The role of sleep difficulties in the vasomotor menopausal symptoms and depressed mood relationships: an international pooled analysis of eight studies in the InterLACE consortium

Short title: VMS, sleep difficulties and depressed mood

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Abstract

Background: Many women experience both vasomotor menopausal symptoms (VMS) and depressed mood at midlife, but little is known regarding the prospective bi-directional relationships between VMS and depressed mood and the role of sleep difficulties in both directions.

Methods: A pooled analysis was conducted using data from 21,312 women (median: 50 years, IQR 49-51) in eight studies from the InterLACE consortium. The degree of VMS, sleep difficulties, and depressed mood were self-reported and categorised as never, rarely, sometimes, and often (if reporting frequency) or never, mild, moderate, and severe (if reporting severity). Multivariable logistic regression models were used to examine the bi-directional associations adjusted for within-study correlation.

Results: At baseline, the prevalence of VMS (40%, range 13-62%) and depressed mood (26%, 8-41%) varied substantially across studies, and a strong dose-dependent association between VMS and likelihood of depressed mood was found. Over three years of follow-up, women with often/severe VMS at baseline were more likely to have subsequent depressed mood compared with those without VMS (OR=1.56, 1.27-1.92). Women with often/severe depressed mood at baseline were also more likely to have subsequent VMS than those without depressed mood (OR=1.89, 1.47-2.44). With further adjustment for the degree of sleep difficulties at baseline, the OR of having a subsequent depressed mood associated with often/severe VMS was attenuated and no longer significant (OR=1.13, 0.90-1.40). Conversely, often/severe depressed mood remained significantly associated with subsequent VMS (OR=1.80, 1.38-2.34).

Conclusions: Difficulty in sleeping largely explained the relationship between VMS and subsequent depressed mood, but it had little impact on the relationship between depressed mood and subsequent VMS.

Keywords: depressed mood; hot flushes; menopausal transition; night sweats; sleep difficulties; vasomotor menopausal symptoms

Introduction

Mood disturbances are prevalent in reproductive-age women and appear to be linked to hormonal fluctuation and reproductive events, such as the premenstrual and postpartum periods and the menopausal transition (Kessler and Gadermann, 2013, Rapkin *et al.*, 2002). Up to 40% of women going through the menopausal transition experience depressive symptoms but the prevalence varies substantially across studies (Harlow *et al.*, 1999, Li *et al.*, 2008, Timur and Sahin, 2010). Numerous factors influence the risk of depressive symptoms, from psychosocial factors to the cumulative effect of lifestyle and hormonal exposures (Harlow *et al.*, 1999, Li *et al.*, 2008, Timur and Sahin, 2010). The Harvard Study of Moods and Cycles found that the risk for depressive symptoms was higher for women who entered perimenopause compared with those who remained premenopausal, and the increased risk was amplified by the presence of vasomotor menopausal symptoms (VMS) (hot flushes and night sweats) (Cohen *et al.*, 2006). A systematic review has recently shown a bi-directional relationship between VMS and depressive symptoms during perimenopause, but a number of limitations of the studies contributing to the review have been identified (Worsley *et al.*, 2014). These included small sample sizes, limited information on confounders, and differences in study design and measures used for variables (Worsley *et al.*, 2014). Moreover, the dearth of longitudinal research, particularly with regard to depressive symptoms and subsequent VMS (Freeman *et al.*, 2009, Gold *et al.*, 2006), has raised questions about the directionality of these two key menopausal symptoms.

The quality of sleep is likely important in the relationship between VMS and depressive symptoms, though its exact role is not yet clear. On the one hand, the "*domino hypothesis*" suggests a causal role of sleep problems in this relationship, postulating that VMS (resulting from low/fluctuating estradiol levels) lead to significant sleep disruption, which in turn cause negative mood (Eichling and Sahni, 2005). There is some recent strong evidence providing empirical data showing that sleep difficulties partly mediate the association of VMS with depressive symptoms, although studies are small (Burleson *et al.*, 2010, Joffe *et al.*, 2016, Vincent *et al.*, 2014). On the other hand, these three symptoms occur frequently and often co-occur around the menopausal transition. In fact, bi-directional relationships have been observed between VMS and depressive symptoms (Worsley *et al.*, 2014) and between insomnia and depression (Alvaro *et al.*, 2013). The *domino hypothesis* has been applied only to the VMS first pathway. However, the relationship may differ depending on whether depressive symptoms or VMS are present first, and it would be reasonable to evaluate sleep problems as a risk factor for VMS.

This study used data from over 20,000 midlife women to examine the cross-sectional and prospective bi-directional associations between VMS and depressed mood over three years and to investigate the role of sleep difficulties in both directions. Individual level data were pooled from eight studies in the UK, USA, Australia, and Japan that all contribute to the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) (Mishra *et al.*, 2013, Mishra *et al.*, 2016).

Methods

Ethics

Participants in each study were recruited under the Institutional Review Board protocols approved at each research centre. Informed written consent was obtained from all participants.

Study participants

Eight studies in the InterLACE consortium had collected information on VMS and depressed mood: Australian Longitudinal Study on Women's Health (ALSWH) (Dobson *et al.*, 2015), MRC National Survey of Health and Development (NSHD) (Wadsworth *et al.*, 2006), National Child Development Study (NCDS) (Power and Elliott, 2006), Study of Women's Health Across the Nation (SWAN) (Sowers *et al.*, 2000), Seattle Midlife Women's Health Study (SMWHS) (Mitchell and Woods, 2011), Healthy Ageing of Women Study (HOW) (Anderson *et al.*, 2004), Japanese Midlife Women's Health Study (JMWHS) (Anderson *et al.*, 2004), and Whitehall II Study (WHITEHALL) (Marmot and Brunner, 2005) (**Table 1**). For the longitudinal studies, data collected at around 50 years of age (analytic baseline) were used to provide some consistency in the variability of menopausal status and symptoms. For HOW and JMWHS, data were included from the baseline surveys when the median age of participants was around 54 years (range 45–60 years).

