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REVIEW

A Systematic Review of Anxiety and Depressive Symptoms Among Women Experiencing Vasomotor Symptoms Across Reproductive Stages in the US

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Purpose: Vasomotor symptoms (VMS) due to menopause affect up to 80% of women and are associated with fatigue, depressive symptoms, and anxiety although the exact nature of these associations is not fully understood. This systematic review aimed to examine the existing evidence on the relationship between VMS, fatigue, depressive symptoms, and anxiety among women in any stage of reproductive aging in the United States.

Methods: A comprehensive search of MEDLINE and Embase databases was performed to identify observational studies (2010–2022) that reported on the target population. Exposure of interest was VMS; data related to the outcomes of interest (measures of fatigue, depressive symptoms, and/or anxiety) were extracted and analyzed descriptively.

Results: Twenty-six studies met the inclusion criteria, with 19 reporting on depressive symptom outcomes, 16 on anxiety outcomes, and none on fatigue. The mean age of women with VMS ranged from 41.3 to 62.0 years; 34.8% to 91.1% of women were premenopausal or in the late stage of reproductive aging, 0.6% to 61% were perimenopausal or in menopause transition, and 0% to 49% were postmenopausal. The most frequent comorbidities were hypertension and diabetes. Baseline depressive symptom rates ranged from 1.4% to 58%, with higher rates and more severe symptoms among women with more frequent and severe VMS. Anxiety rates at baseline ranged from 2.2% to 52%, with higher rates reported among women with frequent VMS. Anxiety levels varied, with the highest levels observed among women with sleep disturbances and severe hot flashes. In regression model analyses, VMS were associated with increased risk, duration, frequency, and severity of both depressive symptoms and anxiety.

Conclusion: VMS are strongly and consistently associated with depressive symptoms and anxiety, negatively affecting a woman's health beyond physical discomfort. There is a need to reduce this burden and improve quality of life for women with VMS.

Keywords: depressive symptoms, hot flashes, menopause transition, night sweats, perimenopausal women, quality of life

Introduction

Vasomotor symptoms (VMS), or hot flashes and night sweats,[1,2] affect up to 80% of women across various stages of reproductive aging[2–4] and can persist for years or decades into postmenopause for a sizable minority of women.[5] The pathophysiology of VMS is centrally mediated, involving the overstimulation of hypothalamic kisspeptin/neurokinin B/dynorphin (KNDy) neurons and consequent thermoregulatory dysfunction, as a result of declining estrogen levels during menopause.[6]

VMS can negatively affect quality of life,[7] causing substantial distress,[8] and have been linked with fatigue, depressive symptoms, and anxiety during menopause.[7,9] Fatigue is a frequent symptom in any stage of reproductive aging, often as a result of disturbed sleep due to hot flashes and night sweats.[10] Studies have also identified a positive association between

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VMS and depressive symptoms,[11,12] even in the absence of a history of depressive symptoms.[12] Moreover, there is strong evidence linking depressive symptoms during menopause to several comorbidities, including metabolic syndrome[13] and cardiovascular disease.[14] This may be further complicated by the presence of anxiety.[9] A recent systematic review reported a strong association between hot flashes and related insomnia and the risk of new-onset anxiety or depressive symptoms, or recurrence of previous depressive episodes.[9] However, the exact nature of the relationship between VMS and anxiety and depressive symptoms remains unclear. The Study of Women's Health Across the Nation (SWAN) reported that frequent VMS was associated with increased odds of anxiety in women with both low and high anxiety at baseline.[15] The Penn Ovarian Aging Study showed that somatic anxiety, but not affective anxiety, is a strong predictor of hot flashes during the menopause transition.[16] Evidence also suggests that during perimenopause there is a positive association between VMS and depressive symptoms. The association is observed to be bidirectional—women with VMS have a greater likelihood of developing depressive symptoms, and women with depressive symptoms have a greater likelihood of developing VMS.[11]

A better understanding of the relationship between fatigue, depressive symptoms, and anxiety and VMS may have substantial implications for the development of management strategies that can help women maintain good quality of life in the menopause transition and beyond. This systematic review aimed to examine existing evidence of the clinical burden and unmet needs associated with fatigue, depressive symptoms, and anxiety among women with VMS in the United States. By identifying gaps in the literature, this review seeks to provide insights that can guide future research and inform clinical practice, enhancing management of VMS in any stage of reproductive aging.

