Journal of Mood & Anxiety Disorders 12 (2025) 100152

Contents lists available at ScienceDirect

Journal of Mood & Anxiety Disorders

journal homepage: www.journals.elsevier.com/journal-of-mood-and-anxiety-disorders

Gender differences in symptom profiles of individuals being treated for mood disorders

Sandra J. Weiss [a,*], Sarah Nagle-Yang [b], Heather Flynn [c], Bruce Cooper [a], Maria Muzik [d], Diana I. Simeonova [e], Aysegul Ozerdem [f]

[a] Department of Community Health Systems, University of California, San Francisco, CA 94158, USA
[b] Department of Psychiatry, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA
[c] Department of Behavioral Sciences and Social Medicine, Florida State University, Tallahassee, FL 32306, USA
[d] Departments of Psychiatry and Obstetrics & Gynecology, University of Michigan, Ann Arbor, MI 48109, USA
[e] Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA 30322, USA
[f] Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN 55905, USA

ARTICLE INFO

Keywords:
Depression
Anxiety
Comorbidity
Sex differences
Symptom profiles

ABSTRACT

Background: A growing body of research suggests that symptoms of mood disorders vary by gender. Such differences could reflect unique mood phenotypes for women and men. We examined whether women and men with mood disorders had comparable or distinct profiles of anxiety and depressive symptoms, along with demographic and clinical variables associated with these profiles.

Methods: Our research involved a secondary analysis of data collected from 36,381 adults (age 18–98; 67.2 % women and 32.8 % men) through the National Network of Depression Center's Mood Outcomes Program. Latent class analysis (LCA) and logistic regression modeling were used to examine the aims. Symptoms included in the LCA were derived from the Patient Health Questionnaire-9 and the Generalized Anxiety Disorder Scale.

Results: Four latent classes were identified and labeled based on their predominant symptoms (BIC: 629,688.56; VLMR: 3787.30, $p < .01$). Women had greater odds of experiencing 'Demoralized Depression' than men (OR = 1.22, $p = .001$), with women of reproductive age having the greatest odds. Men had greater odds than women of having symptom profiles that reflected 'Anxious Arousal' (OR = .88, $p = .001$) or 'Mild Fatigue and Insomnia' (OR = .89, $p = .001$). There was no gender difference in the odds of a 'Comorbid Anxiety and Depression' profile.

Conclusions: Results suggest gender-specific phenotypes that differentially characterize mood disturbances, although effect sizes were small. Further research is needed to confirm these phenotypes and identify sexually dimorphic biomarkers or psychosocial exposures that may underlie gender differences. Understanding the heterogeneity of phenotypes can inform precision-based assessment and treatment of mood disorders, improving affective well-being of women and men in the long term.

1. Introduction

Women are approximately twice as likely to develop *Major Depressive Disorder* and *Generalized Anxiety Disorder* as men [1–3], with *Bipolar Disorder* showing a higher frequency among women as well [4]. It has been proposed that sexually dimorphic biological systems, such as reproductive hormones and stress response pathways, may influence these gender disparities [5–8]. Women's greater exposure to trauma appears also to be a contributing factor [9–11].

In addition, some studies suggest that specific symptoms of mood disorders vary by gender. For instance, women often present with anhedonia, sleep and eating disturbances, fatigue, sadness and feelings of worthlessness [2,12–14]. Men typically report more symptoms of anger, irritability, suicidal ideation, low self-esteem and cognitive problems such as impaired attention or memory [2,3,15,16], although similar levels of irritability have also been found for men and women [14]. However, in a study of individuals with Major Depressive Disorder, Vetter et al. [17] found few differences in specific symptoms endorsed by women and men, and no differences in their overall depression scores.

* Correspondence to: Mission Bay Campus, University of California, 490 Illinois Street, #92P, San Francisco, CA 94158, USA.
E-mail addresses: sandra.weiss@ucsf.edu (S.J. Weiss), sarah.nagle-yang@cuanschutz.edu (S. Nagle-Yang), heather.flynn@med.fsu.edu (H. Flynn), muzik@med.umich.edu (M. Muzik), dsimeon@emory.edu (D.I. Simeonova), Ozerdem.Aysegul@mayo.edu (A. Ozerdem).

https://doi.org/10.1016/j.xjmad.2025.100152
Received 10 June 2025; Received in revised form 23 September 2025; Accepted 24 September 2025
Available online 25 September 2025

Gender differences in symptoms may reflect distinct phenotypes or mood profiles for women and men. A few studies have examined gender-specific profiles or subtypes. For instance, a symptom profile has been identified among women that reflects somatic alterations in the areas of appetite, sleep, and fatigue [18–21]. In addition, comorbidity of depression with anxiety disorders is frequently reported in females, while males more often experience substance use disorders in conjunction with depression [2,14,22–24].

Most research that has examined sex differences simply compared group means or the frequency with which varied symptoms are endorsed by women and men rather than attempting to identify inter-related symptoms that may characterize gender-specific phenotypes in a more nuanced way. A few studies have used latent class analysis (LCA) to identify potential subtypes of depression.

Alexandrino-Silva et al. [25] performed separate LCAs for Brazilian men and women who had completed a survey of symptoms they experienced during the worst depressive episode in their lives. They identified a group in both genders who reported 'mild symptoms', and two more severe symptom groups among women, labeled as 'melancholic' and 'atypical.' Two more severe classes were found for men as well, including 'slowed/decreased psychomotor activity' and 'agitated depression'. Rodgers et al. [26] uncovered three LCA subtypes of depression symptoms experienced in the last 12 months in their longitudinal study of Swiss adults: 'severe atypical' (anhedonia and low energy combined with weight gain and increased appetite), 'severe typical' (anhedonia and low energy combined with loss of weight and decreased appetite), and 'moderate' (less pronounced symptoms overall). Females had a greater probability of being in the severe atypical subtype while males were higher in the severe typical subtype. The proportion of males and females in the moderate group was similar. Ulbricht et al. [27] analyzed depression symptoms within the prior week among participants in the U.S. STAR*D study. Through their LCA, four depression subtypes were identified in which men and women were differentially represented. Men were more likely to have a subtype of 'Mild Symptoms' while subtypes called 'Severe with Increased Appetite' and 'Severe with Insomnia' were more prevalent among women. A group having 'Moderate Symptoms' had approximately equal percents of men and women. Although not using LCA, Vetter et al. [17] and Steen et al. [28] performed network analyses to identify potential relationships among depression symptoms in a sample of Swiss psychiatric patients and a Dutch cohort from the general population, respectively. They found symptom networks were essentially the same for men and women.

