

Research paper

Symptom profiles of women at risk of mood disorders: A latent class analysis

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ARTICLE INFO

Keywords:

Depression
Anxiety
Mood
Women
Symptom clusters
Latent class analysis

ABSTRACT

Background: Depression is the leading cause of disease burden among women worldwide. However, an understanding of symptom profiles among women at risk of mood disorders is limited. We determined distinct profiles of affective symptoms among high risk women, along with their distinguishing characteristics.

Methods: Women were recruited from 17 clinical sites affiliated with the National Network of Depression Centers. They completed measures of depression (Patient Health Questionnaire – 9) and anxiety (Generalized Anxiety Disorder – 7) as well as questions regarding demographics, reproductive status, behavioral/mental health history, and life stress/adversity. Latent class analysis and multinomial logistic regression were used to identify and characterize symptom profiles.

Results: 5792 women participated, ages 18 to 90 ($M = 38$). Three latent classes were identified: generally asymptomatic (48%), elevated symptoms of comorbid anxiety and depression (16%), and somatic symptoms (36%). Financial security and greater social support were protective factors that distinguished asymptomatic women. The profile of the class with elevated anxiety/depressive symptoms constituted a complex mix of adverse social determinants and potentially heritable clinical features, including a diagnosis of Bipolar Disorder. Women in the 3rd latent class were characterized by menstrual irregularity and a stronger expression of neurovegetative symptoms, especially sleep disturbance and fatigue.

Limitations: Limitations included less than optimal racial diversity of our sample and reliance on self-report.

Conclusions: Different symptom profiles may reflect distinct subtypes of women at risk of mood disorders. Understanding the etiology and mechanisms underlying clinical and psychosocial features of these profiles can inform more precisely targeted interventions to address women's diverse needs.

1. Introduction

Seminal data from the National Comorbidity Study (NCS) showed that major depressive disorder (MDD) was twice as common in women than men (Kessler et al., 1993), with increased risk during the reproductive years. MDD is a highly prevalent chronic illness and the leading

cause of disease burden among women worldwide (WHO, 2008). In United States (U.S.) national surveys, the prevalence of a major depressive episode among non-pregnant women of childbearing age ranges from 11.1%–12.2%, with as many as 18.4% and 19.2% reporting major or minor depression during pregnancy or the first 3 postpartum months, respectively (Gavin et al., 2005; Halbreich and Karkun, 2006;

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<https://doi.org/10.1016/j.jad.2021.08.013>

Received 3 June 2021; Received in revised form 3 August 2021; Accepted 6 August 2021

Available online 12 August 2021

0165-0327/© 2021 Published by Elsevier B.V.

Ko et al., 2012; Le Strat, Dubertret, and Le Foll, 2011). Depressive and other mood symptoms are the result of a complex interaction of unique biological and environmental factors which impact neurocircuit connectivity and function (Drevets et al., 2008). Female sex steroids and female-specific psychological stressors associated with the menstrual cycle (Epperson et al., 2012), as well as perinatal and perimenopausal reproductive phases (Bromberger and Epperson, 2018; Guintivano et al., 2018) have distinct effects on the prevalence and expression of mood disorders in women, creating unique challenges for their accurate assessment and treatment.

In addition, depression in women may be more heterogeneous than previously thought, especially in light of reproductive transitions that may influence symptom profiles. Assuming all women have homogeneous profiles can lead to an incomplete understanding of underlying causes and a lack of efficacy in addressing symptoms. Research including both genders has previously focused on the depressive subtypes of atypical, melancholic, or seasonal depression (Nandi et al., 2009). Studies of depression phenotypes in women have asked whether the differences between MDD and postpartum depression (PPD) represent distinct disorders, or rather one disorder (MDD) marked by the timing of onset (Bloch et al., 2005; Causes, 2015). Recent latent class analyses of PPD and perinatal depression (PND) more broadly determined several distinct phenotypes within this reproductive phase (Causes, 2015). An additional analysis of a perinatal population found 5 distinct subtypes, with differences between women who were pregnant versus postpartum as well as for women with perinatal medical complications versus those without (Sun et al., 2019). Latent class analysis of a cohort of middle-aged women identified distinct profiles that distinguished perimenopausal and postmenopausal women (Hickey et al., 2016). Including women older than 30 years, a study of Chinese women with major depression found subtypes that differentiated severity and atypicality of symptoms (Li et al., 2014). These subtypes had unique family histories, degrees of co-morbidity, and other factors, although the role of reproductive status was not considered. Lastly, a study of older adults in Korea demonstrated that men and women differed in subgroups that predicted longitudinal change in depressive symptoms (Lee and Park, 2018). For women, poverty and poor health were influential in distinguishing classes of trajectories.

Although these studies provide important contributions to the literature, they primarily focus on women at specific stages of life or reproductive transition, or they only include women who have been diagnosed with MDD. Our knowledge of potential profiles is limited among a larger spectrum of women who may be at elevated risk for depression (but not yet diagnosed) or who are at various reproductive stages and transitions. Lack of a comprehensive understanding of different symptom profiles or phenotypes that may underlie women's mood disorders may lead to less than optimal treatment. Improved knowledge of these profiles can enable more precisely targeted interventions that address salient characteristics of women with different contexts and needs.

