner as MENQOL items and scored identically. We then treated these items as if they were a part of the instrument and evaluated how they factored among the other items.

We conducted an exploratory factor analysis in the same manner as the first phase of this study. Items loading less than 0.40 and those that cross-loaded were considered candidates for exclusion from the overall instrument. Reliability coefficients were also constructed for the finalized version of the MENQOL with the added vaginal health items.

RESULTS

Table 8 shows basic demographics of the overall Menopause Epidemiology Study and the subset of postmenopausal women from the MEPI study as compared to the Current Population Study (97). The Menopause Epidemiology study is a fairly representative sample of women aged 40-65 in the United States (96). Compared to the US population, there is a slightly smaller percent of women 40-44 years old which is likely due to the MEPI exclusion criteria of pregnancy, breastfeeding, and IUD use. There were fewer women in MEPI with less than a high school diploma, which is indicative of a slightly more educated population than the United States.

In the analyses presented here, 84.0% (n=2,270) were aged 50 years or older, slightly more than three quarters (80%, n=2,171) were of White/Non-Hispanic race/ethnicity, and 23% (n=619) held a Bachelor's or higher degree (Table 8).

Phase I

Parallel analysis suggested the extraction of four domains from the existing MENQOL instrument (77). With few exceptions, the items in the MENQOL overwhelmingly factored into the domains under which they were placed originally. The vasomotor domain contained its original items (hot flashes or flushes, night sweats and sweating) and the sexual domain contained its original items (avoiding intimacy,

decreased sexual desire and vaginal dryness). The psychosocial domain contained all of its original items with the exception of one: 'Accomplishing Less than I Used To' did not load into the Psychosocial domain. It instead loaded into the physical domain. All other items from the physical domain remained the same.

With a four factor extraction from the study sample, one item was a candidate for exclusion based on item loading less than 0.40 (Difficulty Sleeping, item loading: 0.29) (Table 9). Several other items were poor items based on crossloading across factors: 'Feeling Tired or Worn Out', 'Accomplishing Less Than I Used To', 'Changes in Appearance, Texture or Tone of your Skin', 'Difficulty Sleeping', and 'Poor Memory'. These 5 items were removed from the questionnaire, and the data were re-analyzed. After the removal of these 5 items, the remaining items factored well with similar factor loadings; not further item reduction was required.

The revised factor analysis showed that the remaining items clustered well under the domains in which they were originally placed. These clusters were then tested on the other random half of the sample, and additionally on the full sample. Table 3 shows the results as tested on the full sample of postmenopausal women.

Reliability

Reliability coefficients were constructed for each domain of the revised MENQOL. Cronbach's Alpha statistics were acceptable for each of the domains (Table 10). The sexual domain alpha was 0.78, the physical domain alpha was 0.86, the vasomotor domain alpha was also 0.86, and the psychosocial domain alpha was 0.84.

Interfactor Correlations

The correlations between factors are shown in Table 11. These results indicate moderate degree of correlation (0.3-0.5) between the factors and confirms that the oblique rotation was appropriate.

Phase II

An exploratory factor analysis was run in Phase II to evaluate the candidacy of six vaginal health items to the revised MENQOL questionnaire found in Phase I. Similarly to Phase I, these analyses were run on each half of a uniformly randomized split sample, and again on the sample as a whole. The six vaginal health items included 'Vaginal Irritation', 'Vaginal Itching', 'Vaginal Discharge', 'Vaginal Bleeding on Sex', 'Vaginal Pain on Sex', and 'Vaginal Pain, Difficulty or Burning During Urination'.

Since it was unclear how many factors we should extract with the additional items, we again used parallel analysis to guide extraction techniques. Based on the parallel analysis results, five factors were extracted.

Table 12 shows the factor loadings for the revised MENQOL from phase I with the addition of the six vaginal health items. The supplemental items did not all factor into one additional domain; two of the items factored into the sexual domain and the other four clustered into a new domain. 'Vaginal Pain on Sex' and 'Vaginal Bleeding on Sex' clustered on the Sexual Domain, although the loading on 'Vaginal Bleeding on Sex' was under 0.40 and was therefore a candidate for elimination (Table 12). The other four items, 'Vaginal Irritation', 'Vaginal Itching', 'Vaginal Discharge, and 'Vaginal Pain, Difficulty and Burning During Urination' constituted a new Vaginal Health domain.

'Vaginal Bleeding on Sex' was eliminated from the revised MENQOL and the data were re-analyzed. Without this item, the rest of the items held firmly to the same domains with good factor loadings (Table 13).

The data in Table 13 show what we consider to be the final, revised MENQOL, eliminating the original ambiguous items and adding in the pertinent vaginal health items. The subsequent five appended vaginal health items clustered into two domains, 'vaginal pain on sex' with the sexual domain, and the others into a new domain (Vaginal Health).

Reliability

Reliability for each of the five domains for the revised MENQOL was also acceptable. The vasomotor and physical domains each had reliability coefficients of 0.86, the psychosocial domain had a reliability coefficient of 0.84, and the sexual domain with the added item had reliability of 0.77. The new domain, comprising the remaining appended vaginal health items, retained a coefficient of 0.67, slightly lower than the standard 0.70 recommended for adequate reliability (79).

Interfactor Correlations

Interfactor correlations are shown for the five-factor MENQOL in Table 14. Correlations between factors were slightly lower than shown in Table 4, but still show that the oblique rotation used in the factor analysis was appropriate. Coefficients ranged from 0.18 (vaginal health and psychosocial domains) to 0.55 (psychosocial and physical domains).

DISCUSSION

The Menopause-Specific Quality of Life Questionnaire is a useful tool than can be used to evaluate frequent and bothersome symptoms in a postmenopausal population. The existing tool explored symptoms as they impacted a woman's life over four domains; vasomotor, psychosocial, physical and sexual. This is the first study to evaluate the existing tool using a factor analytic approach to eliminate items that were ambiguous across more than one domain or that had poor factor loading indicating weakness as an item. This has been a criticism of this tool in the literature and we aimed to address this issue in this paper. Items which loaded on more than one domain included 'Feeling Tired or Worn Out', 'Accomplishing Less Than I Used To', 'Changes in Appearance, Texture or Tone of Your Skin', 'Difficulty Sleeping', and 'Poor Memory' and were removed based on ambiguity.

The second phase of this study appended the abbreviated MENQOL by adding pertinent vaginal health items which may also impact a woman's quality of life. The vaginal health items that we included are strongly related to vaginal atrophy and were found to cluster both on their own and with the sexual domain, which can be reasonably expected given their nature.

This study is not without its limitations. First, we began our factor analysis with only the 29 items in the original MENQOL. Traditionally, item reduction and exploratory factor analysis is conducted on the entire set of potential items, to which we did not have access. However, the results here hold largely to the expected domains. Second, the reliability of the vaginal health domain for the added vaginal health items is 0.67, slightly below the accepted reliability level of 0.70. The addition of one or two related items to this domain may improve this reliability coefficient. These items could be generated through focus groups or suggestions from key opinion leaders in the field. Yet, the coefficient is close to 0.70 giving us confidence that these important items should remain in the suggested version of this instrument.

This study has several strengths. The Menopause Epidemiology Study population from which the data for this analysis were derived is a large population-based study and is generally representative of women 40-65 years old in the United States. The privacy of the data collection method over the Internet encourages truthful responses, which are particularly useful in a factor analysis approach in determining which items cluster with each other within domains. Furthermore, to ensure that we were not overfitting our data to our factor analysis models, the models presented here have been confirmed after being run on both a split sample. Also, the elimination of unnecessary items reduces the time it takes women to respond to the questionnaire, yet provides similar data to yield high quality results to the researcher or physician collecting the data. Lastly, the addition of the vaginal health items asked in the same manner

ensured the ability to combine them with the MENQOL domains since the items were scored in the same manner.

We present here a final revised MENQOL, a 29 item questionnaire, which eliminated five of the original items and appended five vaginal health items. Scoring for each domain should remain similar to the original domain (2).

Paper 2: Longitudinal Association Between Vasomotor Symptoms and Psychosocial Outcomes among Postmenopausal Women in the United States: a Population-Based Study

Running title: Vasomotor Symptoms and Psychosocial Outcomes

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Key words: Menopause; Postmenopausal; Vasomotor; Psychosocial; MENQOL;

Epidemiology

ABSTRACT

Objective*:* While both vasomotor and psychosocial symptoms persist as common manifestations of the menopausal transition, their explicit association is unclear. We investigated this association among post-menopausal women over a two year period.

Design: The Menopause Epidemiology Study is a cross-sectional population-based study of women 40-65 years old in the United States chosen from a source population selected by random digit dialing and probability sampling. We then followed up participants two years later, including only women who were postmenopausal at baseline and at follow-up (n=1,506) in the analyses. The MENQOL vasomotor domain was used to assess vasomotor symptoms and the MENQOL psychosocial domain was used to assess psychosocial symptoms in this population. The change in symptoms was defined as the difference in the MENQOL domain score from baseline to follow-up two years later. Demographic information, behavioral activities, reproductive history and medication use were included as covariates in the models and were evaluated for effect modification and confounding. Covariate-adjusted linear regression was used to assess the independent relationship between the change in vasomotor symptoms and the change in psychosocial symptoms.

Results: Approximately 25% (n=375) of the women reported an increase in vasomotor symptoms, specifically the degree of bother, over the two-year study period. A larger proportion of women experienced an increase in psychosocial symptoms over the two-year period (41%, n=619). Twenty-two percent of the women reported an increase in both vasomotor and psychosocial symptoms over time. A one unit increase in the vasomotor domain was associated with a 0.21 (95% CI: 0.12, 0.29) unit increase in the psychosocial domain among smokers, after adjustment for demographic, behavioral, medication use, and reproductive history covariates. This association was stronger (0.29, 95% CI: 0.20, 0.39) among past or never smokers.