Each of these previous studies has focused on depressive symptoms only, even though there is a high degree of comorbidity between depression and anxiety [29,30]. Depression and anxiety are both considered internalizing disorders that share a common dimension of affective symptoms such as feelings of upset, insomnia, restlessness, somatic changes, and irritability [31–33]. It has been proposed that their comorbidity may arise as a result of symptoms shared by both disorders that can activate or trigger symptom clusters of each disorder [34]. In light of the robust relationship between depression and anxiety symptoms, it seems essential to consider both sets of symptoms when identifying potential phenotypes of mood disorders.

A study by Curran et al. [35] with older Irish adults did examine gender differences in latent classes involving both anxiety and depression symptoms. Four classes of anxiety and depression were derived from their LCA: 'low frequency of symptoms overall', 'comorbidity of depression and anxiety,' 'anxiety and subthreshold depression', and 'anxiety' symptoms only. Investigators concluded that the symptom patterns did not differ across gender for this older age population.

In sum, previous research has found gender differences in profiles of depressive symptoms although the nature of these profiles differs across studies. However, there is a lack of research examining potential gender differences across the life span in profiles that consider both depression and anxiety symptoms. In this study, we addressed these gaps in knowledge. We determined whether women and men with mood disorders had comparable or distinct profiles of anxiety and depressive symptoms, and whether age, race, ethnicity, marital/partner status, psychiatric diagnosis, or suicidal behavior were associated with these profiles.

2. Methods

This study involved a secondary analysis of data collected through the National Network of Depression Centers (NNDC). This program integrates patient data from clinical sites affiliated with the NNDC, using a standard protocol. Data are collected from patients as part of routine clinical care through an on-line patient portal at the clinic sites. Data are automatically uploaded into a central repository hosted on a secure network which is fully compliant with all HIPAA standards. A de-identified, encrypted database is then created that can be employed for research and other health-related analytic goals. The participants included in this analysis were enrolled from 2011 to 2024 from 18 Centers affiliated with the NNDC. They were ages 18 and older. Self-report measures of mood symptoms were used to determine symptom profiles of women and men while data on demographics, patient diagnoses, and suicidal behavior provided information to better characterize gender differences in symptom profiles. As a secondary analysis of de-identified data, our study received exempt certification from the Institutional Review Boards for Human Research Protection at the University of California, San Francisco and the Mayo Clinic.

2.1. Measures

2.1.1. Mood symptoms

Data from two self-report measures were used to develop our symptom profiles. The Patient Health Questionnaire (PHQ-9) provided information on depressive symptoms. The PHQ-9 is a nine-item questionnaire based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) for major depression [36]. Each item is scored on a 4-point scale for frequency of the symptom (from not at all to everyday). A score of 10 or above is considered the clinical cut-off for follow-up. Testing of PHQ-9 has supported its criterion, discriminant, and construct validity as well as its internal consistency [36,37]. Research also indicates its utility for disparate sex, age and racial/ethnic groups [38].

The Generalized Anxiety Disorder Scale (GAD-7) [39] provided data on anxiety. The GAD-7 has 7-items, each on a 4-point scale reporting the frequency of a respondent's symptoms from not at all to everyday. A score of 8 or above has been identified as the optimal cutoff for clinically relevant levels of anxiety [40]. Internal consistency, convergent validity and internal consistency have been established for the scale in both inpatient and outpatient psychiatric populations [40,41].

2.1.2. Demographics

Five demographic characteristics were available in the data set. These included age, gender (female, male), race (African American/Black, American Indian/Alaskan Native, Asian American/Asian, European American/White, Native Hawaiian/Other Pacific Islander, and other or unknown), ethnicity (Hispanic/Latinx or not), and partner status (single/never married, married/committed relationship, divorced/separated, and widowed).

2.1.3. Primary diagnostic classification

Diagnostic codes for Mental, Behavioral and Neurodevelopmental Disorders from the International Classification of Diseases, Tenth Revision (ICD-10) were available for each participant [42,43]. These were identified by the patient's primary clinician based on clinical assessment. We created binary scores for a person's receipt or not of any ICD-10 code that would fall under the following major diagnostic categories: *Bipolar Disorder*, *Major Depressive Disorder* (MDD), *Anxiety*

Disorder (AD), *Posttraumatic Stress Disorder* (PTSD), and *Substance Use Disorder* (SUD).

2.1.4. Suicidal behavior

The lifetime/recent version of the Columbia-Suicide Severity Rating Scale (C-SSRS) was completed by participants as an assessment of their immediate risk for suicide and any previous suicidal behavior [44]. Questions in the C-SSRS measure the severity of ideation, the intensity of ideation, behavior, and lethality. All items involve binary responses (yes/no) that identify the presence or absence of the thoughts or behaviors. From the items, we calculated 2 scores. The first was a sum score of items indicating the intensity of an individual's suicidal behavior over the past month, from having thoughts about wishing to be dead (a score of 1) to having done something specific or prepared to do something to end their lives (a score of 6). The second was a binary score for whether (or not) the individual reported making an actual suicide attempt at some point during their life. The C-SSRS has excellent psychometric support [44–46] and is used as part of multiple national and international public health initiatives involving the assessment of suicidality.

2.2. Data analysis

We employed descriptive statistics to characterize the sample. Latent class analysis (LCA) was used to detect the presence of unobserved, latent classes or symptom profiles among the total sample of women and men. For these analyses, we examined patterns of association among participants' scores on anxiety and depressive symptoms from the PHQ-9 and the GAD-7. Item 8 on the PHQ-9 (movement/speech slowing or restlessness) was not used in the analyses due to its extreme non-normality (rarely endorsed by participants). Similarly, item 9 on the PHQ-9 (suicidal ideation) was not included in the LCA because of its potential confounding with the C-SSRS when examining our second aim. For the LCA, we used a cross-validation approach. The goal of cross-validation was to determine if any class structure we identified would generalize to an independent dataset not used in estimating it. We randomly split the full sample into two equally sized subsamples of 50 %: an initial calibration sample and a second validation sample. Using the calibration sample, fit indices were estimated for LCA models for 1-class through 5-class solutions. This same procedure was then performed with the validation or hold-out sample to determine whether the same latent class solution would be replicated. Full information maximum likelihood (FIML) was employed to produce unbiased estimates and the expectation-maximization algorithm was used to deal with missingness.

Using the total integrated (calibration and validation) sample, logistic regression modeling was employed to identify variables that best characterized or predicted different latent classes or symptom profiles. In these analyses, we created a binary score for each latent class as the categorical dependent variable. We first examined the association of gender with each class, controlling for patient age. Then, associations of each of the demographic, diagnostic, and suicide variables were determined with each of the latent classes for men and women separately. Bonferroni adjustments were made for multiple testing, with our correction indicating p = .0125 as the value considered significant. LCA was carried out with Mplus and logistic regressions with STATA 18.