The Women and Mood Disorders (WMD) Research Group was formed within the National Network of Depression Centers (NNDC) in 2011 to forge a national research agenda that could effectively address mood-related disorders among women. The group consists of women's mood researchers from NNDC member sites across the U.S. Our initial efforts included development and testing of a standardized women's mental health screening measure that could be feasibly administered in diverse health care settings throughout the network. In addition to demonstrating feasibility, results indicated that 14% and 15% of the women scored at or above the cutoff for depression and anxiety respectively (Flynn et al., 2018). However, it was unclear from our initial data whether women who scored above these cutoffs had particular clusters or profiles of symptoms that put them at risk, and whether specific characteristics of women might predict unique symptom profiles. These gaps in knowledge, in conjunction with very

limited previous research about symptom profiles, catalyzed the study described here. The purpose of this research was to determine whether there are distinct clusters of affective symptoms among women at risk of mood disorders that could inform our understanding of their varied symptom profiles across the lifespan. We also sought to identify factors that characterize any symptom profiles among women. The specific aims were:

- 1 To determine whether there are distinct profiles of depression and anxiety symptoms among women at risk of mood disorders, and
- 2 To identify factors associated with women's sociodemographic and reproductive status, their behavioral and mental health history, and their exposure to stress or adversity that may characterize different symptom profiles.

2. Materials and methods

2.1. Design and structure of a women's mood and health questionnaire

The self-report questionnaire used in this study was a refinement and expansion of a questionnaire designed and evaluated previously by the WMD research group. This refined version included a core questionnaire that acquired data on women's sociodemographic and reproductive status as well as their behavioral and mental health history. We also included a newly developed component on stress and adversity as well as two symptom questionnaires: the Patient Health Questionnaire - Depression (PHQ-9; Kroenke et al., 2001) and the Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al., 2006). Two versions of the questionnaire were developed: a paper and pencil prototype and an electronic format completed via laptop, desktop or smart phone that enabled direct data entry to a Research Electronic Data Capture (REDCap; Harris et al., 2009) web-based platform at the data coordinating center.

2.2. Stress and adversity measures

We incorporated two well-established measures of stress and adversity: The Perceived Stress Scale (PSS; Cohen et al., 1983) and the Adverse Childhood Experiences Questionnaire (ACE; Felitti et al., 1998a). Other items were also included to assess social support, domestic and workplace violence or harassment, and types of government assistance used by the family. For government assistance, women completed a checklist of programs such as WIC and SNAP (nutrition assistance programs), public housing, head start, and others.

The 4-item PSS provided a global assessment of perceived stress over the past month. Each item is rated on a 5-point Likert scale, with 2 positive items that get reverse scored. The total score represents a sum of all items, with higher scores indicative of more perceived stress. This brief measure is based on items selected from the 10-item version and has shown good concurrent validity and internal consistency (Ingram et al., 2016; Karam et al., 2012).

The ACE is a 10-item self-report scale that measures the number and type of traumatic or stressful experiences a person may have experienced in childhood, such as sexual abuse or physical neglect (Felitti et al., 1998b). Content validity was described in initial development of the measure and its predictive validity has been supported in numerous studies [Dube et al., 2001; Chapman et al., 2007].

2.3. Symptom assessment

The Patient Health Questionnaire (PHQ-9) is a nine-item self-report questionnaire based on the DSM criteria for major depression (Kroenke et al., 2001). Scores range from 0 to 27, with higher scores indicating more severe depression. Testing of PHQ-9 indicates that it is equal or superior to other established depression measures in terms of criterion, discriminant, and construct validity. The measure's established internal consistency is also very good (Cronbach's $\alpha=0.86-0.89$)

as well as its test-retest reliability. The PHQ-9 has been found effective across sex, age and racial/ethnic groups (Patel et al., 2019).

Anxiety was assessed using the Generalized Anxiety Disorder Assessment (Spitzer et al., 2006). The GAD-7 is a 7-item scale assessing the degree of anxiety experienced by the patient. Scores can range from 0 to 27, with different cut-points to indicate mild to severe anxiety. Using a cut-point of 10 for various anxiety disorders, sensitivities for the GAD-7 range from 0.66 to 0.89 and specificities range from 0.80 to 0.82. Internal consistency and convergent validity are excellent in both inpatient and outpatient psychiatric populations, with evidence of good variation related to differential severity of treatment groups (Johnson et al., 2019).

2.4. Characterization of symptom profiles

Forty-nine items in the questionnaire were used to examine characteristics that may predict different symptom profiles. These included items acquiring information about the women's sociodemographic and reproductive status, their behavioral and mental health history, and their exposure to adversity. Sociodemographic questions evaluated variables such as age, ethnicity, race, marital/partner status, income, government assistance, and educational level. Reproductive/menstrual status was evaluated by asking women to select from among 5 mutually exclusive categories: having regular menstrual periods, having irregular menstrual periods, being pregnant, having delivered a baby within the last 12 months, or that their periods stopped due to menopause. Questions about behavioral and mental health history assessed family and personal history of mood, anxiety, substance abuse, and other disorders as well as types of treatment for these problems (i.e. psychotherapy, specific classes of medication, self-help approaches). Questions concerning exposure to adversity assessed poverty (current and during childhood), domestic and community violence, sexual harassment, and adverse childhood experiences. Perceived stress and social support were also examined.

2.5. Data collection procedures

The study involved multiple clinical sites affiliated with the National Network of Depression Centers. Eight sites agreed to participate initially, each with a Principal Investigator who was responsible for acquiring Institutional Review Board (IRB) approval (or waiver), collaborating with their clinical site for access to potential participants and mutually agreeable approaches to data collection, supervising data collection, and assuring that their site's de-identified data were integrated into the data management center located at the University of California, San Francisco. All site investigators were psychologists or psychiatrists with expertise in depression. The recruitment sites included clinics in obstetrics-gynecology, psychiatry, primary care, and neonatal care settings that served women facing psychosocial or health-related challenges.