Conclusions: This study provides further evidence of an association between vasomotor symptoms and psychosocial symptoms using a validated instrument in a population-based study. There is a small but significant increase in psychosocial symptoms with increasing vasomotor symptoms. Clinicians may want to take note of this association when treating postmenopausal women with either condition.

INTRODUCTION

Hot flashes are hypothesized to be a symptom caused by the decrease in estrogen associated with the menopausal transition. Hot flashes manifest themselves via a sharp peak soon after the last time of ovulation for a woman and tend to decrease after a period of one to three years (22). The prevalence of hot flashes among post-menopausal women in the United States varies from study to study; two recent population-based studies have shown the prevalence of hot flashes to range from 59% to 75% (25, 98). Hot flashes are also prevalent worldwide; a longitudinal study in Australia showed hot flash prevalence at approximately 27% (24) and a study conducted in Australia among Indian women found the prevalence of hot flashes to be 34% (23).

The characterization and impact on quality of life of these vasomotor symptoms is assessed using the Menopause-Specific Quality of Life (MENQOL) questionnaire. The MENQOL is a 29-item validated tool that measures the existence of, and degree of bother from, hot flashes, night sweats and sweating, along with many other common menopausal symptoms such as psychosocial, physical and sexual symptoms (2).

It has been noted that depression has a significant effect on quality of life; worldwide it is the fourth leading contributor to the global burden of disease (43). This condition is marked by a loss of interest or pleasure in doing things, constant depressed mood, loss of appetite, sleeplessness, feelings of guilt or low self-esteem, poor concentration, and low energy. The prevalence of depressive symptoms during the menopausal transition is somewhere between 40 and 60 percent (26, 51). In general, depression is associated with reduced quality of life (56). Well-conducted studies have shown that depression, specifically in the years surrounding menopause, has a significant impact on physical and mental well-being (57-58).

The association between hot flashes and depression is not well understood, although both are highly prevalent during menopause. Studies have suggested that

prior psychological issues, health related behaviors, socioeconomic status and a woman's attitude toward menopause may confound the relationship between vasomotor and psychosocial symptoms (10, 24, 73). The objective of this analysis is to evaluate the relationship between vasomotor symptoms and depression more rigorously by controlling for many potential confounders and evaluating potential effect modifiers, as has not been previously done to our knowledge.

METHODS

Study Population

The study population included postmenopausal women who participated in the original and follow-up Menopause Epidemiology (MEPI) Study. The original MEPI study was a cross-sectional, population-based study of 4,402 women 40-65 years old in the United States, collected in April 2005 (94, 96, 99). The source population for this study was based on the Knowledge Networks (KN) KnowledgePanel^{SM}. This panel was selected via random digit dialing and members who did not have internet access at home were provided access free of charge. Thus, the KN panel is a reasonably representative sample of the US population, rather than a convenience sample of Internet users.

When participant selection for the study began, there were approximately 11,000 women aged 40-65 years on the Knowledge Networks panel. Just over six thousand (n=6,201) women were randomly selected from this group and invited to participate in the MEPI study. There were 4,923 (79%) women who replied and 4,630 (75%) who consented to the study. Exclusion criteria included missing menstrual periods in the last 12 months due to pregnancy, breastfeeding, intra-uterine device, chemotherapy, strenuous exercise, anorexia, or other medical condition that resulted in lack of a menstrual period. After exclusion criteria were applied, 4,402 women remained in the

study. Postmenopausal status (both natural and surgical) was self-reported and was defined by not having a period in the past 12 months (n=2,703).

A follow-up study was conducted two years later in April 2007 among women who had been participants in the first study. Women were asked the same questions that were in the original study, allowing for direct comparison of their responses over the two-year period. Retention was approximately 60% between the two phases. All eligible postmenopausal women who completed both the initial and follow up questionnaires (n=1,506) were used in this longitudinal analysis. Summaries of the original and follow-up MEPI populations are shown in Table 1. By study design, KnowledgePanel[SM] members are enrolled for three years total, after which they are released from the Panel. Thus, some loss to follow-up between the two phases of the MEPI study likely occurred at random due to participants' completion of three years of overall panel participation.

Measures

The outcome of interest, change in psychosocial symptoms, was assessed using the psychosocial domain of the MENQOL. The change over time was calculated as the follow-up psychosocial domain score minus the original psychosocial domain score, which yields values between (-) 7 to (+) 7.

The MENQOL vasomotor domain was used as a measure of vasomotor symptoms. The change in the vasomotor domain score over the two-year period was constructed by subtracting the original vasomotor score from the follow-up vasomotor score, creating a continuous score ranging from (-) 7 to (+) 7.

Baseline covariates were assessed in 2005 at the time of the original survey. Demographic and socioeconomic status variables were age, race, marital status, and income level. Health behavior factors were smoking status, body mass index, and level of physical activity. Reproductive history covariates were history of hysterectomy and/or oophorectomy, parity, and the number of years that had passed since the start of

menopause. Use of hormone therapy (HT) and depression medication was also included as a covariate. Age, body mass index, and the number of years since menopause were assessed for normality using historgrams and included as continuous variables. All other covariates were categorical in nature.

Statistical Analyses

The objective of the analyses was to evaluate the relationship between vasomotor symptoms and depressive symptoms over time. Prior to modeling, effect modification was explored using stratification by the covariates individually to determine the need for any potential interaction terms. Linear regression was used with a backwards elimination approach to evaluate the association between vasomotor symptoms and psychosocial symptoms. Candidate confounders were selected based on biologic plausibility, association with both vasomotor symptoms and psychosocial symptoms, and the use of a directed acyclic graph (90). Baseline scores for vasomotor symptoms and depression were also controlled for in the models. Confounding variables were assessed via a ten percent change in estimate of the beta during modeling.

To explore this association further, we conducted the same analysis restricted to several different subpopulations: postmenopausal women on hormone therapy (n=298), postmenopausal women not on hormone therapy (1,208), postmenopausal women on depression medication (n=415), postmenopausal women not on depression medication (n=1,019), and postmenopausal women not on any depression or hormone therapy (n=840).

As a sensitivity analysis, these analyses were also run using logistic regression on the full model, classifying the outcome as dichotomous with a change greater than or equal to 1.5 units and less than 1.5 units. Potential confounders were evaluated in the

same manner, and effect measure modifiers were identified using Breslow-Day test of homogeneity with a p-value set at 0.20.

RESULTS

In these analyses, 86% (n=1,297) of the women were aged 50 years or older at baseline, over three-quarters were White non-Hispanic (82.5%, n=1,242), and just over 25 percent (n=383) had a Bachelors degree or higher (Table 15). The baseline study population of the Menopause Epidemiology Study and its follow-up cohort are well representative of the United States, as compared to the US Current Population Survey (96) (Table 15). The exclusion criteria for the MEPI study, including pregnancy, use of any contraceptive device, or use of birth control, could be a reason for this age discrepancy between the CPS and the overall MEPI population. The postmenopausal women remaining in the follow-up survey maintained similar demographics as those in the baseline and the US Current Population Survey, with the exception of being slightly older as expected since they were postmenopausal.

Change in vasomotor score was assessed continuously. The distribution of these scores was approximately normal; median and mode change score was zero. Mean change score was (-) 0.35. Approximately 25% (n=375) of the women reported an increase in the degree of bother from their hot flashes. Likewise, change in psychosocial score was assessed continuously. The distribution of these scores was also approximately normal as assessed via histograms; median change score was zero. The mean change score for psychosocial symptoms was (-) 0.13. Over forty percent (41%, n=618) of the women reported an increase in their psychosocial symptoms over time. Nearly twenty-three percent (n=334) of the women noted an increase in both vasomotor and psychosocial scores over the two-year study period; only 1.75% (n=25) reported a decrease in both symptoms.

The unadjusted model showed that for every one-unit increase in the vasomotor domain score, the average increase in the psychosocial score was 0.20 (95% CI 0.16, 0.24, p<0.0001).

Smoking status, categorized as smoking “currently or some days” versus “past or never” was found to modify the association between the vasomotor domain score and the psychosocial domain score, as assessed via stratification. In the fully adjusted model, for every one-unit change in the vasomotor domain, the average change in psychosocial domain score after two years for current smokers was 0.21 (95% CI: 0.12, 0.29; p<0.0001), after controlling for all covariates (Table 16). For past or never smokers, the association was stronger; for every one point increase in the vasomotor score over the two-year study period, the psychosocial domain score was increased by 0.29 (95% CI: 0.20, 0.39; p<0.0001). The only statistically significant predictors of change in psychosocial score were baseline vasomotor score, baseline psychosocial score, and smoking. However, because there was very little precision gained by reducing the number of covariates in the model, we report results from the full model (92).

These results were confirmed with logistic regression. No effect modifiers were found, and the final model contained the same confounders as the linear regression. However, because precision was not altered, all covariates were retained in the model. The final logistic regression model produced an odds ratio of 1.29 (95% CI 1.14, 1.44).

When subpopulations were examined among those taking (and not taking) hormone therapy, those taking (and not taking) depression medication, and those on no medication at all, all the models found similar results (Table 17).

Because tobacco use was found to modify the association between change in vasomotor score and change in psychosocial score, and because the psychosocial score measure includes an item which takes anxiety into account, a sensitivity analysis

was conducted to explore the effect on an item which measures depression only. The change score of One item from the psychosocial domain, “Feeling Depressed, Down, or Blue” was used as the outcome and the model was reanalyzed. The results of this model did not change; the main effect estimate was similar to that of the full model (Appendix A6).

DISCUSSION

This study found a positive association between an increase in vasomotor symptoms and increase in psychosocial symptoms. These results confirm what has often been hypothesized in literature. There was a difference found in the association between vasomotor symptoms and psychosocial symptoms between women who are current smokers and those who are former/never smokers. The association between change in vasomotor score and change in psychosocial score is weaker for women who are current smokers, perhaps because tobacco use serves as a coping mechanism. It is important to note that the definition of our outcome is broadly defined and included anxiety, which could be highly linked to tobacco use.