For the cross-sectional analysis, a total of 21,312 women who had reported VMS and depressed mood and had complete information on the covariates (listed below) at baseline were included in the analysis. Four cohort studies (ALSWH, NSHD, SWAN, and WHITEHALL) provided longitudinal data for further analyses (n=15,645). Women who did not return or had incomplete data at 3-year follow-up were excluded (n=4,953), leaving 10,692 women for the prospective analysis (nearly 70% were retained). Women who were excluded were more likely to report VMS, depressed mood, or sleep difficulties at baseline and were more likely to be a current smoker, obese, less educated, currently taking menopausal hormone therapy, or having a history of hysterectomy/oophorectomy compared with those who were included (**Supplemental Table 1**). To examine the prospective association between VMS and incident depressed mood, women with the

presence of depressed mood (defined below, n=2,459) at baseline were excluded, while to examine the reverse prospective association, women with the presence of VMS (defined below, n=3,708) at baseline were excluded. There were no differences in characteristics between the two prospective samples.

Depressed mood and vasomotor symptoms

In this study, the term "*depressed mood*" rather than "*depressive symptoms*" is used because the data were from single questions about feeling depressed, blue, sad, or unhappy rather than from validated depression scales. In each study, hot flushes, night sweats, and depressed mood were collected using self-reported menopausal symptom checklists assessing symptoms over a specific period. VMS was defined by having either hot flushes or night sweats. In ALSWH, women were asked how *frequently* they have had the symptoms in the last 12 months (considered as a long-term recall period), and SWAN asked about symptoms in the past 2 weeks (a short-term recall period). The frequency categories were harmonised and categorised as never, rarely, sometimes and often. In the other six studies, women were asked how *severely* they had been bothered by the symptoms in the last 12 months (NSHD, NCDS), in the last 24 hours (SMWHS) and at the moment (HOW, JMWHS, WHITEHALL). The severity of bothersome symptoms was harmonised and categorised as never, mild, moderate and severe. For our pooled analyses, the degree of symptoms was pooled into four categories: never, rarely, sometimes, and often (if reporting frequency) or never, mild, moderate, and severe (if reporting severity). When VMS and depressed mood were considered as an outcome variable, they were coded dichotomously as *present* ("often/sometimes" or "severe/moderate", respectively) and *absent* ("rarely/never" or "mild/never", respectively).

Sleep difficulties and covariates

Data on sleep difficulties were collected at baseline from menopausal symptom checklists or difficulty sleeping-related questions, i.e. "*trouble falling asleep*" and "*difficulty in sleeping*" in the questionnaires. The degree of sleep difficulties was harmonised as never, rarely, sometimes, and often (if reporting frequency) or never, mild, moderate, and severe (if reporting severity). Other baseline covariates included reproductive, socio-demographic, and lifestyle factors. Details of data harmonisation have been reported elsewhere.(Mishra *et al.*, 2016). Menopausal status was collapsed into the simplest level of detail and categorised based on gynecological surgery and menstrual bleeding patterns: 1) hysterectomy/oophorectomy, 2) unknown due to hormone use (menopausal hormone therapy or oral contraceptive hormones before reaching menopause), 3) premenopause (regular menstrual cycles in the last 3 and 12 months), 4) perimenopause (menses in the past 3 months and changes/irregularity in menstrual patterns in the past 12 months; or no menses in the

previous 3 months but menses in the preceding 11 months), and 5) natural postmenopause (amenorrhea for at least 12 months). Information on current use of menopausal hormone therapy (e.g. estrogen), regardless of menopausal status, was collected. Socio-demographic variables included race/ethnicity [Caucasian-Australian, Caucasian-European, Caucasian-American, Japanese, African American/Black, and Other (including Hispanic, Chinese, Middle Eastern, and mixed)] and education level (≤10, 11-12, and >12 years). Lifestyle factors included smoking status (never, past, and current) and body mass index (BMI) (<25, 25-29.9, and ≥30 kg/m^2).

Statistical analyses

As a result of different types of assessment (frequency or severity) and different recall periods (past 12 months or past 2 weeks/less) for menopausal symptoms, studies were grouped as follows: (1) frequency of symptoms in the past 12 months (ALSWH); (2) severity of symptoms in the past 12 months (NSHD, NCDS); (3) frequency of symptoms in the past 2 weeks (SWAN); (4) severity of symptoms in the past 2 weeks (SMWHS, HOW, JMWHS, WHITEHALL). First, the associations between VMS and depressed mood were obtained separately for the four study designs, followed by the overall estimates.

Logistic regression models were used to examine the cross-sectional and prospective bi-directional associations between VMS and depressed mood and the odds ratios (ORs) and 95% confidence intervals (CIs) were obtained. Study variability was adjusted by including study indicator as a covariate in the model. Based on the previous literature, the effect estimates were adjusted for menopausal status, concurrent use of menopausal hormone therapy (Model 1), race/ethnicity, education, smoking status, and BMI (Model 2). To examine the heterogeneity between studies, study-specific logistic regression and random-effect meta-analyses were performed and fully adjusted for the covariates in Model 2. Data for SWAN were additionally adjusted for study site. In the prospective analyses (four studies included), ORs (95%CIs) were estimated for incident depressed mood at 3-year follow-up by the degree of VMS in women without depressed mood at baseline. The odds for incident VMS associated with the degree of depressed mood in women without VMS at baseline were similarly analysed. The models were adjusted for baseline covariates mentioned above and were further adjusted for sleep difficulties at baseline to investigate the role of sleep difficulties in both directions.

To further examine the robustness of the results, multiple sensitivity analyses were performed. First, results for a single-item measure of depressed mood were compared with results using the Center for Epidemiologic Studies Depression Scale (CES-D) collected in ALSWH and SWAN. Second,

the potential influence of previous history of depression and current use of antidepressants (e.g. Prozac, Aropax) on the association between VMS and likelihood of depressed mood was examined by adjusting for these two confounders and excluding women with a history of depression or current use of antidepressants from the prospective analysis using data from ALSWH. Third, we also tested prospective results with all the women included (n=10,692) but conditioning on their baseline symptoms. Analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina), and the METAN command in STATA 14 (StataCorp LP, College Station, Texas) was used to perform meta-analyses.