At the 8 sites, women completed the questionnaire either within the context of routine clinical care or research. Recruitment included varied approaches. Some sites posted flyers or provided handouts that referred women to research assistants or made the survey link or print copies of the survey available at the clinic. At other sites, personnel were present to discuss the survey and provide informed consent if women expressed interest. Still other sites offered participation as a supplement to ongoing research projects. Regardless of the recruitment approach, no reimbursement was provided for participation and it was made clear that a woman's decision to participate was entirely her choice and would have no effect on her clinical care. In addition to recruitment of women who were affiliated with the 8 original sites, *ResearchMatch* was used for recruitment. This service is a web-based recruitment registry that matches individuals wishing to participate in clinical research studies with researchers actively searching for volunteers throughout the United States (Harris et al., 2012). The addition of this recruitment method resulted in participation of women from 9 other sites affiliated

with the NNDC, resulting in participants from 17 NNDC centers representing various regions of the U.S.

All procedures were approved by the IRB of each participating institution. For certain sites, an informed consent was presented to participants and signed prior to completion of the questionnaire. At other sites, IRB exemption allowed anonymous questionnaire completion. In order to maximize feasibility and sustainability, each site determined the best process for data collection at their site.

2.6. Data analysis

Latent class analysis (LCA) was used to detect the presence of unobserved, latent classes or symptom profiles among the women. For these analyses, we examined patterns of association among women's scores on all anxiety and depressive symptoms from the PHQ-9 and the GAD-7. Fit indices were estimated for the LCA models for 1-class through 4-class solutions. Full information maximum likelihood (FIML) was employed to produce unbiased estimates and the expectation-maximization algorithm to deal with missingness.

We used multinomial logistic regression to determine variables that best characterized or predicted different latent classes or symptom profiles. In these analyses, covariates were the predictors and the latent class solution was the categorical dependent variable. We first examined associations between the 49 covariates and the latent classes in bivariate analyses. We followed that step by performing a logistic regression with all variables that showed significant bivariate relationships within their particular set of variables (e.g. behavioral and mental health history). Significant variables from those analyses were then included together in the final multinomial logistic regression to identify a best fitting predictive model. We carried out statistical analyses with Stata 16 and Mplus (StataCorp LLC, 2019). We evaluated all tests of significance with a two-sided alpha of 0.05.

3. Results

3.1. Sample description

The sample included 5792 women who were affiliated with 17 different health care sites. Their age ranged from 18 to 90, with an average age of 38 years. As shown in Table 1, most women described themselves as either menstruating (21% regular menses; 17% irregular menses) or pregnant (39%). 80% of the women were White/Euro-American. 7.3% reported Hispanic/Latina ethnicity. Average income of the women was between \$51,000 and \$65,000 annually, with 27% ($n = 1564$) indicating they were receiving at least 1 type of government assistance. Sixty-six percent of the women had a Bachelor's degree or some type of advanced educational preparation and sixty-five percent were married or in a committed relationship with a partner. More detailed sociodemographics are outlined in Table 1.

3.2. Symptom profiles

In examining fit statistics for 1 through 4 class solutions, the 3-class solution was selected as having the best fit. As shown in Table 2, the Bayesian Information Criterion (BIC) for that solution was smaller than the BIC for the 2-class solution, indicating a better fit for number of classes. In addition, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR) was significant for the 3-class solution at $p < 0.0001$. This significant VLMR indicates that three unique symptom classes fit the data better than two classes. Although the BIC was slightly smaller (1.8%) for the 4-class compared to the 3-class solution, the VLMR was not significant for the 4-class solution, indicating that too many classes had been extracted. In addition, entropy (an estimate of the probability that each person is in each of the classes) was lower for the 4-class solution than a 3-class solution, moving closer to an unacceptable threshold of 0.80 with 4 classes.

Table 1
Characteristics of the Sample.

Variable	N	Percent
Race		
European American/White	4633	80.0
African American/Black	869	15.0
Asian American	266	4.6
Other	24	0.4
Reproductive Status		
Menstruation	2201	38
Pregnancy	2259	39
Postpartum	174	3
Menopause	1158	20
Relationship Status		
Single	1274	22
Married/Partnered	3765	65
Separated/Divorced	637	11
Widowed	116	2
Education		
High School or Less	753	13
Associate Degree	753	13
Bachelor Degree	1969	34
Advanced Degree	1853	32
Unknown	464	8
Annual Income		
<\$21,000	869	15.0
\$21,000 - \$50,000	1378	23.8
\$51,000 - \$75,000	1066	18.4
\$76,000 - \$100,000	898	15.5
\$101,000 - \$150,000	909	15.7
>\$150,000	672	11.6

Table 2
Latent Profile Solutions and Fit Indices for One Through Four Symptom Classes.

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	-86,197.92	172,491.84	172,811.73	n/a	n/a
2 Class	-71,666.77	143,527.53	144,173.96	.93	29,062.32**
3 Class	-67,668.89	135,629.79	136,602.76	.89	7995.74*
4 Class	-66,222.02	132,834.04	134,133.57	.85	2893.74 ^{ns}

^{n/a} Baseline LL, entropy and VLMR not applicable for one class.
^{ns} Not significant; * $p < .05$; ** $p < .0001$

Note: LL = log-likelihood; AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; VLMR = Vuong-Lo-Mendell-Rubin likelihood ratio test for the K vs. K-1 model.