Using different measures to describe outcomes of psychosocial symptoms, other studies have found that vasomotor symptoms are statistically significantly associated with psychological symptoms (100). One study used several different models to examine predictors of being blue for ≥ 6 days in the past two weeks, feeling irritable ≥ 6 days in the past two weeks, feeling nervous ≥ 6 days in the past two weeks, and having a depressed mood for ≥ 6 days in the past two weeks (101). Vasomotor symptoms were significantly associated in all models. The results presented here are similar, except combine all of these outcomes into one cohesive domain, representing one latent variable of psychosocial symptoms. Similarly, another study has found that the inability to cope with hot flashes leads to increasing depressive symptoms, which is consistent with the results seen in this study (70).

Other studies have found that an association between hot flashes and depression persists among pre- and perimenopausal women but that the association was not statistically significant among postmenopausal women (41). This association may have been lost due to the cross-sectional nature of the study.

Although this study provides further evidence of the association between change in vasomotor symptoms and psychosocial symptoms, this study is not without limitations. First, this study pertains only to those who entered our study as postmenopausal and remained postmenopausal throughout the study period. Thus, in a perimenopausal period when vasomotor symptoms may be fluctuating more, this variability is not evaluated in our study. This is due to the use of the MENQOL to define our exposure, which is validated only in postmenopausal women. It may be conceivable that if perimenopausal women had been included, the positive association may have been stronger. Second, our outcome of psychosocial symptoms is not equivalent to a clinically diagnosable condition of depression, but rather a self-reported construct of various symptoms representing mood fluctuations. Third, we recognize the possibility for selection bias in this study. In the period between the baseline and follow up study, if women who were exhibiting more psychosocial symptoms were less likely to participate in the follow up study, this may have weakened the observed association, and this is important to acknowledge. Finally, it is of importance to note that there are additional external factors such as serotonin levels or changing estrogen which may have an important impact on the association, but which go unmeasured in this study.

The use of the MENQOL questionnaire also is a strength of this study. Although there may be other measurements for vasomotor and psychosocial symptoms, the MENQOL is standardized and validated in this postmenopausal population (2). It allows us to quantify change in the domains of interest while taking into account multiple aspects of these conditions. The measures we used to evaluate both the exposure and

the outcome encompass a variety of symptoms that incorporate the degree of bother, instead of just one symptom coded dichotomously. This is a novel approach to evaluating the association between the change in vasomotor and psychosocial symptoms that has not been shown in the literature. Other strengths of this study include the representativeness of the population and the study design. The Menopause Epidemiology Study is well representative of the United States population and the follow-up study maintained a good response rate.

An additional strength of this study was our ability to perform a sensitivity analysis and stratify on various subpopulations, restricting among those taking and not taking both hormone therapy and medications indicated for depression. Several medications have been successful in alleviating depression, such as bupropion, venlafaxine, sertraline, escitalopram and allopregnanalone (60-67). Some of these medications are also used, though not indicated for, the treatment of vasomotor symptoms. Because of this, it is important to note that medication use, either for the treatment of vasomotor symptoms or for depression, could be an important confounder. Our results provide evidence that regardless of medications being taken, that there is an association between vasomotor symptoms and psychosocial symptoms.

The longitudinal nature of this study allows us to draw conclusions about the association that vasomotor symptoms have on psychosocial symptoms in the postmenopausal period. This is a large study which shows that over time, there is a positive association linking increased vasomotor symptoms to subsequent reporting of increased psychosocial symptoms, including feelings of isolation, anxiety, decreased accomplishment, and depression. We evaluated a large number of potential predictors and found very few that were actual confounders of the association.

There are important clinical conclusions that can be drawn from this study. The MENQOL is frequently used in clinic populations and can now help guide physicians in

the treatment of patients. Clinicians seeing women over time with complaints of vasomotor symptoms should be sensitive to the potential for increased psychosocial symptoms. These symptoms encompass more than just depression, and may be indicative of anxiety, feelings of isolation, and lack of productivity.

It is well documented that vasomotor and psychosocial symptoms are common during the postmenopausal period, but this is the first population-based longitudinal study completed in the United States that examines this explicit association. Further research is warranted using clinically-based definitions of depression to confirm the effect of vasomotor symptoms on psychosocial outcomes.

CHAPTER V

DISCUSSION

The Menopause-Specific Quality of Life Questionnaire is a validated tool used in post-menopausal women in many populations. The existing tool is efficiently designed to measure four domains of a postmenopausal woman's quality of life. With areas such as vasomotor symptoms, psychosocial symptoms, physical and sexual symptoms, it seeks to tap all aspects of life not only in terms of frequency but also degree of bother.

One of the criticisms of the MENQOL was that it had never been evaluated for its psychometric properties via factor analysis. This criticism has since been rectified with positive results from this dissertation. The items factored well with a minor amount of crossloading between domains. However, five items were candidates for exclusion: Difficulty Sleeping, Poor Memory, Accomplishing Less Than I Used To, Changes in Appearance, Texture, or Tone of My Skin, and Feeling Tired. These items were likely excluded based on ambiguity due to physical and emotional interpretations. Without these items in the existing MENQOL, the items then factored well into the domains under which they were suggested.

The first part of this study adds to the literature a wealth of information, not only by conducting a frequently-used method of psychometric testing on the instrument, but also by suggesting the deletion of unnecessary items from the tool which are not needed, and only add burden to the respondent filling it out.

The second part of this study appended pertinent information to the MENQOL by adding items relating to vaginal health to the existing instrument. These items were selected for inclusion to the instrument based on their significance in vulvovaginal atrophy as commonly reported symptoms. Five of the six candidate items remained in the instrument after exploratory factor analysis was conducted. The sixth, "Vaginal Bleeding on Sexual Activity" was suggested for exclusion based on poor loading and was indicative of a poorly worded or unimportant item.

After the exclusion of the five existing items and the one new vaginal health item that were not needed, and the addition of the five new vaginal health items, this newer version of the modified MENQOL provides an revised version of a quality of life tool which encompasses an entirely new domain of important items.

We suggest the modification of the existing MENQOL instrument, based on the factor analysis performed herein. In clinic settings, this revised version provides new and important information to physicians and patients alike. Patients will be able to accurately and discreetly report any vaginal symptoms they may be experiencing (as well as degree of bother) without fear of as much embarrassment as bringing it up verbally. Additionally, physicians will be able to take the information from their patients and accurately assess and treat their patients therapeutically as needed.

Physicians may also be able to make better treatment decisions based on the results shown from the second aim presented here. Until this study, the relationship between vasomotor symptoms and psychosocial symptoms has been speculated, but not well quantified among postmenopausal women. Controlling for many potential effect modifiers and confounders, this study found a statistically significant relationship between changing vasomotor scores and changes in psychosocial scores. Moreover, smoking status modified this association. While the association was still significantly positive, women who smoked were less likely to experience an increase in psychosocial

symptoms as a result of increasing vasomotor score. This is likely due to cigarettes being used as a mechanism for not being able to cope with the bothersome vasomotor symptoms. Sensitivity analyses conducted among several populations showed the same results. Smoking was found to modify the association in women who were not on hormone therapy, and in women not on any therapy at all.

Naturally, smoking should not be advocated as a means for reducing psychosocial symptoms, but should be recognized by clinicians a method of coping among women experiencing increases in vasomotor symptoms over time. The recognition of this increase may lead the physician to treat the women with therapies which may reduce the hot flashes and in turn, lead to reduced depressive symptoms.

The results shown here on the association between vasomotor and psychosocial symptoms confirm what has been shown in the literature using a new and innovative way of categorizing both the exposure and outcome with the MENQOL. Using the vasomotor and psychosocial domains for the exposure and outcome definitions, respectively, a broad categorization of various items was used to quantify a single concept. This is an advantage over existing literature, which has used either a single dichotomous outcome, or more than one model to express the relationship between vasomotor symptoms and many psychological outcomes.

We have shown here that the MENQOL is an appropriate tool to use in a population-based sample, that is has good psychometric properties, and that it is well suited to study the relationship between hot flashes and depression over time. However, it is also important to note that the population from which we derived this sample is appropriate to also draw such conclusions. The Menopause Epidemiology Study and its follow up are well suited for such studies. This study is a large, population-based study that is well representative of postmenopausal women in the United States aged 40-65 years.

Despite the conclusions this work may add to menopause literature, there are several limitations to the study conducted. First, the factor analysis provides a wealth of knowledge to the field of menopause quality of life, but it was not possible to perform a true exploratory factor analysis using all 106 items originated in the initial instrument development. There may have been other items which would have been suggested for retention via factor analysis that were excluded by investigators. Second, the reliability coefficients were not as high as suggested by literature when the vaginal health items were added. Though this does not mean that the items are not useful, it does mean that a few additional items, or potentially the re-wording of currently items, could help improve this reliability coefficient.

In the second analysis, it was necessary to restrict to only postmenopausal women, as this is the only population in which the MENQOL is validated. Unfortunately, this precludes studying a highly variable time period during the menopausal period, the perimenopause, where changes in vasomotor symptoms are frequent and most bothersome. We lose this sensitivity in restricting to studying a population that was not only post-menopause at baseline, but remains so two years later at follow-up, after the traditional peak of vasomotor symptoms have passed. There also may exist a selection bias in the time between baseline and follow-up in that women whose psychosocial domain score had increased may have been less likely to participate, which would have driven our estimate toward the null. Finally, there are a number of unmeasured confounders such as serotonin estrogen levels which could have a direct impact on either vasomotor symptoms or psychosocial symptoms which must be taken into consideration.

This is not to say that overall, the studies do not have their strengths. The Menopause Epidemiology Study is a large, population-based study that is well representative of the United States. The MENQOL is a validated instrument used to

measure quality of life and is able to capture not only the existence of frequent menopausal symptoms, but the degree of bother as well. Additionally, the inclusion of supplemental vaginal health items is helpful to the instrument and will be able to provide physicians and researchers as well as patients the ability to explain their current symptom profile.

