ORIGINAL ARTICLE

Lifetime History of Depression and Anxiety Disorders as a Predictor of Quality of Life in Midlife Women in the Absence of Current Illness Episodes

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Context: It is unknown whether a history of depression, anxiety disorders, or comorbid depression and anxiety affects subsequent health-related quality of life (HRQOL) during midlife in women when vasomotor symptoms (VMS) and sleep disturbance commonly disrupt QOL.

Objectives: To evaluate whether previous affective illness is associated with low HRQOL during midlife in the absence of current illness episodes and whether low HRQOL is explained by VMS or sleep disruption.

Design: Longitudinal, community-based study.

Setting: Western Pennsylvania.

Participants: A total of 425 midlife women in the Study of Women's Health Across the Nation who completed the Structured Clinical Interview for *DSM-IV* (SCID) and the 36-Item Short Form Health Survey (SF-36) annually during 6 years of follow-up.

Main Outcome Measures: Scores on the SF-36 scales of social functioning (SF), role-emotional (RE), role-physical (RP), body pain (BP), and vitality.

Results: Ninety-seven women (22.8%) had comorbid affective illness histories, 162 (38.1%) had previous depression only, and 21 (4.9%) had previous anxiety only. Those with comorbid illness histories and depression alone were more likely to report low HRQOL on the SF, RE, RP, and BP domains (odds ratio [OR] = 2.31-3.54 and 1.59-2.28, respectively) than were women with neither disorder. After adjustment for VMS and sleep disturbance, the comorbid group continued to have low HRQOL on these domains (OR = 2.13-3.07), whereas the association was significant on SF and BP only for the depression-alone group (OR = 2.08 and 1.95, respectively). Compared with women with neither disorder, the anxiety-only group had low HRQOL on the RP domain (OR = 2.60). Sleep disturbance, but not VMS, was independently associated with low HRQOL on all the domains except RE.

Conclusions: A history of both depression and anxiety has the most robust negative effect on HRQOL in women during midlife, an association not explained by VMS or sleep disturbance. For the depression-alone group, sleep disturbance may partially explain the negative impact of previous affective illness on HRQOL. Sleep disturbance remains an independent correlate of low HRQOL.

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Depression and anxiety disorders are each associated with compromised functioning and low quality of life (QOL).[1] Relative to individuals with depression alone or an anxiety disorder alone, those with both a depressive disorder and an anxiety disorder have the greatest risk of impaired functioning during an illness episode.[2,3] Limited literature[4-7] also suggests that those with a history of a depressive disorder subsequently have low QOL, with impairment in social and interpersonal functioning, even when they are not currently depressed. However, little is known about the long-term effect of previous depression generally, and of comorbid depression and anxiety in particular,[8] on QOL in midlife women.

The National Comorbidity Survey found that by the time women reach midlife, approximately 23% have experienced at least 1 episode of major depression and 30% have been diagnosed as having an anxiety disorder.[9] Therefore, many women may be at risk for sequelae of previous affective illness during midlife, including low health-related QOL (HRQOL). In the absence of an active depression episode, women aged 42 to 52 years with previous recurrent major depression are susceptible to low HRQOL before they enter the menopause transition.[4] The menopause transition is itself associated with deleterious effects on selected domains of HRQOL in some studies,[10-12] whereas other researchers found that the association with menopause was explained by menopausal symptoms.[10] However, to what ex-

tent previous affective illness contributes to low HRQOL independent of common menopause-related symptoms is not known. No studies, to our knowledge, have examined whether midlife women with previous affective illness are at greater risk for compromised HRQOL in the absence of recurrent illness episodes than are those without previous depression or anxiety disorders.

The impact of previous affective illness on HRQOL during midlife may be due to the association of depression and anxiety with common menopause-associated symptoms: vasomotor symptoms (VMS; 50%-85% of women) and sleep disturbance (approximately 50% of women), which are each associated with low HRQOL.[11] In the absence of current depression, women with a history of depression or anxiety may be at increased risk for sleep disturbance and VMS during midlife.[13] Although less is known about the risk of menopause-related symptoms in women with histories of anxiety and depression, it is expected that such a history confers greater vulnerability to these symptoms than does either disorder alone. Thus, given the prevalence of VMS and sleep disturbance and their deleterious effect on HRQOL, it is plausible that they may, in part, explain the effect of previous affective illness on HRQOL during midlife.[10]

In this study, we sought to determine whether in the absence of current illness episodes, midlife women who have histories of depression and anxiety disorders, depression alone, or an anxiety disorder alone are more susceptible to low HRQOL than are those with no history. We hypothesized that compared with women with no history of affective illness, those with previous depression or anxiety would be more likely to report compromised HRQOL during midlife and that those with histories of both depression and anxiety would be most likely to experience low HRQOL. We also hypothesized that associations between previous psychiatric illness and HRQOL would be, in part, explained by the presence of VMS and sleep disruption, given evidence that these symptoms are more common in women with previous depression and anxiety and independently contribute to poor HRQOL.