3. Results

3.1. Sample description

The sample included 36,381 individuals: 24,431 self-identified as women (67.2 %) and 11,950 as men (32.8 %). As shown in Table 1, the majority was of European/White ancestry, with individuals of African American/Black and Hispanic/Latinx heritage being the next largest groups. On average, women (M = 38.77) and men (M = 39.6) were comparable in age. *Major Depressive Disorder* was the most prevalent primary diagnosis for both women (47.1 %) and men (42.3 %), with an *Anxiety Disorder* being the next most frequent primary diagnosis for both genders (30.7 % and 29.1 % respectively).

Table 1
Characteristics of the sample (N = 36,381) by gender*.

Variable	Women N (%)	Men N (%)
Race		
African American/Black	1881 (7.7)	609 (5.1)
American Indian/Native Alaskan	24 (0.1)	12 (0.1)
Asian American	635 (2.6)	334 (2.8)
European American/White	20,717 (84.8)	10,432 (87.3)
Hawaiian/Pacific Islander	171 (0.7)	71 (0.6)
Other or Unknown Ancestry	1001 (4.1)	478 (4.0)
Ethnicity		
Hispanic American/Latinx	1441 (5.9)	573 (4.8)
Relationship Status		
Single	10,847 (44.4)	6094 (51.0)
Married/Partnered	10,529 (43.1)	4851 (40.6)
Separated/Divorced	2467 (10.1)	908 (7.6)
Widowed	586 (2.4)	107 (0.8)
Primary Diagnosis		
Bipolar Disorder	2711 (11.1)	1410 (11.8)
Major Depressive Disorder	11,507 (47.1)	5055 (42.3)
Other Mood Disorders	1001 (4.1)	621 (5.2)
Anxiety Disorders	7500 (30.7)	3477 (29.1)
PTSD	953 (3.9)	287 (2.4)
Substance Use Disorders	537 (2.2)	717 (6.0)
Lifetime Suicide Risk		
No Suicidal Behavior	15,709 (64.3)	7564 (63.3)
Suicidal Ideation & Suicide Plans	6034 (24.7)	3190 (26.7)
Suicide Attempt	2687 (12.0)	1195 (10.0)
	Mean (SD)	**Mean (SD)**
Age (Range from 18 to 98)	38.77 (15.90)	39.60 (16.11)
Current Depressive Symptoms	11.60 (6.68)	10.95 (6.78)
Current Anxiety Symptoms	10.43 (6.06)	9.59 (6.14)
Current Suicide Severity Risk	4.52 (2.22)	4.21 (2.24)

* Women (n = 24,431); Men (n = 11,950).

3.2. Latent classes

Our latent class analysis (LCA) with the initial calibration sample indicated that there were 4 distinct classes or symptom profiles among our sample participants. The fit indices for the LCA are provided in Table 2. The 4-class solution was selected because the Bayesian Information Criterion (BIC) for that solution was lower than the BIC for the 3-class solution, indicating a better fit. In addition, the Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR) was significant for the 4-class solution, indicating that four classes fit the data better than three classes. Although the BIC was smaller for the 5-class than for the 4-class solution and entropy a bit higher, the VLMR was not significant for the 5-class solution, indicating that too many classes were extracted. Entropy is considered a key measure of effect size as it quantifies the degree to

Table 2
Fit indices for five latent classes.

Model	LL	AIC	BIC	Entropy	VLMR
1 Class	− 326,594.54	653,329.09	653,881.95	n/a	n/a
2 Class	− 319,130.19	638,430.39	639,101.72	0.82	14,928.70‡
3 Class	− 316,168.80	632,537.59	633,327.39	0.84	5922.80+
4 Class	− 314,275.14	628,780.29	629,688.56	0.88	3787.30+
5 Class	− 308,874.98	618,009.95	619,036.70	0.90	ns

Note: Baseline Entropy and VLMR are not applicable for the one-class solution. Abbreviations: AIC = Akaike's Information Criterion; BIC = Bayesian Information Criterion; LL = log-likelihood; n/a = not applicable; ns = not significant; VLMR = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test for the K versus K-1 model

+ p < .01.

‡ p ≤ .00005.

which individuals are distinctly assigned to their respective latent classes. An entropy value above .80 indicates that the latent classes are highly discriminating and provides strong evidence for distinct classes. The 4-class structure we selected had an entropy value of .88. The LCA for the validation sample showed indistinguishable results, yielding a 4-class solution similarly supported by the BIC, entropy and VLMR fit indices. Both the initial calibration sample and the validation sample had the following identical proportions of individuals assigned to each class: class 1 (49 %), class 2 (22 %), class 3 (11 %), and class 4 (18 %).

3.3. Symptom profiles

The specific symptoms that characterized individuals in each class are shown in Table 3. Overall, symptoms in Class 1 were mild, with fatigue and sleep disturbance the most prominent. Thus, Class 1 was labeled 'Mild Fatigue/Insomnia'. In Class 2, three depressive symptoms were most prevalent among individuals. These included 1) feeling down, depressed and hopeless, 2) feeling bad about oneself and a failure, and 3) feeling low energy and fatigue. Other symptoms in Class 2 involved a mix of less prominent depression and anxiety symptoms. Based on this symptom profile, Class 2 was labeled 'Demoralized Depression' since its symptoms align with a syndrome of demoralization that has been described as a psychological state of 'existential distress' involving failure and hopelessness [47]. In contrast, the most prevalent symptoms in Class 3 were indicative of 'Anxious Arousal'. These were: 1) being so restless it was hard to sit still, 2) trouble relaxing, and 3) feeling nervous, anxious and on edge. Individuals in Class 4 had more severe symptoms overall than individuals in other classes. In addition, their symptoms indicated a high degree of comorbidity. Although the class had slightly more symptoms of anxiety than depression, two of the most prevalent symptoms were 'feeling nervous, anxious and on edge', as well as 'feeling bad about oneself and a failure'. We labeled this class 'Comorbid Anxiety and Depression.'

3.4. Gender differences

3.4.1. Gender differences in latent class designation

The logistic regression analyses for gender differences were significant for 3 of the 4 latent classes. As shown in Table 4, women had 11 % lower odds than men of being in Class 1 (Mild Fatigue/Insomnia; OR = .89, $p < .001$). In contrast, men had 12 % (OR = 1.12, $p < .001$) greater odds of being in Class 1. Women had 22 % greater odds than men of being in Class 2 (Demoralized Depression; OR = 1.22, $p < .001$) but 12 % lower odds of being in Class 3 (Anxious Arousal; OR = .88, $p < .001$). Men had 13 % greater odds of being designated as having this Anxious Arousal profile (OR = 1.13, $p < .001$). There were no gender differences for Class 4 (Comorbid Anxiety and Depression). Fig. 1 contrasts the proportion of women and men whose symptom profiles situated them in each class.

Table 3
Means of anxiety and depression symptoms for four latent classes.