Also, the sensitivity analysis conducted on the second study enable us to be a little more confident in the relationship that change vasomotor symptoms have on changing psychosocial symptoms. In looking at the relationship among those taking and not taking hormone therapy and depression medication, there were very similar results as the full model. Furthermore, when it was found that tobacco use was a modifier, and that the outcome contained an anxiety component, we looked at a outcome encompassing depression only and found similar results.

In conclusion, we present an updated version of the Menopause-Specific Quality of Life Questionnaire, complete with a newly added Vaginal Health domain. This research shows that these domains are fully sufficient to stand on their own, but may benefit from one or two additional vaginal health items to strengthen reliability.

Also, we show that an increase in vasomotor symptoms is associated with the increase in psychosocial symptoms over time. Because this association was only quantified over two time points, true causality cannot be determined and further research is warranted and encouraged. Meanwhile, it may be advantageous for clinicians to be aware of this association when treating women who are menopausal and reporting increasingly bothersome hot flashes over time.

TABLES

Table 1. Characteristics of US Women, Menopause Epidemiology Study population

Characteristic	**US CPS* (%)**	**MEPI Study Population n (%) n=4,402**	**MEPI II Study Population n (%) n=2,563**
Age, years			
40-44	24.8	848 (19.3)	255 (9.9)
45-49	23.4	900 (20.4)	465 (18.1)
50-54	20.0	920 (20.9)	544 (21.2)
55-59	16.5	827 (18.8)	508 (19.8)
60-67	15.3	907 (20.6)	791 (30.9)
Race/Ethnicity			
White, non-Hispanic	74.6	3,424 (77.8)	2,074 (80.9)
Black, non-Hispanic	11.8	497 (11.3)	248(9.7)
Hispanic	4.5	150 (3.4)	80 (3.1)
Other, non-Hispanic	9.1	331 (7.5)	161 (6.3)
Education			
Less than high school	12.4	273 (6.2)	145 (5.7)
High school	33.7	1,721 (39.1)	948 (37.0)
Some college	27.7	1,265 (28.7)	746 (29.1)
Bachelor's degree or higher	26.2	1,143(26.0)	724 (28.3)

*CPS: Current Population Survey, 2002.

Table 2. Distribution of domains from the MENQOL.

Domain	Item
Vasomotor	Hot Flashes
	Night Sweats
	Sweating
Psychosocial	Dissatisfaction of Personal Life
	Feeling Anxious or Nervous
	Poor Memory
	Accomplishing less than I used to
	Feeling down, depressed or blue
	Being impatient with other people
	Feelings of wanting to be alone
Sexual	Change in sexual desire
	Vaginal Dryness
	Avoiding intimacy
Physical	Flatulence or gas pains
	Aching muscles or joints
	Feeling tired or worn out
	Difficulty sleeping
	Aches in back of neck or head
	Decrease in physical strength
	Decrease in stamina
	Feeling a lack of energy
	Drying skin
	Weight gain
	Increased facial hair
	Changes in appearance, texture, or tone of skin
	Feeling Bloated
	Low backache
	Frequent urination
	Involuntary Urination

Table 3. Additional Vaginal Health Characteristics appended to original MENQOL Instrument

Vaginal Health Characteristic added to MENQOL
Vaginal Irritation
Vaginal Itching
Pain, Difficulty, or Burning during Urination
Vaginal Pain associated with sexual activity
Vaginal Bleeding associated with sexual activity
Vaginal Discharge

Table 4. Original hypothesized factoring structure for appended vaginal health items.

What could happen?	Likelihood?	Reasoning
All 6 items load into their own 'Vaginal Atrophy' Factor	Unlikely	There are symptoms that appear to be more physical, and those that appear to be more sexual in nature.
Items 1,2,3, and 6 load into the MENQOL Physical Functioning Domain; 4 and 5 load into Sexual Functioning Doman	Possible	1,2,3,4 and 7 have physical qualities; 5 and 6 are associated with sexual activity
Items 1,2,3, and 6 load into the MENQOL Physical Functioning Domain; 4 and 5 do not load well into any MENQOL domain	Possible	5 and 6 are somewhat abstract from the other MENQOL sexual functioning measures.
All 6 items load into MENQOL Physical Functioning Domain	Possible	The 6 additional items all have the potential for some physical functioning aspect.
None of the 6 items are stable enough to load into factors	Possible	The addition of questions to a validated questionnaire may not support the inclusion of standalone factors.

Table 5. Baseline Covariates and Potential Confounders

Covariate	Key	Distribution % (n) (n=1506)	Comment
Age (years)	-	Mean: 58.2 (5.9)	
	40-44	4.52 (n=68)	
	45-49	9.36 (n=141)	
	50-54	22.38 (n=337)	
	55-59	29.02 (n=437)	
	60-65	34.73 (n=523)	
Baseline	-	Mean: 3.11 (2.20)	
VMS*	1-<3	54.91 (n=886)	
	3-<6	29.22 (n=440)	
	6-≤8	11.95 (n=180)	
Baseline	-	Mean: 3.19 (1.75)	
PSY**	1-<3	51.66 (n=778)	
	3-<6	39.64 (n=597)	
	6-≤8	8.70 (n=131)	
Race/Ethnicity	0= White, Non-Hispanic	82.54 (n=1243)	
	1= Other	17.46 (n=263)	
Income	0 = <$25,000	23.71 (n=357)	
	1 = $25,000 – $74,000	56.24 (n=847)	
	2 = $75,000 +	20.05 (n=302)	
BMI†	0= <25	32.04 (n=462)	Deviates from traditional BMI cutpoints. There were few (n=19) with BMI <18.
	1= 25 - <30	32.35 (n=465)	
	2=≥ 30	35.71 (n=515)	
		missing = 64	
Marital Status	0 = Currently Married	62.42 (n=925)	
	1 = Not Currently Married	37.58 (n=557)	
		missing =24	
Physical Activity	0= Never	20.84 (n=313)	
	1= 1-3 days a month	21.57 (n=324)	
	2= 1-3 days a week	23.30 (n=350)	
	3= 3-5 days a week	28.43 (n=427)	
	4= 6-7 days a week	5.86 (n=88)	
Smoking	0 = Non-current smoker	74.85 (n=1125)	
	1= Current smoker	25.15 (n=378)	
Hormone Therapy use	0= No	80.21 (n=1208)	SERMS not included in HT use.
	1= Yes	19.79 (n=298)	

*Vasomotor Score
**Psychosocial Score
†Body Mass Index

Table 5 (cont'd)

Covariate	Key	Distribution % (n) (n=1506)	Comment
Parity	0 = Never given birth 1= 1 2= 2 or more times	25.23 (n=395) 14.28 (n=215 59.50 (n-896))	
Depression Medication	0 = No 1 = Current Depression Medication	28.94 (n=415) 71.06 (n=1,019)	
Hysterectomy	0= No Hysterectomy 1= Hysterectomy with or without oophorectomy	54.80 (n=822) 45.20 (n-678)	

Table 6. Power estimates for main effects analyses using logistic regression.

Odds Ratio	Sample Size	P (Vas inc among those with no change in psy domain)	Power
1.1	1,506	0.23	0.33
1.2	1,506	0.23	0.83
1.3	1,506	0.23	0.98
1.4	1,506	0.23	1.00
1.5	1,506	0.23	1.00
1.6	1,506	0.23	1.00
2.0	1,506	0.23	1.00
2.1	1,506	0.23	1.00

Table 7. Power estimates for difference in mean psychosocial domain score using linear regression.

Detectable Difference in Mean Score (Score change)	Number with Vasomotor Score Increase	Ratio of Vasomotor Increase to those with Decrease or No Change	Standard Deviation of Change in Psychosocial Domain	Power
0.2	899	0.65	1.3	0.82
0.4	899	0.65	1.3	0.99
0.5	899	0.65	1.3	1.00
0.75	899	0.65	1.3	1.00
1.0	899	0.65	1.3	1.00
1.25	899	0.65	1.3	1.00
1.50	899	0.65	1.3	1.00
2.0	899	0.65	1.3	1.00

Table 8. Descriptive statistics of the MEPI study population.

Characteristic	**US CPS, 2002* (%)**	**MEPI Study Population (n=4,402) (%)**	**MEPI Post-Menopausal Study Population (n=2,703) (%)**
Age			
40-44	24.8	19.3	5.0
45-49	23.4	20.4	11.0
50-54	20.0	20.9	22.4
55-59	16.5	18.8	28.7
60-65	15.3	20.6	33.0
Race/Ethnicity			
White, non-Hispanic	74.6	77.8	80.3
Black, non-Hispanic	11.8	11.3	10.6
Hispanic	9.1	7.5	3.1
Other, non-Hispanic	4.5	3.4	6.0
Educational Level			
High school or Less	46.1	45.3	48.3
Some college	27.7	28.7	28.8
Bachelor's degree or higher	26.2	26.0	22.9

* Current Population Survey. US Census Bureau, 2002.

Table 9. Existing MENQOL, restricted to 4 factors, among postmenopausal women 40-65 years old in the United States.