METHODS

STUDY PARTICIPANTS AND PROCEDURES

This study was conducted in participants at the Pittsburgh site of the Study of Women's Health Across the Nation (SWAN), a multisite, community-based cohort investigation of the menopause transition and aging in midlife women. The SWAN study design and sampling procedures have been described previously.[14] Each site recruited Caucasian women and a predetermined minority group. The Pittsburgh site enrolled 162 African American and 301 Caucasian women using random-digit dialing and voter registration list recruitment methods. Eligibility criteria for the SWAN included age 42 to 52 years, an intact uterus, at least 1 menstrual period in the previous 3 months, no use of reproductive hormones in the previous 3 months, and for the Pittsburgh site, self-identifying as Caucasian or African American. Approximately 50% of those eligible to participate in the SWAN in Pittsburgh entered the study. SWAN participants did not differ from those who were eligible but declined to participate by race, marital status, parity, QOL, social support, or perceived stress. Written informed consent was obtained in accordance with University of Pittsburgh institutional review board guidelines.

Of 463 women enrolled at the Pittsburgh SWAN site, 443 (95.7%) participated in the SWAN ancillary Mental Health Study, which began concurrent with the SWAN parent study. There were no significant sociodemographic differences between SWAN participants in Pittsburgh who did and did not participate in the SWAN Mental Health Study.

The Structured Clinical Interview for *DSM-IV* (SCID) was conducted at SWAN Mental Health Study entry to obtain information on previous lifetime psychiatric history and then annually during 6 years of follow-up to establish the presence of current and interim psychiatric disorders occurring during the previous year. The first SCID was administered 2 to 9 months after the SWAN baseline assessment and then annually within 3 months of each SWAN visit. This article focuses on 425 women who completed at least 2 psychiatric interviews (baseline plus 1 follow-up). The mean (SD) number of annual assessments completed per patient was 6.5 (1.3) of a possible 7. Women who completed only 2 SCIDs (n=13) did not differ from those who completed all 7 assessments (n=333).

MEASURES

Assessment of Psychiatric Disorders

Diagnoses of lifetime, annual, and current depressive and anxiety disorders were determined from interviews conducted by trained mental health clinicians using the SCID,[15,16] a semistructured psychiatric interview demonstrated to have good reliability.[15] All the interviewers had extensive clinical experience, had a mental health graduate degree, and were trained to administer the SCID. Qualitative procedures were used to ensure consistency of SCID administration, including centralized training, monitoring for rater drift, and interrater reliability testing.

Baseline SCIDs assessed lifetime and current disorders; subsequent annual SCIDs assessed current disorders and those that occurred during the previous year. Women met the criteria for current depression if they had major or minor depression during the past month, were in partial remission of an episode of major depression that began earlier, or had a current episode of dysthymia. A history of depression was defined as an episode of major or minor depression that occurred before the current visit and was in full remission during the past month. Anxiety disorders (panic disorder or attacks, agoraphobia, social phobia, generalized anxiety disorder, obsessive compulsive, and anxiety not otherwise specified) were defined similarly.

Health-Related QOL

The HRQOL was assessed using the 36-Item Short Form Health Survey (SF-36), a widely used HRQOL measure scored using the original coding algorithm in which raw scores are transformed to a 0 to 100 range.[17] The present study used 5 of the 8 SF-36 HRQOL domains: bodily pain, vitality, role limitations as a result of physical health, role limitations as a result of emotional problems, and social functioning. The scales have been shown to have good reliability and construct validity.[18,19] The SF-36 scales were dichotomized using the 25th percentile of the sample as the cutoff point between good and poor functioning as previously established[18-20] because scores were highly skewed and we were particularly interested in predictors of impaired function.

Menopause Status

Based on SWAN eligibility requirements, all the women were premenopausal or early perimenopausal at baseline. Consis-

tent with the World Health Organization classification system,[21] menopause status for the previous 12 months was assigned at each assessment based on menstrual bleeding patterns during the previous year and was categorized as (1) premenopausal if menstrual periods were present in the past 3 months and there was no change in regularity in the past 12 months; (2) menopausal transition/perimenopausal if menstrual periods were present in the past 3 months but changed in regularity during the previous 12 months (early perimenopause) or if there was menstrual bleeding in the past 12 months but not in the past 3 months (late perimenopausal); (3) postmenopausal if there was no menstrual period during the past 12 months or if the woman had undergone a hysterectomy with bilateral oophorectomy, regardless of the duration of amenorrhea; or (4) unknown status if women had a hysterectomy without bilateral oophorectomy or were using hormone therapy (HT) when premenopausal or perimenopausal because HT can affect bleeding patterns.

Vasomotor Symptoms

At each visit, participants reported the presence of hot flashes and night sweats (termed *vasomotor symptoms* [VMS]) in the previous 2 weeks. The VMS were coded as present if either hot flashes or night sweats were reported and as frequent if they occurred on 6 or more days during this interval.

