NEGATIVE AFFECT AND VASOMOTOR SYMPTOMS IN THE DAILY HORMONE STUDY

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Submitted to the Graduate Faculty of

The School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2011

UNIVERSITY OF PITTSBURGH

SCHOOL OF ARTS AND SCIENCES

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December 9, 2010

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IN THE DAILY HORMONE STUDY

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Purpose: Vasomotor symptoms (VMS) are linked to poorer health and quality of life, and are common in the menopausal transition. Negative affect is consistently associated with self-reported VMS, but interpretation of the temporal and directional nature of this relationship has been limited by potentially biased retrospective recall of VMS. Using prospective data from end-of-day daily diaries, we examined the daily association and the day-to-day temporal relationship between negative affect and VMS.

Methods: Data were from the third wave of the Daily Hormone Study (DHS) (n=625). DHS is a substudy of the Study of Women's Health Across the Nation (SWAN), a multi-site community-based prospective cohort study of the menopausal transition. Daily affect and VMS were reported in diaries over 12-50 days. Multilevel mixed models, with daily observations nested within women, were used to determine the associations between daily diary-reported VMS and negative affect, adjusted by woman-level covariates (antidepressant use, age, education, menopausal status, self-reported health, and race/ethnicity) drawn from annual SWAN visits.

Results: Overall, VMS was reported on at least one day of observation by 327 women (52.3%). Women with higher average negative affect were more likely to ever report VMS (OR 1.79, 95% CI 1.30-2.45, p<.001). Negative affect was also positively associated with VMS (OR 1.76, 95% CI 1.43-2.17, p<.001) within each 24 hour period. Negative affect, adjusted by same day VMS, was not predictive of next day VMS (OR 1.107, 95% CI .85-1.35, p=.55), while VMS, adjusted

by same day negative affect, was predictive of negative affect the next day (OR 1.27, 95% CI 1.03-1.58, p=.01).

Conclusions: VMS and negative affect were positively associated with each other using prospective daily diaries. Assessment of temporal relationships suggests that VMS precedes acute elevations in negative affect, but negative affect does not increase likelihood of VMS.

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1.0 INTRODUCTION

Hot flashes and night sweats, or vasomotor symptoms (VMS), are common during the menopausal transition. These symptoms are reported by an estimated 70-80% of women, and increase in prevalence with advancing menopausal stage (Gold, 2006). The frequency, duration, severity, and bothersomeness of VMS are highly variable, and explanatory mechanisms for these differences in experience are only partially understood. Smoking, obesity, SES, and race are associated with symptom occurrence and characteristics of VMS presentation, while measures of negative affect appear to be among the strongest and most consistent correlates of VMS (Woods, 2005).

VMS have a negative impact on quality of life, and emerging associations with health functioning and cardiovascular risk factors (Thurston, 2008b) suggest that the underlying factors or ramifications of these symptoms have an impact on physical health that has not been previously recognized. Achieving a better understanding of the relationship between VMS and their common correlates may elucidate information about the mechanisms behind these events. Understanding mechanisms may also have an impact on intervention, improving quality of life and alleviating the health concerns related to VMS. While the current literature has established that negative mood and VMS are strongly associated, limitations in study design do not allow for an understanding of the temporal associations of these factors, or whether the association is still present when retrospective recall that may be biased by affect is limited.

This study aimed to use novel data collection to increase our understanding of the association between negative mood and VMS, with a focus on determining the nature of the temporal relationship between these factors. The following pages review the common presentation, course, and prevalence of VMS, the possible health implications of VMS, and current etiological theories. The common correlates of VMS seen in the literature are detailed next, with an emphasis on the relationship between VMS and negative mood. The limitations of the current literature preventing a better understanding of these associations and directionality are discussed. The study design and analytic plan are then presented, followed by results and a discussion of the study's findings.

2.0 LITERATURE REVIEW

2.1 VASOMOTOR SYMPTOMS

Vasomotor symptoms (VMS), commonly referred to as hot flashes and night sweats, are experienced as temporary sensations of intense heat accompanied by sweating and flushing (Thurston, 2009a), peaking within a minute and subsiding altogether within about five minutes (Freedman, 2001). VMS are preceded by an increase in core body temperature, and accompanied by peripheral vasodilation and increased skin temperature, blood flow, sweating, and skin conductance (Freedman, 2005). VMS are a common experience of the menopausal transition, reported by an estimated 70-80% of women. Prevalence increases with advanced

menopausal stages, with symptoms most often occurring in the late perimenopause and early post-menopause (Gold, 2006). An estimated 30% of women with daily VMS report a frequency of 10 or more occurrences each day (Freedman, 2001). VMS are generally experienced over a period of 1-5 years before subsiding, with a median duration of 4 years (Freedman, 2001). However, an estimated 20-30% of women continue to experience VMS for 10-15 years or longer (Barnabei, 2005). In addition to individual variations in duration, the severity, frequency (Woods, 2005), and perceived bother (Thurston, 2008a) of VMS are highly variable.

2.2 ETIOLOGY OF VASOMOTOR SYMPTOMS

The etiology underlying VMS and driving individual differences in symptom presentation is unclear. VMS are common in women during the menopausal transition and following natural and surgical menopause, suggesting an etiological role of estrogen withdrawal. Adding support to this theory is the general efficacy of exogenous estrogen administration in decreasing or eliminating VMS occurrence. However, VMS are not experienced by all women experiencing either gradual or sudden estrogen withdrawal (Freedman, 2005).

The thermoregulatory theory may partially explain VMS etiology. The sweating and peripheral vasodilation characteristic of VMS are heat dissipation events that naturally occur when core body temperature exceeds the upper threshold of the body's thermoneutral zone, the temperature range sufficient for function. In symptomatic women, the entire thermoneutral zone may be narrowed and the upper threshold lowered, allowing VMS to be triggered with small fluctuations in core body temperature (Freedman, 2005). Estradiol affects the hypothalamic thermoregulatory center as well as serotenergic, adrenergic, and norepinephrine

neurotransmitters (Joffe, 2007). Fluctuating estradiol levels typical in the perimenopause may therefore negatively impact thermoregulation. Neural norepinephrine, which seems to be higher in symptomatic women and increases with VMS, may be the mediator for alteration of the thermonetural zone (Keefer, 2005).

2.3 HEALTH IMPLICATIONS OF VASOMOTOR SYMPTOMS

VMS are commonly associated with decreases in quality of life and sleep disturbance (Avis, 2009). VMS may also have a significant clinical impact beyond their effects on quality of life. An estimated one-third of women with VMS seek medical attention, with increased utilization among women with frequent or bothersome VMS (Williams, 2007). Though VMS are a primary driver of treatment-seeking for menopausal problems (Guthrie, 2003), treatment-seeking is not limited to attempts to alleviate these symptoms.

VMS have increasingly been associated with overall poor health, with an emerging literature linking VMS to cardiovascular risk factors and indices of subclinical cardiovascular disease (Thurston, 2008b). VMS occurrence was associated with significant health decline over time in a prospective analysis of Whitehall II, with concordance between the severity of health decline over the menopausal transition and the severity of self-reported symptoms (Kumari, 2005). In the Melbourne Women's Midlife Health Project, a longitudinal sample of midlife women in Australia, bothersome VMS were associated with declining ratings of self-rated health (Dennerstein, 2003). In recent studies, associations between VMS, cardiovascular disease risk factors, and subclinical coronary heart disease have also been found. VMS may be associated with higher BMI, waist-hip ratio, total cholesterol level, LDL level, triglycerides level, glucose

level, and systolic and diastolic blood pressure (Gast, 2010), reduced high-frequency heart rate variability (Thurston, 2010a; Hoikkala, 2010), impaired endothelial function (Thurston, 2008b; Bechloulis, 2010) increased aortic calcified plaque (Thurston, 2008b; Thurston, 2010b), and increased intima media thickness (Thurston, in press). At this time, it is not known whether VMS increases health risks, occur more frequently due to poor health, or whether underlying factors increase the risk for both VMS and poor health among women in midlife.

2.4 COMMON CORRELATES OF VASOMOTOR SYMPTOMS

Research on the menopausal transition has elucidated several factors that tend to be associated with VMS. Both active and passive smoke exposure are associated with VMS, though the mechanisms linking exposure with symptoms is unclear (Gold, 2004). Regular physical activity may be associated with a lower prevalence and lower severity of VMS (Ivarsson, 1998; Gold, 2004), though evidence of this association is highly mixed (Greendale, 2005). Self-reported VMS have been associated with difficulty falling asleep and sleep disruption in SWAN and other samples, and women often report sleep disruption due to night sweats (Kravitz, 2008). Higher body fat percentage (Thurston, 2008b) and body mass index (BMI) (Freeman, 2001), as well as increasing body fat over the menopausal transition are associated with increased self-reported VMS (Thurston, 2009b). VMS experience appears to vary by race/ethnicity, with the highest prevalence seen among African American women and the lowest seen among Asian women. Whether these differences are due to physiological or cultural reporting issues is unclear (Gold, 2006). VMS is also more likely to be reported among women with low socioeconomic status, generally measured by educational attainment (Gold, 2006; Schwingl, 1994). As described

below, the prevalence, frequency, severity (Woods, 2005), and bothersomeness of VMS are associated with anxiety, depressive symptoms, and other measures of negative affect (Thurston, 2008a).

2.5 NEGATIVE AFFECT AND VASOMOTOR SYMPTOMS

Evidence relevant to the associations between self-reported VMS and measures of negative affect come from three types of literatures: (1) cross-sectional studies where concurrent measures of negative mood and VMS are examined; (2) longitudinal and experimental studies where concurrent measures of negative mood and VMS are examined over time; and (3) studies that use longitudinal data, experimental findings, and/or statistical methods such as path analysis to examine the associations of negative mood at one point in time in relation to VMS at another point in time, and vice versa. We now discuss each of these types of evidence, as noted in Tables 1 – 3.

2.5.1 Findings from cross-sectional studies

There are 17 cross-sectional studies relevant to this topic in the literature. Thirteen found an association between concurrently measured negative affect and VMS (table 1). This relationship was obtained in studies representing varied populations, varied characteristics of VMS, and varied measures of mood. Mood and VMS were generally self-reported, using either validated questionnaires or ad hoc symptom reporting to assess mood and VMS experience in the previous 2-4 weeks. Associations were found between the presence, frequency, severity, and bother of

self-reported VMS and depressive symptoms (Blumel, 2004; Brown, 2008; Joffe, 2002; Thurston, 2009b; Thurston, 2008a; Cheng, 2008; Hunter, 2009; Li, 2008; Seritan, 2010), anxiety (Blumel, 2004; Cheng, 2008; Hunter, 2009; Li, 2008; Seritan, 2010; Thurston, 2009b; Thurston, 2008a), psychologic distress (Bromberger, 2001; Bromberger, 2003; Ishizuka, 2008), and negative affect (Collins, 1994; Thurston, 2008a). These associations have been seen in samples in the US (Bromberger, 2003; Bromberger, 2001; Brown, 2009; Joffe, 2002; Seritan, 2010; Thurston, 2008a; Thurston, 2009b), Chile (Blumel, 2004), Taiwan (Cheng, 2008), Japan (Ishizuka, 2008), China (Li, 2008), Sweden (Collins, 1994), India, and the UK (Hunter, 2008). Findings also indicate that negative affect is a significant correlate of VMS bother, even adjusting for frequency (Thurston, 2008a), implicating a role of mood in the subjective experience of symptoms.

Although the majority of studies reported this association, there were some notable exceptions. Though significantly associated in unadjusted models, VMS and depressive symptoms were no longer associated in adjusted models in two community samples. In one study, this may have been due to the simultaneous entry of hot flashes and night sweats entered separately, rather than considered together as highly correlated measures of VMS (Bosworth, 2001). In the second study, prevalence of VMS and depressed mood were low, which may have limited their ability to find associations. Additionally, the association was not longer seen after adjusting for insomnia, though VMS continued to predict fatigue, which was associated with depressed mood (Elavsky, 2009). The relationship between VMS and depressed mood may be mediated by sleep disturbance attributable to night sweats. No association between VMS and depression was seen in two investigations that used current SCID-diagnosed depression (Ozturk, 2006; Schmidt, 2004a) rather than a more commonly reported measure of depressive symptoms.