Symptoms	Class 1	Class 2	Class 3	Class 4
Symptoms of Anxiety				
Feeling nervous, anxious, on edge	0.89	2.09	2.15	2.67
Not able to stop or control worrying	0.76	2.00	1.86	2.62
Worrying too much about different things	0.85	2.08	1.97	2.65
Trouble relaxing	0.79	1.84	2.26	2.66
Being so restless it's hard to sit still	0.32	0.54	2.40	2.56
Becoming easily annoyed or irritable	0.84	1.76	1.84	2.42
Feeling afraid/something awful will happen	0.50	1.52	1.29	2.23
Symptoms of Depression				
Little interest or pleasure in doing things	0.74	1.92	1.32	2.21
Feeling down, depressed, or hopeless	0.70	2.26	1.20	2.37
Trouble with sleep	1.03	2.03	1.84	2.42
Feeling tired or having little energy	1.15	2.24	1.79	2.47
Poor appetite or overeating	0.69	1.71	1.32	2.18
Feeling bad about yourself, a failure	0.48	2.40	0.69	2.67
Trouble concentrating on things	0.64	1.70	1.64	2.33

Table 4
Logistic regression results for effects of gender on latent class affiliation.

	Estimate	SE	OR	p-value	95 % CI
Class 1					
Mild Fatigue/Insomnia	− .116	.02	.89	.001	.853,.930
Class 2					
Demoralized Depression	.205	.02	1.22	.001	1.161, 1.290
Class 3					
Anxious Arousal	− .127	.03	.88	.001	.823,.943
Class 4					
Comorbid Depression/ Anxiety	.046	.03	1.04	.110	.990, 1.108

Note: Reference group is women; Controlling for age and race; SE = Standard error; OR = Odds ratio; CI = Confidence interval.

3.4.2. Gender differences in latent class based on race and ethnicity

In addition to gender differences in overall class designation, certain variables provided a more in depth understanding of gender differences within different classes. A number of these differences were based on race and ethnicity. For Class 1 (Mild Fatigue/Insomnia), one gender difference emerged. Women of European American/White ancestry had lower odds of being in Class 1 than did European/White men (B = -.11 (.02), OR = .89, $p < .001$). Three gender differences for Class 2 (Demoralized Depression) were related to racial heritage. African American women (B = .29 (.11), OR = 1.34, p = .008), Asian American women (B = .36 (.16), OR = 1.43, p = .03), and European American women (B = .19 (.03), OR = 1.21, p = .001) all had greater odds of being in Class 2 than their male counterparts of the same racial background. For Class 3 (Anxious Arousal), women of African American (B = -.44 (.13), OR = .64, p = .001) and European American (B = -.11 (.03), OR = .89, p = .003) ancestry had lower odds of being in this class than men in their respective racial groups. On the other hand, African American men had 56 % greater odds of being in Class 3 (OR = 1.56) than African American women. European American men also had 12 % greater odds of being in this class than European American women (OR = 1.12). No gender differences were found among individuals in Class 4 (Comorbid Anxiety/Depression) based on racial heritage. Of note, there were no significant gender differences in latent class among individuals of Hispanic/Latinx heritage.

3.4.3. Gender differences in latent class based on primary diagnosis

Two of the diagnostic categories predicted the odds of being in a particular latent class for one gender but not the other. The first finding was that men with a *Substance Use Disorder* (SUD) had a 39 % greater

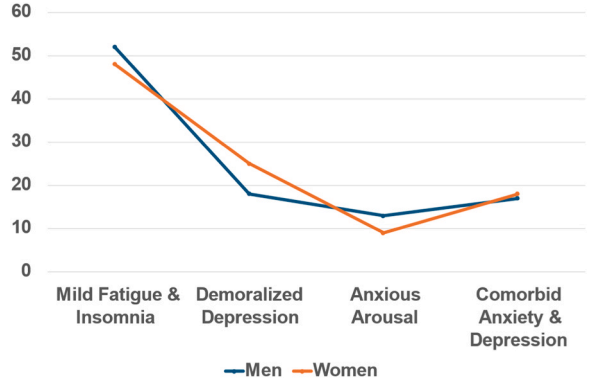

Fig. 1. Proportion of men and women in each symptom profile (latent class).

odds of being in Class 3 (Anxious Arousal) than men without a SUD (B = .33(.11), OR = 1.39, p = .002). For women, having a SUD did not predict being in any latent class, including Class 3. The gender difference in Odds Ratios for the effect of a SUD on the likelihood of experiencing a profile of 'Anxious Arousal' is shown in Fig. 2. *Bipolar Disorder* was the second diagnostic category showing a gender-specific relationship to a latent class. Women with a diagnosis of *Bipolar Disorder* had a 22 % lower odds of being in Class 2 (Demoralized Depression) than women without this diagnosis (B = -24 (.05), OR = .78, p = .001). For men, a diagnosis of *Bipolar Disorder* had no relationship to being in any latent class, including Class 2.

3.4.4. Gender differences in latent class based on age

One latent class (Class 2 – Demoralized Depression) showed gender-specific effects by age. Younger women (age 18–45) had 10 % greater odds of being in Class 2 than women of other ages (B = .09 (.03), OR = 1.10, p = .002). However, for men, it was those in middle age (46–60) who showed greater odds of being in the 'Demoralized Depression' class (B = .23 (.05), 1.26, p = .001); they had an increased probability of 26 %.

3.4.5. Sample characteristics showing similar relationships to latent class across gender

Some demographic and clinical variables predicted being in a particular latent class for both men and women, showing an analogous effect across gender. Individuals of older age (61–95 years) had 78 % greater odds of being in Latent Class 1 (Mild Fatigue/Insomnia; OR = 1.78, p = .001) than did younger (18–45) or middle aged (46–60) persons. Older persons also had lower odds of being in all other latent classes. In contrast, younger persons of both genders had greater odds of being in Class 3 (Anxious Arousal; OR = 1.36, p = .001) and Class 4 (Comorbid Anxiety and Depression; OR = 1.34, p = .001) than either middle aged or older persons.

Partner status also had similar effects across gender in predicting latent class. For both women and men, being married or living with a partner was associated with 27 % greater odds of having a symptom profile of 'Mild Fatigue/Insomnia' (Class 1; B = .24 (.02), OR = 1.27, p = .001) and lower odds of being in all other latent classes.