Materials and Methods

Study Protocol

Prespecified Population, Exposure, Comparator, Outcomes, and Study design criteria (PECOS) guided the design and implementation of this systematic review, which followed Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.[17]

Search Strategy

On October 4, 2022, we conducted a search of MEDLINE and Embase electronic databases covering the years 2010 to 2022. Search terms related to the PECOS criteria were used. The population of interest was women of any age in the United States, while the exposure of interest was VMS. Allowed study designs included observational studies of any design (prospective or retrospective), while outcomes of interest included measures of fatigue, depressive symptoms, or anxiety. Search filters related to study design and outcomes were applied to ensure specificity of the results (Supplemental Tables 1 and 2).[18,19] Results were then saved and imported into EndNote, and the total number of hits from each database and the date on which the search was implemented were recorded. Deduplication was performed according to EUnetHTA guidelines.[20,21] The formal search strategy was supplemented by a manual search of the bibliography of relevant systematic reviews and a grey literature search.

Inclusion and Exclusion Criteria

To help with statistical reliability, generalizability, and potential bias, only observational studies that included at least 100 women of any age and assessment of VMS were included. Those who experienced VMS due to conditions other than menopause (eg, drug side effects), were excluded. Reports of studies conducted in other populations, non-English language publications, and abstracts from conferences before 2019 were also excluded.

Study Selection and Quality Assessment

Abstracts and full-text articles were screened for eligibility by two independent reviewers (EB, MV) and, in the event of differences in opinion, a third reviewer (FOS) was consulted to make the final decision. The Newcastle-Ottawa Scale was used to assess the quality of identified studies.[22]

Data Extraction and Synthesis

For each study, extracted parameters included author, year, study design, population demographics (age, race, smoking status, body mass index [BMI], education level, and employment status), menopausal status (as reported by the authors), comorbidities, and outcomes (fatigue, depressive symptoms, and anxiety). All studies underwent double data extraction by two reviewers (EB, MV), and conflicting opinions were resolved through discussion. The means, medians, standard deviations (SD), 95% confidence intervals (CI), and ranges for continuous variables and numbers and proportions of participants for dichotomous and categorical variables were extracted. The analyses were descriptive and selected according to the type of extracted data; baseline participant demographic and clinical characteristics were described using counts, proportions, and medians. Results are presented as prevalence or rates depending on how these were reported in the original sources.

Results

Study Characteristics

The initial search identified 7613 citations. Reports of 26 observational studies that met the PECOS criteria were included in the systematic review (Figure 1). The characteristics of these studies are presented in Supplemental Table 3. Of these studies, 17 were prospective,[5,15,23–37] three were retrospective,[38–40] three were cross-sectional,[41–43] and three were population or community based.[44–46]