This suggests that VMS may be more strongly related to mood symptoms rather than clinically significant mood disorders, or may be due to decreased power to identify an association given the lower number of individuals meeting diagnostic criteria. Additionally, subanalyses of some studies suggest that mood and VMS associations may be strongest in perimenopausal women. VMS were associated with anxiety in perimenopausal and post-menopausal Taiwanese women, though not premenopausal women (Cheng, 2008). Seritan et al. found a larger effect of VMS in perimenopausal women compared to post-menopausal women (Seritan, 2010), and in Joffe et al.'s (2002) sample of women seeking primary care, depressive symptoms were only linked to VMS in perimenopausal women, with no relationship seen among premenopausal and postmenopausal women.

Table 1. Cross-sectional studies

Author (year)	Sample	Subject	VMS measure	Affect measure	Supports VMS/affect association?
Blumel (2004)	N=300 Age=40-59 Sample=Chilean community sample	Role of biological and psychosocial factors in prevalence of menopausal symptoms	Self-reported VMS current bother (Greene Climacteric Scale)	Anxiety (Greene Climacteric Scale), depression (Greene Climacteric Scale)	Yes
Bromberger (2003)	N=3302 Age=42-52 Sample=SWAN	Persistent mood symptoms in pre- and early perimenopause	Self-reported VMS frequency in previous two weeks	Psychologic distress (frequency of feling blue or depressed, irritability of grouchiness, feeling tense or nervous, frequent mood changes)	Yes
Bromberger (2001)	N=16,065 Age: 42-54 Sample=SWAN screener	Psychologic distress and menopause	Self-reported VMS occurrence in previous two weeks	Psychologic distress (frequency of feeling tense/nervous, feeling blue or depressed, and feeling irritable or grouchy in previous 2 weeks)	Yes
Brown (2009)	N=639 Age=45-54 Sample=Population-based community sample	Menopausal symptoms, sleep disturbance, and depressive symptoms	Self-report: occurrence and frequency of daytime and nocturnal hot flashes in previous 30 days	Depressive symptoms (CES-D)	Yes
Cheng (2008)	N=1113 Age=43-57 Sample=Taiwanese community sample	Relationship between sleep disturbance, mood, menopausal status, and VMS.	Self-reported VMS occurrence in previous 2 weeks	Anxiety (Chinese version of the Hospital Anxiety Depression Scale (HADS)), depression (Chinese version of the Hospital Anxiety Depression Scale (HADS))	Yes
Collins (1994)	N=2011 Age=48 Swedish community sample	Reproductive health, use of estrogen and experience of menopausal symptoms in perimenopausal women	Self-reported frequency of VMS (adapted from The Menopause Symptom Inventory (MENSI))	Negative mood (self-reported tension, feeling depressed, spells of crying; adapted from The Menopause Symptom Inventory (MENSI))	Yes
Hunter (2008)	N=153 Age=45-55 Caucasian and Southeast Asian women in UK, Southeast Asian women in India	Cultural differences in the menopausal experience	Self-reported VMS occurrence in previous two weeks (Women's Health Questionnaire, vasomotor subscale)	Anxiety, depressed mood (Women's Health Questionnaire, anxiety subscale, depression subscale)	Yes

Table 1 (Continued)

Ishizuka (2008)	N=1169 Age=50 Urban Japanese community sample	Prevalence and characteristics of menopausal symptoms in Japanese women	Self-reported VMS occurrence	Psychological stress (endorsing unease or anxiety)	Yes
Joffe (2002)	N=476 Age=40-60 Primary care patients	VMS in depression in perimenopausal v. pre- and postmenopausal women	Self-report: occurrence of VMS within previous 30 days	Depressive symptoms (CES-D)	Yes
Li (2008)	N=1280 Age=45-59 Urban Chinese community sample	Prevalence of depression and anxiety, and their influence, in menopause	Self-reported VMS occurrence in previous year	Anxiety (Zung Self-rating Anxiety Scale), depression (Zung Self-rating Depression scale)	Yes
Seritan (2010)	N=487 Age=40-64 Retrospective chart review, California menopausal sx patients	Anxiety, depressive symptoms, and VMS in perimenopause	Self-reported occurence and bothersomeness of VMS in previous several weeks	Depressive symptoms (clinical intervew and response to "I have more depressed moods." Anxiety symptoms (clinical interview and response to, "I feel more anxious than usual." (anxiety and depressive symptoms combined)	Yes
Thurston (2008)	N=1042 Age=49-61 SWAN visit 7	Predictors of VMS bother	Self-report of VMS occurrence, frequency, and bother in previous 2 weeks	Negative affect (index comprised of negative mood—PANAS, depressive symptoms—CES-D, trait anxiety—Spielberger State Trait Anxiety Inventory, anxious symptoms—sum score of responses to 4 questions about irritability, nervousness, heart punding, and feeling fearful in past 2 weeks, and perceived stress—Perceived Stress Scale)	Yes
Thurston (2009b)	N=30 Age=40-60 Sample=late peri- and postmenopausal women with VMS	Laboratory hot flash classification methods	Self-reported VMS as occurring in laboratory (event marker)	Depressive symptoms (CES-D), anxiety (Spielberger State Trait Anxiety Inventory)	Yes
Bosworth (2001)	N=581 Age=45-54 Community sample	Predictors of depression in perimenopause	Self-reported VMS occurrence	Depressive symptoms (CES-D)	No

Table 1 (Continued)

Elavsky (2009)	N=212 Age=45-65 TREMIN Research Program on Women's Health	Depressed mood and fatigue as mediators between physical activity, BMI, VMS, and perceived stress	Self-reported VMS bother in previous year	Depressed mood (degree to which self-reported "feeling depressed/having the blues" in previous year)	No
Ozturk (2006)	N=151 Age=40-54 Depressed and non-depressed pre-and perimenopausal Turkish sample recruited from University perimenopause and outpatient psychiatry clinics	Comparison of depression and rsik factors in perimenopausal and premenopausal women	Self-reported current VMS bother (Greene Climacteric Scale)	Depression (SCID, Hamilton Depression Scale, Montgomery Asberg Depression Scale)	No
Schmidt (2004a)	N=100 Age=44-55 depressed and non-depressed perimenopausal women	Stressful life events, loss, and depression in the perimenopause	Presence v. absence of VMS based on mean severity/frequency of VMS self-reported on Daily Rating Form in previous 8 weeks	Depression (SCID)	No

2.5.2 Findings from longitudinal studies

As noted in Table 2, there are 12 reports on concurrently measured associations across time in longitudinal studies. The presence, frequency, and severity of VMS were associated with measures of negative affect over a range of 3 to 15 years in 9 studies. This relationship was found in 4 studies that used repeated measures regression models with depressive symptoms as the outcome, with VMS as a covariate and both factors assessed at all annual observations over 3-8 years (Avis, 2001; Avis, 1994; Bromberger, 2010; Dennerstein, 1999) and 2 studies that used repeated measures regression models with VMS as the outcome, with anxiety (Freeman, 2005; Gold, 2006) and depressive symptoms (Gold, 2006) as independent variables, and both factors assessed at all annual observations over 6-8 years. In two samples of women followed over the menopausal transition, ever reporting VMS during the observed period was associated with an increased risk of depression during that same period (Schmidt, 2004b; Cohen, 2006). Schmidt et al. followed premenopausal women until they reported amenorrhea for at least 6 months, a mean of 5 years; depression was assessed with SCID every 6 months, and daily VMS reports were collapsed into ever/never VMS over the observed period. Depressive symptoms were assessed every 6 months for 3 years, and VMS in the previous 6 months were self-reported at the final follow-up in Cohen et al.(2006). Finally, in an assessment of changing risk for depressive symptoms within women over eight years of the menopausal transition, it was found that women were twice as likely to report VMS at annual visits concurrent with high levels of depressive symptoms relative to those visits when their depressive symptoms were low (Freeman, 2006). These positive findings were seen in varied samples of women in the US (Avis, 2001; Avis,

1994; Freeman, 2006; Freeman, 2005; Gold, 2006; Schmidt, 2004b) and Australia (Dennerstein, 1999).

This relationship was not seen in all studies. Two analyses of the Seattle Midlife Women's Health Study (SMWHS) did not find a relationship between self-reported VMS severity and self-reported severity of depressed or sad mood. In a small subsample, both variables were reported concurrently in daily diaries over a period of three days every 1-3 months for a mean of 6 years, with within-woman correlations of individual annual averages of mood and VMS assessed (Woods, 2007). In a separate SMWHS analysis, depressed mood as measured annually for up to 15 years by the CES-D was related to retrospectively self-reported past-year VMS in unadjusted though not adjusted models (Woods, 2008). The authors speculate that sleep disturbance, which was related to VMS and to depressed mood in the first paper and not assessed in the second, may mediate the relationship between VMS and mood. Among the three longitudinal studies that examined diagnosed depression and VMS, one small sample (Schmidt, 2004b) found an association between ever reporting VMS over a mean of 5 years observation and perimenopausal depression as assessed by SCID every 6 months, while two other analyses of large, population-based samples (Bromberger, 2009; Freeman, 2006) with annual measures of VMS and depression did not. In one within-woman analysis of the Penn Ovarian Aging Study (POAS), depression as diagnosed by PRIME-MD was not associated with VMS, while depressive symptoms as measured by CES-D were (Freeman, 2006). All VMS and mood assessments were completed every 8-12 months over 8 years of observation. The authors suggested that power may have been limited to find a relationship in the small number of women with diagnosable depression. This outcome is consistent with the previously reviewed findings

of SCID-diagnosed depression in the cross-sectional literature; the relationship between VMS and depressive symptoms may be stronger than that between VMS and clinical diagnoses.

Overall, findings from cross-sectional and longitudinal studies in which VMS and mood are assessed concurrently largely support an association between measures of negative mood and self-reported VMS. This relationship is present in a variety of samples, with varying measures of mood and self-reported VMS, and persists over time. The relationship appears strongest in the perimenopause, and with measures of symptoms rather than diagnosable mood disorders. However, the nature of this relationship is not known. The temporal relationship between these factors cannot be determined from the literature reviewed, and few investigators purposefully attempt to address it.

Table 2. Longitudinal studies

Author (year)	Sample	Subject	VMS measure	Affect measure	Outcome of interest	Supports VMS/affect association?
Avis (2001)	N=309 Age=43-53 Sample=Massachussetts Women's Health Study Timeframe=3 years	Association between depression and estradiol in menopause	Self-reported VMS occurrence	Depressive symptoms (CES-D)	Depressed mood	Yes
Avis (1994)	N=2565 Age=43-53 Sample=Massachussetts Women's Health Study Timeframe=5 years	Menopausal status and depression	Self-reported VMS occurrence	Depression	Depressed mood	Yes
Bromberger (2010)	N=3302 Age=42-52 Sample=Study of Women's Health Across the Nation Timeframe=8 years	Hormone levels and depressive symptoms in menopause	Self-reported VMS occurrence in previous two weeks	Depressive symptoms (CES-D)	Depressed mood	Yes
Cohen (2006)	N=460 Age=36-45 Sample=premenopausal women with no history of depression from Harvard Study of Mood and Cycles Timeframe=3 years	Menopausal transition and risk for new onset of depression	Self-reported VMS presence in previous 6 months	Depressive symptoms (CES-D)	Depressed mood	Yes
Dennerstein (1999)	N=354 Age=45-55 Sample=MWMHP (Australia) Timeframe=6 years	Predictors of negative mood in menopause	Self-reported bothersome VMS in previous 2 weeks	Negative moods (Affectometer-2 subscale)	Negative mood	Yes
Freeman (2006)	N=231 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=8 years	Menopausal status and hormonal changes as predictors of depression in menopause	VMS occurrence, frequency, and severity in previous month	Depressed mood (CES-D)	Depressed mood	Yes

Table 2 (Continued)

Freeman (2005)	N=436 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=6 years	Anxiety and hormonal changes as predictors of VMS	VMS occurrence, frequency, and severity in previous month	Anxiety (Zung Anxiety Index)	VMS	Yes
Gold (2006)	N=3198 Age=42-54 at baseline Sample=SWAN Timeframe=6 years	Race/ethnicity and VMS	Self-reported VMS occurrence in previous 2 weeks	Anxiety (sum score of responses to four questions), depressive symptoms (CES-D)	VMS	Yes
Schmidt (2004b)	N=29 Age=45-55 Sample=asymptomatic premenopausal volunteers Timeframe=mean 5 years (until postmenopausal)	Menopausal status and depression	Self-reported VMS occurrence (confirmed by daily ratings)	Depression (SCID)	Depression	Yes
Bromberger (2009)	N=266 Age=42-52 Sample=Study of Women's Health Across the Nation Timeframe=7 years	Predictors of incident depression in midlife	Self-reported VMS occurrence in previous two weeks	Depression (SCID)	Depression	No
Woods (2008)	N=302 Age=35-55 Sample=Seattle Midlife Women's Health Study Timeframe-15 years	Depressed mood in the menopausal transition	Self-reported occurrence and severity of VMS in previous year	Depressed mood (CES-D)	Depressed mood	No
Freeman (2006) (repeat entry; separate analysis)	N=231 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=8 years	Menopausal status and hormonal changes as predictors of depression in menopause	VMS occurrence, frequency, and severity in previous month	Depression (PRIME-MD)	Depression	No
Woods (2007)	N=41 Age=35-47 Sample=SMWHS Timeframe=8 years	Menopausal symptoms and hormonal changes in the menopausal transition	VMS occurrence and severity self-reported in daily diaries for 3 days	Depressed mood (daily diary)	Depressed mood, VMS	No

2.5.3 Studies addressing temporal association

2.5.3.1 Treatment studies Though not specifically designed to test the temporal relationship between mood and VMS, experimental studies examining interventions for VMS that are traditionally used to alleviate negative mood symptoms and/or reduce stress, such as pharmacological treatment with SSRIs or SNRIs, could be utilized to assess the temporal relationship between mood and VMS. VMS reduction secondary to improvements in mood would suggest that mood precipitates and influences VMS presentation; simultaneous improvement in mood and VMS may suggest that a third factor affected by the treatment, such as serotenergic function, underlies both factors. However, evidence from these trials is limited. Studies are generally small, of short duration, and largely comprised of women with a history of breast cancer, which may have a different influence on VMS etiology and treatment (Suvanto-Luukkonen, 2005). Further, mood changes are not often measured, and the temporal association between changes in mood and VMS is not usually tested.