Results

Baseline characteristics

The present study pooled data from 21,312 midlife women (median age 50 years, IQR: 49-51) **(Table 1)**. Among these women, 19% were premenopausal, 27% were perimenopausal, 19% were postmenopausal, and 20% had had a hysterectomy or oophorectomy at study entry (**Table 2**). Nearly 20% of the women were taking menopausal hormone therapy (10% with an unknown menopausal status). At baseline, nearly 40% of the women (range 13-62% among studies) reported that they had experienced VMS, 41% (11-56%) reported sleep difficulties, and 26% (8-41%) had depressed mood (all dichotomised: "*present*" indicating sometimes/moderate or often/severe). The prevalence of symptoms was substantially higher in ALSWH, NSHD and NCDS where symptoms were recalled over a longer period (12 months) compared with that over a shorter period (≤2 weeks). We observed racial/ethnic differences in the menopausal symptom experience. Japanese women (from JMWHS) were less likely to use menopausal hormone therapy and less likely to report severe symptoms of hot flushes and night sweats compared with other Caucasian cohorts, even though it could be partly attributable to a lower proportion of women at the perimenopausal stage, a lower proportion being current smokers and being obese, and to the collection of data on symptoms over a short period.

At baseline, the prevalence of VMS (dichotomised) was 19.8%, 42.9%, and 45.8% in premenopausal, perimenopausal, and postmenopausal women, respectively. The increased prevalence of VMS in the peri- and postmenopausal periods suggested that VMS were potentially attributable to endocrine changes at menopause. However, the prevalence of sleep difficulties (32.6%, 40.3%, and 38.0%, respectively) and depressed mood (21.6%, 26.4%, and 21.8%, respectively) were reasonably comparable across menopausal stages, reflecting normal variation in women at midlife regardless of menopausal status.

Cross-sectional associations

At baseline, a dose-dependent association between VMS and odds of depressed mood was found in all study designs, although the estimated effects were higher if the symptoms were recalled over a shorter period rather than a longer period **(Table 3)**. In the pooled analysis, this association changed little after full adjustment (Model 2), with the adjusted ORs (95%CI) of 1.23 (1.11-1.35), 1.82 (1.67-1.98), and 2.59 (2.35-2.85) for increasing degree of VMS, compared with those without VMS. We observed that women who were currently taking menopausal hormone therapy were more likely to report an experience of VMS (OR: 1.34, 1.21-1.47), depressed mood (OR: 1.40, 1.26-1.55), and sleep difficulties (OR: 1.32, 1.20-1.46) (data not shown), but hormone therapy use, as well as menopausal status, did not affect the observed associations.

In the study-specific analysis, the dose-response relationship between VMS and odds of depressed mood was present in each study. Random-effects meta-analysis of the estimates from eight studies yielded a pooled OR of 1.50 (1.04-2.15), 2.85 (1.91-4.26), and 3.95 (2.52-6.18) for increasing degree of VMS compared with non-VMS **(Supplemental Fig. 1)**. The effect size was much larger for WHITEHALL than all other studies, while the estimates were not statistically significant in SMWHS. Although significant heterogeneity between studies was detected (all I^2>87%, p<0.001), the pattern of results was similar across studies and random-effects models provided a partial soulaution to studuy hetergeneity.

Prospective bi-directional associations

During the 3-y follow-up, 31.0% of the women experienced VMS only, 10.1% experienced depressed mood only, 14.3% had concurrent symptoms, 3.5% had VMS first then depressed mood, 4.4% had depressed mood first then VMS, and 36.6% had neither symptoms (n=10,692, data not shown). In the pooled analysis, **Table 4 & 5** show dose-dependent associations between VMS and depressed mood in both directions (Model 2). Women with VMS at baseline were more likely to report subsequent depressed mood than those without VMS, with the adjusted ORs of 1.00 (0.83-1.21), 1.16 (0.96-1.39) and 1.56 (1.27-1.92) for increasing degree of VMS. The prospective relationship was much weaker than the cross-sectional relationship, with significant OR only for often/severe VMS after adjustment. On the other hand, the relationship between baseline depressed mood and subsequent VMS was stronger, with the adjusted ORs of 1.42 (1.24-1.63), 1.43 (1.22-1.67), and 1.89 (1.47-2.44) (all significant) for increasing degree of depressed mood.

Role of sleep difficulties

At baseline, we observed a moderate correlation (polychoric correlation 0.43, 95%CI 0.41-0.46) between sleep difficulties and VMS for the depressed mood subgroup and a moderate correlation (0.54, 0.52-0.56) between sleep difficulties and depressed mood for the VMS subgroup (data not shown). In the prospective analyses, with adjustment for the degree of sleep difficulties at baseline, the OR of having subsequent depressed mood associated with often/severe VMS was attenuated from 1.56 (1.27-1.92) to 1.13 (0.90-1.40) and no longer significant, with nearly a 30% reduction in the OR, while sleep difficulties remained an independent predictor for incident depressed mood with little change in odds ratios (**Table 4**). Conversely, baseline sleep difficulties did not appear to affect the relationship between baseline depressed mood and subsequent VMS as the OR reduced little to 1.80 (1.38-2.34) for often/severe depressed mood, with a <5% reduction in the OR, and sleep difficulties were not a predictive factor for incident VMS (**Table 5**).

Sensitivity analyses

Associations between VMS and depressed mood were robust in multiple sensitivity analyses (data not shown). Of note, it was found that a single question about depressed mood was highly correlated with the dichotomised CES-D score (dichotomised at 10 in ALSWH for the 10-item short form; 16 in SWAN). The tetrachoric correlation for these two definitions for depressed mood was 0.74 (95%CI 0.72-0.76) in ALSWH and 0.79 (95%CI 0.75-0.83) in SWAN. Similar results were obtained in a sensitivity analysis in which dichotomised CES-D score was used as the outcome variable. In the ALSWH study, 8.1% of the women reported a history of depression (more than two years ago) at baseline, and 5.9% reported current use of antidepressants (during the past four weeks). A sensitivity analysis, in which models were further adjusted for prior history of depression and current use of antidepressants at baseline, yielded similar findings. We found women with a history of depression had a nearly 3-fold increased odds of reporting depressed mood at follow-up (OR: 2.84, 2.09-3.84), and current users of antidepressants had an over 4.5-fold increased odds of experiencing depressed mood at follow-up (OR: 4.65, 2.08-10.41). Further exclusion of women with a history of depression or current use of antidepressants at baseline did not alter the observed relationships. In the prospective analysis with all the women included (n=10,692), baseline depressed mood, even adjusted by baseline VMS, was significantly associated with subsequent VMS.