Sleep Disturbance

Information about sleep disturbance was collected annually using 3 sleep questions taken from the Women's Health Initiative Insomnia Rating Scale.[22] Participants were asked how often in the past 2 weeks they experienced trouble falling asleep, waking up several times a night, and waking up earlier than planned without being able to fall asleep again: (1) none, (2) less than 1 time a week, (3) 1 or 2 times a week, (4) 3 or 4 times a week, or (5) 5 or more times a week. Sleep disturbance was determined to be present if at least 1 of the 3 was reported to have occurred at least 3 times a week, consistent with the frequency criterion commonly used in insomnia research.[23,24]

Covariates

Sociodemographic factors relevant to the present analyses included age, race, level of educational attainment, number of medical conditions (0, 1, or ≥2), and use of mental health treatment (psychotropic medications and psychotherapy/counseling). Use of HT at each visit was included as a separate covariate because HT users have been shown to have low HRQOL relative to nonusers.[25] At each visit, women indicated whether they had experienced and were upset by 1 or more of 18 negative life events during the past year to categorize women as having experienced at least 1 "very upsetting" event vs none/somewhat upsetting event for that interval.

STATISTICAL ANALYSIS

Four anxiety/depression groups were defined based on the presence or absence of depression and anxiety disorders occurring before study entry or each annual visit during the 6-year prospective follow-up study period: (1) comorbid depression and anxiety, (2) depression only, (3) anxiety only, and (4) neither. Women who had lifetime histories of either disorder at baseline were always considered to have a past disorder. Women who did not have a lifetime history of either disorder at baseline but met the criteria for 1 or both between 2 annual visits were considered to have a history of the disorder from that visit forward. For example, a woman first diagnosed as having an episode occurring between annual visits 2 and 3 would be categorized at visit 3 and thereafter as having a past disorder. If the episode occurred in the month before visit 3, it would be coded as current only and would not be categorized as a past disorder until visit 4. Thus, at the end of 6 years, the final anxiety/depression groups reflect a cumulative indicator of previous disorders.

Initial analyses compared the characteristics at study entry of the 4 final groups using analysis of variance and χ^2 tests. Longitudinal associations between HRQOL and previous lifetime history of depression or anxiety disorder were evaluated by separate repeated-measures multilevel logistic regression models for each of the 5 HRQOL outcomes. Preliminary analyses showed that 123 women met the criteria for a current depression episode (new-onset or recurrent) and 85 women met the criteria for a current anxiety disorder at 1 or more of the annual SCID assessments. Data for that study visit at which the mood or anxiety episode was present were excluded from analysis to ensure that HRQOL measures were not affected by current mood or anxiety episodes.

Models were first adjusted for age, race, menopause status, HT use, medical conditions, mental health treatment, and upsetting life events. The VMS and sleep disturbance were subsequently added separately and together to the models. Interactions of previous psychiatric history with VMS, sleep disturbance, and menopause status were examined. We also examined the relative influence of distant and proximal affective illness and single vs recurrent major depressive episodes on HRQOL domains. Analyses were performed using commercially available software programs (SAS, version 9.1.2; SAS Institute, Inc; and STATA, version 9.2; StataCorp LP).

RESULTS

PARTICIPANT CHARACTERISTICS

The mean age of participants at study entry was 46 years. One-third of the sample was African American. The population was evenly divided between premenopausal and early perimenopausal women. Forty percent of women reported VMS, and one-third reported sleep disturbance before study entry (**Table 1**).

At the end of 6 annual follow-up visits, 97 participants (22.8%) met the lifetime criteria for depression and anxiety disorders, 162 (38.1%) for depression disorders only, and 21 (4.9%) for anxiety disorders only. For those with depression or anxiety disorders recorded at any point up through the end of their study participation, most women (82.2%) with a history of anxiety disorders also had a history of depression disorders, whereas only 37.5% of women with previous depression disorders also had a history of anxiety disorders.

Table 1 lists the baseline characteristics of the study population by final diagnostic group. Groups differed significantly by previous use of mental health treatment, number of medical illnesses, and upsetting life events in the previous 12 months. There was no difference between groups in age, race, marital status, educational level, or menopausal status. Women without a history of depression and anxiety disorders were less likely to have experienced VMS and sleep disturbance before study entry, symptoms that were reported most commonly by women who had already experienced depression and anxiety disorders (52.6% and 43.3%, respectively).