Several psychiatric diagnoses predicted the same latent class for both genders. A diagnosis of MDD increased the odds for men (OR = 1.71) and women (OR = 1.67) of being in Class 2 (Demoralized Depression) while a diagnosis of anxiety disorder decreased the odds for both men (OR = .65) and women (OR = .62) of being in this class (all at p < .001). A diagnosis of PTSD increased the odds for both men (OR = 1.48) and women (OR = 1.36) of being in Class 3 (Anxious Arousal) as did a diagnosis of any anxiety disorder for men (OR = 1.29) and women (OR = 1.32), all at p.< .001. Of particular interest was the finding for both genders that while PTSD *increased* their odds of being in Class 4 (Comorbid Anxiety and Depression; men's OR = 2.04; women's OR = 1.63, p < .001), their diagnosis of any anxiety disorder (e.g. generalized anxiety disorder, panic disorder) *decreased* the odds of being in this class (men's OR = .85; women's OR = .74, p < .001)

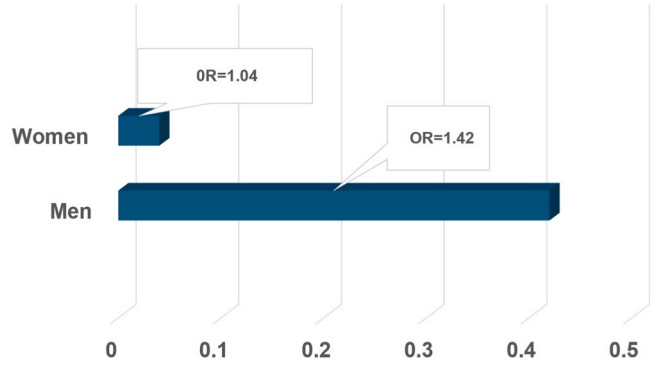

Fig. 2. Gender difference in odds ratios (OR) for the effect of having a substance use disorder on the likelihood of experiencing 'anxious arousal'.

Lastly, suicidal behavior showed associations with all latent classes that were similar for men and women. Intensity of suicidal behavior (i.e. having done something specific to end their lives) predicted lower odds of being in Class 1 (Mild Fatigue/Insomnia) and Class 3 (Anxious Arousal) for all individuals in the sample. Women with more intense suicidal behavior had an 81 % lower probability of being in Class 1 (B = -1.67 (.03), OR = .19, p = .001) while men had an 80 % lower probability (B = -1.58 (.04), OR = .20, p = .001). For Class 3, women with more intense suicidal behavior had a reduced odds of 43 % (B = -.55 (.04), OR = .57, p = .001) and men had reduced odds of 32 % (B = -.38 (.04), OR = .68, p = .001). Conversely, more intense suicidal behavior predicted greater odds of being in Class 2 (Demoralized Depression) and Class 4 (Comorbid Anxiety and Depression) for both women and men. For Class 2, more intense suicidal behavior among women increased their odds of being in this class by 68 % (B = .52 (.02), OR = 1.68, p = .001) and increased men's odds by 81 % (B = .60 (.02), OR = 1.81, p = .001). The effect of more intense suicidal behavior was the strongest for Class 4 (Comorbid Anxiety/Depression). It increased the odds of being in Class 4 by approximately 2 ½ times (~ 150 %) for both women (B = .91 (.02), OR = 2.48, p = .001) and men (B = .92 (.02), OR = 2.52, p = .001). Results for actual suicide attempts paralleled the findings for intensity of suicidal behavior. Men and women who had attempted suicide at some time in their lives had greater odds of being in Class 2 (men's OR = 1.47, women's OR = 1.34) as well as Class 4 (men's OR = 1.79, women's OR = 1.95), all at p < .001.

4. Discussion

4.1. Heterogeneous symptom profiles

Our study is the first to examine symptom profiles using latent class analysis of both depression and anxiety symptoms in a sample of women and men across the lifespan (ages 18–98). A more nuanced understanding of specific phenotypes that integrate depressive and anxiety symptoms is necessary to advance research on both the etiology and precision treatment of mood and anxiety disorders. Even advances in understanding the genetics of depression alone have been drastically limited by the lack of attention to phenotypic heterogeneity [48]. Studies have developed evidence on metabolomic and proteomic markers characterizing distinctive depression subtypes such as depression with melancholic, atypical or anxious features [49,50]. This research supports a biological basis for subtypes of depression that are homogeneous in symptom presentation. However, such studies have typically not given anxiety equal footing in these analyses but considered it as something that might co-occur with depression. In light of the growing evidence for complex, robust biological and psychological linkages between anxiety and depression [51–53], our research provides potential phenotypes that reflect the important interconnection between their symptoms. In an era of individualized medicine, better definition of such phenotypes will support more refined treatment targets and better treatment outcomes.

We identified four distinct latent classes, indicating symptom profiles that differentially reflect the nature of mood disturbances. One of the profiles we identified ('Comorbid Anxiety and Depression') is congruent with a profile reported by a previous study that examined gender differences through LCA with both depression and anxiety symptoms (but only in older adults) [35]. However, in that study, Curran et al. [35] did not find any profile similar to our 'Demoralized Depression' group or any unique depression profile for that matter. Because their study included only older adults (M = 68.7 years), our findings extend knowledge in the field by showing that women of reproductive age had the highest odds of experiencing a cluster of symptoms indicating 'Demoralized Depression'.

While exploratory in nature, our results may advance the field in a number of ways. First, the distinct nature of the symptom profiles we identified reinforces the heterogeneity that can exist among individuals with mood disorders and the importance of nuanced assessment and treatment of patients in individualized, tailored ways. If future research supports the presence of these profiles across various populations and clarifies potential biological and psychological mechanisms that underlie the different profiles, the use of profile-based scores in assessment could assist clinicians in prioritizing treatment goals and better tailoring interventions to meet individual needs. For instance, the neurovegetative symptoms of the 'Fatigue and Insomnia Profile' will likely respond to different medications or psychotherapeutic strategies than the cognitive-emotional symptoms of failure and hopelessness in the 'Demoralized Depression' profile.

4.2. Gender differences in symptom profiles

Although women and men were significantly different in their odds of experiencing three of the profiles we identified, the effect sizes for gender differences were small. Thus, further research is needed to confirm the validity of the gender differences we found and whether they are clinically meaningful. Until such data are available, the credibility of these gender differences remains uncertain.

Still, our findings accentuate potential areas for attention by clinicians. The somewhat higher prevalence of the 'Fatigue and Insomnia' profile we found for men highlights the need to carefully assess somatic symptoms when screening men for mood disorders. Somatic symptoms have often been viewed as more prevalent among women [e.g. [13,20]] but need to be seriously assessed in men as well. Milder physical symptoms, like fatigue and insomnia, cannot be overlooked as potential precursors of more severe illness [54] since they have been associated with greater odds of developing major depressive disorder or an anxiety disorder over time [55].

Our results also suggest that assessment and treatment of women who are in the reproductive stage of their lives may need to attend more carefully to their symptoms of failure and hopelessness. Our finding that women of this age had the greatest odds of 'Demoralized Depression' (driven substantially by their perceived failure and hopelessness) is congruent with a hypothesized role for sex hormones. Fluctuating sex hormones, particularly estrogen, have been proposed as likely contributors to female-specific risk for depression because of their impact on a woman's brain morphology and neurochemistry [56]. Women who present with this phenotype may be helped, in particular, by pharmaceutically addressing alterations of their hormone levels or by targeting symptoms of failure and hopelessness through cognitive restructuring, behavioral activation, or other strategies. These hypotheses should be tested in future research.