Six studies assessed mood as well as VMS changes, but the sample sizes in four are too small for interpretation (Joffe, 2007; Ladd, 2005; Schmidt, 2000; Soares, 2006). In the two trials with sufficient sample size (Gordon, 2006; Suvanto-Luukkonen, 2005), there was improvement in both mood and VMS, but changes in these factors were not related (Suvanto-Lukkonen, 2005), and VMS reductions were not attributable to treatment effects on mood (Gordon, 2006). However, the trial duration in one trial of sufficient sample size was only 4 weeks (Gordon, 2006), and it is possible that this timeframe was not sufficient to see possible VMS reductions attributable to continued mood improvement. Further, there was a substantial VMS reduction in response to placebo in both trials, an effect which has been reported to exceed

30% in several treatment studies (van Die, 2009). The placebo effect may be specific to the subjective experience of symptoms; placebo response was seen with self-reported VMS, but not with physiologically measured VMS, in one study of breast cancer survivors (Carpenter, 2007). Overall, pharmacological treatment appears to have an effect on VMS that may be mediated by central nervous system changes or mood effects on appraisal, but current investigations do not adequately examine these relationships to contribute to conclusions.

2.5.3.2 Epidemiological Studies Data from epidemiological studies can offer information about the temporal relationship between affect and VMS assessed in annual assessments. To that end, six analyses of longitudinal samples are discussed below. Two analyses of the Penn Ovarian Aging Study (POAS) that set out to examine the temporal association between these factors suggest that mood precedes VMS. In a lagged analysis predicting self-reported VMS in the past month at each annual assessment over 6 years, previous-year anxiety scores (Zung Anxiety Scale) and anxiety score change over the past year predicted VMS as well as initial VMS onset (Freeman, 2005). However, the alternate pathway, VMS preceding anxiety, was not tested. In another within-woman assessment of women without VMS or depressive symptoms at baseline, depressed affect occurred prior to VMS in 24% of the women who subsequently experienced both over the 10-year observed period; this relative risk is twice what would be expected if the two symptoms were due to entirely independent processes (Freeman, 2009). In the POAS, both anxiety and depressive symptoms seem to precede VMS onset when both are measured annually and assessed over the menopausal transition. Other longitudinal studies confirmed predictive pathways over the menopausal transition with either VMS or depressive symptoms as the outcome. Consistent with Freeman et al. (2004, 2009), two studies predicted VMS at follow-up from baseline measures of depressive symptoms four years (Freeman, 2001)

and nine years (Guthrie, 2005) previously, and one survival analysis with depressive symptoms as a biennially measured time-varying covariate predicted the onset of VMS and other menopausal symptoms over a 10 year period (Sabia, 2008). In contrast, depressive symptoms in the final study visit were predicted from annual observations of VMS and other factors over the previous 10 years in another epidemiological sample (Dennerstein, 2004). While these longitudinal samples suggest that measures of affect at one point in time can predict VMS at another, and that VMS over time can predict later depressive symptoms, only the analyses of the POAS were purposefully designed to test which factor appears to precede the other over time.

2.5.3.3 Ambulatory and Daily Diary Studies As opposed to the summary measures of mood and VMS collected in treatment and epidemiological studies, ambulatory and daily diary data can be utilized to investigate the relatively acute effects of mood on VMS, and vice versa. These prospective data collection methods also limit the potential bias of long-term retrospective recall. Thurston et al. (2005) investigated the effect of acute emotional arousal on VMS over the course of two days using ambulatory physiologic and self-report VMS measurement. Mood ratings were collected on a fixed schedule three times an hour, self-reported VMS were self-reported as they occurred, and skin conductance was continually monitored for physiologically measured VMS. Self-reported VMS not accompanied by physiological evidence were more likely in women whose responses to psychometric questionnaires at the initiation of data collection indicated overall increased depression, state anxiety, trait anxiety, and somatization, and self-reported VMS tended to occur after periods of increased frustration. This relationship was not seen with physiologically measured VMS, which were more likely after positive rather than negative emotional states. Self-reported VMS was both precipitated by negative emotion and more common in women with increased negative mood (Thurston, 2005). The difference

between physiologically measured and self-reported VMS suggests the importance of mood specifically in the subjective experience of symptoms.

Other studies have used daily diaries and path analysis to examine VMS as a precipitant of negative mood. VMS reported in daily diaries over five days were used in a structural equation model analysis designed to test a proposed pathway from VMS to an annual measure of depressed mood in women in midlife. This analysis of the Seattle Midlife Women's Health Study (SMWHS) did not find a direct effect of VMS on depressed mood (Woods, 1997). The lack of association in this study may stem from several factors. First, VMS severity rather than occurrence or frequency was used to assess VMS. However, severity was low in this sample, with a mean value suggesting that most women experienced no symptoms, or few symptoms with limited severity. The limited symptom experience may explain the absence of an association, and may be due to the fact that data were drawn from the first year of collection, when only a small percentage of women appeared to have begun the transition to perimenopause. As previously discussed, the association between mood and VMS may not be consistently seen in women outside of perimenopause.

Burleson et al. (2010) collected daily diary ratings of VMS and mood items from 55 healthy women in midlife over up to 5 years. They created a structural equation model using 252 contiguous, highly symptomatic days for each woman to test the direct relationship between VMS and next-day mood, and a mediated relationship between VMS and mood by way of sleep problems. VMS predicted lower next-day positive mood and higher next-day negative mood, but only in women who did not have high depression scores at study entry (Burleson, 2010). While the findings supported the theory that VMS precedes mood over short periods of time, the effect on acute mood states was only seen in women without high stable measures of negative

affect. Further, although a number of models indicating potential causal pathways can be statistically supported when two factors are significantly correlated (SPSS Wikia, 2010), alternate path models were not reported; interpretation may have been biased by a priori assumptions of directionality. Finally, only half of this small sample had reached perimenopausal status at the initiation of data collection, and as previously reported, the association between affect and VMS may not be present or as strong in non-perimenopausal women. This analysis did not adjust for menopausal status or any other woman-level covariates. Overall, studies that test or offer information about the temporal associations between mood and VMS are few, and yield mixed evidence. Though the efficacy of mood-alleviating treatments for VMS would suggest that mood precipitates VMS, the mood-independent efficacy of treatment tend to offer more support to the third factor theory than to either theory of temporal relationship. The theory that mood precedes VMS is supported by some epidemiological and ambulatory data, suggesting that both stable affect and short-term, acute mood states may influence VMS presentation. There is also limited evidence from diary studies that VMS precedes mood when both are measured on a daily basis.

Table 3. Temporal relationships

Author (year)	Sample	Subject	VMS measure	Affect measure	Outcome of interest	Directionality of effect
Treatment studies						
Gordon (2006)	N=102 Age=40-65 Sample=Healthy women with VMS Timeframe=4 weeks	Sertraline for the treatment of VMS	VMS presence/severity self-reported in daily diary	Depressive symptoms (Medical Outcomes Study) at baseline and week 4	VMS reduction	3rd factor >VMS, mood?
Joffe (2007)	N=20 Age=40-60 Sample= Depressed women with frequent VMS Timeframe=8 weeks	Duloxetine for the treatment of depression and VMS in depressed women	VMS presence/severity self-reported with the Greene Climacteric Scale vasomotor subscale at two and eight weeks	Depressive symptoms (Montgomery-Asberg Depression Rating Scale), anxiety (Beck Anxiety Inventory) at two and eight weeks	VMS and depressive symptom reduction	3rd factor >VMS, mood?
Ladd (2005)	N=16 Age=42-51 Sample= Depressed perimenopausal women Timeframe=8 weeks	Venlaxafine for the treatment of depression and VMS in depressed women	VMS presence/severity self-reported with the Greene Climacteric Scale vasomotor subscale at two and eight weeks	Depressive symptoms (Hamilton Rating Scales for Depression), anxiety (Hamilton Rating Scales for Anxiety)	VMS and depressive symptom reduction	3rd factor >VMS, mood?
Schmidt (2000)	N=34 Age=44-55 Sample=Depressed women with and without VMS Timeframe=6 weeks	Hormone therapy for the treatment of perimenopausal depression in women with and without VMS	VMS presence as self-reported in daily diaries during screening phase	Depressive symptoms (CES-D, Ham-D)	Depressed mood	3rd factor >VMS, mood?
Soares (2006)	N=40 Age=40-60 Sample=Depressed women with frequent VMS Timeframe=8 months	Hormone therapy v. escitalopram for the treatment of VMS and depression	VMS presence/severity self-reported with the Greene Climacteric Scale vasomotor subscale at two, four, and eight weeks	Depressive symptoms (Montgomery-Asberg Depression Rating Scale)	VMS and depressive symptom reduction	3rd factor >VMS, mood?

Table 3 (Continued)

Suvanto-Luukkonen (2005)	N=150 Age=45-66 Sample=Healthy postmenopausal women with VMS (Finland) Timeframe=9 months	Citalopram and fluoxetine for the treatment of VMS in non-depressed women	VMS frequency self-reported in daily diary for 9 months	Depressive symptoms (Beck Depression Inventory)	VMS reduction	3rd factor >VMS, mood?
Epidemiological studies						
Dennerstein (2004)	N=438 Age=45-55 Sample=MWMHP (Australia) Timeframe=11 years	Predictors of depressed mood in menopause	Self-reported bothersome VMS in previous 2 weeks	Depressive sympotoms (CES-D)	Depressed mood	VMS > Mood
Freeman (2009)	N=170 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=10 years	VMS and depressed mood in menopause	VMS occurrence, frequency, and severity in previous month	Depressed mood (CES-D)	VMS, depressed mood	Mood > VMS
Freeman (2005)	N=436 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=6 years	Anxiety and hormonal changes as predictors of VMS	VMS occurrence, frequency, and severity in previous month	Anxiety (Zung Anxiety Index)	VMS	Mood > VMS
Freeman (2001)	N=375 Age=35-47 Sample=Penn Ovarian Aging Study Timeframe=9 months	Predictors of VMS in late reproductive years	VMS occurrence, frequency, and severity in previous month	Anxiety (Zung Anxiety Index)	VMS	Mood > VMS
Guthrie (2005)	N=350 Age=45-55 Sample=Melbourne Women's Midlife Health Project (MWMHP) Timeframe=9 years	Predictors of VMS presence, severity, and frequency	Self-reported severity and frequency of bothersome VMS in previous 2 weeks	Negative moods (Affectometer-2 subscale)	VMS	Mood > VMS

Table 3 (Continued)