Discussion

The findings from this pooled analysis provide robust evidence for a dose-dependent, bi-directional relationship between VMS and depressed mood. Prospective results showed that women with VMS were more likely to have a subsequent depressed mood, and women with depressed mood were also

more likely to experience VMS subsequently. Sleep difficulties largely explained the relationship between VMS and subsequent depressed mood but did not appear to affect the relationship of depressed mood with subsequent VMS. The strength of the associations varied among studies according to differences in study designs and distributions of race/ethnicity and menopausal status.

Previous prospective studies have also shown that VMS predict subsequent onset of depressive symptoms and the association is independent of marked changes in reproductive hormones during the menopausal transition (Avis *et al.*, 2001, Bromberger *et al.*, 2010, Freeman *et al.*, 2006). The Penn Ovarian Aging Study (POAS) (Freeman *et al.*, 2006) and Massachusetts Women's Health Study (Avis *et al.*, 2001) found that associations between VMS and depressive symptoms remained unchanged after adjustment for levels of estradiol. Again, the association was consistent with previous results from SWAN showing that elevated depressive symptoms (CES-D scores ≥16) were more likely to occur in women with VMS even after adjustment for multiple psychosocial factors and concurrent levels of testosterone (Bromberger *et al.*, 2010). Moreover, evidence from the SWAN Daily Hormone Study, which included daily diary reports of VMS and mood over a month, indicated that negative mood more often followed reports of VMS (Gibson *et al.*, 2011). Other studies highlight the importance of night-time VMS (but not daytime) in the association of VMS with depressive symptoms (Joffe *et al.*, 2016). However, the current literature does not suggest a relationship between VMS and a clinical diagnosis of major depression (Freeman *et al.*, 2006, Joffe *et al.*, 2011, Worsley *et al.*, 2014).

In line with the findings of the present study, results from two mediation analyses which evaluated the *domino hypothesis* (a temporal relationship between VMS, sleep, and mood) in midlife women showed that the relationship between VMS and subsequent depressed mood might partly result from sleep disturbance (Burleson *et al.*, 2010, Vincent *et al.*, 2014). One study of 114 breast cancer survivors reported that results were consistent with the hypothesis in which VMS have an indirect effect on negative mood which is mediated by sleep difficulties (Vincent *et al.*, 2014). However, in another study with a sample of 55 healthy women, sleep problems accounted for only a small portion of the relationship between VMS and next day negative mood, suggesting that the *domino hypothesis* may be true in some cases, but that is not the complete explanation (Burleson *et al.*, 2010). Additional mechanistic studies have identified that sleep interruption and night-time VMS are independently associated with emergence of depressive symptoms during menopause (Joffe *et al.*, 2016). It is vital for future research to examine the temporal relationship and formally quantify the mediating effect of sleep disturbance in these associations.

Recent intervention studies have shown the effectiveness of online insomnia programmes, such as Sleepio (Elison *et al.*, 2017) and SHUTi (Christensen *et al.*, 2016), for improvement and prevention of mental health difficulties. Internet-based cognitive behaviour therapy for insomnia (CBT-I) could be a practical and effective intervention to reduce depression symptoms in midlife women with insomnia. However, CBT-I services are limited, particularly amongst general practitioners (Asnis *et al.*, 2015). In clinical practice, the first-line pharmacotherapy treatment for insomnia is often hypnotic medication (e.g. zaleplon, zolpidem and benzodiazepines) (Asnis *et al.*, 2015). A double-blind randomised controlled trial found adding a hypnotic agent (zolpidem) to serotonin-norepinephrine reuptake inhibitors/selective-serotonin reuptake inhibitors improved sleep and optimised the quality of life in breast cancer women with hot flushes (Joffe *et al.*, 2010). Long-term effects of sleep loss and sleep disorders have been linked to a range of adverse health consequences including hypertension, obesity, diabetes, cardiovascular disease and depression (Institute of Medicine, 2006). Although clinicians are often reluctant to prescribe hypnotics, treatment approaches should include consideration of longer term use of hypnotic therapy targeting sleep disturbance, which may have profound implications for the mental health of women during midlife.

One major finding is that VMS also follow the onset of depressed mood, which is consistent with results from two prospective cohorts. POAS examined the temporal relationship between hot flushes and depressive symptoms in women with no previous experience of either symptom and found that among women who developed both symptoms, depressive symptoms were twice as likely to precede hot flushes, with an average of 1.5 years before the onset of hot flushes (Freeman *et al.*, 2009). SWAN study also found that baseline depressive symptoms were associated with subsequent VMS (Gold *et al.*, 2006), and women who reported more depressive symptoms when first experiencing VMS had a longer duration of VMS (Avis *et al.*, 2015). Although the relationships between depressed mood and subsequent VMS are established in a few studies, the underlying mechanism remains unclear; sleep difficulties do not seem to explain the relationship. One interpretation is that women with negative emotions tend to over-report symptoms via a negative reporting style and be highly self-attentive and sensitive to bodily sensations (Aronson *et al.*, 2006). It is possible that somatic symptoms in depression amplify experiences of physical sensations such as VMS. Hunter et al found that women with depressed mood were more likely to report VMS as problematic (Hunter and Liao, 1995). A systematic review of 13 studies also suggests that women with more negative attitudes towards the menopause report more menopausal symptoms, but more prospective studies are needed to determine causality (Ayers *et al.*, 2010). In addition to negative mood, anxiety was also found to be a predictor of VMS even after the adjustment of depression (Freeman and Sammel, 2016). The SWAN study even found that the

association with anxiety appeared to be stronger than the association with depressive symptoms (Gold *et al.*, 2006). Given that anxiety data were not available in all studies, however, it is important to understand these as forming another triad of symptoms: anxiety, sleep, and VMS.