Table 1. Baseline Characteristics of 425 Midlife Women Participating in the SWAN Pittsburgh Mental Health Study According to Cumulative Depression and Anxiety Disorder Status at the Final Annual Study Visit

Characteristic	All (N = 425)	Ever Lifetime Depressive and Anxiety Disorders (n = 97)	Ever Lifetime Depressive Disorder (n = 162)	Ever Lifetime Anxiety Disorder (n = 21)	Never Lifetime Depressive or Anxiety Disorder (n = 145)
Age, mean (SD), y	45.6 (2.5)	45.0 (2.4)	45.8 (2.4)	45.2 (2.2)	45.7 (2.7)
Race, No. (%)					
Caucasian	**278** (65.4)	66 (68.0)	107 (66.0)	15 (71.4)	90 (62.1)
African American	**147** (34.6)	31 (32.0)	55 (34.0)	6 (28.6)	55 (37.9)
Marital status, No. (%)					
Married	**281** (66.1)	66 (68.0)	96 (59.3)	14 (66.7)	105 (72.4)
Never married	**54** (12.7)	9 (9.3)	22 (13.6)	3 (14.3)	20 (13.8)
Separated/widowed/divorced	**90** (21.2)	22 (22.7)	44 (27.1)	4 (19.0)	20 (13.8)
Employed, No. (%)	**364** (85.6)	78 (80.4)	139 (85.8)	19 (90.5)	128 (88.3)
Educational status, No. (%)					
High school or less	**100** (23.5)	18 (18.5)	30 (18.5)	9 (42.9)	43 (29.7)
Some college	**158** (37.2)	35 (36.1)	69 (42.6)	7 (33.3)	47 (32.4)
College graduate	**72** (16.9)	21 (21.7)	27 (16.7)	2 (9.5)	22 (15.2)
More than college	**95** (22.4)	23 (23.7)	36 (22.2)	3 (14.3)	33 (22.8)
Menopause status, No. (%)					
Premenopausal	**224** (52.7)	50 (51.6)	82 (50.6)	10 (47.6)	82 (56.6)
Early perimenopausal	**201** (47.3)	47 (48.4)	80 (49.4)	11 (52.4)	63 (43.4)
Lifetime history of depression or anxiety before study entry, No. (%)[a]	**220** (51.8)	88 (90.7)	121 (74.7)	11 (52.4)	NA
Upsetting life event, No. (%)[b]	**222** (52.4)	62 (63.9)	95 (58.6)	7 (33.3)	58 (40.3)
Medical illness before study entry, No. (%)[c]					
0	**136** (32.0)	22 (22.7)	47 (29.0)	8 (38.1)	59 (40.7)
1	**143** (33.6)	32 (33.0)	53 (32.7)	7 (33.3)	51 (35.2)
≥2	**146** (34.4)	43 (44.3)	62 (38.3)	6 (28.6)	35 (24.1)
Mental health treatment before study entry, No. (%)[b,d]	**187** (44.0)	68 (70.1)	89 (54.9)	4 (19.1)	26 (17.9)
VMS at study entry, No. (%)[a]	**172** (40.6)	51 (52.6)	69 (42.6)	8 (38.1)	44 (30.6)
Sleep disturbance at study entry, No. (%)[b,e,f]	**132** (31.1)	42 (43.3)	50 (30.9)	6 (28.6)	34 (23.4)

Abbreviations: NA, not applicable; SWAN, Study of Women's Health Across the Nation; VMS, vasomotor symptoms (defined as a report of hot flashes or night sweats during the previous 2 weeks).

[a] $P = .007$.

[b] $P < .001$.

[c] $P = .02$, between-group differences.

[d] Mental health treatment includes the use of psychotropic medications and psychotherapy/counseling.

[e] Sleep disturbance is defined categorically as trouble falling asleep, waking up several times at night, or waking up earlier than planned and unable to fall asleep again for 3 or more nights per week during the previous 2 weeks.

[f] $P = .01$.

Table 2 provides the characteristics of the study population at the end of follow-up by final diagnostic group. The number of annual assessments during which SCIDs were conducted did not differ between groups ($P = .70$). At their final assessment, few women (5.2%) remained premenopausal; most were perimenopausal or postmenopausal (41.5% and 44.4%, respectively), and the rest (9%) were of undetermined menopause status, primarily because they had started using HT before their final menstrual period or they had undergone a hysterectomy without bilateral oophorectomy. The proportion that was not yet postmenopausal did not differ between groups. Hormone therapy was used by 31.1% of women at some point during the study, but this proportion did not differ between groups. Overall, 81.6% of all the study participants experienced VMS and 70.1% reported sleep disturbance during follow-up, with women who had no history of affective illness being least likely to report these symptoms. Women with a history of comorbid affective illness were most likely to experience at least 2 lifetime major depressive episodes and to seek mental health treatment and report a medical illness during the study.