Sabia (2008)	N=28,118 Age=50-75 Sample= French E3N Timeframe=biannual questionnaires over 10 years	Risk factors for onset of menopausal symptoms	Self-reported occurrence of menopausal symptoms (list of 5, including VMS)	History of depression at baseline (self-report)	VMS (among other menopausal symptoms)	Mood > VMS
Ambulatory and daily diary studies						
Burleson (2010)	N=55 Age=42-52 Sample=healthy volunteers Timeframe=36 contiguous weeks within 5 years of data collection	SEM model testing direct effects of VMS on mood and indirect effect via sleep disruption	Self-reported VMS occurrence and frequency self-reported in daily diaries for up to 5 years (36 contiguous weeks used in analyses)	Negative mood (mean composite score from daily diary checklist: anxious, depressed, distressed, nervous, hostile, ashamed, guilty, irritable)	Negative mood	VMS > mood
Thurston (2005)	N=42 Age=40-60 Sample=peri- and postmenopausal women with VMS Timeframe=Two noncontiguous 24 hour periods	Emotional antecedents of VMS	Self-reported VMS as occurring (behavioral diary, event marker), physiologically measured VMS (sternal skin conductance)	Depressive symptoms, state anxiety, trait anxiety	VMS	Mood > VMS
Woods (1997)	n=337 age=35-47 Sample=Seattle Midlife Women's Health Study Timeframe=5 days	Depressed mood in the menopausal transition	VMS occurrence and severity self-reported in daily diaries for 5 days	Depressed mood (CES-D, SCL-90)	Depressed mood	Not seen

2.5.4 Summary of current literature

Vasomotor symptoms are common in the menopausal transition, and are linked to decreased quality of life and declining health status. However, the frequency, severity, duration, and perception of these common events are highly variable. The mechanisms behind these events and reasons for their variable presentation are not well understood. Measures of negative affect are consistently associated with self-reported VMS when both are measured concurrently or at one point in time relative to another, though the nature of this relationship is not currently understood. This relationship seems to be strongest in perimenopausal women and with measures of anxiety, and is not always seen in non-perimenopausal women or women with diagnosed depression. Negative mood may precipitate VMS, a theory which is supported by ambulatory measurement of self-reported mood and VMS and findings from longitudinal analyses comparing the onset of VMS to the onset of anxious and depressive symptoms over the menopausal transition. It is also possible that VMS instead precipitates negative mood, which is assumed in studies attributing an increase in negative mood over the menopausal transition to an increase in VMS, and supported by one investigation into VMS as a daily precursor to negative mood. Alternatively, a third, unmeasured factor may underlie both mood and VMS. This perspective may be supported by treatment studies, in which interventions typically used to treat mood also effectively treat VMS, without strong evidence that the treatment effect is acting via mood changes.

2.5.5 Limitations of the current literature addressed in study

Interpretation of the relationship between affect and VMS is currently limited by potentially biased retrospective recall of VMS, infrequent measurement of VMS and affect, and limited investigations into the temporal relationship between these factors. Cross-sectional studies provide information about the association between affect and VMS, but interpretation of the association is difficult and could be due to any possible pathway between or underlying these factors. Affect and VMS are assessed only at one point in time, and may not represent stable patterns. Further, VMS in these studies are largely reported by retrospective recall; the association between negative affect and VMS may be due to recall biased by affect at the time of reporting (Thurston, 2005). Longitudinal studies offer more robust evidence of the association over time, but are also subject to the third factor issue and potentially biased VMS reporting based on the same retrospective recall methods. While longitudinal studies can be utilized to help elucidate the directionality of the association between affect and VMS, few have purposefully done so.

The proposed study will attempt to address these limitations. Interpretation of associations seen in the current literature, based largely on findings from one-time and annual assessments, will be expanded by utilizing novel data collection to assess acute associations between measures of negative affect and VMS over time. Daily prospective measures of mood and VMS will limit the potential bias of retrospective recall while allowing examination of temporal relationships on a day-to-day basis between factors. While this is not the first study to specifically look at acute changes in affect or VMS in relation to the other with prospective diary data, the few existing studies are hampered by small sample sizes, short observation periods, statistical conclusions biased by *a priori* assumptions, no consideration of woman-level

covariates, and observation during periods of limited symptom experience. In contrast, the proposed study will utilize a large, ethnically diverse sample followed over several weeks, resulting in over 21,000 observations. This primarily perimenopausal sample is expected to have a high level of VMS as well as negative mood symptoms, and represent the cohort most likely to exhibit a relationship between these factors. While *a priori* hypotheses regarding the temporal associations between VMS and affect will be made, bidirectional relationships will be tested and reported.

3.0 SPECIFIC AIMS

Using the daily diaries of the SWAN Daily Hormone Study (DHS), prospectively recorded affect and vasomotor symptoms among women in the menopausal transition was examined to evaluate the day-to-day associations between negative affect and VMS over the course of one menstrual cycle or comparable period, with a breadth of contributing factors taken into account. The temporal relationship between day-to-day affect and VMS occurrence was evaluated. The use of prospective daily diary data limited the retrospective bias inherent in most existing studies of VMS.

4.0 HYPOTHESES

VMS and measures of negative affect are generally associated in cross-sectional and longitudinal measurements of both factors. To that end, we expected to replicate this relationship in this sample, with daily measurements of VMS and affect across a menstrual cycle among women in midlife.

H1: Negative affect in a given 24-hour period will be associated with vasomotor symptoms in that same 24-hour period over the course of a menstrual cycle or comparable period.

Negative affect may impact the subjective experience of symptoms, influencing symptom perception via increased cognitive catastrophization, vigilance to somatic symptoms, or anxiety sensitivity, creating an environment in which symptoms are more commonly perceived and reported (Hannisch, 2008; Thurston, 2008a). Negative emotional arousal and stress may serve as an acute trigger for VMS, which has been anecdotally reported and supported by ambulatory measurement of self-reported symptoms (Thurston, 2005). This influence of mood on subjective experience is further suggested by the association of negative mood with self-reported, but not objectively measured VMS, the strong effect of placebo treatment on self-reported symptoms, and the influence of negative affect on subjective characteristics of experience such as symptom bother (Thurston, 2008a). This relationship has also been supported by analyses indicating that anxiety (Freeman, 2005) and depressive symptoms

(Freeman, 2009), precede the onset of self-reported VMS. Therefore, we hypothesized that mood would precede VMS.

H2: Negative affect in a given 24-hour period will be associated with vasomotor symptoms in the subseqent 24-hour period adjusting for VMS in the prior 24 hours over the course of a menstrual cycle or comparable interval .

While perimenopausal depression and an increase in negative mood over the menopausal transition are often attributed to increased VMS (Keefer, 2005), this relationship is not always seen when explicitly tested. Further, the lack of a relationship between objective measures of VMS and negative mood implies that mood influences symptom perception rather than that symptoms themselves precipitate mood. Therefore, we hypothesized that VMS would not precede mood in this sample.

H3: Vasomotor symptoms in a given 24-hour period will not be associated with negative affect in the subsequent 24-hour over the course of a menstrual cycle or comparable period.

5.0 STUDY IMPLICATIONS

Better understanding the relationship between negative mood and VMS may help elucidate the mechanisms underlying VMS, influencing intervention strategies for women in the menopausal transition. Examining this relationship in a daily fashion also provided the opportunity to uncover potential shortcomings or biases in typical measurement.

6.0 METHODS

6.1 PARTICIPANTS

The Study of Women's Health across the Nation (SWAN) is a multiethnic, community-based natural history cohort study of 3,302 women at seven sites across the United States followed annually as they approach and traverse the menopause. The details of recruitment and enrollment have been reported elsewhere in detail (Sowers, 2000). Briefly, eligible women were, at baseline, aged 42–52 years, self-identified with one of five racial/ethnic groups (Caucasian, African-American, Chinese, Japanese, or Hispanic), reported at least one menstrual period in the prior 3 months, did not use sex-steroid hormones in the prior 3 months, had an intact uterus and at least one ovary, and were not currently pregnant or breastfeeding (Skurnick, 2009). SWAN is a unique study in its large sample size, geographic distribution, and multiethnic composition. The ability to follow this number of women over the course of the menopausal transition has enhanced our understanding of the physical and emotional symptoms and experiences of menopause. By following this diverse population over time, we are able to advance our knowledge of the menopause in women overall and in specific, understudied populations.

Of the 3,302 women in the SWAN cohort, 1,443 were screened for Daily Hormone Study (DHS) eligibility. Inclusion criteria for recruitment into the DHS were: 1) an intact uterus and at least one ovary, 2) at least one menstrual period in the previous 3 months, 3) no use of sex steroid

hormones in the previous 3 months, and 4) not pregnant. Of the 1,219 eligible women invited to complete the baseline urine collection, 848 (69.6%) women agreed to participate and provided a sufficiently complete cycle for analysis. The present analysis used the third year of DHS (DHS 3), which includes 651 of the original 848 women. Reasons for discontinuation or non-participation in DHS 3 included current or recent (within the previous 3 months) HT use (n=65), fertility medication use (n=1), and oral contraceptive use (n=3), bilateral oopherectomy (n=7), more than one year of amenorrhea (n=7) (women were eligible in the first year of becoming postmenopausal), refusal or inability to participate in that year's DHS visit (n=40), and attrition from SWAN (n=74). Women who had a hysterectomy were eligible as long as they retained one or both ovaries. More information on the details of data collection based on different eligibility parameters is available in figure 1. SWAN DHS maintains the diversity of the larger SWAN cohort, while adding knowledge of the day-to-day experience of menopause and hormonal changes to the information gained in annually collected measures. DHS 3 was chosen as the analytic sample because it is comprised of a larger percentage of perimenopausal women (80%) than other available years. We therefore expected the greatest frequency of VMS (Gold, 2006) and negative mood (Bromberger, 2010), and the strongest association between VMS and mood (Seritan, 2009), in this over other available samples.

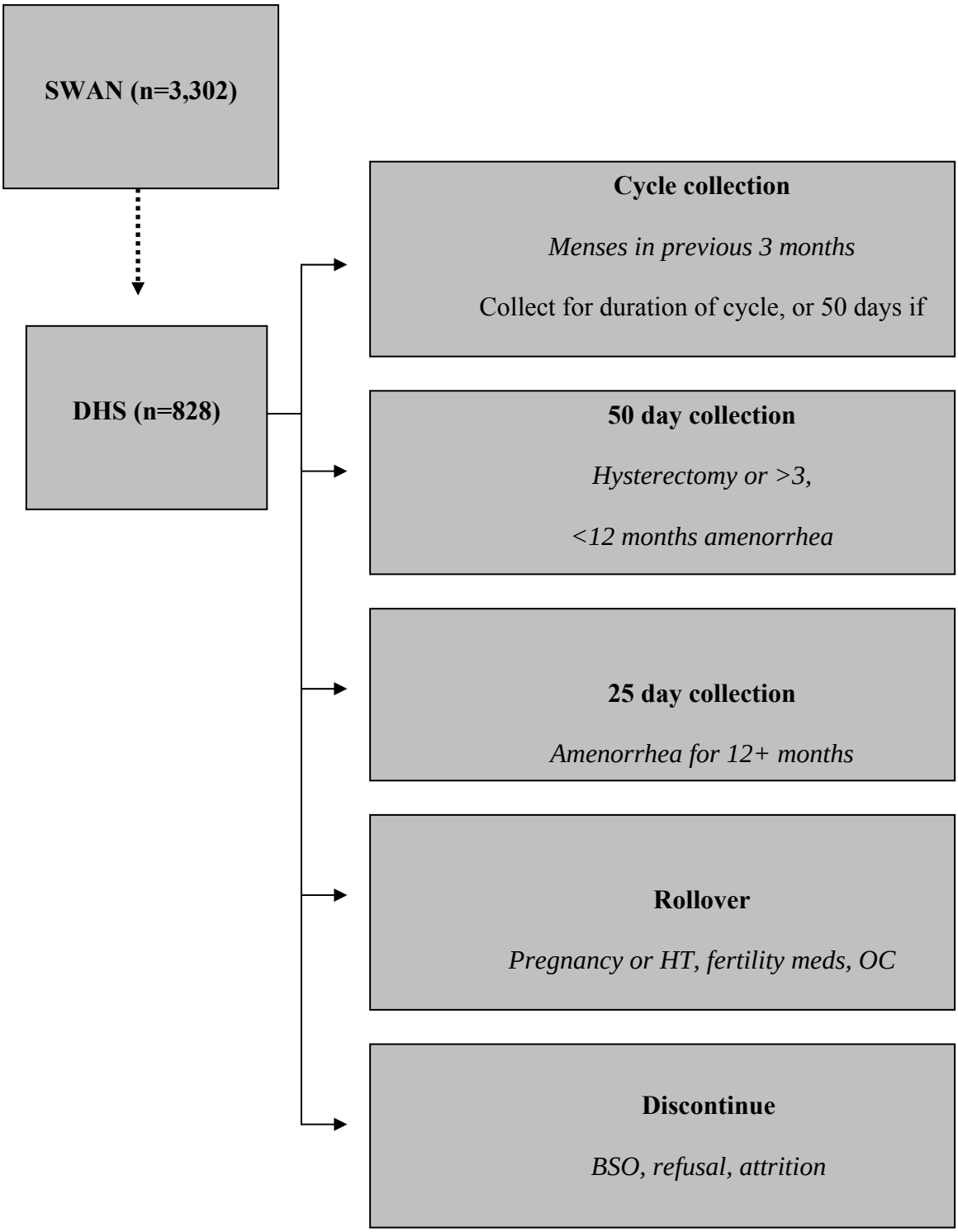


Figure 1. Daily Hormone Study Schematic

6.2 PROCEDURE

DHS enrollees completed a daily diary in which they recorded experience of any vasomotor symptoms within the preceding 24 hours for an entire menstrual cycle ending in bleeding or 50 days, whichever came first. Women who did not have a bleeding cycle coincident with 1-year follow-up began on the next convenient day and collected for 50 days or until a menstrual cycle began. Women who had no menses for the 12 months before an annual follow-up kept a daily diary for 25 days (Skurnick, 2009). Parameters for data collection are detailed in figure 1.