Strengths and limitations

To our knowledge, this is the first study pooling individual-level data from multiple observational studies across different geographic regions, races, and cultures to quantify the dose-response relationships between VMS and depressed mood. The scale of these analyses ensures sufficient statistical power to examine the prospective relationship in both directions. Furthermore, this study included three nationally representative studies, which increases the generalisability of findings. However, some limitations should be considered in interpreting the findings. First, data used to define depressed mood were not based on structured clinical interviews or diagnoses. ALSWH and SWAN had data from the validated CES-D depression scale, and the scores were highly correlated with the single questions about depressed mood. Second, a significant limitation of this study was the variation in measurement tools used to assess VMS across studies. This variation restricted the ability to pool data, resulted in four analysis groups being created (based on frequency/severity and length of recall period), and limited the usefulness of research to inform clinical practice. For future research, it is important to develop standardised measures to collect and report menopausal symptoms across different populations. The COMMA initiative (Core Outcome set in Menopause; part of the CROWN project: Core Outcomes in Women's and Newborn Health) is a new international collaboration established to achieve consensus on standardised measures for menopause which will enhance the availability of comparable data across diverse ethnic groups and advance understanding of factors influencing women's experience of menopause to facilitate evidence-based patient care (Duffy *et al.*, 2017, The CROWN initiative, 2016). Third, sleep is a complicated variable to study and how it is assessed and defined may influence its link to the menopausal transition and symptoms (Shaver and Woods, 2015). Given that data on insomnia disorder and awakenings were not available, however, the specific type of sleep problems, such as night-time and early morning awakening, may be differentially associated with the transition and symptoms and need to be investigated further. Fourth, of the eight studies, four cohort studies provided longitudinal data on menopausal symptoms. It should be noted that women who were excluded due to the missing data at follow-up had a higher prevalence of VMS, depressed mood, and sleep difficulties at baseline compared with those included, which may have led to an underestimation of these symptoms. However, as there was sufficient variation in the distributions of VMS, depressed mood and sleep difficulties, we do not expect the nature of relationships observed in this paper to change substantively. Fifth, in the study-specific analysis, few studies

showed conflicting results where no significant association between VMS and depressed mood was found (i.e. SMWHS in the cross-sectional analysis; NSHD and SWAN in the prospective analysis). We observed that the effect estimates were consistently in the same direction, although the confidence intervals were wide and overlapping potentially due to small sample size. When we pooled the estimates under the random-effects model, these studies made relatively small contributions or weightings towards the combined effect. Sixth, it is possible that women who experienced VMS at baseline were still experiencing them at follow-up, so that prospective results might partly be attributed to cross-sectional associations. Last, although the models were adjusted for a range of confounding factors, some variables of interest, such as lifelong mental health history, anxiety, adverse life events and poor social support, were not available in all studies.

Conclusions and clinical implications

Our findings provide detailed insight into the bi-directionality of the relationship between VMS and depressed mood and different role of sleep difficulties plays in the two pathways, which build evidence to inform practical and public health recommendations for women with VMS and depressed mood. Midlife women who seek clinical help for VMS are likely to have concurrent and subsequent depressed mood, which may be largely explained by sleep difficulties. Effective interventions for sleep disturbance may have profound implications for prevention of depressive symptoms in midlife women. Women with depressed mood, however, are likely to have subsequent VMS regardless of whether sleep difficulties co-occur with depressed mood. Management and treatment of negative moods, such as social supports and more tailored treatment options (hormonal and non-hormonal) for negative emotions, may help reduce the burden from depression during the menopausal transition.

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Conflict of interest

Dr Joffe reports receiving grant funding from NIH, Merck, and SAGE, as well as serving as a consultant to NeRRe Therapeutics, Mitsubishi Tanabe, Merck, and SAGE. Other authors have no conflict of interest to declare.

Ethical standards

The authors assert that all precedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experiementation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1 Baseline characteristics of individual studies in the InterLACE consortium whose data were used for this study

Study	Country	Survey (year) selected for analytic baseline	N	Age in years at baseline Median (Q1, Q3)	Survey (year) selected for 3-y follow-up
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	Survey 2 (1998)	10242	50 (48, 51)	Survey 3 (2001)
MRC Survey of Health and Development (NSHD)	UK	Survey 1996 (1996)	1040	50[a]	Survey 1999 (1999)
National Child Development Study (NCDS)	UK	Survey 8 (2008)	3982	50[a]	N/A
Study of Women's Health Across the Nation (SWAN)	USA	Visit 4 (2000-2002)	2336	50 (48, 52)	Visit 7 (2003-2005)
Seattle Midlife Women's Health Study (SMWHS)	USA	Survey 2000 (2000)	187	50 (46, 53)	N/A
Healthy Ageing of Women Study (HOW)	Australia	Survey 1 (2001)	760	54 (52, 57)	N/A
Japanese Midlife Women's Health Study (JMWHS)	Japan	Survey 1 (2002)	738	N/A[b]	N/A
Whitehall II Study (WHITEHALL)	UK	Survey 3 (1991-1994)	2027	50 (45, 55)	Survey 4 (1995-1996)
Overall			21312	50 (49, 51)	

Abbreviation: N/A: not applicable; Q1 – 25th percentile; Q3 – 75th percentile.
[a] Participants in the NSHD (1946 British birth cohort) and NCDS (1958 British birth cohort) were at age 50 years in the 1996 and 2008 survey, respectively.
[b] JMWHS provided age by category only (≤55 and >55 years), and 48% of women were aged more than 55 (range 45–60 years).