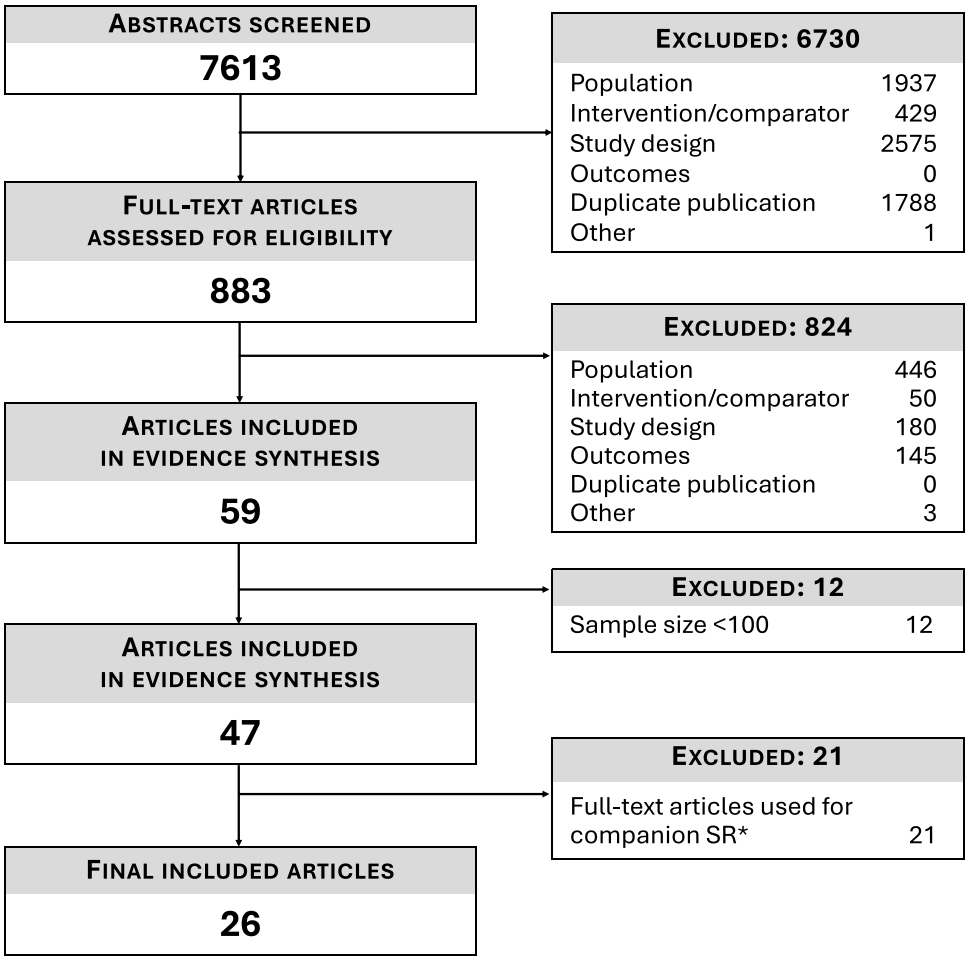

Figure 1 PRISMA Flow Diagram of the Study Selection Process.*A companion systematic review was undertaken using the same search, but focusing on perimenopausal women and women aged over 65 years with VMS in the United States.

The studies varied considerably in duration (3 days–55 years) and in the number of participants in the population of interest (77–252,273 women reporting VMS in the United States).[37,39] Menopause status, as reported by the authors, also varied; two studies focused exclusively on premenopausal women,[44,45] and 13 studies included both premenopausal and perimenopausal women.[15,23,25–31,33–35,43] Two studies included women in late perimenopause or postmenopause.[24,41] Another two studies focused solely on postmenopausal women,[36,40] and three studies included women with surgical menopause.[32,39,40]

Only three studies reported VMS-related treatment use. Of these, two evaluated hormone therapy (HT)[36,40] and one described medical cannabis use.[23]

None of the studies included in this review reported outcomes related to fatigue.

Participant Characteristics

The mean age of women with VMS ranged from 41.3 to 62.0 years across all studies evaluated. Smoking prevalence was reported in 19 studies and ranged from 1.1% to 42%.[25–37,39,42–46] BMI was reported in 14 studies and varied between 25.6 and 31.3 kg/m^2 (Supplemental Table 4).[24,25,27–32,34–37,43,44]

Hot flashes/VMS symptoms were reported in all studies as this was a requirement for inclusion in the systematic review. Menopause status of the study population, as reported by the authors, was only described in detail in 19 studies (Supplemental Table 5); 12.7% to 91.1% of women were premenopausal or in late reproductive stages, 0.6% to 67% were perimenopausal, and 0% to 100% were postmenopausal (Supplemental Table 6).[15,23–35,40,43,44,46] Definitions of the stages of reproductive aging were generally aligned across these studies.

Hypertension, diabetes, obesity, and migraine were the most frequently reported comorbidities across 11 studies.-[15,23,25–27,32,34–36,40,42] Two of these studies[15,27] included women who experienced severe negative life events that were found to correlate with elevated baseline anxiety levels (Supplemental Table 7).

Outcomes

Depressive Symptoms

Of the 26 studies in this analysis, 19 reported outcomes related to depressive symptoms (Table 1).[5,23–29,31–34,36,37,39–42,44] Of these studies, six reported general measures of depressive symptoms[23,25,26,39,40,42] and 12 reported validated measures.[5,24,27–29,31–34,36,41,44] One study reported both general and validated measures.[37] Only two studies recorded data related to depression history among participants.[37,42]

Eleven studies provided data on the percentage of women who had depressive symptoms at baseline, which varied between 1.4% and 58%.[5,23,25–29,37,39,40,42] Depressive symptoms were identified in 1.4% to 45% of women measured using general measures,[24,26,27,38,40,41,43] and in 17% to 58% of women measured using only validated measures, primarily the Center for Epidemiologic Studies Depression Scale (CES-D).[27–29] One study reported depressive symptoms using the Hamilton Depression Scale.[37]

Baseline mean and median depressive symptoms scores were evaluated in nine studies that used only validated instruments.[24,31–34,36,37,41,44] These predominantly included the CES-D scale; mean (SD) scores ranged from 7.6 (7.7) to 17.9 (15.0).[24,31–34,41,44] Notably, high depressive symptoms scores were reported in studies that stratified by moderate or high VMS severity, with means ranging from 8 to 17.9[31,32,34,44] and the highest mean values observed among women with severe VMS.[32]