Table 3 provides the numbers and proportions of women in each group for the 3-class solution. The largest symptom profile class included 48% of the women while the other 2 classes included approximately 36% and 16%. Table 4 displays differences in the probability estimates for the 3 latent classes on each of the anxiety and depression symptoms in the latent class analysis. These estimates are portrayed graphically in Figs. 1 and 2. Women in Class 1 endorsed almost no symptoms (labeled asymptomatic). Class 2 was high on symptoms of both anxiety and depression (labeled comorbid anxiety/depressive symptoms). Class 3 appeared to have generally mild symptoms associated with irritability, nervousness and appetite, but with primary symptoms of sleep disturbance and tiredness/fatigue (labeled somatic symptoms).

Table 3
Number and Proportion of Women in Each of Three Symptom Classes.

	N	Proportion
Class 1 - Asymptomatic	2789	0.48153
Class 2 - Comorbid Anxiety/Depressive Symptoms	899	0.15521
Class 3 - Somatic Symptoms	2104	0.36326

Table 4
Probability Estimates for Individual Symptoms by Latent Class.

Symptoms	Class 1	Class 2	Class 3
Symptoms of Anxiety			
Feeling nervous, anxious, or on edge	0.013	0.831	0.203
Not being able to stop or control worrying	0.001	0.795	0.115
Worrying too much about different things	0.004	0.836	0.174
Trouble relaxing	0.004	0.794	0.194
Being so restless it is hard to sit still	0.004	0.464	0.076
Becoming easily annoyed or irritable	0.017	0.690	0.241
Feeling afraid/something awful might happen	0.003	0.561	0.074
Symptoms of Depression			
Little interest or pleasure in doing things	0.004	0.570	0.090
Feeling down, depressed, or hopeless	0.000	0.642	0.055
Trouble with sleep	0.062	0.774	0.344
Feeling tired or having little energy	0.101	0.864	0.437
Poor appetite or overeating	0.027	0.857	0.223
Feeling bad about yourself, a failure	0.000	0.670	0.097
Trouble concentrating on things	0.006	0.581	0.102
Moving/speaking slowly or fidgety/restless	0.000	0.218	0.014
Better off dead or wanting to hurt self	0.000	0.210	0.005

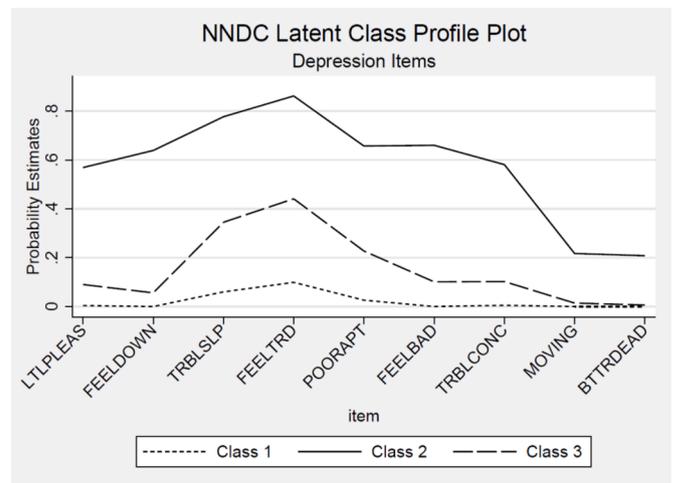


Fig. 1. Graph of Probability Estimates for Specific Symptoms of Depression by Latent Class.

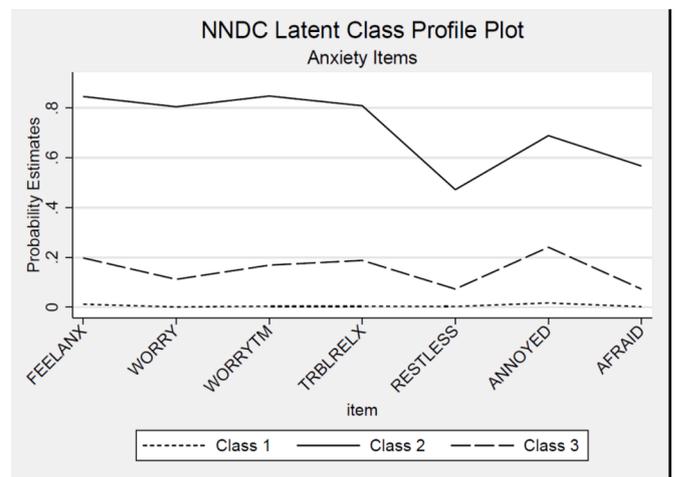


Fig. 2. Graph of Probability Estimates for Specific Symptoms of Anxiety by Latent Class.

3.3. Predictors of symptom profiles

The final multinomial logistic regression model provided a window into potential factors that characterize the 3 different latent classes (symptom profile groups). Variables that were significant in preliminary analyses and then remained significant in the final model are shown in Table 5. Evidence of having depression at some point in their lifetime was a significant predictor that distinguished women in each class from one another to varying degrees. However, the relative risk ratio (RRR) for the model that compared the asymptomatic group (Class 1) and the group with more severe comorbid anxiety and depressive symptoms (Class 2) had the highest level of significance, indicating that women who experienced a 2 week period of depression at some point in their lives were over 5 times more likely to have more severe comorbid symptoms (Class 2) than to be symptom free (Class 1). Women’s perceived stress was a second factor that distinguished each class from the other. As shown in Table 5, the largest difference was again between Classes 1 and 2, with women who had higher levels of stress being 2.34 times more likely to have more severe comorbid anxiety and depressive symptoms than be asymptomatic. Having an anxiety diagnosis was a

Table 5
Relative Risk Ratios for Final Significant Predictors of Latent Class Membership.