Table 2 Baseline characteristics of study sample

Study	Overall	ALSWH	NSHD	NCDS	SWAN	SMWHS	HOW	JMWHS	WHITEHALL
n	21312	10242	1040	3982	2336	187	760	738	2027
Birth year									
<1940	3.7	N/A	N/A	N/A	N/A	0.5	N/A	N/A	39.3
1940-1949	54.9	74.3	100	N/A	41.3	46.5	85.8	47.6[c]	48.6
1950-1959	41.4	25.7	N/A	100	58.7	52.9	14.2	52.4[c]	12.1
Race/ethnicity									
Caucasian- Australian/New Zealander	41.1	79.3	N/A	N/A	N/A	N/A	83.8	N/A	N/A
Caucasian- European	40.2	16.9	100	98.2	N/A	N/A	12.8	N/A	87.8
Caucasian- American	6.3	0.7	N/A	N/A	48.1	85.6	N/A	N/A	N/A
Japanese	4.6	0.1	N/A	N/A	10.5	N/A	N/A	100	N/A
African American/Black	2.9	N/A	N/A	0.1	25.9	5.3	N/A	N/A	N/A
Other	4.8	3.0	N/A	1.7	15.6	9.1	3.4	N/A	12.2
Education level									
≤10 years	45.9	48.0	67.3	62.2	5.6	0.0	51.4	9.5	54.0
11-12 years	17.4	17.1	26.3	10.3	15.8	13.4	15.8	59.3	16.3
>12 years	36.7	34.9	6.4	27.5	78.6	86.6	32.8	31.2	29.7
Body mass index									
Normal weight (<25 kg/m^2)	48.5	48.2	63.1	44.5	36.6	50.3	42.6	85.8	52.8
Overweight (25-29.9 kg/m^2)	30.4	31.6	24.4	33.0	27.5	25.7	32.4	13.0	32.1
Obese (≥30 kg/m^2)	21.0	20.2	12.5	22.6	35.9	24.1	25.0	1.2	15.1
Smoking status									
Never	55.0	56.2	34.4	48.8	59.4	51.3	62.5	86.7	52.2
Past smoker	27.6	26.8	40.5	29.3	26.5	38.5	27.9	3.9	31.0
Current smoker	17.4	17.0	25.1	21.9	14.0	10.2	9.6	9.3	16.8
Menopausal status									

Hysterectomy/oophorectomy	19.8	25.6	18.1	16.9	4.5	3.2	28.4	11.0	15.9
Unknown due to hormone use	14.2	16.1	21.8	13.1	11.4	25.7	7.6	2.3	12.0
Premenopause	19.4	23.1	19.4	18.8	6.6	26.2	3.4	19.9	22.2
Perimenopause	27.4	24.2	24.2	30.1	56.2	31.0	11.4	11.4	18.4
Natural postmenopause	19.1	11.0	16.4	21.0	21.2	13.9	49.1	55.4	31.4
Current use of menopausal hormone therapy									
No	80.9	76.7	79.5	90.4	80.5	78.6	64.9	96.7	84.9
Yes	19.1	23.3	20.5	9.6	19.5	21.4	35.1	3.3	15.1
Frequency/severity of sleep difficulties[a]									
Never	39.0	29.2	32.2	38.6	55.7	66.3	36.3	48.2	68.4
Rarely/mild	20.0	21.0	24.1	5.1	30.2	16.6	39.5	40.5	15.3
Sometimes/moderate	26.9	32.7	31.4	37.0	7.8	10.2	17.9	7.5	8.8
Often/severe	14.2	17.1	12.2	19.3	6.3	7.0	6.3	3.8	7.4
Frequency/severity of hot flushes[a]									
Never	47.2	44.8	48.4	35.5	56.0	67.4	56.3	54.9	63.8
Rarely/mild	17.1	15.7	21.2	8.6	26.5	17.1	28.6	33.2	17.6
Sometimes/moderate	22.2	24.8	20.1	36.5	6.9	9.1	11.1	7.7	10.6
Often/severe	13.4	14.6	10.4	19.4	10.6	6.4	4.1	4.2	8.0
Frequency/severity of night sweats[a]									
Never	57.4	55.1	58.1	48.3	63.4	77.5	62.1	75.3	69.2
Rarely/mild	15.0	14.3	19.0	6.9	24.7	13.9	25.9	20.7	15.2
Sometimes/moderate	17.8	19.6	14.7	31.2	4.9	2.7	8.4	2.8	8.7
Often/severe	9.9	11.0	8.2	13.7	7.1	5.9	3.6	1.1	7.0
Frequency/severity of vasomotor symptoms[b]									
Never	42.0	40.4	42.6	30.1	47.5	63.1	49.9	49.5	59.5
Rarely/mild	18.4	16.6	22.5	8.4	31.7	18.7	32.8	37.7	17.6
Sometimes/moderate	24.2	26.9	22.1	39.1	8.3	9.1	12.0	8.5	12.3

Often/severe	15.4	16.1	12.8	22.5	12.6	9.1	5.4	4.3	10.6
Frequency/severity of depressed mood[a]									
Never	52.5	49.8	42.3	56.4	44.8	47.6	53.6	47.0	74.6
Rarely/mild	21.6	22.8	21.3	2.3	41.3	29.4	37.9	45.0	15.6
Sometimes/moderate	17.9	21.0	24.3	25.1	7.3	12.3	6.8	5.1	6.4
Often/severe	8.0	6.4	12.1	16.2	6.6	10.7	1.7	2.8	3.5

Abbreviation: N/A: not applicable; ALSWH: Australian Longitudinal Study on Women's Health; NSHD: MRC National Survey of Health and Development (1946 British Birth Cohort); NCDS: National Child Development Study (1958 British Birth Cohort); SWAN: Study of Women's Health Across the Nation; SMWHS: Seattle Midlife Women's Health Study; HOW: Healthy Ageing of Women; JMWHS: Japanese Midlife Women's Health Study; WHITEHALL: Whitehall II study.

[a] Sleep difficulties, hot flushes, night sweats, and depressed mood were collected using self-reported menopausal symptom checklists assessing either frequency or severity of the symptoms: frequency of symptoms in the past 12 months (ALSWH), severity of symptoms in the past 12 months (NSHD and NCDS), frequency of symptoms in the past 2 weeks (SWAN), and severity of symptoms in the past 2 weeks or less (SMWHS, HOW, JMWHS, and WHITEHALL).

[b] Vasomotor symptoms were defined by having either hot flushes or night sweats.

[c] JMWHS provided age by category only (≤55 and >55 years). Thus, birth year was categorised based on age categories.