Variable	Factor Loading
PHYSICAL	
Aches in Muscles	0.739
Decrease in Physical Strength	0.735
Decrease in Stamina	0.687
Feeling a Lack of Energy	0.652
Low Backache	0.643
Feeling Tired or Worn Out	0.595 / 0.348*
Aches in back of Head or Neck	0.587
Feeling Bloated	0.543
Accomplishing Less than I Used To	0.4934 / 0.394*
Flatulence (Wind) or Gas Pains	0.493
Increased Facial Hair	0.421
Changes in Appearance, Texture or Tone of your Skin	0.344 / 0.245*
Weight Gain	0.496
Dry Skin	0.443
Involuntary Urination when Laughing or Coughing	0.425
Frequent Urination	0.464
Difficulty Sleeping	0.291 / 0.251/ 0.247*
PSYCHOSOCIAL	
Down, Depressed, or Blue	0.866
Being Dissatisfied with my Personal Life	0.813
Feeling Anxious or Nervous	0.789
Feelings of Wanting to be Alone	0.699
Being Impatient with Other People	0.593
Poor Memory	0.415 /0.242*
VASOMOTOR†	
Hot Flashes	0.847
Night Sweats	0.841
Sweating	0.777
SEXUAL†	
Avoiding Intimacy	0.775
Decreased Sexual Desire	0.765
Vaginal Dryness	0.708

* Crossloading

† Classified the same as in the existing instrument

Table 10. Existing MENQOL, modified after dropping Accomplish, Memory, Sleeping, Tired, and Skin Tone, among postmenopausal women 40-65 years old in the United States.

Variable	Factor Loading
PHYSICAL (ALPHA=0.86)	
Aches in Muscles	0.747
Decrease in Physical Strength	0.737
Decrease in Stamina	0.680
Feeling a Lack of Energy	0.630
Low Backache	0.672
Aches in back of Head or Neck	0.620
Feeling Bloated	0.560
Flatulence (Wind) or Gas Pains	0.514
Increased Facial Hair	0.407
Weight Gain	0.495
Dry Skin	0.438
Involuntary Urination when Laughing or Coughing	0.444
Frequent Urination	0.491
PSYCHOSOCIAL (ALPHA=0.84)	
Down, Depressed, or Blue	0.868
Being Dissatisfied with my Personal Life	0.823
Feeling Anxious or Nervous	0.786
Feelings of Wanting to be Alone	0.708
Being Impatient with Other People	0.590
VASOMOTOR* (ALPHA=0.86)	
Hot Flashes	0.871
Night Sweats	0.859
Sweating	0.798
SEXUAL* (ALPHA= 0.78)	
Avoiding Intimacy	0.801
Decreased Sexual Desire	0.794
Vaginal Dryness	0.740

* Domains classified the same as in the existing instrument

Table 11. Inter-factor Correlations, Existing MENQOL, after Factor Analysis.

	Physical	**Psychosocial**	**Vasomotor**	**Sexual**
Physical	1.00	0.53	0.33	0.34
Psychosocial	0.53	1.00	0.29	0.33
Vasomotor	0.33	0.29	1.00	0.23
Sexual	0.34	0.33	0.23	1.00

Table 12. Revised MENQOL, after removing Cross Loading Factors and Including Vaginal Health Items, among postmenopausal women 40-65 years old in the United States.

Variable	Factor Loading
PHYSICAL	
Decrease in Physical Strength	0.768
Decrease in Stamina	0.717
Aches in Muscles	0.728
Feeling a Lack of Energy	0.659
Low Backache	0.645
Aches in back of Head or Neck	0.606
Weight Gain	0.552
Flatulence Gas or Wind Pains	0.502
Increased Facial Hair	0.443
Feeling Bloated	0.567
Dry Skin	0.450
Involuntary Urination when Laughing or Coughing	0.465
Frequent Urination	0.472
PSYCHOSOCIAL	
Down, Depressed, or Blue	0.861
Being Dissatisfied with my Personal Life	0.821
Feeling Anxious or Nervous	0.785
Feelings of Wanting to be Alone	0.715
Being Impatient with Other People	0.600
SEXUAL	
Vaginal Dryness	0.736
Vaginal Pain on Sex*	0.724
Avoiding Intimacy	0.732
Decreased Sexual Desire	0.718
Vaginal Bleeding on Sex – Suggest dropping*	0.344
VASOMOTOR	
Night Sweats	0.865
Hot Flashes	0.876
Sweating	0.799
VAGINAL HEALTH	
Vaginal Irritation*	0.731
Vaginal Itching*	0.726
Vaginal Pain Difficulty or Burning during Urination*	0.539
Vaginal Discharge*	0.569

Note: To begin this analysis, we started with the 24 item MENQOL found in Phase I, eliminating Accomplish, Memory, Sleeping, Tired and Skin Tone from the original pool.
* Added Vaginal Health items

Table 13. Final Suggested Revised MENQOL, after removing Cross Loading Factors and Including Five Suggested Vaginal Health Items, among postmenopausal women 40-65 years old in the United States.

Variable	Factor Loading
Physical (ALPHA =0.86)	
Decrease in Physical Strength	0.768
Decrease in Stamina	0.717
Aches in Muscles	0.735
Feeling a Lack of Energy	0.657
Low Backache	0.652
Aches in back of Head or Neck	0.613
Weight Gain	0.542
Increased Facial Hair	0.440
Feeling Bloated	0.563
Dry Skin	0.443
Flatulence or wind Pains	0.496
Involuntary Urination when Laughing or Coughing	0.452
Frequent Urination	0.459
PSYCHOSOCIAL (ALPHA=0.84)	
Down, Depressed, or Blue	0.860
Being Dissatisfied with my Personal Life	0.821
Feeling Anxious or Nervous	0.784
Feelings of Wanting to be Alone	0.717
Being Impatient with Other People	0.601
VAGINAL SEXUAL (ALPHA =0.77)	
Vaginal Dryness	0.750
Vaginal Pain on Sex*	0.701
Avoiding Intimacy	0.756
Decreased Sexual Desire	0.742
VASOMOTOR (ALPHA =0.86)	
Night Sweats	0.866
Hot Flashes	0.877
Sweating	0.800
VAGINAL HEALTH (ALPHA=0.67)	
Vaginal Irritation*	0.754
Vaginal Itching*	0.748
Vaginal Pain Difficulty or Burning during Urination*	0.549
Vaginal Discharge*	0.569

* Added vaginal health items.

Table 14. Inter-factor Correlations for Phase II, Modified MENQOL

	Physical	Psychosocial	Vasomotor	Sexual	Vaginal Health
Physical	1.00	0.55	0.35	0.35	0.27
Psychosocial	0.55	1.00	0.29	0.32	0.18
Vasomotor	0.34	0.29	1.00	0.22	0.22
Sexual	0.35	0.32	0.22	1.00	0.28
Vaginal Health	0.27	0.18	0.22	0.28	1.00

Table 15. Demographics of the MEPI Study Population.

Characteristic	**US CPS* (%)**	**MEPI Baseline Study Population (n=4,402) (%)**	**Postmenopausal Women in MEPI baseline and Follow up (n=1,506) (%)**
Age			
40-44	24.8	19.3	4.5
45-49	23.4	20.4	9.4
50-54	20.0	20.9	22.4
55-59	16.5	18.8	29.0
60-65	15.3	20.6	34.7
Race/Ethnicity			
White, non-Hispanic	74.6	77.8	82.5
Black, non-Hispanic	11.8	11.3	9.30
Hispanic	9.1	7.5	5.4
Other, non-Hispanic	4.5	3.4	2.8
Educational Level			
High school or Less	46.1	45.3	45.0
Some college	27.7	28.7	29.5
Bachelor's degree or higher	26.2	26.0	25.4

* United States Current Population Survey. US Census Bureau, 2002.

Table 16. Association Between Change in MENQOL* Vasomotor Domain Score and MENQOL Psychosocial Domain Score among Postmenopausal Women in the United States: Fully Adjusted Model (N=1,506).

Parameter	**Mean Change in Psychosocial Score (SE)**	**95% CI**	**P-value**
Change in Vasomotor Score (1 unit change)			
Current /Some Day Smoker	0.21 (0.04)	(0.12, 0.29)	<0.0001
Past /Never Smokers	0.29 (0.05)	(0.20, 0.39)	<0.0001
Smoking			
Past / Never Smoker	Ref.		0.10
Current /Some Day Smoker	- 0.05 (0.03)	(-0.11, 0.01)	
Change in Vasomotor Score *Smoking	- 0.04 (0.02)	(-0.07, 0.01)	0.02
Baseline Vasomotor Score (1 unit change)	0.11 (0.02)	(0.08, 0.15)	<0.0001
Hysterectomy/Oophorectomy			
No Hysterectomy or Oophorectomy	Ref.		0.22
Hysterectomy and/or oophorectomy	- 0.10 (0.08)	(-0.26, 0.06)	
Use of Hormone Therapy			
No	Ref.		0.32
Yes	0.08 (0.08)	(-0.08, 0.25)	
Physical Activity			
Never	Ref.		
1 to 3 times a month	0.14 (0.10)	(-0.06, 0.34)	
1 to 3 times a week	0.18 (0.10)	(-0.01, 0.38)	0.37
3 to 5 times a week	0.07 (0.10)	(-0.13, 0.26)	
6 to 7 times a week	0.13 (0.16)	(-0.17, 0.44)	
Age (5 year change)	- 0.09 (0.03)	(-0.15, -0.02)	0.01

Table 16 (Cont'd)

Parameter	Mean Change in Psychosocial Score (SE)	95% CI	P-value
Married			
Not Currently Married	Ref.		0.71
Currently Married	0.03 (0.07)	(-0.11, 0.17)	
Baseline Psychosocial Score (1 unit change)	- 0.40 (0.02)	(-0.44, -0.35)	<0.0001
Body Mass Index (1 unit change)	0.02 (0.01)	(0.01, 0.03)	<0.01
Income Level			
Less than $25,000	Ref.		
$25,000 - $74,999	0.01 (0.05)	(-0.10, 0.11)	0.92
$75,000 and up	0.01 (0.11)	(-0.20, 0.22)	
Race			
White non-Hispanic	Ref.	-	0.53
Other	0.06 (0.09)	(-0.12, 0.23)	
Parity			
Never	0		
1	0.002 (0.04)	(-0.07, 0.08)	0.97
2 or more	0.003 (0.08)	(-0.15, 0.16)	
Years Since Menopause (5 year change)	0.01 (0.02)	(-0.03, 0.06)	0.51
Depression Medication			
Not Currently Taking	Ref.		0.01
Currently Taking	0.20 (0.08)	(0.05, 0.35)	