Class 1 (Asymptomatic)* versus Class 3 (Somatic Symptoms)					
	RRR	SE	z	p	[98.33% CI]
Government Assistance	1.71	.41	2.24	0.025	.9639873 - 3.049111
Social Support	.96	.01	-2.17	0.030	.9339681 - 1.003388
Irregular Menses	2.92	1.62	1.93	0.054	.7719814 - 11.06639
Lifetime History of Depression	1.96	.34	3.82	0.000	1.287809 - 3.001706
Anxiety Diagnosis	1.48	.27	2.13	0.033	.9528549 - 2.301474
Perceived Stress	1.54	.04	14.28	0.000	1.435786 - 1.660833
Class 1 (Asymptomatic)* versus Class 2 (Comorbid Anxiety/Depressive Symptoms)					
	RRR	SE	z	p	[98.33% CI]
Government Assistance	2.57	.84	2.90	0.004	1.179806 - 5.634411
Social Support	.94	.01	-2.83	0.005	.8961375 - 0.9908729
History of Anxiety in the Family	1.77	.47	2.16	0.031	.9392503 - 3.371225
Lifetime History of Depression	5.27	2.22	3.94	0.000	1.919993 - 14.50188
Anxiety Diagnosis	2.58	.68	3.61	0.000	1.376514 - 4.852418
Anti-Anxiety Medication	1.99	.63	2.18	0.029	.9352243 - 4.269206
Adverse Childhood Events	1.10	.05	1.99	0.047	.9789113 - 1.256942
Perceived Stress	2.34	.10	19.17	0.000	2.105255 - 2.603566
Class 3 (Somatic Symptoms)* versus Class 2 (Comorbid Anxiety/Depressive Symptoms)					
	RRR	SE	z	p	[98.33% CI]
Lifetime History of Depression	2.68	1.07	2.48	0.013	1.033359 - 6.97033
Bipolar Diagnosis	2.29	.72	2.64	0.008	1.079819 - 4.87039
Anxiety Diagnosis	1.74	.36	2.68	0.007	1.061888 - 2.868317
Anti-Anxiety Medication	1.56	.33	2.12	0.034	.9432712 - 2.607953
Adverse Childhood Events	1.07	.04	1.93	0.053	.98186 - 1.187546
Perceived Stress	1.51	.05	12.56	0.000	1.40057 - 1.641167

* The defined referent group.

third factor that distinguished each group from the other. Women who had received a diagnosis of an anxiety disorder were 2.58 times more likely to have more severe comorbid anxiety and depressive symptoms (Class 2) than to be asymptomatic (Class 1). A diagnosis of Bipolar Disorder distinguished Class 2 and Class 3 from one another, placing women at 2.29 times greater risk of having more severe comorbid anxiety and depressive symptoms (Class 2) than experiencing primarily sleep disturbance and fatigue (somatic symptoms; Class 3).

One factor was of special importance to the group having primarily somatic symptoms. Women who reported having irregular menses were 2.92 times more likely to be in Class 3 (i.e. experience somatic symptoms) than to be in Class 1 (asymptomatic). Irregular menses involved variation in the length of time a woman’s period lasted each month and/or the time between menstrual cycles. Fig. 3 highlights the significantly higher means scores of women with irregular menses for symptoms associated with sleep, fatigue and appetite than for other reproductive groups. The largest differences for symptoms of sleep and appetite disturbance were between women with irregular menses and pregnant women who had very few symptoms. The largest difference for symptoms of fatigue was between women with irregular menses and women in menopause who had minimal fatigue.

Lastly, receiving government assistance distinguished Class 1 from both Classes 2 and 3, with women receiving assistance being significantly more likely to not be symptom free. Women who had received assistance were approximately 70% more likely to have somatic symptoms than be asymptomatic and approximately 2.5 times (250%) more likely to have elevated symptoms of anxiety and depression. Receipt of governmental assistance was strongly linked to annual income, with a significant difference found between women receiving assistance and those who did not receive assistance in their annual income (Chi-Square = 2.33, $p=.000$). Women receiving the highest percent of governmental assistance (72%) were those with an annual income of <\$15,000. A second characteristic of asymptomatic women was their increased likelihood of social support. Women who reported greater satisfaction with support provided by friends and family were 94 to 96% more likely to be asymptomatic than to be in Class 2 or Class 3 respectively.

4. Discussion

4.1. Interpretation of results

We identified distinct symptom profiles of depression and anxiety in a sample of 5792 women across the lifespan, among seventeen healthcare sites in the U.S. Analysis resulted in three classes, characterized by unique symptom profiles among women at risk for affective symptoms. Class 1 was generally asymptomatic, Class 2 had elevated symptoms of both anxiety and depression, and Class 3 experienced primarily somatic symptoms of fatigue and sleep disturbance. These distinct symptom profiles may represent subtypes among women at risk of mood disorders.