Table 3 Cross-sectional association between vasomotor symptoms and odds of depressed mood at baseline

Vasomotor symptoms (VMS)	n	Case (%)[a]	Crude OR (95% CI)	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)
Frequency of VMS in the past 12 months (ALSWH)	10242	27.4			
Never	4135	21.2	Reference	Reference	Reference
Rarely	1696	25.4	1.26 (1.10-1.44)	1.24 (1.08-1.41)	1.22 (1.07-1.40)
Sometimes	2758	31.6	1.71 (1.53-1.91)	1.64 (1.46-1.83)	1.61 (1.43-1.80)
Often	1653	37.9	2.27 (2.00-2.57)	2.17 (1.90-2.47)	2.08 (1.83-2.38)
Severity of VMS in the past 12 months (NSHD, NCDS)	5022	40.2			
Never	1640	32.0	Reference	Reference	Reference
Mild	568	28.0	0.83 (0.67-1.02)	0.85 (0.68-1.05)	0.84 (0.68-1.03)
Moderate	1787	43.0	1.60 (1.39-1.85)	1.62 (1.40-1.87)	1.59 (1.38-1.84)
Severe	1027	55.5	2.65 (2.26-3.12)	2.65 (2.24-3.14)	2.54 (2.14-3.02)
Frequency of VMS in the past 2 weeks (SWAN)	2336	13.9			
Never	1109	9.7	Reference	Reference	Reference
Rarely	740	12.6	1.33 (0.99-1.79)	1.31 (0.97-1.76)	1.25 (0.92-1.69)
Sometimes	193	24.4	2.98 (2.03-4.38)	2.95 (2.01-4.35)	2.62 (1.76-3.89)
Often	294	26.2	3.29 (2.37-4.56)	3.38 (2.40-4.74)	3.11 (2.18-4.43)
Severity of VMS in the past 2 weeks (SMWHS, HOW, JMWHS, WHITEHALL)	3712	9.9			
Never	2068	4.2	Reference	Reference	Reference
Mild	919	10.8	3.01 (2.21-4.09)	3.11 (2.28-4.25)	3.01 (2.20-4.11)
Moderate	420	21.4	6.69 (4.85-9.23)	7.06 (5.06-9.83)	6.89 (4.93-9.64)
Severe	305	29.8	10.1 (7.26-14.1)	10.5 (7.43-14.7)	9.79 (6.90-13.9)
Overall sample: VMS	21312	25.9			
Never	8952	17.8	Reference	Reference	Reference
Rarely/mild	3923	19.9	1.25 (1.13-1.38)	1.25 (1.13-1.38)	1.23 (1.11-1.35)
Sometimes/moderate	5158	34.4	1.90 (1.75-2.06)	1.87 (1.72-2.03)	1.82 (1.67-1.98)
Often/severe	3279	41.6	2.78 (2.54-3.05)	2.71 (2.47-2.98)	2.59 (2.35-2.85)

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Study level variability was adjusted by including study indicator as a covariate in the crude and multivariable model.

[a] Depressed mood was defined by "often or sometimes" having depressed mood or having "severe or moderate" depressed mood.

[b] Model 1 was adjusted for menopausal status and concurrent use of menopausal hormone therapy.

[c] Model 2 was adjusted for model 1 plus following socio-demographic and lifestyle factors: race/ethnicity, education, smoking status, and BMI. Data for SWAN were additionally adjusted for study site.

Table 4 Prospective association between vasomotor symptoms at baseline and incident depressed mood at the 3-year follow-up

Vasomotor symptoms (VMS)	n	Case (%)[a]	Crude OR (95% CI)	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)	Model 2+sleep OR (95% CI)
Frequency of VMS in the past 12 months (ALSWH)	4378	14.4				
Never	1903	13.0	Reference	Reference	Reference	Reference
Rarely	775	14.3	1.12 (0.88-1.43)	1.09 (0.85-1.39)	1.08 (0.84-1.38)	0.97 (0.76-1.25)
Sometimes	1113	14.8	1.17 (0.94-1.44)	1.08 (0.87-1.35)	1.06 (0.85-1.32)	0.91 (0.72-1.14)
Often	587	18.1	1.48 (1.15-1.90)	1.35 (1.04-1.76)	1.29 (0.99-1.68)	0.96 (0.73-1.26)
Severity of VMS in the past 12 months (NSHD)	577	16.5				
Never	269	18.2	Reference	Reference	Reference	Reference
Mild	147	13.6	0.71 (0.40-1.24)	0.71 (0.40-1.27)	0.71 (0.39-1.27)	0.64 (0.35-1.16)
Moderate	111	14.4	0.76 (0.41-1.40)	0.73 (0.39-1.37)	0.71 (0.38-1.36)	0.66 (0.34-1.29)
Severe	50	20.0	1.12 (0.53-2.40)	1.08 (0.50-2.35)	1.03 (0.47-2.26)	0.83 (0.35-1.94)
Frequency of VMS in the past 2 weeks (SWAN)	1710	8.1				
Never	856	6.5	Reference	Reference	Reference	Reference
Rarely	539	6.7	1.02 (0.66-1.58)	1.07 (0.69-1.65)	1.04 (0.67-1.63)	0.97 (0.62-1.52)
Sometimes	123	12.2	1.98 (1.08-3.63)	2.06 (1.12-3.79)	1.88 (1.01-3.50)	1.70 (0.90-3.21)
Often	192	16.2	2.75 (1.72-4.40)	3.19 (1.93-5.27)	2.96 (1.75-4.98)	2.25 (1.30-3.89)
Severity of VMS in the past 2 weeks (WHITEHALL)	1568	9.0				
Never	1014	8.3	Reference	Reference	Reference	Reference
Mild	268	7.8	0.94 (0.57-1.55)	1.09 (0.65-1.82)	1.07 (0.64-1.81)	1.03 (0.57-1.86)
Moderate	165	12.1	1.53 (0.91-2.56)	1.84 (1.07-3.17)	1.93 (1.12-3.35)	1.74 (0.90-3.38)
Severe	121	13.2	1.69 (0.95-2.99)	2.12 (1.16-3.85)	2.03 (1.10-3.75)	1.64 (0.77-3.50)
Overall sample: VMS	8233	12.2				
Never	4042	10.8	Reference	Reference	Reference	Reference
Rarely/mild	1729	10.9	1.02 (0.85-1.22)	1.02 (0.85-1.23)	1.00 (0.83-1.21)	0.90 (0.74-1.08)
Sometimes/moderate	1512	14.3	1.21 (1.01-1.44)	1.19 (0.99-1.43)	1.16 (0.96-1.39)	0.98 (0.81-1.18)
Often/severe	950	17.2	1.62 (1.33-1.98)	1.63 (1.33-2.01)	1.56 (1.27-1.92)	1.13 (0.90-1.40)
Overall sample: sleep difficulties	8233	12.2				
Never	3937	8.3	Reference	Reference	Reference	Reference
Rarely/mild	2059	11.9	1.42 (1.18-1.69)	1.42 (1.19-1.70)	1.42 (1.19-1.70)	1.44 (1.19-1.72)
Sometimes/moderate	1627	17.1	1.99 (1.66-2.38)	1.99 (1.66-2.39)	1.96 (1.63-2.35)	1.94 (1.61-2.35)
Often/severe	610	25.1	3.35 (2.68-4.17)	3.36 (2.69-4.20)	3.28 (2.62-4.11)	3.18 (2.51-4.02)