* MENQOL: Menopause-Specific Quality of Life Questionnaire

Table 17. Association Between Change in MENQOL[*] Vasomotor Domain Score and MENQOL Psychosocial Domain Score among Postmenopausal Subpopulations in the United States: Fully Adjusted Main Effects (N=1,506)

Population / Main Effect	**Adj[**] Mean Change in Psychosocial Score (SE)**	**95% Confidence Interval**	**P-value**
Those on Hormone Therapy (N=298)			
Smokers: Change in Vasomotor Score	0.13 (0.09)	(-0.06, 0.31)	0.17
Non-smokers: Change in Vasomotor Score	0.14 (0.09)	(-0.04, 0.33)	0.12
Those not on Hormone Therapy (N=1,208)[†]			
Smokers: Change in Vasomotor Score	0.24 (0.02)	(0.14, 0.33)	<0.0001
Non-smokers: Change in Vasomotor Score	0.34 (0.06)	(0.23, 0.46)	<0.0001
Those on Depression Medication (N=415)			
Smokers: Change in Vasomotor Score	0.26 (0.08)	(0.11, 0.41)	<0.001
Non-smokers: Change in Vasomotor Score	0.29 (0.08)	(0.14, 0.44)	<0.001
Those not on Depression Medication (N=1,019)			
Smokers: Change in Vasomotor Score	0.17 (0.05)	(0.07, 0.28)	0.001
Non-smokers: Change in Vasomotor Score	0.26 (0.06)	(0.14, 0.38)	<0.0001
Those not on Hormone Therapy or Depression Medication (N=840)[†]			
Smokers: Change in Vasomotor Score	0.23 (0.06)	(0.12, 0.35)	<0.0001
Non-smokers: Change in Vasomotor Score	0.35 (0.07)	(0.22, 0.49)	<0.0001

[*] MENQOL: Menopause-Specific Quality of Life Questionnaire

[**] Adjusted for Baseline Vasomotor Score, Hysterectomy/Oophorectomy, Smoking Status, Physical Activity, Age, Marital Status, Baseline Psychosocial Status, Body Mass Index, Income, Race, Parity, and Years Since Menopause.

[†]True effect modifiers.

FIGURES

Figure 1: Conceptual Model of Study

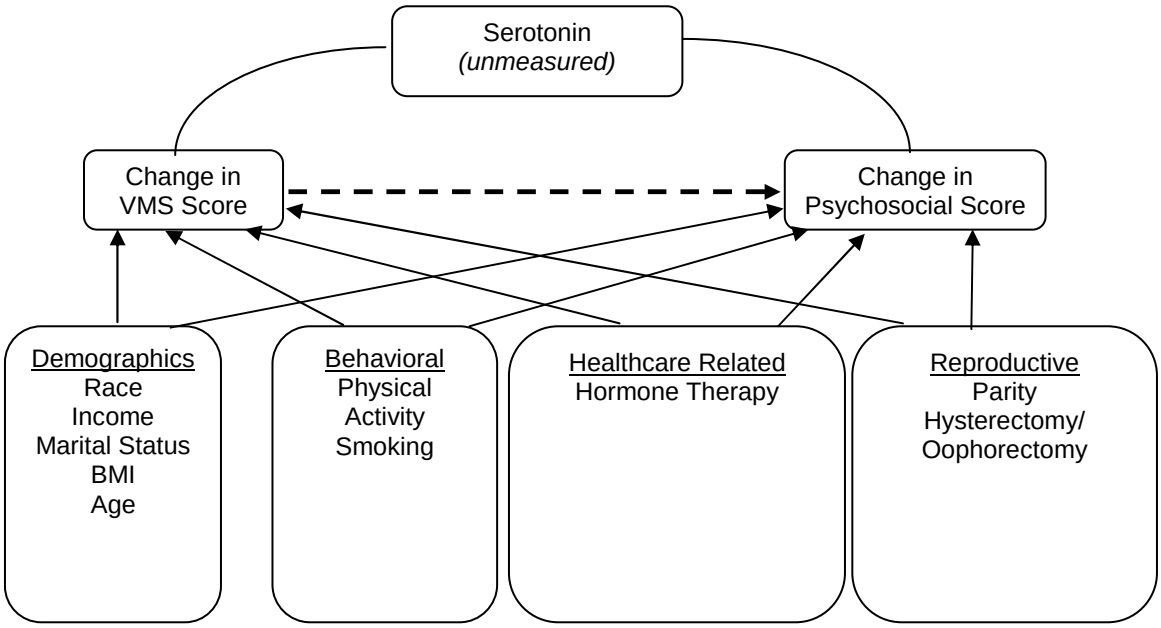


Figure 2. Enrollment of population of postmenopausal women from the Menopause Epidemiology (MEPI) Study, women 40-65 years old in the United States in 2005.

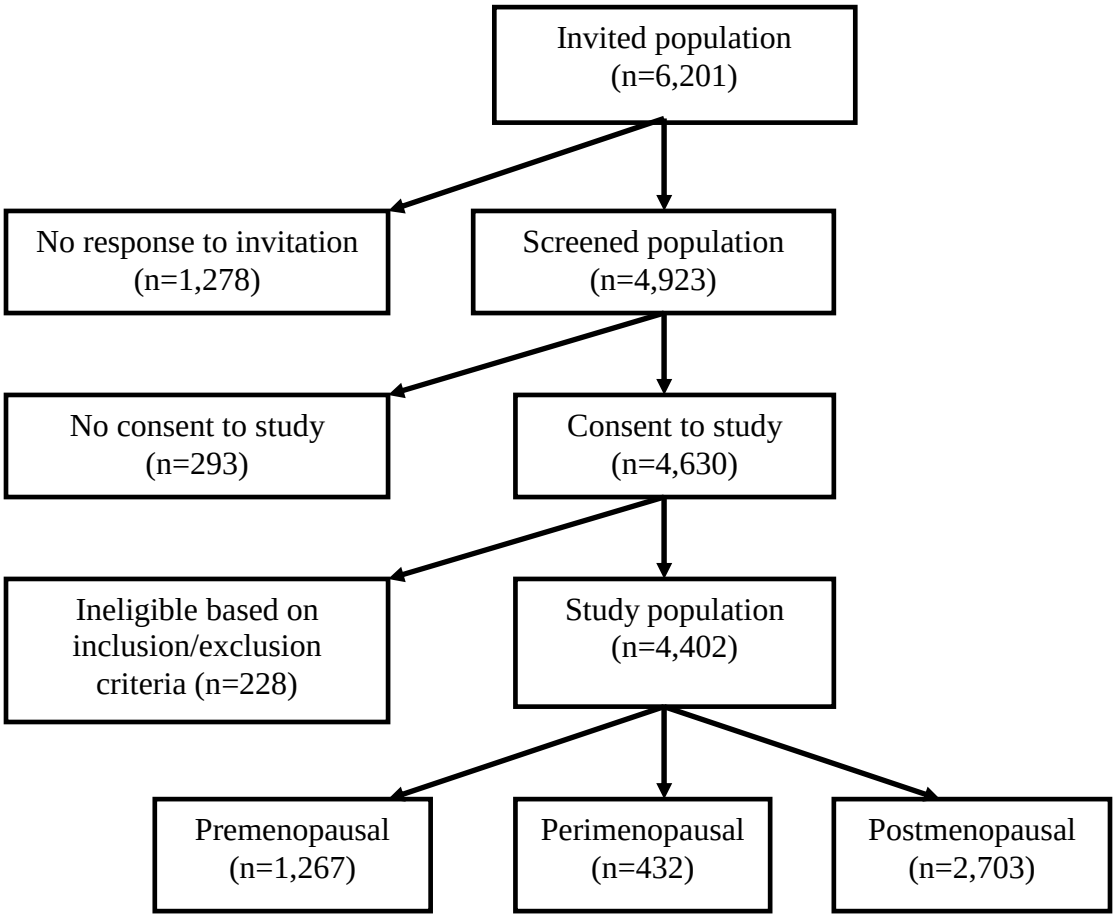
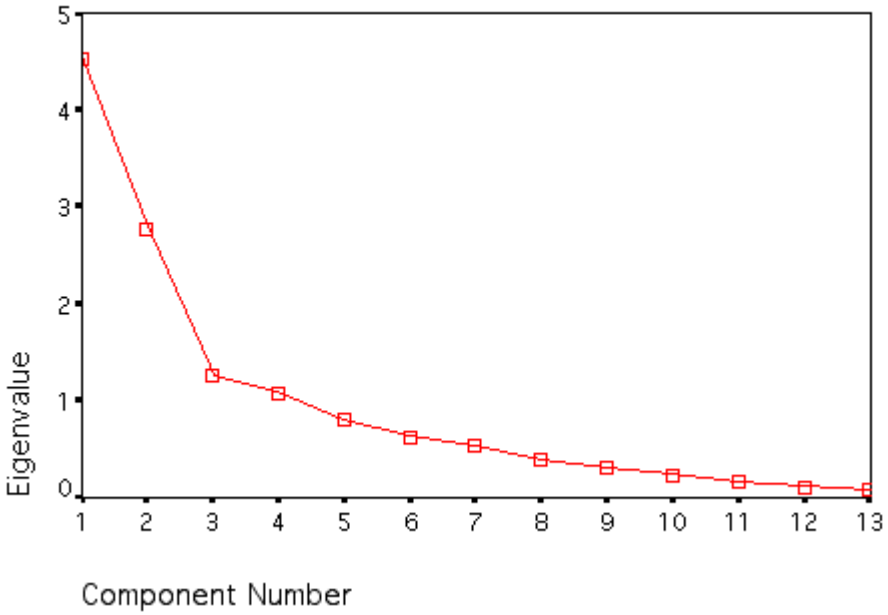
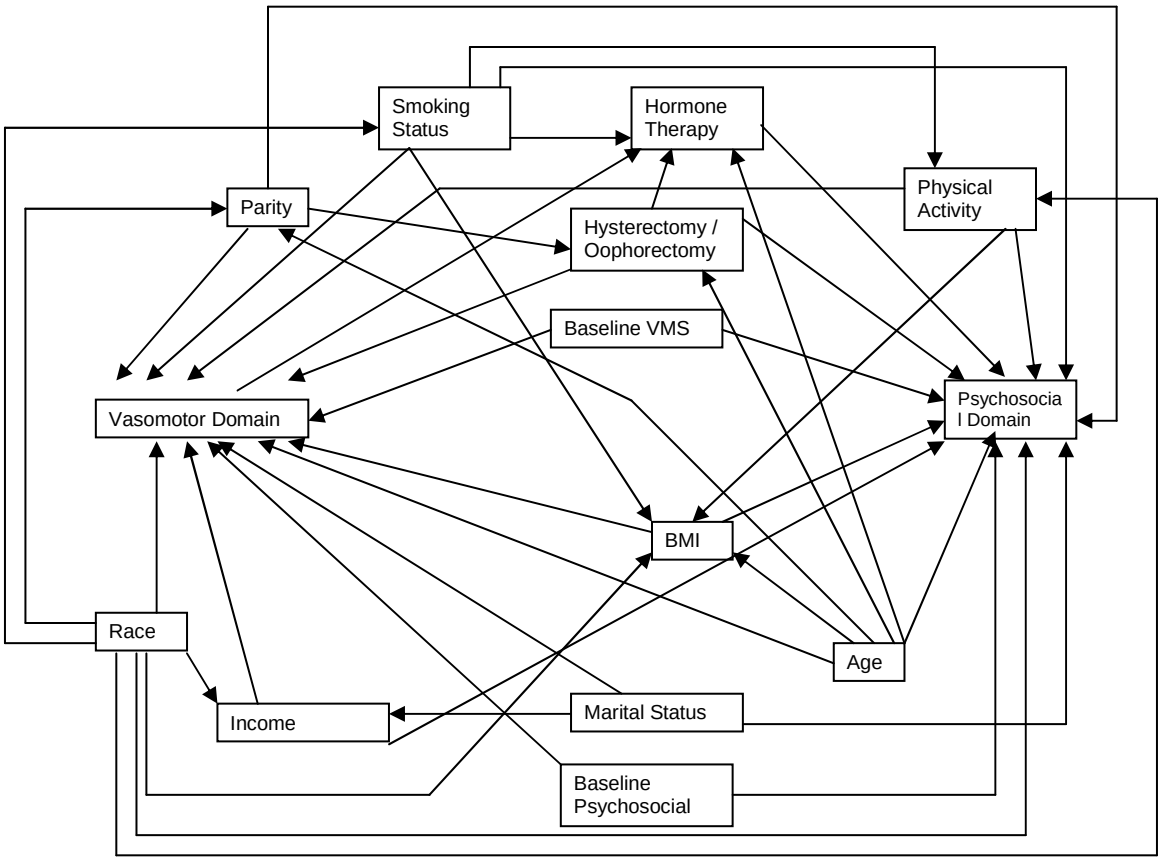