The largest group of women fell into the asymptomatic group (Class 1). Most notably, these women were distinguished by their minimal reliance on governmental assistance such as food, public housing or educational and developmental services for their children. As would be expected, reduced use of governmental services among women in our study was related to a higher annual income. Financial stability is known to benefit mental health via multiple pathways including increased access to healthcare providers and reduced psychological stress (Braveman et al., 2010; Dubay and Lebrun, 2012). In contrast, income inequality and financial insecurity have been identified as causal factors in the onset of depressive and anxiety symptoms, often through the mediating experience of stressful life events (Fine and Hewstone, 2015; Patel et al., 2018). The possibility of a bidirectional relationship should also be considered since a healthy state of mind may have contributed to the relative financial stability of women in the asymptomatic group. There is evidence that poor mental health increases the likelihood of remaining on governmental assistance (Danziger et al., 2000).

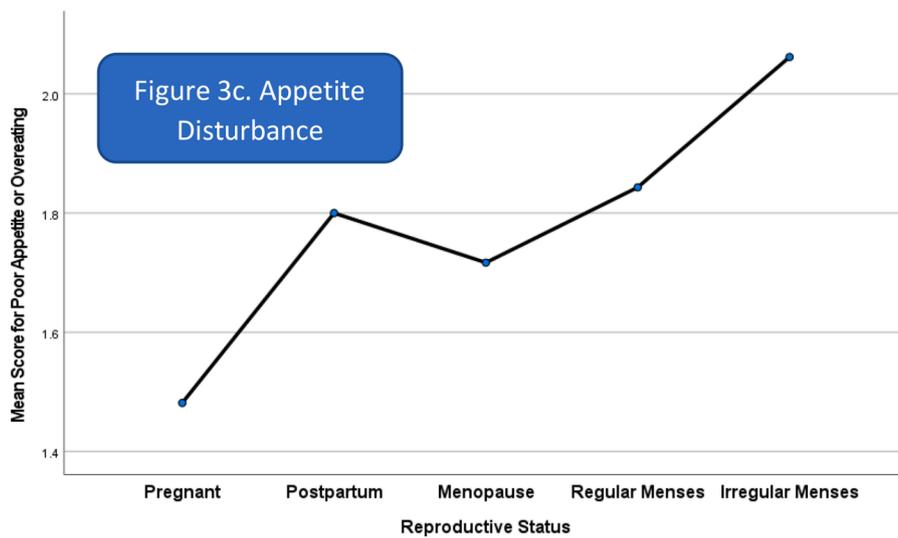
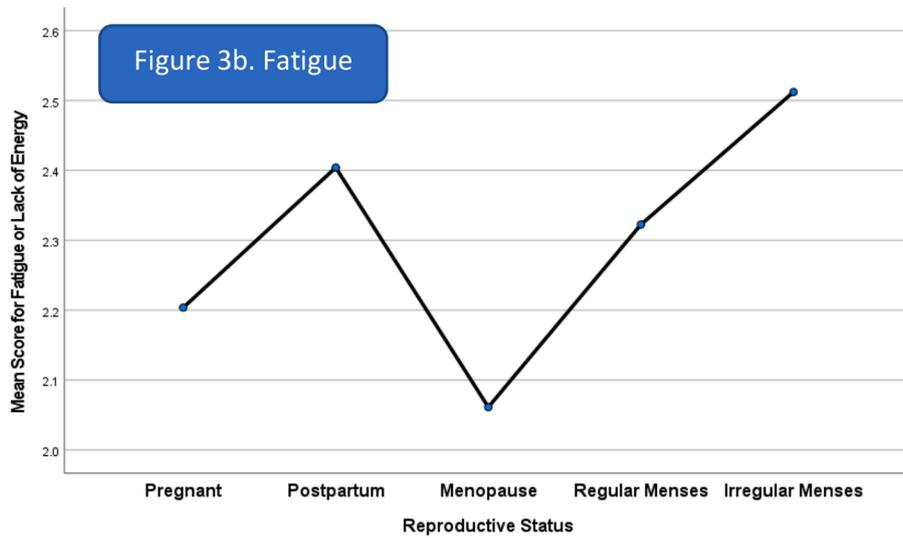
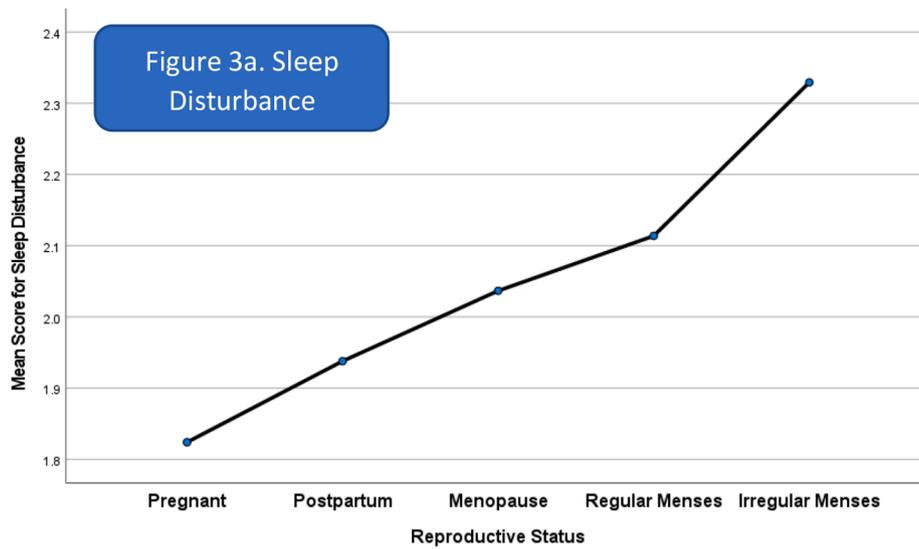


Fig. 3. Mean Scores for Somatic Symptoms by Reproductive Group.