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Study level variability was adjusted by including study indicator as a covariate in the crude and multivariable model.

[a] Depressed mood was defined by "often or sometimes" having depressed mood or having "severe or moderate" depressed mood.

[b] Model 1 was adjusted for menopausal status and concurrent use of menopausal hormone therapy at baseline.

[c] Model 2 was adjusted for model 1 plus following socio-demographic and lifestyle factors: race/ethnicity, education, smoking status, and BMI at baseline. Data for SWAN were additionally adjusted for study site.

Table 5 Prospective association between depressed mood at baseline and incident vasomotor symptoms at the 3-year follow-up

Depressed mood	n	Case (%)[a]	Crude OR (95% CI)	Model 1[b] OR (95% CI)	Model 2[c] OR (95% CI)	Model 2+sleep OR (95% CI)
Frequency of depressed mood in the past 12 months (ALSWH)	3494	38.9				
Never	1904	35.2	Reference	Reference	Reference	Reference
Rarely	774	44.1	1.45 (1.22-1.72)	1.43 (1.20-1.70)	1.41 (1.18-1.67)	1.37 (1.14-1.65)
Sometimes	650	41.2	1.29 (1.08-1.55)	1.33 (1.10-1.60)	1.30 (1.08-1.57)	1.25 (1.03-1.53)
Often	166	48.8	1.76 (1.28-2.41)	1.82 (1.32-2.53)	1.77 (1.28-2.46)	1.65 (1.16-2.33)
Severity of depressed mood in the past 12 months (NSHD)	594	25.1				
Never	292	17.5	Reference	Reference	Reference	Reference
Mild	124	26.6	1.71 (1.04-2.82)	1.74 (1.04-2.90)	1.66 (0.98-2.80)	1.59 (0.93-2.71)
Moderate	123	35.0	2.54 (1.57-4.10)	2.76 (1.68-4.55)	2.70 (1.63-4.46)	2.60 (1.52-4.44)
Severe	55	40.0	3.15 (1.70-5.85)	2.84 (1.50-5.37)	2.80 (1.46-5.34)	2.55 (1.28-5.08)
Frequency of depressed mood in the past 2 weeks (SWAN)	1550	19.1				
Never	769	17.0	Reference	Reference	Reference	Reference
Rarely	626	20.3	1.24 (0.95-1.62)	1.20 (0.92-1.58)	1.19 (0.90-1.58)	1.19 (0.90-1.58)
Sometimes	87	25.3	1.65 (0.98-2.77)	1.67 (0.99-2.84)	1.52 (0.89-2.62)	1.62 (0.94-2.82)
Often	68	23.5	1.50 (0.83-2.71)	1.45 (0.79-2.63)	1.41 (0.77-2.59)	1.49 (0.80-2.78)
Severity of depressed mood in the past 2 weeks (WHITEHALL)	1346	13.3				
Never	1116	11.5	Reference	Reference	Reference	Reference
Mild	166	21.1	2.06 (1.36-3.13)	2.07 (1.34-3.19)	1.94 (1.25-3.01)	1.61 (0.96-2.69)
Moderate	47	21.3	2.09 (1.01-4.30)	2.05 (0.97-4.31)	2.22 (1.05-4.70)	1.95 (0.84-4.53)
Severe	17	35.3	4.21 (1.53-11.6)	3.95 (1.40-11.2)	3.58 (1.25-10.3)	3.22 (1.03-10.1)
Overall sample: depressed mood	6984	28.4				
Never	4081	24.0	Reference	Reference	Reference	Reference
Rarely/mild	1690	31.7	1.46 (1.28-1.67)	1.45 (1.27-1.66)	1.42 (1.24-1.63)	1.38 (1.20-1.59)
Sometimes/moderate	907	37.8	1.45 (1.24-1.70)	1.47 (1.25-1.72)	1.43 (1.22-1.67)	1.39 (1.17-1.64)
Often/severe	306	40.9	1.95 (1.52-2.50)	1.96 (1.53-2.52)	1.89 (1.47-2.44)	1.80 (1.38-2.34)
Overall sample: sleep difficulties	6984	28.4				
Never	3512	22.9	Reference	Reference	Reference	Reference
Rarely/mild	1649	30.5	1.21 (1.05-1.39)	1.24 (1.08-1.42)	1.23 (1.07-1.42)	1.12 (0.97-1.30)
Sometimes/moderate	1319	36.2	1.22 (1.05-1.41)	1.23 (1.06-1.43)	1.21 (1.04-1.41)	1.05 (0.90-1.23)
Often/severe	504	39.7	1.48 (1.21-1.81)	1.51 (1.23-1.86)	1.47 (1.19-1.80)	1.17 (0.94-1.46)

Logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI). Study level variability was adjusted by including study indicator as a covariate in the crude and multivariable model.

[a] Vasomotor symptoms (VMS) were defined by "often or sometimes" having VMS or having "severe or moderate" VMS.

[b] Model 1 was adjusted for menopausal status and concurrent use of menopausal hormone therapy at baseline.

[c] Model 2 was adjusted for model 1 plus following socio-demographic and lifestyle factors: race/ethnicity, education, smoking status, and BMI at baseline. Data for SWAN were additionally adjusted for study site.