ASSOCIATION OF DEPRESSION, ANXIETY, AND A COMBINED HISTORY OF DEPRESSION AND ANXIETY DISORDERS WITH QOL

Multivariate-adjusted models were used to determine the associations of previous comorbid anxiety and depression disorders, depression disorders, and anxiety disorders with HRQOL during follow-up. After adjusting for potential confounders (age, race, menopause status, HT use, medical conditions, mental health treatment, and upsetting life events), there was a strong association between a comorbid history of previous depression and anxiety and of previous depression alone with low HRQOL (**Table 3**, model A). Women with a history of comorbid disease and depression disorders alone had worse HRQOL in all the SF-36 domains (odds ratio [OR] = 2.31-3.54 and 1.59-2.28, respectively) except for vitality. In general, the

Table 2. Characteristics at the Final Annual Study Visit of 425 Midlife Women Participating in the SWAN Pittsburgh Mental Health Study According to Cumulative Depression and Anxiety Disorder Status

Characteristic	All (N = 425)	Ever Lifetime Depressive and Anxiety Disorders (n = 97)	Ever Lifetime Depressive Disorder (n = 162)	Ever Lifetime Anxiety Disorder (n = 21)	Never Lifetime Depressive or Anxiety Disorder (n = 145)
Age, mean (SD), y	51.3 (2.8)	50.6 (2.7)	51.4 (2.6)	50.8 (3.4)	51.6 (3.0)
No. of annual SCID assessments, mean (SD)	6.5 (1.3)	6.5 (1.2)	6.5 (1.2)	5.9 (1.9)	6.5 (1.3)
Menopause status, No. (%)					
Premenopausal	**22** (5.2)	6 (6.2)	6 (3.7)	1 (4.8)	9 (6.2)
Early perimenopausal	**129** (30.4)	33 (34.0)	52 (32.1)	6 (28.6)	38 (26.2)
Late perimenopausal	**47** (11.1)	10 (10.3)	15 (9.3)	3 (14.3)	19 (13.1)
Natural postmenopausal	**151** (35.5)	27 (27.8)	64 (39.5)	5 (23.8)	55 (37.9)
Surgical postmenopausal	**38** (8.9)	11 (11.3)	12 (7.4)	6 (28.6)	9 (6.2)
Cannot determine	**38** (8.9)	10 (10.3)	13 (8.0)	0	15 (10.3)
Episode of depression or anxiety during the study, No. (%)[a]	**160** (37.6)[b]	82 (84.5)	61 (37.7)	11 (52.4)	NA[b]
Lifetime No. of episodes of major depression, No. (%)[c]					
1	**71** (27.4)	19 (19.6)	52 (32.1)	NA	NA
≥2	**121** (46.7)	58 (59.8)	63 (38.9)		
Minor depression only	**67** (25.9)	20 (20.6)	47 (29.0)		
Mental health treatment during the study, No. (%)[a,d]	**155** (36.5)	63 (65.0)	65 (40.1)	5 (23.8)	22 (15.2)
Upsetting life event during the study, No. (%)[a]	**376** (88.5)	92 (94.9)	151 (93.2)	19 (90.5)	114 (78.6)
Medical illness during the study, No. (%)[e]					
0	**118** (27.8)	20 (20.6)	41 (25.3)	7 (33.3)	50 (34.5)
1	135 (31.8)	28 (28.9)	51 (31.5)	5 (23.8)	51 (35.2)
≥2	**172** (40.5)	49 (50.5)	70 (43.2)	9 (42.9)	44 (30.3)
VMS during the study, No. (%)[f]	**347** (81.6)	87 (89.7)	135 (83.3)	14 (66.7)	111 (76.6)
Sleep disturbance during the study, No. (%)[g,h]	298 (70.1)	77 (79.4)	120 (74.1)	16 (76.2)	85 (58.6)

Abbreviations: NA, not applicable; SCID, Structured Clinical Interview for *DSM-IV*; SWAN, Study of Women's Health Across the Nation; VMS, vasomotor symptoms (defined as a report of hot flashes or night sweats during the previous 2 weeks).

Between-group differences: [f] $P = .02$, [h] $P = .002$, [a] $P < .001$, [e] $P = .05$, and [c] $P = .005$ (depression and anxiety group vs depression-alone group; data available for the number of discrete episodes of major depressive disorder but not minor depression or anxiety disorders).

[b] Six women had a single episode of a depressive or anxiety disorder during 6-year follow-up and no history of depression or anxiety episodes before study entry. Because data from visits during an active illness episode were not included in the model, these women contributed data only for visits when they did not have a depression/anxiety episode and are, therefore, included in the group that never had a lifetime episode of a depressive or anxiety disorder.

[d] Mental health treatment includes the use of psychotropic medications and psychotherapy/counseling.

[g] Sleep disturbance is defined categorically as trouble falling asleep, waking up several times at night, or waking up earlier than planned and unable to fall asleep again for 3 or more nights per week during the previous 2 weeks.

magnitude of the association between a comorbid depression and anxiety disorder history and HRQOL was larger than that for depression alone. Further adjustment for a history of recurrent major depression attenuated the association between previous affective illness and low HRQOL on selected domains for the comorbid group, with associations becoming trends for role-emotional ($P = .08$) and role-physical ($P = .06$) and losing significance for body pain but remaining significant for social functioning. The significant association of depression alone with low HRQOL was preserved for all domains except role-physical ($P = .08$, trend). Recurrent depression was independently associated with low HRQOL only on the role-physical and body pain domains.