Figure 3. Scree plot example



In the figure above, an 'elbow' can be seen at component number 3, suggesting that 2 factors should be extracted from the data. Figure source: http://janda.org/workshop/factor%20analysis/SPSS%20run/SPSS08.htm

Figure 4. Directed Acyclic Graph of Study



APPENDIX

Appendix I

THE MENOPAUSE-SPECIFIC QUALITY OF LIFE QUESTIONNAIRE

Primary Care Research Unit
Department of Family and Community Medicine
Sunnybrook Health Science Centre
University of Toronto

The development of this questionnaire was funded by CIBA-Geigy Canada Ltd., Mississauga, Canada

INSTRUCTIONS

Each of the items in the questionnaire is in the form of the examples below:

		Not at all bothered	0 1 2 3 4 5 6	Extremely bothered
NIGHT SWEATS	☐ No	☐ Yes →	0 1 2 3 4 5 6	

Indicate whether or not you have experienced this problem in the ***last month.***

IF YOU ***HAVE NOT*** EXPERIENCED THE PROBLEM:

Mark "No"

NIGHT SWEATS	☐ No	☐ Yes →	0 1 2 3 4 5 6

Go to the next item.

IF YOU ***HAVE*** EXPERIENCED THE PROBLEM:

Mark "Yes", then circle how ***bothered*** you were by the problem

NIGHT SWEATS	☐ No	☐ Yes →	0 1 2 3 4 5 6

Go to the next item.

This questionnaire is completely confidential. Your name will not be associated with your responses. However, if for any reason you do not wish to complete an item, please leave it and go on to the next one.

Primary Care Research Unit
Department of Family and Community Medicine
Sunnybrook Health Science Centre
University of Toronto

The Menopause-Specific Quality of Life Questionnaire

For each of the following items, indicate whether you have experienced the problem in the **PAST MONTH.** If you have, rate how much you have been ***bothered*** by the problem.

		Not at all bothered									Extremely bothered
				0	1	2	3	4	5	6	
1.	HOT FLUSHES OR FLASHES	❑ No	❑ Yes	→	0	1	2	3	4	5	6
2.	NIGHT SWEATS	❑ No	❑ Yes	→	0	1	2	3	4	5	6
3.	SWEATING	❑ No	❑ Yes	→	0	1	2	3	4	5	6
4.	BEING DISSATISFIED WITH MY PERSONAL LIFE	❑ No	❑ Yes	→	0	1	2	3	4	5	6
5.	FEELING ANXIOUS OR NERVOUS	❑ No	❑ Yes	→	0	1	2	3	4	5	6
6.	EXPERIENCING POOR MEMORY	❑ No	❑ Yes	→	0	1	2	3	4	5	6
7.	ACCOMPLISHING LESS THAN I USED TO	❑ No	❑ Yes	→	0	1	2	3	4	5	6
8.	FEELING DEPRESSED, DOWN OR BLUE	❑ No	❑ Yes	→	0	1	2	3	4	5	6
9.	BEING IMPATIENT WITH OTHER PEOPLE	❑ No	❑ Yes	→	0	1	2	3	4	5	6
10.	FEELINGS OF WANTING TO BE ALONE	❑ No	❑ Yes	→	0	1	2	3	4	5	6
11.	FLATULENCE (WIND) OR GAS PAINS	❑ No	❑ Yes	→	0	1	2	3	4	5	6

Primary Care Research Unit
Department of Family and Community Medicine
Sunnybrook Health Science Centre
University of Toronto

The Menopause-Specific Quality of Life Questionnaire

	Not at all bothered								Extremely bothered	
		0	1	2	3	4	5	6		
12. ACHING IN MUSCLES AND JOINTS	❑ No	❑ Yes	→	0	1	2	3	4	5	6
13. FEELING TIRED OR WORN OUT	❑ No	❑ Yes	→	0	1	2	3	4	5	6
14. DIFFICULTY SLEEPING	❑ No	❑ Yes	→	0	1	2	3	4	5	6
15. ACHES IN BACK OF NECK OR HEAD	❑ No	❑ Yes	→	0	1	2	3	4	5	6
16. DECREASE IN PHYSICAL STRENGTH	❑ No	❑ Yes	→	0	1	2	3	4	5	6
17. DECREASE IN STAMINA	❑ No	❑ Yes	→	0	1	2	3	4	5	6
18. FEELING A LACK OF ENERGY	❑ No	❑ Yes	→	0	1	2	3	4	5	6
19. DRYING SKIN	❑ No	❑ Yes	→	0	1	2	3	4	5	6
20. WEIGHT GAIN	❑ No	❑ Yes	→	0	1	2	3	4	5	6
21. INCREASED FACIAL HAIR	❑ No	❑ Yes	→	0	1	2	3	4	5	6
22. CHANGES IN APPEARANCE, TEXTURE OR TONE OF YOUR SKIN	❑ Yes	❑ No	→	0	1	2	3	4	5	6
23. FEELING BLOATED	❑ No	❑ Yes	→	0	1	2	3	4	5	6

Primary Care Research Unit
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Sunnybrook Health Science Centre
University of Toronto

The Menopause-Specific Quality of Life Questionnaire

	Not at all bothered		0	1	2	3	4	5	6	Extremely bothered
24. LOW BACKACHE	☐ No	☐ Yes	→	0	1	2	3	4	5	6
25. FREQUENT URINATION	☐ No	☐ Yes	→	0	1	2	3	4	5	6
26. INVOLUNTARY URINATION WHEN LAUGHING OR COUGHING	☐ No	☐ Yes	→	0	1	2	3	4	5	6
27. CHANGE IN YOUR SEXUAL DESIRE	☐ No	☐ Yes	→	0	1	2	3	4	5	6
28. VAGINAL DRYNESS DURING INTERCOURSE	☐ Yes	☐ No	→	0	1	2	3	4	5	6
29. AVOIDING INTIMACY	☐ No	☐ Yes	→	0	1	2	3	4	5	6

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Sunnybrook Health Science Centre
University of Toronto

Appendix A2. MENQOL Scoring

Selection on MENQOL	Original MENQOL Score	Rescaled MENQOL Score
I did not experience the problem in the last month.	'No'	1
I did experience the problem, but it was not at all bothersome.	'Yes', 0	2
I did experience the symptom, and marked bothersome as a '1'	'Yes', 1	3
I did experience the symptom, and marked bothersome as a '2'	'Yes', 2	4
I did experience the symptom, and marked bothersome as a '3'	'Yes', 3	5
I did experience the symptom, and marked bothersome as a '4'	'Yes', 4	6
I did experience the symptom, and marked bothersome as a '5'	'Yes', 5	7
I did experience the symptom, and marked bothersome as a '6'	'Yes', 6	8

Each item is rescaled and then items within domains are averaged.