6.3 MEASURES

6.3.1 Outcomes

6.3.1.1 Diary overview Participants in DHS were asked to complete a daily diary every evening before bed for the duration of the study. The diary was one page long, with 14 feelings and physical states (happy, bored, headaches, blue/down, tired, aches/pains, calm, forgetful, mood swings, irritable, anxious, confident/in control, difficulty concentrating, feelings easily hurt) listed along with three yes/no questions about other symptoms. A 1-4 scale was listed beside each item (1=not at all, 2=a little bit, 3=moderately, 4=a lot). Before bed, participants were asked to mentally review their day and record how strongly they felt each item during the previous 24 hours. A sample diary is depicted in figure 2.

BEDTIME DIARY

Date _____ DATE

Day DAY_____ **Time** DIAHOUR, DIAMIN **PM/AM** DPMAM

Circle the number that best describes how strongly (or intensely) you felt each of the following during the past 24 hours.

	Not at all	A little bit	Mode-rately	A lot
happy HAPPY	1	2	3	4
bored BORED	1	2	3	4
headaches HEADACH	1	2	3	4
blue/down BLUE	1	2	3	4
tired TIRED	1	2	3	4
aches/pains ACHES	1	2	3	4
calm CALM	1	2	3	4
forgetful FORGET	1	2	3	4
mood swings MOODY	1	2	3	4
Irritable IRRITA	1	2	3	4
anxious ANXIOUS	1	2	3	4
confident/in control CONFI	1	2	3	4
difficulty concentrating CONCEN	1	2	3	4
feelings easily hurt EHURT	1	2	3	4

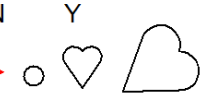
Think back over the last 24 hours and indicate whether or not you had any of the following.

Trouble sleeping? N Y TSLEEP

Hot flashes/ night sweats? N Y NSWEAT

Abdominal pain/cramps? N Y APAIN

Comments? _____ DIA_SP

HEART → 

_____

_____

Figure 2. Daily Hormone Study Daily Diary

(underlined text from codebook, not included in participant version)

6.3.1.2 Vasomotor symptoms A single question in the daily diary asked if participants had experienced hot flashes/night sweats in the previous 24 hours. A binary variable was created from these yes/no responses.

6.3.1.3 Measure of negative affect A principal components analysis (PCA) was conducted with oblique rotation in SPSS (SPSS, 2008) on the 14 items of the daily diary. Because the number of observations differed between women in this sample, the PCA was run with data from only the first twelve observations, the minimum number of observations available for all participants. PCA revealed the presence of three components with eigenvalues exceeding 1. The relatively high correlations between factors and comparison of the pattern and structure matrix suggested that oblique rotation was most appropriate for this data.

The first component was comprised of seven variables related to negative mood: mood swings, feelings easily hurt, irritable, difficulty concentrating, forgetful, anxious, and blue/down, with factor loadings ranging from .53 (blue/down) to .85 (mood swings) (Tables 4, 5). This component explained 39.0% of the variance and had a Cronbach's alpha of .87. These items were summed, and a mean score calculated for each daily observation. This daily negative mood variable was dichotomized due to its non-normal distribution, with scores ≥ 2 indicating the presence of negative mood. For the purposes of preliminary analysis, the overall mean negative mood score across all observations for each participant was also calculated, and also dichotomized with scores ≥ 2 indicating the presence of higher overall negative mood.

6.3.1.4 Measure of positive affect A positive affect variable was drawn from the second factor of the PCA, comprised of 3 items: confident/in control, happy, and calm. This item explained 10.2% of the variance, and has a Cronbach's alpha of .77. Daily and overall mean composite positive mood variables were created for each participant, and treated as continuous variables.

Table 4. Principal Component Analaysis Pattern Matrix

	Component		
	1	2	3
Past 24h-mood swings	.851		
Past 24h-feelings easily hurt	.838		
Past 24h-irritable	.741		
Past 24h-anxious	.653		
Past 24h-difficulty concentrating	.649		
Past 24h-forgetful	.595		
Past 24h-blue/down	.534		
Past 24h-bored	.338		
Past 24h-confident/in control		.807	
Past 24h-calm		.775	
Past 24h-happy		.765	
Past 24h-aches/pain			-.821
Past 24h-headaches			-.685
Past 24h-tired			-.664

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

a. Rotation converged in 6 iterations.

Table 5. Principal Components Analaysis Structure Matrix

	Component		
	1	2	3
Past 24h-mood swings	.823	-.347	
Past 24h-irritable	.779	-.371	-.360
Past 24h-feelings easily hurt	.766	-.308	
Past 24h-difficulty concentrating	.710		-.460
Past 24h-anxious	.689	-.426	
Past 24h-blue/down	.684	-.531	-.349
Past 24h-forgetful	.603		-.425
Past 24h-bored	.419		
Past 24h-confident/in control	-.377	.825	
Past 24h-happy	-.371	.788	
Past 24h-calm	-.352	.787	
Past 24h-aches/pain	.305		-.803
Past 24h-tired	.409	-.314	-.723
Past 24h-headaches	.312		-.695

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

6.3.2 Covariates

Potential covariates were selected due to their associations with VMS and negative mood in the literature. Covariates considered were site, age, education, and race, drawn from baseline, and physical activity, self-rated health, BMI, smoking, menopausal status, and antidepressant use, assessed anually and drawn for this analysis from the annual SWAN visit preceding and most proximal to DHS 3 data collection. The coordinating SWAN site of each participant was recorded. Age was calculated using date of birth and the date of the first day of DHS 3 data collection. Education and race/ethnicity were self-reported at SWAN baseline. Education, a proxy for socioeconomic status, was determined using one question that asks the highest grade completed or degree attained (Centers for Disease Control and Prevention, 1994), and coded as "less than high school", "high school graduate", "some college", "college graduate", and "post-college". Race/ethnicity was self-determined by study participants and was obtained by asking the following open-ended question: "How would you describe your primary racial or ethnic group?" The responses were categorized as Caucasian (white), African American, Chinese, Japanese, or Hispanic. Physical activity was assessed at baseline and at annual follow-up visits 3, 5, and 6 with the Kaiser Physical Activity Survey (KPAS) (Sternfeld, 1999), an adaptation of the Baecke physical activity questionnaire (Baecke, 1982). Self-rated health was assessed by response to the following question: "In general, would you say your health is excellent, very good, good, fair or poor?". Responses were categorized into four categories, with responses of "fair" and "poor" collapsed into a single category. Body mass index (BMI) was calculated using weight (kg) and height $(m)^2$. This variable was also categorized (underweight/normal: <25;

overweight: 25-30; obese: >30) for descriptive analysis. Smoking status (never, ever, current) was self-reported at each visit. Menopausal status was assessed annually in SWAN and was defined as indeterminant (pre- and perimenopasual women who used hormones in the past year), premenopausal (bleeding in the last 3 months with no cycle irregularity in the previous 12 months), early perimenopausal (bleeding in the last 3 months with some change in cycle regularity in the last 12 months), late perimenopausal (bleeding >3 months ago but within the last 12 months), postmenopausal (no bleeding in the last 12 months). Menopausal status was collapsed into three categories: premenopausal, perimenopausal (early and late perimenopausal), and postmenopausal. For this analysis, records were reviewed to reclassify women defined as indeterminant as premenopausal (n=1) or perimenopausal (n=9), based on their status at annual visits before and after the annual visit coinciding with DHS 3. Current antidepressant use was self-reported in response to questions about medications used currently and in the previous year during each annual SWAN visit.

7.0 ANALYTIC PLAN

7.1 DATA SOURCE

For all analyses, daily-level variables (VMS, mood) were drawn from the daily diaries of DHS 3, and woman-level covariates were drawn from the annual SWAN follow-up visit closest to the DHS visit date for each participant.

7.2 PRELIMINARY ANALYSES

We identified and addressed outliers, examined the distribution of study variables, and categorized variables as needed. Differences in key factors between those women who ever reported vasomotor symptoms over the observed time period and those who did not, and between those women with overall average negative mood ≥ 2 or <2, were assessed using logistic regression. Associations between key factors and overall positive mood were assessed with linear regression. Descriptive analysis was conducted to evaluate the overall proportions of days that women experienced mood and vasomotor symptoms over the observed period. Analyses were conducted with SPSS v. 17 (SPSS, 2008).

7.3 PRIMARY ANALYSES

Daily observations, nested within women, were examined with two-level hierarchical generalized linear models (HGLM). Analyses were conducted with HLM 6.08 (HLM, 2009). To address the first hypothesis, daily negative affect was regressed on same day VMS; in separate models, daily VMS was regressed on same day negative affect. To address the second and third hypotheses, regarding the temporal association between affect and VMS, a lagged analysis was utilized. Specifically, negative affect at time t, adjusted by vasomotor symptoms at time t, was examined as a predictor of vasomotor symptoms at time t+1; vasomotor symptoms at time t, adjusted by negative affect at time t, was examined as a predictor of negative affect at time t+1. Woman-level covariates were regressed on the daily-level intercept in adjusted models. Regression equations are detailed in appendix 3.

The final models used to address study hypotheses were determined as follows, with equations again detailed in appendix 3. Intercepts-only models were run to determine the variance in each level present for each daily outcome, and to verify that random intercepts were appropriate for these models. Associations between daily predictors and daily outcomes were assessed with random-coefficients models. In order to determine whether expected daily outcomes varied as a function of participant characteristics, associations between potential woman-level covariates and each daily outcome were determined individually with means-as-outcomes models. Covariates were retained in final models if they exhibited significant associations with the daily outcome, $p<.20$, and those included in fully adjusted final models therefore varied by outcome. The intercept for all analyses was modelled as a function of race/ethnicity, menopausal status, self-rated health, and age. Education was included in models with VMS as the outcome; antidepressant use was included in models with negative mood as the

outcome. Age was grand-centered around the sample mean of 48.8; all other variables were uncentered. Site was not considered as a covariate for daily outcomes, due to the confounded relationship between race/ethnicity and site in SWAN. In order to determine whether the relationship between mood and VMS varied as a function of participant characteristics, slopes-and-intercepts as outcomes models were used to test for potential cross-level interactions. Due to the differences in VMS reporting by race/ethnicity, menopausal status, and BMI suggested in the literature, as well as the possible moderating effect of menopausal status on the relationship between mood and VMS suggested by some studies, these covariates were of particular interest. No significant cross-level interactions were seen, and no interaction terms were entered into the final models.

Outcomes for all models were set as a Bernoulli distribution, indicating that for each daily observation, an outcome of 0 (absent) or 1 (present) was possible. Outcomes were also corrected for overdispersion. Restricted maximum likelihood estimation was utilized for all models, and unit-specific models with robust standard errors were interpreted. A random intercept was postulated for all models. Random slopes best fit the data and were retained for all models, after confirming that the random effects of variance components was significant at $p < .05$, and that standard errors and robust standard errors were closer in random than fixed effects models.