Overall, a positive correlation was observed across multiple studies between depressive symptoms and VMS severity and frequency, showing that women with more intense and recurrent VMS had higher mean depressive symptom scores compared with those who experienced milder and less frequent VMS.[32–34,44] Additionally, two studies found greater proportions of women with depressive symptoms at baseline among those who had frequent VMS (≥6 days over the previous 2 weeks), compared with women with less frequent VMS (<6 days over the previous 2 weeks).[27,29]

Table 1 Baseline and End of Study Depressive Symptoms Outcomes

First Author, Year	Subgroup/Arm	N	Measure Name	Timepoint Measured	Mean (SD)	n	%	*p* Value	Comparator
General measures									
Dibonaventura, 2012[42]	HF	3632	Percentage experiencing depressive symptoms in the past 12 months	Baseline	—	1165	32.1	—	—
Thurston, 2013[37]	HF	77[a]	Percentage experiencing depressive symptoms	Baseline	—	23	13.6[a]	<0.05	Comparing participants with HF and participants without HF, adjusted estimates
		20[a]		52 weeks postpartum	—	5	6.9[a]	<0.05	
Gallicchio, 2014[25]	HF	285	Percentage using antidepressant medication	Baseline	—	37	13	0.3	No HF
Sarrel, 2015[39]	Untreated VMS	252,273	Percentage experiencing depressive symptoms	Baseline	—	8588	3.4	—	—
Gallicchio, 2015[26]	History of HF	332	Percentage experiencing depressive symptoms	Baseline	—	85	25.6	0.0002	—
Tang, 2018[40]	CE tablet cohort	1404	Percentage experiencing depressive symptoms	Baseline	—	100	7.12	0.2452	Untreated cohort, crude estimates
		1404	Percentage experiencing a major depressive disorder		—	98	6.98	0.0923	
		1404	Percentage using antidepressant medication		—	28	1.99	0.1311	
	Untreated VMS cohort	3096	Percentage experiencing depressive symptoms		—	192	6.2	—	—
		3096	Percentage experiencing a major depressive disorder		—	176	5.68	—	—
		3096	Percentage using antidepressant medication		—	43	1.39	—	—
Dahlgren, 2022[23]	Overall	251	Percentage experiencing depressive symptoms	Baseline	—	113	45	—	—

(*Continued*)

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Table 1 (Continued).

First Author, Year	Subgroup/Arm	N	Measure Name	Timepoint Measured	Mean (SD)	n	%	*p* Value	Comparator
Validated measures									
Thurston, 2010[36]	HF at any study visit	139	Beck Depression Inventory	Baseline	5.4 (4.8)	—	—	—	—
Chen, 2010[41]	US participants	121	CES-D	—	15.4 (0.9)[b]	—	—	0.000	US participants compared with Taiwanese participants adjusted for maternal age, number of children, marital status, maternal education, and employment
Freeman, 2011[44]	Moderate/severe HF	259	CES-D	Baseline	16.9 (15.6–18.1)[c]	—	—	<0.001	Mild HF and no HF
	Mild HF	90	CES-D		13.5 (11.6–15.3)[c]	—	—	—	—
Thurston, 2012[34]	HF frequency 1–5 d/2 wk	575	CES-D	Baseline	10 (5.0–18.0)[d]	—	—	—	—
	HF frequency ≥6 d/2 wk	227			13 (6.0–24.0)[d]	—	—	—	—
Gold, 2013[28]	VMS at baseline	1070	CES-D[e] ≥16	Baseline	—	351	58	—	—
		1070	CES-D[e] <16		—	719	34	—	—
Thurston, 2013[37]	HF	77[a]	HAM-D[f]	Baseline	18.5 (8.3)	—	—	<0.05	Comparing participants with HF and participants without HF, adjusted estimate
		20[a]		52 weeks postpartum	7.3 (6.6)	—	—	<0.05	
Avis, 2015[5]	Total VMS duration population (frequent VMS)	1383	CES-D	At first VMS report	—	386	27.9	—	—
Tepper, 2016[33]	Overall	1455	CES-D	Baseline	9.9 (9.1)	—	—	—	—
	Low: low probability of VMS with a slight increase around FMP	400			7.6 (7.7)	—	—	—	—
	Early onset: probability of VMS before FMP, decreasing after FMP	247			11.7 (9.1)	—	—	<0.001	Comparing across VMS trajectory subgroups, crude estimates
	Late onset: probability of VMS sharply increased after FMP, decreased later	435			8.7 (8.2)	—	—	<0.001	
	High: high probability of VMS throughout the MT	373			12.7 (10.4)	—	—	<0.001	