Appendix A3. Methodological Considerations for Inclusion of Covariates

The ultimate goal for this analysis is to evaluate the extent to which depression is exacerbated (or initiated) by bothersome hot flashes. To do so, several important confounders and effect modifiers must be considered. To date, many studies have attempted to examine associations between depression and hot flashes, but have skirted the epidemiologic issues that are inherent in conducting studies of association, namely, including crucial confounders in analysis. The following sections detail covariates that will be available from the MEPI I and its followup study and that are important potential confounders for this analysis.

Race. Race and ethnicity may be potential confounders and/or effect modifiers, but have been understudied in the specific role they play in a study on depression and hot flashes. Recent studies have shown that African American women are more likely than Caucasian women to experience hot flashes, due to differences found in estrogen levels and body mass index, even after controlling for differences in age and menopausal status (28, 102). Additionally, it was found that African American and Hispanic menopausal women had some of the highest depression scores, compared to white, non-Hispanic women (103).

Marital Status. The impact that marital status has on both vasomotor and psychosocial outcomes has been debated. While some studies have shown that separated women have significantly high MENQOL scores for vasomotor and psychosocial domains (13), others have demonstrated that married women actually exhibit the most bothersome scores (14). Given this inconsistency, and that both of these studies were performed in women of other countries, marital status is something that should be controlled for in the model, and should be done so with finer granularity than just “married vs non-married”.

Income. Though these studies were performed in various countries, the prevalence of hot flashes among low income women supersedes that of higher income women (5, 23). Also, lower income levels are a risk factor for depression, which makes income a covariate that should be controlled for (104).

Body Mass Index. Obesity and increased body mass index is a risk factor for hot flashes (105). Additionally, BMI was found to be associated not only with the existence of hot flashes, but increased frequency, and increase severity (30). On the contrary, abdominal fat increases circulating estrogen and may actually reduce the frequency and intensity of hot flashes in obese women (21) Conversely, increased body mass index has been found to lower depressive symptoms, in post-menopausal women with lower education (106). These inconsistent finding provide support for the inclusion of body mass index in models.

Smoking Status. Smoking status is known to exacerbate hot flashes (28). Additionally, smoking is associated with depression, but the true direction of causality is debated in literature (107). Smoking status' potential influence on both the exposure and outcome requires that it be included for adjustment as a confounder in the modeling algorithm.

Physical Activity Levels. The literature surrounding the association between hot flashes and physical activity is unclear. Some studies have found a dose response relationship that demonstrated increased physical activity was helpful in reducing hot flashes (108). On the contrary, other studies have found that in general, physical activity levels are not associated with hot flashes, but may be associated with decreased hot flashes in women with a history of depression (108-109). Given these contradictory results, it is possible that physical activity levels may modify the association between depression and hot flashes, and thus, must be included in analysis.

Healthcare Seeking. Women who are seeking care for their menopausal symptoms are likely to be prescribed medication, advice, and/or complementary medicine (110). This

pattern of behavior may make women who seek healthcare different from women who do not seek this service or who have limited access to care. The inclusion of this variable will prove valuable as a potential effect modifier or confounder.

Hormone Therapies. The use of estrogen alone, or combined estrogen + progestin compounds were common for the relief of hot flashes (111). This use was decreased substantially after initial reports of the potential cardiovascular threats that these compounds posed, and prescribing rates were greatly diminished (112). However, it should be noted that the effect that these compounds have on hot flashes and depression makes controlling for hormone use imperative (113).

Depression Medication. Depression medication may be the biggest potential confounder of all listed here. Depression medication, for the most obvious of reasons, is used to treat depression. However, after the results of the Women Health Initiative, many women discontinued use of hormone replacement therapy, and that this decrease was correlated with an increased use of depression medication (114). Since then, some studies have shown that depression medications such as escitalopram are more helpful than hormone therapy at reducing menopausal symptoms (115-116). Other drugs such as venlafaxine and paroxetine have been effective at reducing hot flashes and depression, but are not without side effects (64-65, 117). Other medications such as sertraline and fluoxetine have been shown to be not as effective (118).

Prior Depression Diagnosis. A history of depression earlier in life is associated with the recurrence of depression during the menopausal transition (119). Prior depression has also been associated with an increase in hot flashes (120).

History of Breast Cancer. Breast cancer is a likely confounder in this analysis due to its causal effects on both the exposure and the outcome. Breast cancer is likely to occur around the same time as the menopausal transition. Breast cancer patients often report hot flashes; this quality of life issue is only exacerbated when estrogenic compounds are

contraindicated and cannot be used for treatment (121). Breast cancer is also a known cause of depression, especially in the absence of family support (122).

Parity. Parity may play a role of a confounder in this proposed association, but literature is conflicting. In a small sample of Ecuadorian women a parity of four children or greater were associated with increased number of hot flashes (123). Likewise, post-partum depression is associated with parity and is likely to contribute to the association of parity with depression, though causal mechanisms are unclear (52).

Hysterectomy and/or Oophorectomy. The removal of a woman's uterus and, more specifically, ovaries causes the onset of surgical menopause (24). This procedure will produce hot flashes in the same manner as would a natural menopause. It has been suggested that a hysterectomy would also cause feelings of depression; if so, this is an important potential confounder which would need to be controlled for in analysis (124).

Appendix A4. Baseline covariate distribution of Women Lost to Follow-up in Menopause Epidemiology Study

Covariate	Key	Distribution % (N) (N=1506)
Age	-	Mean: 55.45 (6.2)
	40-44	5.54 (n=66)
	45-49	12.95 (n=155)
	50-54	22.39 (n=268)
	55-59	28.32 (n=339)
	60-65	30.83 (n=369)
Baseline VMS Score	-	Mean: 3.26 (2.26)
	1-<3	53.14 (n=635)
	3-<6	29.54 (n=353)
	6-≤8	17.32 (n=207)
		Missing=2
Baseline PSY Score	-	Mean: 3.38 (1.83)
	1-<3	47.58 (n=569)
	3-<6	41.39 (n=495)
	6-≤8	11.04 (n=132)
Race/Ethnicity	0=White, Non-Hispanic	77.53 (n=928)
	1= Other	22.47 (n=268)
Income	0 = <$25,000	26.02 (n=312)
	1 = $25,000 – $74,000	55.47 (n=664)
	2 = $75,000 +	18.46 (n=221)
BMI	0= <25	33.16 (n=380)
	1= 25 - <30	28.18 (n=323)
	2=≥ 30	38.66 (n=443)
		missing = 51
Marital Status	0 = Currently Married	58.90 (n=705)
	1 = Not Currently Married	41.10 (n=492)
Physical Activity	0= Never	23.06 (n=276)
	1= 1-3 days a month	25.81 (n=309)
	2= 1-3 days a week	22.14 (n=265)
	3= 3-5 days a week	23.89 (n=286)
	4= 6-7 days a week	5.01 (n=60)
Smoking	0 = Non-current smoker	74.10 (n=884)
	1= Current smoker	25.90 (n=310)
Hormone Therapy use	0= No	80.70 (n=966)
	1= Yes	19.30 (n=231)

Appendix A5. Demographics of the Subpopulations used for Analysis in Aim #2. Numbers shown are in percentages.

Characteristic	**Postmenopausal Women in MEPI baseline and Follow up (n=1,506)**	**Women on HT (n=298)**	**Women not on HT (n=1,208)**	**Women on Depression Med (n=415)**	**Women not on Depression Med (n=1,019)**	**Women not on Any Medication (n=840)**
Age						
40-44	4.5	6.0	4.1	6.5	3.8	3.6
45-49	9.4	12.1	8.7	10.6	8.9	8.2
50-54	22.4	20.1	22.9	26.8	20.9	21.6
55-59	29.0	26.9	30.0	26.0	29.9	30.7
60-65	34.7	34.9	34.7	30.1	36.4	36.0
Race/Ethnicity						
White, non-Hispanic	82.5	82.9	82.5	84.10	82.1	81.9
Black, non-Hispanic	9.30	6.4	10.0	8.0	9.8	10.2
Hispanic	5.4	7.4	4.9	6.3	4.9	5.00
Other, non-Hispanic	2.8	3.4	2.7	1.7	3.1	2.9
Educational Level						
High school or Less	45.0	43.0	45.6	46.3	44.9	45.1
Some college	29.5	28.2	29.8	32.8	27.8	28.6
Bachelor's degree or higher	25.4	28.9	24.6	21.0	27.4	26.3

Appendix A6. Association Between Change in MENQOL* Vasomotor Domain Score and MENQOL "Feeling Down, Depressed, or Blue" Score among Postmenopausal Subpopulations in the United States: Fully Adjusted Main Effects (N=1,506)

Parameter	**Mean Change in Psychosocial Score (SE)**	**P-value**
Change in Vasomotor Score	0.20 (0.04)	<0.0001
Baseline Vasomotor Score	0.17 (0.03)	<0.0001
Hysterectomy/Oophorectomy	- 0.08 (0.14)	0.54
Smoking	- 0.08 (0.05)	0.09
Physical Activity		
Never	0	0.34
1 to 3 times a month	0.22 (0.17)	
1 to 3 times a week	0.40 (0.17)	
3 to 5 times a week	0.24 (0.16)	
6 to 7 times a week	0.06 (0.26)	
Age (5 year change)	-0.13 (0.06)	0.02
Married	0.12 (0.12)	0.32
Baseline Psychosocial Score	- 0.62 (0.02)	<0.0001
Body Mass Index	0.02 (0.01)	0.02
Income Level		
Less than $25,000	0	0.99
$25,000 - $74,999	0.01 (0.09)	
$75,000 and up	0.01 (0.18)	
Other Race (vs White)	- 0.07 (0.15)	0.62
Parity		
Never	0	0.07
1	0.11 (0.06)	
2 or more	0.23 (0.13)	
Years Since Menopause (5 year change)	0.04 (0.04)	0.34
Any Depression Medication	0.57 (0.13)	<0.0001

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