7.4 SECONDARY ANALYSES

In order to evaluate whether positive mood has a differential association with VMS, all models were re-run with positive mood in place of negative mood. These were run with 2-level HLM,

as positive mood was assumed to follow a normal distribution. Significant covariates included in adjusted models were education, race/ethnicity, menopausal status, self-rated health, and age.

8.0 RESULTS

8.1 CHARACTERISTICS OF SAMPLE

The final sample was comprised of 625 women. Sample characteristics of the sample are detailed in table 4. Participants completed daily diaries over a period of 12-50 days (mean 33.91, SD 10.85), and were excluded from analysis if they were missing information daily diary data on all observations (n=26). Women who were excluded were more likely to be from the New Jersey site ($p<.01$), to be Hispanic ($p<.01$), to have a high school education or less ($p<.01$), to report fair/poor self-rated health ($p=.02$), and to have a higher BMI ($p=.02$) than women included in the final analytic sample (data not shown).

Table 6. Characteristics of sample: Between-women study variables

	Total (n=625) ***n, column %***
Site	
Michigan 11	63 (10.1)
Boston 12	68 (10.9)
Chicago 13	68 (10.9)
UC-Davis 14	175 (28.0)
UCLA 15	143 (22.9)
New Jersey 16	46 (7.4)
Pittsburgh 17	62 (9.9)
Race/ethnicity	
Black	123 (19.7)
White	191 (30.6)
Chinese	122 (19.5)
Hispanic	46 (7.4)
Japanese	143 (22.9)
Education	
College/post-college	To
Some college	198 (31.9)
High school/<hs	145 (23.3)
Self-rated health	
Excellent	100 (16.2)
Very good	238 (38.4)
Good	208 (33.6)
Fair/poor	73 (11.8)
Categorical BMI	
Normal/underweight (<=24.9)	269 (43.5)
Overweight (25-30)	162 (26.2)
Obese (>30)	187 (30.3)
Smoking status	
Current smoker	57 (9.2)
Current non-smoker	563 (90.8)
Menopausal status	
Postmenopausal	30 (4.8)
Perimenopausal	510 (81.6)
Premenopausal	84 (13.4)
Antidepressant use	
Yes	60 (9.6)
No	565 (90.4)
VMS	
Yes	327 (52.3)
No	298 (47.7)
	Mean, SD
BMI	27.73 (6.77)
Age	48.80 (2.51)
Physical activity	7.69 (1.73)
Negative mood	1.66 (.57)
Positive mood	2.86 (.64)

Over the observed period, 52.3% of participants (n=327) ever reported VMS. Ever reporting VMS was less common in Chinese women, but did not otherwise vary significantly by race (table 5). Ever reporting VMS was more common in older women, perimenopausal women, among women with poorer self-rated health, and among women at the Michigan, Boston, and Chicago SWAN sites compared to the Pittsburgh site (table 5). Ever reporting VMS was associated with higher mean negative mood and lower mean positive mood over the course of the daily diary collection.

Table 7. Univariate relationships between study variables and ever reporting VMS during daily diary collection

	Odds Ratio	95% CI	p-value
Site			**.01**
Michigan 11	**2.11**	**1.03-4.30**	**.04**
Boston 12	**2.38**	**1.12-4.82**	**.02**
Chicago 13	**2.90**	**1.42-5.92**	**<.01**
UC-Davis 14	1.19	.66-2.14	.55
UCLA 15	1.33	.73-2.4	.36
New Jersey 16	1.39	.64-2.98	.41
Pittsburgh 17	--	--	--
Race/ethnicity			**.02**
White	--	--	--
Black	1.05	.66-1.67	.83
Chinese	**.50**	**.32-.79**	**<.01**
Hispanic	.72	.45-1.37	.72
Japanese	.69	.45-1.07	.69
Education			.24
College/post-college	--	--	--
Some college	1.42	.95-2.13	.09
High school/<hs	1.14	.79-1.64	.49
Self-rated health			**.03**
Excellent	--	--	--
Very good	1.16	.73-1.86	.53
Good	1.48	.92-2.39	.11
Fair/poor	**2.35**	**1.26-4.38**	**.01**
BMI	1.02	.99-1.04	.15
Categorical BMI			.65
Normal/underweight (<=24.9)	--	--	--
Overweight (25-30)	1.17	.79-1.73	.43
Obese (>30)	1.16	.80-1.68	.44
Smoking status	.94	.55-1.62	.83
Menopausal status			**<.01**
Postmenopausal	2.00	.86-4.67	.11
Perimenopausal	**2.51**	**1.55-4.09**	**<.001**
Premenopausal	--	--	--
Antidepressant use	1.53	.88-2.63	.13
Age	**1.07**	**1.00-1.14**	**.04**
Physical activity	1.02	.93-1.12	.74
Overall negative mood	**1.79**	**1.30-2.45**	**<.001**
Overall positive mood	**.68**	**.52-.90**	**<.01**

All variables entered independently into logistic regression models.

Over 15% of participants (n=96) had an overall mean negative mood score ≥2. Overall negative mood (≥2) was associated with poorer health, perimenopausal status, site, and race/ethnicity, with women from the New Jersey SWAN site and Hispanic women exhibiting higher average negative mood scores than their counterparts. Similarly, less education, poorer health, and perimenopausal status were associated with decreased overall average positive mood. Positive mood also varied by race/ethnicity, with decreased average positive mood seen among Hispanic women. Higher average positive mood was associated with increased levels of self-reported physical activity (table 6).

Table 8. Univariate relationships between study variables and overall mean negative mood (≥ 2), positive mood

	Negative mood (≥ 2)			Positive mood		
	Odds Ratio	**95% CI**	**p-value**	**Beta Coefficient**	**95% CI**	**p-value**
Site			.13			**<.01**
Michigan 11	1.36	.44-4.17	.59	.09	-.03-.34	.10
Boston 12	1.07	.40-3.38	.91	-.02	-.21-.15	.75
Chicago 13	1.61	.55-4.72	.39	.07	-.07-.29	.23
UC-Davis 14	1.48	.58-3.82	.41	.05	-.09-.21	.44
UCLA 15	2.37	.93-6.05	.07	-.03	-.19-.12	.68
New Jersey 16	**3.29**	**1.13-9.59**	**.03**	.-10	-.41-.00	.05
Pittsburgh 17	--	--	--	--	--	--
Race/ethnicity			**.03**			**<.01**
White	--	--	--	--	--	--
Black	.75	.36-1.57	.45	.08	-.01-.23	.08
Chinese	1.28	.67-2.46	.45	-.03	-.16-.08	.54
Hispanic	**2.46**	**1.12-5.38**	**.03**	**-.12**	**-.41--.08**	**.01**
Japanese	1.77	.98-3.20	.06	-.06	-.19-.04	.21
Education			.44			**<.01**
College/post-college	--	--	--	--	--	--
Some college	.89	.53-1.50	.65	-.03	-.13-.07	.56
High school/<hs	1.29	.76-2.19	.35	**-.14**	**-.28--.07**	**<.01**
Self-rated health			**<.001**			**<.001**
Excellent	--	--	--	**--**	**--**	**--**
Very good	1.77	.75-4.20	.19	**-.21**	**-.33--.09**	**<01**
Good	**2.88**	**1.23-6.70**	**.01**	**-.40**	**-.52--.28**	**<.001**
Fair/poor	**6.11**	**2.45-15.23**	**<.001**	**-.57**	**-.72--.42**	**<.001**
BMI	1.01	.97-1.04	.73	-.03	-.01-.00	.44
Categorical BMI			.20			.56
Normal/underweight (<=24.9)	--	--	--	--	--	--
Overweight (25-30)	1.50	.89-2.51	.13	-.01	-.11-.10	.89
Obese (>30)	.94	.55-1.62	.82	-.05	-.15-.05	.30
Smoking status	.77	.34-1.75	.53	-.02	-.18-.11	.59
Menopausal status			**.03**			**<.01**
Postmenopausal	1.76	.39-7.84	.46	.05	-.10-.34	.30
Perimenopausal	**3.30**	**1.30-8.37**	**.01**	**-.10**	**-.26--.02**	**.02**
Premenopausal	--	--	--	--	--	--
Antidepressant use	1.79	.94-3.41	.08	-.06	-.25-.03	.12
Age	.97	.89-1.06	.52	.04	-.01-.02	.37
Physical activity	.94	.83-1.07	.35	**.11**	**.01-.06**	**<.01**

All variables entered independently into logistic (negative mood) and linear (positive mood) regression models.

8.1.1 Daily diary: VMS

Symptomatic women reported VMS on 2-100% of daily observations. Overall, and among all groups but Hispanic women, most participants with VMS reported symptoms on 2-30% of days collected (data not shown). Most of the variance (95%) in VMS reporting was seen between women, with 5% of the variance occurring within women's daily observations (table 7). Significant woman-level predictors of daily VMS were similar to the significant predictors of ever reporting VMS reported in the previous section (table 8).

8.1.2 Daily diary: Mood

Most of the variance (96%) in negative mood reporting was seen between women, with 4% of the variance occurring within women's daily observations (table 7). Daily negative mood (≥2) was reported on 20% of observations (n=4194) (data not shown). Significant woman-level predictors of daily negative mood (≥2) were similar to those associated with overall negative mood (table 8). The expected unadjusted positive mood score was 2.88 (SE .02) on a 1-4 scale. Most of the variance (64%) in positive mood reporting was seen between women, with 36% of the variance occurring within women's daily observations. Significant woman-level predictors of daily positive mood were similar to those associated with overall positive mood (data not shown).

Table 9: Between- and within-woman variance for daily within-woman outcomes: Daily VMS, daily negative mood, daily positive mood

	VMS	Negative mood	Positive mood
Between	95%	96%	64%
Within	5%	4%	36%

Table 10: Unadjusted associations of between-women covariates and daily within-woman daily VMS and daily negative mood

Between-women covariates	Intercept (VMS) OR (95% CI)	Association with VMS OR (95% CI)	p-value	Intercept (negative mood) OR (95% CI)	Association with negative mood OR (95% CI)	p-value
Age	**.05 (.04-.06)**	**1.18 (1.07-1.31)**	**<.01**	**.07 (.06-.09)**	**0.90 (0.82-0.99)**	**.03**
Antidepressant use	.05 (.04-.06)	1.50 (0.66-3.40)	.33	**.06 (.05-.08)**	**3.48 (1.51-8.05)**	**<.01**
BMI	.05 (.04-.06)	1.03 (.99-1.07)	.20	.07 (.05-.09)	1.92 (.99-1.06)	.27
BMI (cat)	.04 (.03-.07)			.06 (.04-.08)		
Normal/underweight		Ref			Ref	
Overweight		.91 (.49-1.70)	.76		1.55 (.83-2.87)	.17
Obese		1.38 (.73-2.62)	.32		1.35 (.76-2.38)	.30
Education	**.03 (.02-.05)**			.07 (.05-.11)		
High School or less		**2.12 (1.13-4.01)**	**.02**		1.06 (.55-2.06)	.86
Some College		**2.03 (1.10-3.75)**	**.03**		.76 (.44-1.33)	.34
College +		**Ref**			Ref	
Menopausal status	**.01 (.01-.03)**			**.03 (.02-.05)**		
Postmenopausal		**9.19 (1.89-44.67)**	**.02**		.41 (.11-1.54)	.22
Perimenopausal		**4.19 (2.05-8.58)**	**<.01**		**3.13 (1.65-5.92)**	**<.01**
Premenopausal		**Ref**			Ref	
Health	**.04 (.02-.08)**			**.02 (.01-.04)**		
Excellent		Ref			Ref	
Very Good		.87 (.39-1.93)	.73		**2.32 (1.19-4.53)**	**.01**
Good		1.48 (.66-3.68)	.34		**4.02 (1.97-8.19)**	**<.001**
Fair/poor		**4.54 (1.57-13.14**	**.01**		**13.42 (5.38-33.46)**	**<.001**
Race/ethnicity	**.06 (.04-.09)**			**.08 (.05-.12)**		
White		Ref			Ref	
Black		1.24 (.60-2.57)	.56		**.42 (.20-.86)**	**.01**
Chinese		**.33 (.16-.67)**	**<.01**		.81 (.40-1.63)	.55
Hispanic		1.13 (.32-4.01)	.85		**3.56 (1.26-10.10)**	**.03**
Japanese		.75 (.37-1.54)	.44		.95 (.49-1.84)	.86
Physical activity	.05 (.04.06)	1.08 (0.91-1.29)	.31	.05 (.04-.06)	1.11 (0.93-1.32)	.21
Smoking status	.05 (.04-.07)	1.24 (0.44-3.47)	.68	.07 (.05-.09)	1.14 (0.50-2.61)	.77

All variables entered independently into hierarchical generalized linear models.
Age has been grand-centered; all other variables entered uncentered.