An additional defining feature of women who were essentially symptom free was their satisfaction with the support provided by friends and family. A systematic review of studies in Western countries has substantiated the role of social support in protecting individuals against depression, with partner/spousal support identified as most protective (Gariépy et al., 2016). Social support may provide an important buffer to daily life stressors via access to tangible resources (e.g., financial support), emotional support (e.g., love, empathy, caring), and informational support (e.g., advice). The positive effects of social support on physical and mental health have been well documented (e.g., Feeney and Collins, 2015; Holt-Lunstad and Uchino, 2015). Overall, our findings suggest that women with an asymptomatic profile have greater access to protective factors such as financial security and social support that may enhance their resilience in the face of elevated risk.

A second group of women (Class 2) reported elevated comorbid anxiety and depressive symptoms. Previous studies show that MDD and generalized anxiety disorder are commonly comorbid (Coplan et al., 2015; Zbozinek et al., 2012), with comorbidity more prevalent in women than men (Luo et al., 2019) and especially among women who are mothers (Pino et al., 2019; Ramakrishna et al., 2019).

A number of significant clinical features distinguished women in this symptom profile group. A history of having previous depression was the strongest characteristic of these women. Our results are in alignment with prior research reporting a history of prior depression as a risk factor for depression recurrence (van Loo, Aggen, Gardner, and Kendler, 2015) and for more severe comorbid anxiety and depression (Cancino et al., 2018). Another very salient characteristic of women with this comorbid symptom profile was their increased likelihood of having a Bipolar Disorder diagnosis. This characteristic distinguished them in particular from women in the somatic symptom group, having greater than 2 times the risk for elevated comorbid symptoms. It has been estimated that approximately 71% of patients with bipolar disorder have a comorbid anxiety disorder (Krishnan, 2005), with the presence of co-morbid depression and anxiety associated with greater illness severity, greater functional impairment, higher ratings of suicidal ideation (Lee and Dunner, 2008) and poorer treatment response to mood stabilizers (Henry et al., 2003; Huang et al., 2020).

A prominent role for anxiety also characterized women in this symptom group, including a family history of anxiety disorder, their own personal diagnosis of an anxiety disorder, and use of anti-anxiety medications. Previous research has shown that individuals with an anxiety diagnosis are 6.1 times more likely to have a first-degree family member with an anxiety disorder (Hettema et al., 2001). Prior data demonstrate that these familial patterns reflect a combination of shared genetic factors as well as shared lifestyle and other exposures that ultimately contribute to risk (Shimada-Sugimoto, Otowa, and Hettema, 2015). In addition, other research has shown that individuals with comorbid anxiety and depression have an anxiety diagnosis and treatment with benzodiazepines as key clinical features (Dold et al., 2017).

Lastly, evidence of life stress and early adversity was also apparent for women in this symptom profile group, significantly more than for women in the other two groups. Recent results from a study of pregnant women who presented with severe comorbid anxiety and depressive symptoms are in concert with our findings, highlighting their high levels of perceived stress and greater exposure to adverse childhood experiences (Premji et al., 2020). Prior work has consistently demonstrated that early life stress is a risk factor for later life mental health problems ((Ishikawa et al., 2015; Kalmakis and Chandler, 2015; Vargas et al., 2016), with adverse childhood events having a particular impact on a greater likelihood of depression in women at various ages and reproductive stages (Ångerud et al., 2018; Epperson et al., 2017; Racine et al., 2020; Weiss et al., 2016). In epigenetic studies, early-life stress has been associated with the expression of genes which increase the risk of both anxiety and depression (Alyamani and Murgatroyd, 2018; Gillespie et al., 2019; Vaiserman, 2015). Similarly, ongoing life stress has been correlated with severity of anxiety and depression (McEwen et al., 2012) as well as

comorbid anxiety and depression (Funke et al., 2017), including among postpartum women (Farr et al., 2014).

The symptom profile of this group of women constitutes a more complex subtype than the others, integrating a mix of potentially heritable clinical features and social determinants. Comorbid anxiety and depression create substantially greater challenges for treatment and higher risk of poor mental health outcomes than occurs for either depression or anxiety alone (Coplan et al., 2015).

The last group of women (Class 3) was characterized by somatic symptoms of primarily sleep disturbance and fatigue, with milder symptoms associated with appetite and irritability. A unique feature of these women was their significantly greater likelihood of experiencing irregular menstrual cycles than other classes of women. We considered the possibility that the class might include primarily perimenopausal women who commonly have irregular menses as they approach menopause and who suffer symptoms such as hot flashes that disrupt sleep and lead to fatigue. However, women in this symptom profile group had a mean age in their 30's, indicating that perimenopausal status was not a driving factor. Another potential explanation is that these women may have disorders such as polycystic ovary syndrome (PCOS), uterine fibroids, endometriosis, or thyroid disease, each of which is associated with irregular bleeding and symptoms such as fatigue and mood changes (Cooney and Dokras, 2017; Cooney et al., 2017; Go et al., 2020; Ram-in-Wright et al., 2018; Smorgick et al., 2013; Thannickal et al., 2020; van Barneveld et al. 2021). For instance, women with PCOS experience irregular menstrual cycles (e.g. oligomenorrhoea) and are at a 2–4 times increased risk for depressive and anxiety symptoms. Those with uterine fibroids report significantly more depressive symptoms than those without fibroids, as well as pain, fatigue, and poor sleep. The potential role played by these conditions in shaping mood-related symptoms should be examined in future research.