A lifetime history of an anxiety disorder alone was significantly associated with low HRQOL on the role-physical domain, and the ORs on other SF-36 domains (social functioning, body pain, and vitality) were increased but not statistically significant. Post hoc pairwise comparisons of the depression and anxiety groups revealed no significant differences in HRQOL between groups. Menopause status was not associated with HRQOL in unadjusted or adjusted models, and there were no interactions between menopause status and previous affective illness.

IMPACT OF ADJUSTMENT FOR VMS AND SLEEP DISRUPTION ON THE ASSOCIATION BETWEEN LIFETIME HISTORIES OF DEPRESSION AND ANXIETY DISORDERS AND QOL

Sleep disruption and VMS were added separately and then jointly to the adjusted multivariate models to determine whether they explained the association between previous psychiatric illness and HRQOL. For women with a history of depression and anxiety, associations between psychiatric history and HRQOL were not altered by further adjustment for current VMS alone (Table 3, model B), current sleep disturbance alone (Table 3, model C), or concurrent adjustment for both symptoms (Table 3, model D), with associations between comorbid psychiatric history and low HRQOL remaining statistically significant for all SF-36 scales. Adjustment for VMS alone (Table 3, model B), sleep disturbance alone (Table 3, model C), and both symptoms together (Table 3, model D) attenuated the association of previous depression with several HRQOL domains. Associations between previous depression alone and low HRQOL remained strong for the social functioning and body pain domains and became nonsignificant for the role-emotional and role-

Table 3. Effect of Cumulative Lifetime History of Depression and Anxiety Disorders, Depression Only, and Anxiety Only on Quality of Life as Measured by SF-36 Outcomes for Repeated-Measure Analysis During 6-Year Follow-up of 425 Midlife Women Participating in the SWAN Pittsburgh Ancillary Mental Health Study[a]

	OR (95%CI)				
Model	**Social Functioning**	**Role-Emotional**	**Role-Physical**	**Body Pain**	**Vitality**
A: Basic model					
No depression or anxiety	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Both depression and anxiety	3.54 (1.85-6.77)[b]	2.48 (1.32-4.67)[c]	2.35 (1.18-4.67)[d]	2.31 (1.21-4.40)[d]	1.27 (0.66-2.45)
Depression only	2.28 (1.40-3.71)[b]	1.59 (0.99-2.56)[d]	1.71 (1.03-2.82)[d]	2.03 (1.27-3.24)[c]	1.45 (0.89-2.34)
Anxiety only	2.26 (0.90-5.66)	1.02 (0.37-2.81)	2.72 (1.08-6.83)[d]	2.05 (0.82-5.12)	2.01 (0.82-4.93)
B: Basic model + VMS					
No depression or anxiety	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Both depression and anxiety	3.29 (1.72-6.29)[b]	2.22 (1.20-4.10)[e]	2.27 (1.14-4.53)[d]	2.24 (1.18-4.26)[d]	1.21 (0.62-2.33)
Depression only	2.20 (1.35-3.59)[c]	1.51 (0.95-2.39)	1.68 (1.02-2.78)[d]	2.01 (1.26-3.20)[c]	1.42 (0.88-2.30)
Anxiety only	2.27 (0.91-5.67)	1.00 (0.37-2.71)	2.71 (1.08-6.83)[d]	2.04 (0.82-5.09)	2.00 (0.82-4.92)
VMS (yes/no)	1.47 (1.00-2.17)[d]	1.66 (1.12-2.44)	1.20 (0.81-1.77)	1.21 (0.86-1.71)	1.39 (0.99-1.94)
C: Basic model + sleep disturbance					
No depression or anxiety	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Both depression and anxiety	3.24 (1.70-6.20)[b]	2.37 (1.26-4.47)[e]	2.17 (1.08-4.33)[d]	2.21 (1.16-4.19)[d]	1.17 (0.61-2.27)
Depression only	2.13 (1.31-3.47)[c]	1.55 (0.96-2.48)	1.61 (0.97-2.65)	1.96 (1.23-3.13)[c]	1.36 (0.84-2.20)
Anxiety only	2.15 (0.86-5.38)	0.99 (0.36-2.72)	2.60 (1.03-6.56)[d]	1.97 (0.79-4.90)	1.94 (0.79-4.75)
Sleep disturbance	1.98 (1.33-2.93)[b]	1.42 (0.95-2.12)	1.88 (1.27-2.81)[c]	1.76 (1.24-2.50)[c]	2.23 (1.56-3.13)[b]
D: Basic model + VMS + sleep disturbance					
No depression or anxiety	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Both depression and anxiety	3.07 (1.60-5.88)[b]	2.14 (1.16-3.98)[d]	2.13 (1.06-4.26)[d]	2.17 (1.14-4.12)[d]	1.14 (0.59-2.20)
Depression only	2.08 (1.28-3.40)[c]	1.48 (0.93-2.34)	1.59 (0.96-2.64)	1.95 (1.22-3.11)[c]	1.34 (0.83-2.17)
Anxiety only	2.16 (0.86-5.40)	0.98 (0.36-2.63)	2.60 (1.03-6.55)[d]	1.96 (0.79-4.89)	1.93 (0.79-4.76)
VMS (yes/no)	1.36 (0.92-2.02)	1.60 (1.08-2.36)[d]	1.10 (0.74-1.64)	1.12 (0.79-1.58)	1.24 (0.89-1.75)
Sleep disturbance	1.90 (1.28-2.83)[b]	1.33 (0.90-1.98)	1.86 (1.25-2.79)[c]	1.73 (1.21-2.47)[e]	2.17 (1.54-3.06)[b]