8.2 DAILY COVARIANCE OF VMS AND NEGATIVE AFFECT

The first hypothesis was that VMS and negative affect would be associated with each other within each 24-hour period. This hypothesis was confirmed. The association was significant in unadjusted and adjusted models with daily VMS set as the outcome, predicted by same day daily negative mood (≥2) (table 9), and with daily negative mood (≥2) set as the outcome, predicted by same day VMS (table 10). Older age, poorer health, and perimenopausal status increased the likelihood of reporting VMS on a given day, while being Chinese was associated with reduced odds of VMS. The association between education and VMS was no longer significant in the fully adjusted model (table 9). Results for unadjusted and adjusted models were equivalent when the continuous daily negative mood variable was used as a predictor (data not shown). With daily negative mood as the outcome, poorer health and perimenopausal status continued to increase the likelihood of daily negative mood (≥2), while Black women and older women had decreased odds of daily negative mood (table 10).

Table 11. Hypothesis 1: Association between daily negative mood and daily VMS, adjusted by between-women covariates
Outcome: VMS

	OR (95% CI)	p-value
Unadjusted		
Intercept (VMS)	**0.04 (0.03-0.06)**	**<.001**
Slope (negative mood)	**1.89 (1.53-2.33)**	**<.001**
Adusted		
Intercept (VMS)	**0.02 (0.01-0.05)**	**<.001**
Slope (negative mood)	**1.72 (1.39-2.13)**	**<.001**
Age	**1.15 (1.04-1.28)**	**.01**
Education		
High school or less	1.60 (.80-3.21)	.19
Some college	1.57 (.84-2.92)	.16
College+	Ref	
Health		
Excellent	Ref	
Very Good	.76 (.35-1.68)	.50
Good	1.27 (.56-2.90)	.57
Fair/poor	**3.70 (1.21-11.35)**	**.02**
Race/ethnicity		
White	Ref	
Black	.86 (.40-1.83)	.69
Chinese	**.26 (.13-.54)**	**<.01**
Hispanic	.48 (.14-1.68)	.25
Japanese	.52 (.25-1.05)	.07
Menopausal status		
Postmenopausal	5.17 (1.01-26.39)	.05
Perimenopausal	**3.09 (1.50-6.38)**	**<.01**
Premenopausal	Ref	

All daily-level predictors and woman-level covariates simultaneously entered into hierarchical generalized linear models.
Age has been grand-centered; all other variables entered uncentered.

Table 12. Hypothesis 1: Association between daily VMS and daily negative mood, adjusted by between-women covariates
Outcome: Negative mood (>2)

	OR (95% CI)	p-value
Unadjusted		
Intercept (negative mood)	**.06 (.05-.08)**	**<.001**
Slope (VMS)	**1.72 (1.39-2.12)**	**<.001**
Adjusted		
Intercept (negative mood)	**.01 (.00-.01)**	**<.001**
Slope (VMS)	**1.76 (1.43-2.17)**	**<.001**
Age	**0.87 (0.79-0.96)**	**.01**
Antidepressant use	**3.18 (1.49-6.78)**	**<.01**
Health		
Excellent	Ref	
Very Good	**2.87 (1.48-5.56)**	**<.01**
Good	**4.38 (2.17-8.88)**	**<.001**
Fair/poor	**13.11 (5.22-32.95)**	**<.001**
Race/ethnicity		
White	Ref	
Black	**.32 (.16-.64)**	**<.01**
Chinese	.82 (.41-1.65)	.58
Hispanic	1.88 (.63-5.62)	.26
Japanese	.84 (.45-1.58)	.59
Menopausal status		
Postmenopausal	.74 (.19-2.85)	.66
Perimenopausal	**3.18 (1.65-6.12)**	**<.01**
Premenopausal	Ref	

All daily-level predictors and woman-level covariates simultaneously entered into hierarchical generalized linear models.
Age has been grand-centered; all other variables entered uncentered.

8.3 NEGATIVE AFFECT AS A PREDICTOR OF NEXT DAY VMS

The second hypothesis was that negative affect, adjusted by same day VMS, would predict next day VMS. This hypothesis was not confirmed. Negative mood (≥2) was not associated with next day VMS in unadjusted or adjusted models. In the fully adjusted model, previous day VMS, higher age, poor health, and perimenopausal status increased the odds of reporting next day VMS; being Chinese was negatively associated with next day VMS (table 11). Equivalent results were found in the unadjusted and adjusted models when using the continuous negative mood variable (data not shown).

Table 13. Hypothesis 2: Association between previous day negative mood and next day VMS, adjusted by previous day VMS and between-women covariates
Outcome: Next day VMS

	OR (95% CI)	p-value
Unadjusted		
Intercept (VMS)	**.03 (.03-.04)**	**<.001**
Slope (previous day VMS)	**8.62 (7.26-10.24)**	**<.001**
Slope (previous day negative mood)	1.14 (.91-1.43)	.26
Adjusted		
Intercept (VMS)	**.01 (.01-.03)**	**<.001**
Slope (previous day VMS)	**8.96 (7.55-10.64)**	**<.001**
Slope (previous day negative mood)	1.07 (.85-1.35)	.55
Age	**1.11 (1.02-1.20)**	**.02**
Education		
High school or less	1.64 (.94-2.84)	.08
Some college	1.48 (.90-2.42)	.12
College+	Ref	
Health		
Excellent	Ref	
Very Good	.85 (.45-1.59)	.60
Good	1.27 (.65-2.45)	.49
Fair/poor	**2.88 (1.20-6.91)**	**.02**
Race/ethnicity		
White	Ref	
Black	.92 (.50-1.69)	.80
Chinese	**.34 (.19-.60)**	**<.001**
Hispanic	.49 (.18-1.33)	.16
Japanese	.57 (.32-.99)	.05
Menopausal status		
Postmenopausal	3.60 (.98-13.19)	.05
Perimenopausal	**2.57 (1.42-4.64)**	**<.01**
Premenopausal	Ref	

All daily-level predictors and woman-level covariates simultaneously entered into hierarchical generalized linear models.
Age has been grand-centered; all other variables entered uncentered.

8.4 VMS AS A PREDICTOR OF NEXT DAY NEGATIVE AFFECT

The final hypothesis was that VMS, adjusted by same day negative affect, would not predict next day negative affect. This hypothesis was not confirmed. VMS was significantly associated with next day negative affect in unadjusted and adjusted models. In the fully adjusted model, previous day negative mood, antidepressant use, poorer health, and perimenopausal status increased the odds of reporting negative mood (≥2) the next day. Older women and Black women were less likely to report next day negative mood (table 12).

Table 14. Hypothesis 3: Association between previous day VMS and next day negative mood, adjusted by previous day negative mood and between-women covariates
Outcome: Next day negative mood (>2)

	OR (95% CI)	p-value
Unadjusted		
Intercept (negative mood)	**.05 (.04-.06)**	**<.001**
Slope (previous day VMS)	**1.28 (1.02-1.59)**	**.03**
Slope (previous day negative mood)	**4.65 (4.01-5.40)**	**<.001**
Adjusted		
Intercept (negative mood)	**.00 (.00-.01)**	**<.001**
Slope (previous day VMS)	**1.27 (1.03-1.58)**	**.01**
Slope (previous day negative mood)	**4.86 (4.20-5.62)**	**<.001**
Age	**0.90 (0.83-0.98)**	**.01**
Antidepressant use	**2.57 (1.37-4.82)**	**<.01**
Health		
Excellent	**Ref**	
Very Good	**2.42 (1.24-4.05)**	**<.01**
Good	**3.54 (1.90-6.60)**	**<.001**
Fair/poor	**8.74 (4.03-18.96)**	**<.001**
Race/ethnicity		
White	Ref	
Black	**.41 (.23-.73)**	**<.01**
Chinese	.82 (.45-1.50)	.52
Hispanic	1.38 (.53-3.53)	.51
Japanese	.81 (.48-1.40)	.46
Menopausal status		
Postmenopausal	.70 (.22-2.18)	.53
Perimenopausal	**2.80 (1.58-4.95)**	**<.01**
Premenopausal	Ref	

All daily-level predictors and woman-level covariates simultaneously entered into hierarchical generalized linear models.
Age has been grand-centered; all other variables entered uncentered.

8.5 SECONDARY ANALYSES

The first hypothesis was confirmed with positive mood in the place of negative mood in unadjusted and adjusted models; higher positive mood reduced the risk of VMS, and VMS was associated with lower positive mood. For hypotheses 2 and 3, no relationship was seen between positive affect and next day VMS, nor between VMS and next day positive affect (data not shown).

9.0 DISCUSSION

This study utilized prospective daily diary reports of mood and VMS to expand our current understanding of the commonly reported relationship between these factors. In this sample of women in the menopausal transition, higher average negative affect over the course of daily diary collection was associated with an increased risk of ever reporting VMS. On a day-to-day basis, higher negative affect was positively associated with VMS within each 24-hour period. This relationship was maintained regardless of whether negative affect or VMS was the predicted outcome. This study also sought to shed light on the potential directionality of effect between these factors. Contrary to hypotheses, negative affect, adjusted by VMS, was not associated with next day VMS. However, VMS, adjusted by negative affect, was associated with next day negative affect.

The daily association between negative affect and VMS mirrors the common association between these factors found in the literature. However, this association is generally seen with retrospective recall of VMS and mood symptoms in previous weeks. Usual measurement casts doubt on this relationship, with the introduction of retrospective recall bias that may be influenced by current mood. Our results suggest that the often-reported association between negative affect and VMS on a daily as well as general basis, and exist even with limited bias from retrospective reporting.

This study also offers a contribution to our understanding of the temporal relationship between negative affect and VMS. It was hypothesized that negative mood would precede VMS, due in part to the potential influence of negative mood on the subjective experience of symptoms. Negative mood may increase awareness of and attention to bodily sensations, increase symptom sensitivity, and decrease symptom tolerance (Thurston, 2008a). Women experiencing negative mood may be more likely to negatively interpret bodily sensations, and to amplify the experience due to attentional bias, leading to increased reporting and possible over-reporting due to misinterpreted signals (Hunter, 2010). However, the findings in this study did not support this relationship. Negative affect, adjusted by VMS, was not associated with next day VMS. While this may indicate that negative affect preceding VMS is not the temporal relationship that exists between these factors, alternate explanations are also possible. The ability to predict VMS from previous-day mood may have been limited by the small amount of within-woman variance in symptom occurrence in this study. Further, 24-hour periods may not have been the appropriate timeframe in which to see this effect. In Thurston et al. (2005), self-reported VMS were more likely within 30 minutes of increased frustration. Our ability to detect such transient changes in mood and VMS experience was limited, and acute effects of negative mood on subjective symptom experience may have been better captured with more frequent data collection. It is also possible that a longer, rather than shorter, timeframe would have yielded significant results. If sustained negative mood is necessary to influence subjective symptom experience, accumulated negative mood indicative of periods of increased stress or general negative affectivity, rather than a single day's fluctuation, could predict later VMS. Future research should address these variations in temporal resolution.

An alternate theory of temporal association is that VMS leads to increased negative mood. Women often report distress and embarrassment due to symptom experience, particularly when they occur in public (Kronenberg, 1990). Women vary in their behavioral and emotional reactions to these unpredictable and uncontrollable events, but those who report them as more distressing and bothersome in general may experience negative thoughts during and about the symptoms as well as a catastrophization of symptoms. These negative cognitive appraisals may be transient and limited to the duration of symptom experience, or could extend into more persistent negative beliefs about the self and the menopausal transition (Hunter, 2010). Symptoms may therefore precede subsequent negative mood for a short or longer period of time by activating negative schemas and triggering feelings of lack of control, embarrassment, and shame. This theory is particularly related to the experience of daytime VMS, or hot flashes. Nighttime VMS, or night sweats, may lead to next-day negative mood by alternate mechanisms. The domino hypothesis posits that sleep disturbance resulting from night sweats leads to next-day impairment and negative mood. With frequent VMS, this cycle of chronic sleep disruption and impaired daytime functioning and well-being may lead to significant depressive symptoms. Studies testing this theory result in mixed findings, with a noted disparity between self-reported and objectively measured sleep disruptions due to VMS (Joffe, 2009). Though the mechanism linking VMS to subsequent negative mood in this sample is unclear, this temporal relationship was supported by our findings, in which VMS, adjusted by negative affect, was associated with next day negative affect. These results suggest that daily changes in negative mood do not increase risk of day-to-day VMS, while VMS does have a significant impact on day-to-day mood.