The finding that men had greater odds of an 'Anxious Arousal' profile suggests that arousal could reflect an important male-specific phenotype of anxiety, characterized by a propensity to monitor the external environment for threat as well as hypervigilance and hyperarousal of the sympathetic nervous system [57,58]. Research suggests that men experience anxiety at a more physiological level than women and have greater activation in motor areas of the brain during anxiety [59–61]. Our discovery that men with *Substance Use Disorder* had greater odds of this symptom profile is also important since anxious arousal, specifically, has been associated with greater substance abuse [62]. It has been proposed that anxiety and substance abuse share underlying, mutually exacerbating, neurobiological processes that involve a dysregulated stress-response system [63,64]. In light of this, it is possible that beta blockers, sympatholytics, or other methods to regulate the sympathetic nervous system could be effective in treating individuals with this profile. Research is needed to examine this hypothesis, along with gender-specific responses to such interventions. Our findings implicate the need for research to study shared biological mechanisms underlying anxious arousal and substance abuse as well as to develop integrated interventions for these co-occurring mental health problems.

4.3. 'Comorbid anxiety and depression'

The lack of gender difference we found for the symptom profile of 'Comorbid Anxiety and Depression' is congruent with the previous LCA study which examined both anxiety and depression symptoms among older men and women [35]. Individuals with moderate to severe symptoms of either anxiety or depression are often more likely to experience the other disorder, with the severity of symptoms in both conditions increasing when they co-occur [65,66]. Our most important contributions related to this profile are the identification of suicidal behavior (activities to prepare for suicide and an actual suicide attempt) and a diagnosis of PTSD as core characteristics of individuals with the profile.

The increased suicide risk of patients with this profile may be due to a cumulative or escalating effect of the overlapping depression and anxiety symptoms, resulting in greater psychological distress, impairment in more areas of functioning, and demands beyond the threshold of the individual's ability to cope. Our results emphasize the need for attention in clinical assessment to the salience of comorbidity for imminent or future suicide risk. The finding that patients with a comorbid profile had 2 ½ times greater odds of doing something specific to end their lives suggests the value of more in depth screening questions about their suicidal behavior as well as potential development of a safety plan that includes a list of coping strategies and sources of support for their use during any emerging suicidal crisis.

The significant role of a PTSD diagnosis for individuals who had this comorbid profile suggests that trauma exposure and its re-experiencing likely increase the development or exacerbation of both depression and anxiety [67,68]. In addition, research indicates that PTSD, depression, and anxiety share genes, neural pathways and neurotransmitter systems that are involved in regulating emotion, mood, and stress response [69–71]. The shared biological underpinnings of these three disorders may serve as bridges from one disorder to another and sources of mutual activation. Considering our findings that individuals with PTSD had significantly increased odds of a comorbid depression/anxiety profile, trauma-informed interventions could be particularly useful for patients with this phenotype. Trials of trauma-informed versus other interventions can be conducted to compare their effectiveness in reducing the severity of comorbid symptoms.

4.4. Strengths and limitations

This study was the first to perform a latent class analysis (LCA) of both depression and anxiety symptoms to identify symptom profiles of a national sample of men and women with mood disorders across the adult lifespan. We used the most widely accepted, robust approach to LCA, employing items derived from patient self-report of the symptoms they experience. The size and geographic representation of the sample are strengths that enhance generalizability of our findings. In addition, we had an excellent age distribution from 18 to 98. All participants received a clinician-derived diagnosis for their disorders and data on an array of disorders was available. We examined both depression and anxiety symptoms in our profiles and used cross-validation to determine if the class structure we identified would generalize to an independent dataset not used in estimating it.

However, most participants were of European/White ancestry, limiting the generalizability of our findings. The smaller size of some racial and ethnic subsamples may have also limited the power to detect significant effects of race or ethnicity. In addition, because only certain participant data was available in the dataset we used, we could not fully characterize potential psychological, social and biological predictors of the symptom profiles. For example, variables such as women's reproductive stage, the presence of thyroid or autoimmune disorders, sex hormone levels, family history of mood disorders, adverse childhood

experience, or ongoing treatment for mood disorders (e.g., psychotherapy and medication type/dose) would help in understanding factors that influence symptom profiles. The absence of such variables in model testing reduced our ability to effectively characterize patients within each profile and identify potential assessment and treatment implications of the profiles. In particular, conducting sensitivity analyses for various stages in the continuum of care and types of treatment being received by patients would provide critical insights regarding the impact of these conditions on symptom profiles. Different profiles or gender differences may have emerged in treatment naïve versus treatment intensive conditions.

Lastly, issues related to our measures should be noted. Our latent class analysis included 15 symptoms that were available from the measures in the dataset. A more extensive aggregate of symptoms may have aided in understanding more nuanced symptom profiles. In addition, a meta-analysis indicated that the PHQ-9 may have a higher false positive rate for women than men [72]. This suggests that certain items in the measure might have less validity for women. Although the measure has shown excellent validity and reliability overall among women from varied populations [e.g., [73,74]], the gender-specific accuracy of specific items in the depression measure could introduce some degree of measurement bias into the profiles that we generated. However, investigators of large population cohorts in both the U.S. and Germany examined measurement invariance across sexes and found that items functioned similarly for women and men [75,76]. Still, because of mixed findings about the measure, an analysis of 'differential item functioning' between men and women from multiple samples would help in identifying whether all items in the PHQ-9 are equivalent in their ability to accurately assess depressive symptoms of men and women.

4.5. Conclusions

For decades, research has focused on gender differences in the prevalence of depression and anxiety, with less attention on elucidation of symptom profiles or phenotypes. Understanding symptom profiles is important given the widely recognized heterogeneity of mood disorders and the need for personalized assessment and treatment. Research aimed at identifying more precise sub-types may also help advance our understanding of genetic underpinnings and varied biological mechanisms, which has been limited, in part, by attempts to characterize depression and anxiety each as one large diagnostic group and without consideration of the interconnectedness of the two entities. This exploratory study is the first to examine symptom profiles of depression and anxiety together in a sample of men and women across the entire adult life span, offering symptom phenotypes for future examination and potential hypothesis-testing. Our findings for the four different symptom profiles had strong effect sizes that were supported through cross-validation within our sample. However, the effect sizes we found for gender differences are small overall, requiring further study to determine their real world, clinical significance.