Fisher, 2016[24]	Daily HF	152	CES-D[g]	Baseline	6 (7.6)[h]	—	—	—	—
Gold, 2017[27]	VMS 1–5 d/2 wk	902	CES-D	Baseline	—	276	35.8	—	—
	VMS ≥6 d/2 wk	353			—	159	20.7	—	—
Matthews, 2020[31]	VMS symptoms	1407	CES-D[i]	Baseline	7.0 (3.0–13.0)[d]	—	—	<0.0001	Comparing the differences between groups of all women and women with different ethnicity, crude estimates
	Group 1: Low VMS/sleep problems/high FSH rise	552		Baseline	7.8 (8.0)	—	—	—	—
				At FMP	5.9 (6.1)				
	Group 2: Moderate VMS and sleep problems/low FSH rise	169		Baseline	11.5 (9.2)	—	—	—	—
				At FMP	8.8 (8.4)				
	Group 3: Lower VMS/high sleep problems/high FSH rise	203		Baseline	8.7 (8.5)	—	—	—	—
				At FMP	8.5 (9.1)				
	Group 4: High VMS/lower sleep problems/high FSH rise	297		Baseline	8.6 (8.5)	—	—	—	—
				At FMP	6.9 (7.0)				
	Group 5: High VMS/high sleep problems/intermediate FSH rise	186		Baseline	13.2 (10.5)	—	—	—	—
				At FMP	11.4 (9.6)				
Peterson, 2022[32]	Overall	874	CES-D	3-wave follow-up, 29 years after study recruitment	16.1 (15.1)				
	Low VMS severity	251			15.2 (17.2)	—	—	0.02	Comparing differences between low, medium, and high VMS severity
	Medium-low VMS severity	280			14.6 (12.7)				
	High VMS severity	343			17.9 (15.0)				
	HT users	580			15.9 (14.2)			0.702	Comparing differences between HT and non-HT users
	Non-HT users	294			16.3 (16.6)				
Gold, 2022[29]	Less frequent VMS (1–5 d/2 wk)	949	CES-D <16	Baseline	—	787	82.9	—	—
			CES-D ≥16		—	161	17	—	—
	Frequent VMS (≥6 d/2 wk)	338	CES-D <16		—	264	78.1	—	—
			CES-D ≥16		—	74	21.9	—	—

Notes: — Not reported. [a] Exact n not given, but 18% of 429 participants reported HF at baseline (77 calculated) and 10% of 201 reported HF at week 52 (20 calculated). [b] Mean (SE). [c] Mean (95% CI). [d] Median (IQR). [e] Score on a 20-item scale of the extent to which each item was experienced in the previous week. [f] 29-item Structured Interview Guide for the HAM-D with Atypical Depression Supplement. Scores: <7: absence of depression; 7–17: mild; 18–24: moderate; 25+: severe depression. [g] Score of ≥16 denotes a participant is depressed. [h] Median (SD). [i] Depressive symptoms in the last week were based on the 20-item CES-D, with the sleep item removed for analyses.

Abbreviations: CE, conjugated estrogen; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; FSH, follicle stimulating hormone; FMP, final menstrual period; HAM-D, Hamilton Rating Scale for Depression; HF, hot flashes; HT, hormone therapy; IQR, interquartile range; MT, menopause transition; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

Anxiety

Overall, 15 studies evaluated anxiety at baseline[15,23,24,27–30,33–35,39–41,43,44] and one assessed anxiety at first report of VMS[5]; 12 used general measures,[5,15,23,27–30,33–35,39,40] and four used validated measures (Table 2).[24,41,43,44] The proportion of women reporting anxiety ranged from 2.2% to 52%.

Of the studies that used general measures, five were drawn from SWAN and found high anxiety (scores ≥4 on a questionnaire assessing irritability, nervousness, tension, feeling fearful for no reason, and heart-pounding or racing symptoms) in 14% to 52% of women.[27,28,30,33] Notably, in one of these studies, although most women did not report anxiety, the largest proportion of those who did, reported high levels of anxiety and frequent VMS (≥6 days per week in the previous 2 weeks).[29] Consistent with these results, another study reported higher mean (interquartile range) anxiety scores among women with high versus low frequency of hot flashes (4 [2–6] and 2 [1–4], respectively).[34]

Three of the four studies that used validated scales found mean (SD) anxiety scores ranging from 10.9 (NR) to 39.7 (1.10), as measured with the State Trait Anxiety Inventory score,[24,41,43] with one study reporting the highest mean values among women with sleep disturbances.[43] In another study, which used the Zung scale for anxiety, moderate or severe hot flashes were associated with higher mean anxiety scores compared with mild or no hot flashes (36.3, 32.8, and 33.0, respectively).[44]

There were no studies that reported follow-up anxiety scores.