Additional factors may play a role in these relationships, and should be investigated in future studies. Despite significant associations, little variance in either VMS or mood outcomes was explained by the daily predictors and woman-level covariates. Unmeasured factors related to both outcomes may remain to better explain these relationships. These may include hormonal fluctuations (Joffe, 2007), measures of somatization (Thurston, 2005), and self-reported sleep disturbance (Kravitz, 2008). Further, within the explored predictors, specific aspects of mood may have differential associations with VMS. While negative and positive mood were correlated, findings related to the temporal relationship between VMS and each mood factor differed. VMS increased the risk of higher negative mood the following day, without an associated decrease in positive mood. This may suggest that VMS contributes to a specific aspect of negative mood over time, rather than just increasing negative relative to positive affect on a daily basis. An investigation into individual mood components is warranted in the future.

Several commonly reported correlates of traditionally measured VMS were also seen with the overall and daily reports of VMS in this prospective daily diary collection. As with past investigations, the risk of ever reporting VMS increased with age (Gold, 2006), poorer health (Dennerstein, 2003), and perimenopausal status (Gold, 2006). The risk of reporting VMS on any given day was also associated with these factors, as well as with postmenopausal status and lower educational attainment. These associations were consistent with past investigations of traditionally-measured VMS (Gold, 2006; Schwingl, 1994), and, with the exception of educational attainment, maintained when entered into models simultaneously.

Some factors commonly associated with VMS did not exhibit a relationship in this sample. Physical activity was not linked to VMS in this sample, contrary to the findings of some studies (Gold, 2004) but consistent with others (Greendale, 2005). This association may be

better explained by the relationship between overall physical health and VMS. Smoking may increase risk of VMS, potentially through its effects on estradiol and estrone levels (Gold, 2004), but a relationship with current smoking was not seen in our sample. Few women (9.2%) in our sample reported current smoking; results may differ with a higher prevalence of smoking and/or with assessment of smoking history. Black women are thought to have more VMS and Asian women less VMS than White women (Gold, 2006). While overall and daily VMS reporting varied significantly by race/ethnicity, this effect was driven by the reduced reporting seen only in Chinese women relative to other ethnic groups. Increased bother related to VMS, independent of VMS frequency, has also been seen in Black women compared to White women (Thurston, 2008). The high level of bother attributed to VMS experience by Black women may contribute to inflated retrospective reporting. Daily prospective reporting, with decreased retrospective bias, may better sample the true symptom experience of this population. The reporting patterns in the other ethnic groups are relatively consistent with past findings in SWAN (Gold, 2006; Gold 2000). Finally, BMI had no association with VMS in this sample, though increased BMI has been seen to increase risk of VMS in numerous cross-sectional and longitudinal studies, including SWAN (Thurston, 2009b).

Some additional findings in this study deserve mention. Past studies utilizing retrospectively self-reported VMS have indicated that VMS occur on a daily basis at some point in the menopausal transition for 20-25% of women (Freeman, 2005). In contrast, the findings of this study suggest that the majority of women who experience VMS do not have them daily; only 6.1% of symptomatic women reported VMS on every observation, while 56.7% of symptomatic women reported symptoms on just 2-30% of their daily observations (data not shown). Prospective daily diary reporting may provide a more accurate representation of symptom

frequency, with limited retrospective recall bias and error. The menopausal transition is also considered a vulnerable period for higher levels of depressive symptoms (Bromberger, 2010). In this sample, prospective ratings of negative mood were very low, with most women reporting no to little endorsement of negative mood symptoms on a daily basis. In contrast, positive mood ratings were consistently relatively high. This snapshot of the menopausal transition did not appear to represent a period of highly negative mood as measured with prospective daily reports in our large, multiethnic, largely perimenopausal sample.

Several limitations of this study should be noted. As previously discussed, the relationship between mood and daytime hot flashes or night sweats may differ, but the time at which VMS occurred cannot be determined in this study. Frequency, severity, and bother of VMS were also not assessed, and these characteristics of VMS experience may play an important role in the relationship between daily VMS and daily mood (Thurston, 2008). Interpretation of these findings is also limited by the low levels and limited heterogeneity of daily negative mood reported in this sample, as the negative mood reported may not be of meaningful severity. Finally, the generalizability of this highly compliant, highly motivated sample is limited. In addition to annual SWAN visits, these women complied with annual completion of a month or more of daily diaries and daily urine collection.

This study also has considerable strengths. Foremost among these is the contribution of prospective daily measurement of mood and VMS, rather than the typical 2 week retrospective recall. This both confirms the stable relationship typically seen between these factors and elucidates the relationship between these transient and fluctuating factors on a day-to-day basis, adjusting by stable woman-level characteristics related to symptom experience. The size of the sample and length of data collection lends validity, model stability, and the ability to examine

over 21,000 separate observations. The multiethnic makeup of the sample provides valuable information about symptom experience in understudied populations. Finally, the large number of symptomatic women in this sample provided novel information about day to day symptom experience in a diverse sample of women in the menopausal transition.

10.0 CONCLUSIONS

This study contributes to our knowledge about the relationship between negative affect and VMS. The association between these factors commonly observed in studies using traditional retrospective measurement of VMS continued to be seen when mood and VMS were prospectively reported in daily diaries. Researchers should be assured that prospective daily measurement of VMS largely replicates findings of studies using typical retrospective measurement, though frequency estimates may be inflated. Assessment of temporal relationships between these factors suggests that VMS precedes elevated daily negative affect, while daily fluctuations in negative affect do not increase the likelihood of VMS. Women with VMS may be at increased risk for subsequent negative mood symptoms. Health care practitioners should be aware of this potential detrimental effect of VMS experience in menopausal women, and consider addressing VMS as an appropriate route to alleviating both VMS and mood symptoms in the menopausal transition. Women and practitioners should be aware that negative mood symptoms do not appear to be causing or creating VMS, which may alleviate feelings of guilt or responsibility in women who are concerned that their emotional states are creating false symptoms. This study takes us one step closer toward better understanding the relationship between negative mood and VMS, which may help influence intervention strategies to improve quality of life and health in women as and after they traverse the menopause.

APPENDIX A

HIERARCHICAL GENERALIZED LINEAR MODEL EQUATIONS

Model Building:

Intercepts-only models:
$\eta = \gamma_{00} + u_0 + r$

Means-as-outcomes models:
$\eta = \gamma_{00} + \gamma_{01}$*Covariate $+ u_0 + r$

Random-coefficients models:
for one level 1 predictor (ie, hypothesis 1):
$\eta = \gamma_{00} + \gamma_{10}$*Predictor $+ u_0 + u_1$*Predictor $+ r$

for two level 2 predictors (ie, hypotheses 2 and 3):
$\eta = \gamma_{00} + \gamma_{10}$*Predictor1 $+ \gamma_{20}$*Predictor2 $+ u_0 + u_1$*Predictor1 $+ u_2$*Predictor2 $+ r$

Slopes-and-intercepts as outcomes models:
$\eta = \gamma_{00} + \gamma_{01}$*Covariate $+ \gamma_{10}$*Predictor $+ \gamma_{11}$*Covariate*Predictor $+ u_0 + u_1$*Predictor $+ r$

For all equations, "covariate" refers to between-women variables, and "predictor" refers to within-woman variables

Hypothesis Testing:

Hypothesis 1: VMS and negative mood will covary within each 24-hour period

Unadjusted, VMS as outcome
$\eta = \gamma_{00} + \gamma_{10}$*negative mood $+ u_0 + u_1$*negative mood $+ r$

Adjusted, VMS as outcome
$\eta = \gamma_{00} + \gamma_{01}$***age*** $+ \gamma_{02}$*education (high school or less) $+ \gamma_{03}$*education (some college) $+ \gamma_{04}$*self-rated health (very good) $+ \gamma_{05}$*self-rated health (good) $+ \gamma_{06}$*self-rated health (poor) $+ \gamma_{07}$*race/ethnicity (Black) $+ \gamma_{08}$*race/ethnicity (Chinese) $+ \gamma_{09}$*race/ethnicity (Hispanic) $+ \gamma_{010}$*race/ethnicity (Japanese) $+ \gamma_{011}$*Menopausal status (postmenopausal) $+ \gamma_{012}$*Menopausal status (perimenopausal) $+ \gamma_{10}$*negative mood $+ u_0 + u_1$*negative mood $+ r$

Unadjusted, negative mood as outcome
$\eta = \gamma_{00} + \gamma_{10}$*VMS $+ u_0 + u_1$*VMS $+ r$

Adjusted, negative mood as outcome

$\eta=\gamma_{00} + \gamma_{01}$***age*** $+ \gamma_{02}$*antidepressant use $+ \gamma_{03}$*self-rated health (very good) $+ \gamma_{04}$*self-rated health (good) $+ \gamma_{05}$*self-rated health (poor) $+ \gamma_{06}$*race/ethnicity (Black) $+ \gamma_{07}$*race/ethnicity (Chinese) $+ \gamma_{08}$*race/ethnicity (Hispanic) $+ \gamma_{09}$*race/ethnicity (Japanese) $+ \gamma_{010}$*Menopausal status (postmenopausal) $+ \gamma_{011}$*Menopausal status (perimenopausal) $+ \gamma_{10}$*VMS $+ u_0 + u_1$*VMS $+ r$

Hypothesis 2: Negative mood will be associated with next day VMS

Unadjusted
$\eta=\gamma_{00} + \gamma_{10}$*lagged VMS $+ \gamma_{20}$*lagged negative mood $+ u_0 + u_1$*lagged VMS $+ u_2$*lagged negative mood $+ r$

Adjusted
$\eta=\gamma_{00} + \gamma_{01}$***age*** $+ \gamma_{02}$*education (high school or less) $+ \gamma_{03}$*education (some college) $+ \gamma_{04}$*self-rated health (very good) $+ \gamma_{05}$*self-rated health (good) $+ \gamma_{06}$*self-rated health (poor) $+ \gamma_{07}$*race/ethnicity (Black) $+ \gamma_{08}$*race/ethnicity (Chinese) $+ \gamma_{09}$*race/ethnicity (Hispanic) $+ \gamma_{010}$*race/ethnicity (Japanese) $+ \gamma_{011}$*menopausal status (postmenopausal) $+ \gamma_{012}$*menopausal status (perimenopausal) $+ \gamma_{10}$*lagged VMS $+ \gamma_{20}$*lagged negative mood $+ u_0 + u_1$*lagged VMS $+ u_2$*lagged negative mood $+ r$

Hypothesis 3: VMS will be associated with next day negative mood

Unadjusted
$\eta=\gamma_{00} + \gamma_{10}$*lagged VMS $+ \gamma_{20}$*lagged negative mood $+ u_0 + u_1$*lagged VMS $+ u_2$*lagged negative mood $+ r$

Adjusted
$\eta=\gamma_{00} +$ ***age*** $+ \gamma_{02}$*antidepressant use $+ \gamma_{03}$*self-rated health (very good) $+ \gamma_{04}$*self-rated health (good) $+ \gamma_{05}$*self-rated health (poor) $+ \gamma_{06}$*race/ethnicity (Black) $+ \gamma_{07}$*race/ethnicity (Chinese) $+ \gamma_{08}$*race/ethnicity (Hispanic) $+ \gamma_{09}$*race/ethnicity (Japanese) $+ \gamma_{010}$*menopausal status (postmenopausal) $+ \gamma_{011}$*menopausal status (perimenopausal) $+ \gamma_{10}$*lagged VMS $+ \gamma_{20}$*lagged negative mood $+ u_0 + u_1$*lagged VMS $+ u_2$*lagged negative mood $+ r$

Legend:

η: Outcome
γ_{00}: Intercept
γ_{0x}: Slope term for level 2 explanatory variable *x*
γ_{1x}: Slope term for level 1 explanatory variable *x*
u_0: Unique increment to the intercept associated with level 2 grouping variable
u_x: Unique increment to the slope associated with level 2 grouping variable
r: Level 1 residual variance
bold italics: grand-centered term

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