Independent of any physical condition or illness that may have contributed to symptoms of women in this group, their sleep problems and fatigue may instead reflect a depressive phenotype characterized by physical symptoms rather than mood symptoms. In two previous studies, symptom clusters have been reported that distinguish adults who have sad mood and lack of interest from those with more prominent neurovegetative symptoms such as appetite and sleep perturbations (Li et al., 2014; Toenders et al., 2020). In concert with these previous findings, our results for this profile suggest a potential subtype of depression that involves a stronger expression of neurovegetative symptoms.

4.2. Limitations

Limitations included less than optimal racial diversity among our sample of women and reliance on their self-report. Our percent of Black/African American participants was slightly more than national percentages (15% versus 12.8%), based on the most recent *Census Bureau Statistics* (2019). However, our percent of Asian participants was slightly less (4.6% versus 5.7%) and our percent of Hispanic/Latina participants was substantially less (7.3% versus 18.4%). Although some of our self-report data was ideally based on perception and subjective assessment (e.g. feelings of stress, symptom experience), confirmation of other data (e.g. diagnosis and treatment information) with medical records or clinician reports would have reduced any potential for error.

5. Conclusions

This study extends existing knowledge in the field by identifying distinct clusters of affective symptoms, along with clinical, psychological and social factors, that differentiate unique groups of women who are at risk of mood disorders. To our knowledge, this is the first study to identify symptom clusters among high risk women across the life span and at varied reproductive stages. The research had a number of strengths, including substantial geographic, age (18–90), and clinical diversity of women that enhances generalizability. We used standardized measures

across sites, enabling integration of multi-site data into a common, centralized data management center. In addition, our study leveraged an existing network of women's health investigators who had developed effective working relationships through previous collaborative research.

Three distinct symptom profiles were identified through this latent class analysis, representing potential subtypes of mood disorders among women. Profiles include: 1) essentially asymptomatic women with greater likelihood of protective socioeconomic factors in their lives, 2) women who have elevated affective symptoms of both anxiety and depression characterized by complex clinical features and greater stress and adversity in their lives, and 3) women who experience primarily somatic symptoms with menstrual irregularity.

Results suggest the need to further examine potential biological mechanisms that may underlie the neurovegetative symptoms found for women with a somatic profile. In particular, neuroendocrine factors may explain the link between irregular menses and disturbances of sleep and appetite as well as fatigue. The influence of both genetic contributions and social determinants should be further explored as mechanisms underlying the more severe comorbid symptoms found among one group of women. Diagnosis with Bipolar Disorder was a unique, more prevalent feature of these women. The prominent role of anxiety should also receive attention in light of the prevalence of a family history of anxiety disorders, their own probability of an anxiety diagnosis, and their use of anti-anxiety medications. An interaction between a potential diathesis for anxiety and the high levels of stress and adversity in their lives may contribute to their more severe comorbid symptom profile. Lastly, social determinants of financial security and social support were protective factors characterizing the asymptomatic group of women. Our findings indicate that safety nets may be critical preventive interventions for women who have little access to social and economic resources. However, further study of the asymptomatic group is warranted to better understand potential psychological and biological mechanisms that may contribute to their resilience.

Research to identify the complex biology and psychological processes underlying these distinct symptom clusters may lead to targeted psychotherapies and pharmacotherapies. For example, women with somatic symptoms of primarily sleep disturbance and fatigue may have a better response to chronotherapies and cognitive behavioral therapy for insomnia as compared to other interventions. In contrast, a carefully planned medication regimen may be warranted for women with comorbid anxiety/depressive symptoms since a diagnosis of Bipolar Disorder and a history of familial anxiety characterized women with this symptom profile. Ultimately, improved understanding of the etiology and mechanisms underlying unique features of these different profiles can inform more precisely targeted interventions to address women's diverse needs (Buch and Liston, 2021).

CRedit authorship contribution statement

Sandra J. Weiss: Formal analysis, Project administration, Conceptualization, Investigation, Writing – original draft, Writing – review & editing. **Heather Flynn:** Investigation, Conceptualization, Writing – original draft, Writing – review & editing. **Lisa Christian:** Investigation, Conceptualization, Writing – original draft, Writing – review & editing. **Liisa Hantsoo:** Conceptualization, Writing – original draft, Writing – review & editing. **Teresa Lanza di Scalea:** Investigation, Conceptualization, Writing – original draft, Writing – review & editing. **Sara L. Kornfield:** Writing – original draft, Writing – review & editing. **Maria Muzik:** Conceptualization, Writing – original draft, Writing – review & editing. **Diana I. Simeonova:** Conceptualization, Writing – original draft, Writing – review & editing. **Bruce A. Cooper:** Formal analysis, Writing – original draft, Writing – review & editing. **Anna Strahm:** Writing – original draft, Writing – review & editing. **Kristina M. Deligiannidis:** Investigation, Conceptualization, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

All authors declare that they have no actual or potential conflict of interest (including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work related to this publication) that could inappropriately influence, or be perceived to influence, their work.

Acknowledgments

The Women and Mood Disorders Task Group of the National Network of Depression Centers contributed to development of the overall questionnaire from which data for this study was analyzed. We are also grateful to Sharon Kidd, PhD who assisted in organization and coordination of data acquired through the Research Electronic Data Capture (REDCap) system housed at the University of California, San Francisco.

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