Abbreviations: OR, odd ratio; SF-36, 36-Item Short Form Health Survey; SWAN, Study of Women's Health Across the Nation; VMS, vasomotor symptoms (coded as yes/no during the 2 weeks before the study visit).

[a]The basic model is adjusted for age, race (white vs African American), menopause status (perimenopausal, postmenopausal/surgical menopause, unknown vs premenopausal/reference), hormone therapy use (current use vs no current use), medical conditions (0, 1, or ≥2), mental health treatment, and upsetting life events and compares the groups with (1) a cumulative lifetime history of a depressive and an anxiety disorder, (2) a cumulative lifetime history of a depressive disorder, and (3) a cumulative lifetime history of an anxiety disorder against a reference group of women who have no cumulative lifetime history of depression or anxiety. All categorical SF-36 outcomes are dichotomized as the 25th percentile or less vs greater than the 25th percentile and are presented as ORs (95% CIs). Sleep disturbance is defined categorically as trouble falling asleep, waking up several times at night, or waking up earlier than planned and unable to fall asleep again for 3 or more nights per week during the previous 2 weeks.

[b] $P \leq .001$.

[c] $P \leq .005$.

[d] $P \leq .05$.

[e] $P \leq .01$.

physical domains. There was no significant interaction of previous affective illness with VMS or sleep disturbance ($P \geq .12$ for all interactions). Results of parallel analyses examining the impact of adjusting for frequent vs infrequent/no VMS were consistent with analyses adjusting for the presence vs absence of VMS.

For women with a history of anxiety disorders alone, adjustment for VMS and/or sleep disturbance did not alter the significant negative association between previous psychiatric illness and the role-physical domain, and neither were the ORs for the associations with social functioning, body pain, and vitality substantially reduced (Table 3, models B through D). As confirmation of the findings for the anxiety-alone group, models restricted to a 2-group comparison between the anxiety-alone and no previous affective illness groups similarly showed an association between previous anxiety alone and the role-physical domain in the fully adjusted model (OR = 2.80; 95% CI, 0.98-8.00; $P = .05$).

The association with low HRQOL during midlife was observed for all women with previous depression or anxiety compared with those with neither, irrespective of the timing of episodes, whether affective illness episodes occurred only before, only during, or before and during the study. For example, the associations between depression and anxiety occurring only before midlife were significant for the HRQOL domains of social functioning, role-physical, and body pain (OR = 2.08-2.64, $P \leq .02$), and there was a nonsignificant trend for the role-emotional domain (OR = 1.74, $P = .06$). Adjusting for VMS and sleep disturbance did not alter these associations.

ASSOCIATION OF VMS AND SLEEP DISRUPTION WITH QOL

In unadjusted models, low HRQOL was strongly associated with VMS (OR = 1.43-1.90, $P < .05$ for all the HRQOL domains except role-physical) and sleep disturbance (OR = 2.04-2.96, $P < .05$ for all the HRQOL domains). In models that adjusted for psychiatric illness history, VMS, sleep disturbance, and other potential confounders (age, race, menopause status, HT use, up-

setting life events, medical illness, and mental health treatment), perceived sleep disturbance had independent associations with low HRQOL across all the domains except role-emotional (Table 3, model D), regardless of whether VMS were included as a covariate.

In contrast to the strong independent association between sleep disturbance and low HRQOL, the association between VMS and HRQOL was less robust. After adjusting for previous psychiatric illness and other potential confounders, VMS was significantly associated only with low HRQOL in the social functioning and role-emotional domains (Table 3, model B). After further adjustment for sleep disturbance, the independent effect of VMS on HRQOL remained only for the role-emotional domain. Results of analyses that categorized VMS into frequent vs infrequent/none were consistent with those that classified VMS as present vs absent. Frequent VMS was independently associated with low HRQOL on the vitality domain only, whereas an association between sleep disturbance and low HRQOL was seen for all the HRQOL domains (OR = 1.73-2.08) except role-emotional ($P = .096$, trend).

COMMENT

The results of this study show that in the absence of a current illness episode, women with previous histories of depression and anxiety disorders and those with previous depression only are at risk for compromised QOL in multiple domains during midlife, whereas a history of anxiety disorders alone seems to have a more limited effect on HRQOL. The negative impact of a combined history of depression and anxiety disorders on subsequent HRQOL was not explained by the experience of VMS or sleep disturbance, which are known to reduce QOL and to occur more frequently in those with previous depression and anxiety. The present findings for women with previous depression alone suggest that sleep disturbance seems to partially explain the negative effect of previous depression on selected HRQOL domains. After adjusting for previous affective illness, sleep disturbance, but not VMS, was a significant and independent predictor of low HRQOL in midlife women.