Regression Model Analyses

Studies evaluating the relationship between depressive symptoms and anxiety and VMS due to menopause using regression models used different methodologies and covariates, making comparisons challenging.

Three studies found statistically significant associations between hot flash severity and depressive symptoms across various subgroups, with one study also reporting a significant association between hot flash severity and anxiety.[26,31,37] Three studies examined the relationship between hot flash frequency and depressive symptoms, finding statistically significant associations between frequent hot flashes and depressive symptoms.[26,29,33] Similar associations were observed between hot flash frequency and anxiety.[15,29,33]

One study found a positive correlation between depressive symptoms and hot flash history,[36] and an unadjusted analysis found a significant association between depressed mood and hot flash duration.[44] Similar findings were reported for anxiety.[45] Significant associations were found in the same study between depressive symptoms or anxiety and the risk of developing hot flashes.[45]

A total of 14 studies examined the role of BMI in menopause-related outcomes including VMS, depression, and anxiety.[24,25,27–32,34–37,43,44] Although BMI was often associated with VMS, it was inconsistently linked to depression and anxiety. Three studies found that higher BMI was associated with more frequent or severe VMS, particularly in the early stages of menopause.[27,28,30] However, some studies found no significant relationship between the two.[25,32] Stage of menopause appeared to modify this relationship, showing a positive association between BMI and VMS in the early stages of menopause but an inverse relation in later stages.[27] Although some studies included BMI in models that assessed depressive symptoms,[31,44] none explored BMI directly as a primary variable in the context of depression or anxiety.

Discussion

VMS, comprising hot flashes and night sweats, are highly prevalent during the menopause transition and early postmenopause, significantly affecting relationships, work productivity, and overall quality of life.[4,7] This systematic review aimed to comprehensively describe the published evidence on the relationship between VMS, fatigue, depressive symptoms, and anxiety in women in any stage of reproductive aging in the United States. These data may have important implications, in that a better understanding of the clinical burden and unmet needs associated with VMS in the real world can provide insights into the broader impact of emerging therapies beyond merely controlling VMS frequency and severity.

Table 2 Baseline and End of Study Anxiety Outcomes

First Author, Year	Subgroup/Arm	N	Measure Name	Timepoint of Reported Estimate	Mean (SD)	n	%	*p* Value	Comparator
General measures of anxiety									
Thurston, 2012[34]	HF frequency 1–5 d/2 wk	575	Anxious symptoms[a]	Baseline	2 (1.0, 4.0)[b]	—	—	—	—
	HF frequency ≥6 d/2 wk	227			4 (2.0, 6.0)[b]	—	—	—	—
Gold, 2013[28]	VMS at baseline	1070	Anxiety score ≤4[a]	Baseline	—	833	77.9[c]	—	—
			Anxiety score >4[a]		—	237	22.1[c]	—	—
			Perceived stress scale[d]		8.9 (2.9)	—	—	—	—
Bromberger, 2013[15]	Low baseline anxiety	2304	Symptom checklist[a]	Baseline	—	157	6.8	—	—
	High baseline anxiety	652			—	160	24.5	—	—
Avis, 2015[5]	Total VMS duration population (frequent VMS)	1403	Anxiety score ≥4[a]	At first VMS report	—	488	34.8	—	—
Sarrel, 2015[39]	Untreated VMS	252,273	Percentage experiencing anxiety	Baseline	—	5492	2.2	—	—
Thurston, 2016[35]	Consistently low VMS	228	Anxiety	Baseline	1 (0, 3.0)[e]	—	—	—	—
	Early-onset VMS	134			2 (0, 4.0)[e]	—	—	—	—
	Late-onset VMS	225			1 (0, 3.0)[e]	—	—	—	—
	Consistently high VMS	224			3 (1.0, 6.0)[e]	—	—	<0.0001	Compared with consistently low VMS

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Table 2 (Continued).