4.5.1. Research implications

Results provide a foundation for advancing knowledge of specific mood phenotypes. Replication of our analyses should be performed with diverse sociodemographic and clinical populations. Psychosocial risk trajectories can be examined that may influence development of the 4 symptom profiles. Studies of the neurobiological substrates of the profiles can be initiated to identify biomarkers that may distinguish different profiles or phenotypes. Distinct neurobiological systems (e.g., genetic, immune or endocrine) may align with specific profiles, helping to clarify risk for mood-related subtypes, aiding in their assessment, and explicating treatment approaches [77–79]. Hypotheses specific to key dimensions of the profiles might also be tested. For instance, 'Will CBT focused specifically on thoughts and behaviors related to demoralization improve the depressive profile of women more effectively than other therapeutic approaches?' Or 'Will medications to reduce autonomic nervous system arousal of men significantly improve their symptoms of anxious arousal?' Such questions stem directly from key symptoms of the 'demoralized depression' and 'anxious arousal' profiles we found for women and men respectively. Clinical trial designs such as adaptive and optimization designs can also be employed to test personalized treatments, timing, dosing and sequencing based on specific treatment response of each phenotype, considering its unique symptom profile, social determinants, and biosignature. The ultimate goal is to improve assessment and treatment of mood disorders as well as affective well-being of women and men in the long term.

4.5.2. Clinical implications

Although this study was exploratory, our results may have implications for potential development of personalized, more tailored assessment and treatment of mood disorders over time. The effectiveness of antidepressants (the most prescribed treatment for depression and anxiety) varies substantially, with some individuals experiencing significant improvement and others realizing little benefit [80,81]. Differences in how men and women respond to treatments for depression and anxiety have long been recognized, including response to pharmacotherapy and psychotherapy [82–84]. Understanding unique symptom profiles can lead to advances in differentiating mechanisms of action of medications, psychotherapy and other treatments that are targeted to specific symptoms and patient clinical or demographic characteristics. Results may eventually yield gender-specific biomarkers or digital interventions that can inform screening and treatments for distinct symptom profiles rather than the broad-spectrum treatments of the past several decades such as CBT and antidepressants.

Importantly, our findings support the presence of variable phenotypes and symptom presentations in adults, especially when both depression and anxiety are considered together. This implies that selective screening based on patient report or overt presentation of customary symptoms, which is still a common practice in primary care, will not be effective for all individuals. Rather, our results support the recommendation that universal screening for depression and anxiety be conducted [85]. Moreover, findings suggest the need for innovations to commonly used depression and anxiety screening tools in order to improve the detection of more precise symptom profiles that would lead to personalized treatment. For example, Computerized Adaptive Tests (CAT) for depression and anxiety use statistically derived algorithms to determine items that can capture multiple dimensions of a disorder with high precision [86]. CAT-based screening might assist in identifying specific symptom and severity profiles, even at subclinical levels. Assessment tools that enable more precise identification of symptom profiles could then improve outcomes by aligning interventions to target specific symptoms. Precision treatments based on symptom profiles have the potential to improve clinical and functional outcomes while also reducing inefficiencies and health care system costs.

Declaration of Interest Statement

The authors have no financial or other relationships relevant to the research reported in this article.

Acknowledgement/Funding

We are grateful to the National Network of Depression Centers (NNDC; Ann Arbor, MI) for the access they provided to their de-identified Mood Outcomes Program data and support for the study through a Momentum Grant. The NNDC played no role in the design of the analysis, interpretation of the results, or writing of this publication.

References

[1] Parker G, Brotchie H. Gender differences in depression. Int Rev Psychiatry 2010; 22:429–36.