These study results derive from 6-year longitudinal follow-up of 425 Caucasian and African American women participating in the community-based SWAN in Pittsburgh who were observed annually using SCID-rated psychiatric interviews. To our knowledge, this study is the first to examine QOL longitudinally in midlife women who previously had depression and/or anxiety disorders but were not currently experiencing an episode of depression or anxiety. The magnitude and pervasive nature of the deleterious effects of previous depression on HRQOL in the absence of current illness is striking. Although recurrence of major depression in the comorbid disease group may explain, in part, the especially strong association between previous comorbid affective illness and low HRQOL in midlife, the association between previous affective illness and low HRQOL was observed even in women who had experienced only affective illness episodes before study enrollment. These findings suggest that previous depression, with or without previous anxiety, has an enduring effect on subsequent QOL and that the constitutional makeup of those who experience mental illness confers a vulnerability to poor HRQOL during midlife.

The present results also indicate that women with previous anxiety alone may not share the same broad susceptibility to poor QOL during midlife, as a statistically significant association was seen only on the role-physical domain. However, the absence of statistical significance on the other HRQOL domains may be due to the small size of this anxiety disorder group (n = 21). Future studies involving more women with a history of anxiety disorders but not depression are needed to fully examine the specific effect of previous anxiety on subsequent QOL in midlife women.

The pathways through which previous affective illness confers susceptibility to low overall HRQOL in midlife women are unknown. Consistent with other studies,[10] we found that specific stages of the menopause transition were not associated with low HRQOL. Given that the common menopause-related symptoms of VMS and sleep disturbance are more frequently reported in women with previous depressive or anxiety symptoms[13] and that both symptoms correlate with low QOL, we hypothesized that the experience of these symptoms would, in part, explain the association between previous affective illness and low HRQOL during midlife. However, neither sleep disturbance nor VMS explained the robust association between previous comorbid affective illness history and poor HRQOL, whereas for women with previous depression alone, the present results suggest that the presence of sleep disturbance, but not VMS, may partially explain the association with poor HRQOL. The absence of significant interactions between previous affective illness and sleep disturbance indicates that the effect of each predictor is independent and not increased by the presence of both.

Consistent with previous studies conducted during midlife[10] and other life stages, we observed that sleep disturbance has a strong association with low QOL. However, in contrast with other studies,[10] we did not observe a broad association between VMS and multiple domains of HRQOL in adjusted models but only an independent association between VMS and the role-emotional domain. Therefore, although VMS may be associated with compromised QOL,[10] after accounting for the effect of previous depression or anxiety disorders, the association is substantially reduced. Taken together, these findings suggest that disturbed sleep, but not VMS or specific menopause stage status, has a robust and independent association with low QOL, even in the absence of a current affective illness episode in those with and without previous affective illness.

This study has notable strengths and several limitations. Important strengths are its large size overall and of the group with comorbid depression and anxiety, which enabled us to distinguish the HRQOL burden for women who previously experienced both depression and anxiety disorders from those with previous depression alone. We also could determine whether previous affective illness showed an independent association with low HRQOL in

the absence of a current disorder that compromises functioning. Other strengths include the long-term follow-up and the racial composition of the study population, of which one-third were African American women.

The limitations of this study include the small size of the anxiety-alone group and that, although most women had become perimenopausal, not all had became postmenopausal before the study end. However, most women had the opportunity to develop VMS and sleep disturbance, symptoms that peak in midlife women during perimenopause,[26,27] and the statistical approach used to analyze these data allowed women to contribute data for variable times corresponding to their menopausal stage at each assessment. Another limitation is that all the SWAN and SCID data were collected annually. However, misclassification bias is unlikely to have occurred in the assessment of current illness episodes, for which data were excluded from the analysis for that period of observation to avoid confounding of low HRQOL with current or recent affective illness. Finally, although VMS frequency data were available, we do not have data describing the severity or bothersomeness of VMS, limiting our ability to discern whether severe or bothersome VMS contributed independently to low HRQOL.

In summary, in the absence of an acute illness episode, women with a history of both depression and anxiety disorders have the greatest risk of low QOL during midlife. This effect is not explained by an increased vulnerability to menopause-related symptoms of VMS and sleep disturbance, which are known to reduce QOL. Sleep disturbance has a strong effect on reducing QOL and may, in part, explain why women with previous depression only are also susceptible to experiencing compromised QOL during midlife. The pathways through which the previous affective illness affects subsequent HRQOL in midlife women remain largely unknown and warrant further research. Midlife women with a history of affective illness should be monitored during the menopause transition because of their increased risk of recurrence of depression, emergence of VMS and sleep disturbance, and, in the absence of an acute illness episode, impairment of QOL.

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