First Author, Year	Subgroup/Arm	N	Measure Name	Timepoint of Reported Estimate	Mean (SD)	n	%	*p* Value	Comparator
Tepper, 2016[33]	Overall	1455	Anxiety score ≥4[a]	Baseline	—	280	19.2	—	—
	Low: low probability of VMS with a slight increase around FMP	400			—	44	11	—	—
	Early onset: probability of VMS before FMP, decreasing after FMP	247			—	66	26.7	<0.001	Comparing across VMS trajectory subgroups, crude estimate
	Late onset: probability of VMS sharply increased after FMP, decreased later	436			—	54	12.4	<0.001	
	High: high probability of VMS throughout the MT	373			—	116	31.1	<0.001	
Jackson, 2016[30]	Infrequent VMS (1–5 d/2 wk)	794	Anxiety score ≥4[a]	Baseline	—	226	28.5	<0.0001	Comparing the differences between no VMS, less frequent VMS, and frequent VMS; crude estimate
	Frequent VMS (≥6 d/2 wk)	298			—	155	52	<0.0001	
Gold, 2017[27]	VMS (1–5 d/2 wk)	902	Anxiety score ≥4[a]	Baseline	—	266	36.6	—	—
	VMS (≥6 d/2 wk)	353			—	189	26	—	—
Tang, 2018[40]	CE tablet cohort	1404	Percentage of participants with GAD at baseline	Baseline	—	18	1.28	0.7335	Compared with the untreated cohort, crude estimate
	Untreated VMS cohort	3096			—	36	1.16	—	—
Gold, 2022[29]	Less frequent VMS (1–5 d/2 wk)	949	Anxiety score <4[a]	Baseline	—	816	86	—	—
			Anxiety score ≥4[a]		—	133	14	—	—
	Frequent VMS (≥6 d/2 wk)	338	Anxiety score <4[a]		—	281	83.1	—	—
			Anxiety score ≥4[a]		—	57	16.9	—	—

Dahlgren, 2022[23]	Overall	251[f]	Percentage experiencing anxiety	Baseline	—	102	40.6	—	—
		223[g]			4.4 (2.5)	—	—	—	—
	Perimenopause	127			4.9 (2.5)	—	—	—	—
Validated measures of anxiety									
Chen 2010[41]	US participants	121	State Trait Anxiety Inventory-state anxiety	—	37.9 (1.2)[h]	—	—	0.444	US participants compared with Taiwanese participants adjusted for maternal age, number of children, marital status, maternal education, and employment
			State Trait Anxiety Inventory-trait anxiety		39.7 (1.1)[h]	—	—	0.869	
Freeman, 2011[44]	Premenopause with moderate to severe HF	259	Zung scale for anxiety	Baseline	36.3 (35.3, 37.3)[j]	—	—	<0.001	Mild HF and no HF, *P* values are from F-test
	Premenopause with mild HF	90			32.8 (31.2, 34.4)[j]	—	—	—	—
	Premenopause with no HF	55			30.2 (28.4, 32.0)[j]	—	—	—	—
Kravitz, 2011[43,i]	87% sleep efficiency	116	State Trait Anxiety Inventory score	Baseline	11.1 (—)	—	—	—	—
	85% sleep efficiency				16.0 (—)				
	83% sleep efficiency				20.7 (—)				
	81% sleep efficiency				25.3 (—)				
	79% sleep efficiency				30.0 (—)				
	78% sleep efficiency				32.1 (—)				
	11 min sleep latency				10.9 (—)				
	12 min sleep latency				12.8 (—)				
	13 min sleep latency				14.4 (—)				
	14 min sleep latency				16.0 (—)				
	15 min sleep latency				17.7 (—)				
	16 min sleep latency				19.2 (—)				
	17 min sleep latency				20.4 (—)				
	18 min sleep latency				21.5 (—)				

(*Continued*)

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Table 2 (Continued).

First Author, Year	Subgroup/Arm	N	Measure Name	Timepoint of Reported Estimate	Mean (SD)	n	%	*p* Value	Comparator
	19 min sleep latency				22.6 (—)				
	20 min sleep latency				23.7 (—)				
	21 min sleep latency				24.9 (—)				
	22 min sleep latency				26.1 (—)				
	23 min sleep latency				26.9 (—)				
	24 min sleep latency				28.0 (—)				
	25 min sleep latency				28.7 (—)				
	26 min sleep latency				29.6 (—)				
	27 min sleep latency				30.3 (—)				
	28 min sleep latency				31.1 (—)				
	29 min sleep latency				31.9 (—)				
Fisher, 2016[24]	Daily HF	152	State Trait Anxiety Inventory score	Baseline	33.0 (9.8)	—	—	—	—

Notes: — Not reported. [a] Women were asked if they had experienced each of these symptoms in the previous 2 weeks and, if so, how frequently: irritability, nervousness, or tension; feeling fearful for no reason; and heart-pounding or racing. Those with a score of ≥4 were identified as having high anxiety (0 = no days and 4 = every day). [b] Mean (IQR). [c] Proportions presented here reflect those calculated based on reported sample size and event rates. [d] A summed scale asking how often over the prior 2 weeks that four aspects of stress were experienced, ranging from 1=never to 5=very often. [e] Median (IQR). [f] Participants who self-reported a medical condition including depression. [g] Participants with anxiety scores. [h] Mean (SE). [i] Cross-sectional study, so only baseline measure reported. [j] Mean (95% CI).

Abbreviations: CE, conjugated estrogen; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; FSH, follicle-stimulating hormone; FMP, final menstrual period; GAD, generalized anxiety disorder; HF, hot flashes; IQR, interquartile range; MT, menopause transition; SD, standard deviation; SE, standard error; VMS, vasomotor symptoms.

This review identified 26 studies focusing on depressive symptoms and anxiety in women of any stage of reproductive aging with VMS in the United States. Importantly, none of the studies included in this review specifically addressed the relationship between fatigue and VMS, exposing a significant evidence gap and the need for further research in this area. Only three studies discussed treatments for the management of VMS: two evaluated HT, and one examined medical use of cannabis. None of these studies assessed the impact of VMS treatment on depressive symptoms or anxiety.

Consistent with existing literature showing an association between depressive symptoms and anxiety and VMS,[4,11,47] high rates of depressive symptoms and anxiety were found among the women included in the studies considered. For example, one study reported that 52% of women with frequent VMS (≥6 days in the previous 2 weeks) had high anxiety (score ≥4).[30] Furthermore, studies that stratified participants by hot flash frequency or severity consistently found higher mean anxiety scores and higher proportions of anxiety among those with more severe symptoms, a trend also observed for depressive symptoms, as indicated by higher CES-D scores among women with more frequent or severe VMS in four studies.[31,32,34,44]

VMS are associated with several comorbidities, including diabetes and cardiovascular disease.[48,49] In this review, hypertension was the most frequently reported comorbidity, followed by diabetes. However, data on comorbidities were sparse, making it challenging to determine their prevalence among women with VMS due to menopause.

This systematic review has several strengths, including a comprehensive search strategy, thorough reference list screening, and inclusion of grey literature, which ensured a broad capture of relevant studies. The rigorous methodology and inclusion of numerous studies allowed for in-depth exploration of the impact of depressive symptoms and anxiety on women with VMS in various stages of reproductive aging in the United States.

Nevertheless, there are limitations to consider. First, the absence of data on fatigue did not allow for the exploration of outcomes relating to one of the objectives of this systematic review. This was due to the absence of studies meeting the inclusion criteria for fatigue assessments, highlighting a critical research gap. Second, variability of outcome results within studies using the same data source, such as SWAN, was observed. For instance, the proportion of women experiencing anxiety varied from 14% to 55% in five SWAN studies that used the same definition of anxiety. This may have been due to measurements taken at different timepoints over the follow-up period or related to different subsamples. Estimates of individuals with VMS experiencing depressive symptoms were wide ranging, irrespective of whether studies used validated or general measures for their estimations. Several factors may have contributed to the observed heterogeneity, including differences in study populations, comparison groups, and study design features. Third, excluding studies published before 2010 limited historical context; however, this ensured that the review focused on more recent data on the association between VMS, depressive symptoms, and anxiety. Fourth, our literature search was conducted through 2022, and it is possible that new studies meeting our PECOS criteria have been published since then; therefore, we recommend that similar studies with updated literature searches be conducted in the future. Fifth, findings from single-site studies included in the review may lack generalizability. Finally, as VMS frequency and severity reporting methods varied across studies, the identified evidence shows a degree of heterogeneity.

Notwithstanding the limitations, this review offers detailed insights into the relationship between VMS, depressive symptoms, and anxiety among women in various stages of reproductive aging. The findings show that high frequency and severity of VMS correlate with high levels of anxiety and depressive symptoms. Additionally, VMS were significantly and positively associated with risk, duration, frequency, and severity of both depressive symptoms and anxiety in several regression models reported in the included studies. This knowledge could guide healthcare decision-making by highlighting the potential benefits that effective VMS treatments could have on improving the quality of life for women in the menopause transition.

Conclusion

Women across all stages of reproductive aging experiencing VMS in the United States are at risk of depressive symptoms and anxiety, which worsen as the intensity and frequency of VMS increase. This highlights the substantial impact that VMS can have on a woman's health, often leading to reduced quality of life and increased healthcare utilization. Clinicians should aim to screen for mental health concerns in women reporting VMS and prioritize evidence-based management strategies. Addressing the burdens of VMS not only improves well-being and quality of life among affected

women but also helps to reduce societal costs associated with untreated mental health conditions. Future research should focus on identifying effective interventions that are accessible among diverse populations with VMS.

Data Sharing Statement

The data used in this systematic review were extracted from the existing studies cited in the manuscript, which are available in the public domain; however, some are behind a paywall and require a fee for access. The data extracted from each study are described in Table 1 and Table 2 and Supplemental Tables 3–7.

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Disclosure

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