[2] Rainville JR, Hodes GE. Inflaming sex differences in mood disorders. Neuropsychopharmacology 2019;44(1):184–99.
[3] Shi P, Yang A, Zhao Q, Chen Z, Ren X, Dai Q. A hypothesis of gender differences in self-reporting symptoms of depression: implications to solve under-diagnosis and under-treatment of depression in males. Front Psychiatry 2021;2021(12):589687. https://doi.org/10.3389/fpsyt.2021.589687.
[4] Dell'Osso B, Cafaro R, Ketter TA. Has bipolar disorder become a predominantly female gender-related condition? Analysis of recently published large sample studies. Int J Bipolar Disord 2021;9(1):3. https://doi.org/10.1186/s40345-020-00207-z.
[5] Di Benedetto MG, Landi P, Mencacci C, Cattaneo A. Depression in women: potential biological and sociocultural factors driving the sex effect. Neuropsychobiology 2024;83(1):2–16.
[6] Kropp DR, Hodes GE. Sex differences in depression: an immunological perspective. Brain Res Bull 2023;196:34–45.
[7] Labaka A, Goñi-Balentziaga O, Lebeña A, Pérez-Tejada J. Biological sex differences in depression: a systematic review. Biol Res Nurs 2018;20(4):383–92.
[8] Mohammadi S, Seyedmirzaei H, Salehi MA, Jahanshahi A, Zakavi SS, Dehghani Firouzabadi F, et al. Brain-based sex differences in depression: a systematic review of neuroimaging studies. Brain Imaging Behav 2023;17(5):541–69.
[9] Gaine ME, Jagodnik KM, Baweja R, Bobo WV, McGlade EC, Weiss SJ, et al. Targeted research and treatment implications in women with depression. Focus 2025;23(2):141–55.
[10] Hantsoo L, Jagodnik KM, Novick AM, Baweja R, di Scalea TL, Ozerdem A, et al. The role of the hypothalamic-pituitary-adrenal axis in depression across the female reproductive lifecycle: current knowledge and future directions. Front Endocrinol 2023;14:1295261. https://doi.org/10.3389/fendo.2023.1295261.
[11] Kofman YB, Selbe S, Szentkúti P, et al. Sex differences in psychopathology following potentially traumatic experiences. JAMA Netw Open 2024;7(2):e240201. https://doi.org/10.1001/jamanetworkopen.2024.0201.
[12] Altemus M, Sarvaiya N, Neill Epperson C. Sex differences in anxiety and depression clinical perspectives. Front Neuroendocr 2014;35:320–30.
[13] Cavanagh A, Wilson CJ, Kavanagh DJ, Caputi P. Differences in the expression of symptoms in men versus women with depression: a systematic review and meta-analysis. Harv Rev Psychiatry 2017;25(1):29–38.
[14] Marcus SM, Kerber KB, Rush AJ, Wisniewski SR, Nierenberg A, Balasubramani GK, et al. Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the sequenced treatment alternatives to relieve depression study. Compr Psychiatry 2008;49(3):238–46.
[15] Marcus SM, Young EA, Kerber KB, Kornstein S, Farabaugh AH, Mitchell J, et al. Gender differences in depression: findings from the STAR*D study. J Affect Disord 2005;87:141–50.
[16] Sabic D, Sabic A, Bacic-Becirovic A. Major depressive disorder and difference between genders. Mater Sociomed 2021;33(2):105–8.
[17] Vetter JS, Spiller TR, Cathomas F, Robinaugh D, Brühl A, Boeker H, et al. Sex differences in depressive symptoms and their networks in a treatment-seeking population – a cross-sectional study. J Affect Disord 2021;278:357–64.
[18] Halbreich U, Kahn LS. Atypical depression, somatic depression and anxious depression in women: are they gender-preferred phenotypes? J Affect Disord 2007;102:245–58.
[19] Kapfhammer HP. Somatic symptoms in depression. Dialog Clin Neurosci 2006;8:227–39.
[20] Kim JH, Cho MJ, Hong JP, Bae JN, Cho SJ, Hahm BJ, et al. Gender differences in depressive symptom profile: results from nationwide general population surveys in Korea. J Korean Med Sci 2015;30:1659–66.
[21] Weiss SJ, Flynn H, Christian L, Hantsoo L, di Scalea TL, Kornfield SL, et al. Symptom profiles of women at risk of mood disorders: a latent class analysis. J Affect Disord 2021;295:139–47.
[22] Parker G, Fletcher K, Paterson A, Anderson J, Hong M. Gender differences in depression severity and symptoms across depressive sub-types. J Affect Disord 2014;167:351–7.
[23] Seney ML, Sibille E. Sex differences in mood disorders: perspectives from humans and rodent models. Biol Sex Differ 2014;5(1):17. https://doi.org/10.1186/s13293-014-0017-3.
[24] Weiss SJ, Simeonova D, Kimmel M, Battle C, Maki, Flynn H. Anxiety and physical health problems increase the odds of women having more severe symptoms of depression. Arch Women's Ment Health 2016;19(3):491–9.
[25] Alexandrino-Silva C, Wang YP, Carmen Viana M, Bulhões RS, Martins SS, Andrade LH. Gender differences in symptomatic profiles of depression: results from the São paulo megacity mental health survey. J Affect Disord 2013;147(1-3):355–64.
[26] Rodgers S, Ajdacic-Gross V, Müller M, Hengartner MP, Grosse Holtforth M, Angst J, et al. The role of sex on stability and change of depression symptom subtypes over 20 years: a latent transition analysis. Eur Arch Psychiatry Clin Neurosci 2014;264:577–88.
[27] Ulbricht CM, Rothschild AJ, Lapane KL. The association between latent depression subtypes and remission after treatment with citalopram: a latent class analysis with distal outcome. J Affect Disord 2015;188:270–7.
[28] Steen OD, van Borkulo CD, van Loo HM. Symptom networks in major depression do not diverge across sex, familial risk, and environmental risk. J Affect Disord 2021;294:227–34.
[29] Choi KW, Kim YK, Jeon HJ. Comorbid anxiety and depression: clinical and conceptual consideration and transdiagnostic treatment. Adv Exp Med Biol 2020;1191:219–35.
[30] Demyttenaere K, Heirman E. The blurred line between anxiety and depression: hesitations on comorbidity, thresholds and hierarchy. Int Rev Psychiatry 2020;32(5-6):455–65.
[31] Lei H, Chen C, Hagiwara K, Kusumi I, Tanabe H, Inoue T, et al. Symptom patterns of the occurrence of depression and anxiety in a Japanese general adult population sample: a latent class analysis. Front Psychiatry 2022;13:808918. https://doi.org/10.3389/fpsyt.2022.808918.
[32] Sultson H, Murd C, Havik M, Konstabel K. Negative affect instability predicts elevated depressive and generalized anxiety disorder symptoms even when negative affect intensity is controlled for: an ecological momentary assessment study. Front Psychol 2024;15:1371115. https://doi.org/10.3389/fpsyg.2024.1371115.
[33] van Loo HM, Beijers L, Wieling M, de Jong TR, Schoevers RA, Kendler KS. Prevalence of internalizing disorders, symptoms, and traits across age using advanced nonlinear models. Psychol Med 2023;53(1):78–87.
[34] Groen RN, Ryan O, Wigman JTW, Riese H, Penninx BWJH, Giltay EJ, et al. Comorbidity between depression and anxiety: assessing the role of bridge mental states in dynamic psychological networks. BMC Med 2020;18(1):308. https://doi.org/10.1186/s12916-020-01738-z.
[35] Curran E, Rosato M, Ferry F, Leavey G. Prevalence and factors associated with anxiety and depression in older adults: gender differences in psychosocial indicators. J Affect Disord 2020;267:114–22.
[36] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13.
[37] Levis B, Benedetti A, Thombs BD, DEPRESSion Screening Data (DEPRESSD) Collaboration. Accuracy of patient health questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. BMJ 2019;365:l1476. https://doi.org/10.1136/bmj.l1476.
[38] Patel JS, Oh Y, Rand KL, Wu W, Cyders MA, Kroenke K, et al. Measurement invariance of the patient health questionnaire-9 (PHQ-9) depression screener in U.S. adults across sex, race/ethnicity, and education level: NHANES 2005–2016. Depress Anxiety 2019;36(9):813–23.
[39] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–7.
[40] Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: a systematic review and diagnostic meta-analysis. Gen Hosp Psychiatry 2016;39:24–31.
[41] Johnson SU, Ulvenes PG, Øktedalen T, Hoffart A. Psychometric properties of the general anxiety disorder 7-Item (GAD-7) scale in a heterogeneous psychiatric sample. Front Psychol 2019;10:1713. https://doi.org/10.3389/fpsyg.2019.01713.
[42] NCHS. National Center for Health Statistics. ICD-10 classification of mental and behavioral disorders; 2024 ⟨https://www.cdc.gov/nchs/icd/icd-10-cm/index.html⟩
[43] WHO. World Health Organization. ICD-10 classification of mental and behavioral disorders: clinical descriptions and diagnostic guidelines; 2024. ⟨https://www.who.int/classifications/classification-of-diseases⟩
[44] Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-suicide severity rating scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry 2011;168(12):1266–77.
[45] Bjureberg J, Dahlin M, Carlborg A, Edberg H, Haglund A, Runeson B. Columbia-suicide severity rating scale screen version: initial screening for suicide risk in a psychiatric emergency department. Psychol Med 2021;52(16):1–9.
[46] Madan A, Frueh BC, Allen JG, Ellis TE, Rufino KA, Oldham JM, et al. Psychometric reevaluation of the Columbia-suicide severity rating scale: findings from a prospective, inpatient cohort of severely mentally ill adults. J Clin Psychiatry 2016;77(7):e867–73.
[47] Costanza A, Baertschi M, Richard-Lepouriel H, Weber K, Berardelli I, Pompili M, et al. Demoralization and its relationship with depression and hopelessness in suicidal patients attending an emergency department. Int J Environ Res Public Health 2020;17(7):2232. https://doi.org/10.3390/ijerph17072232.
[48] Nguyen TD, Kowalec K, Pasman J, Larsson H, Lichtenstein P, Dalman C, et al. Genetic contribution to the heterogeneity of major depressive disorder: evidence from a sibling-based design using Swedish National Registers. Am J Psychiatry 2023;180(10):714–22.
[49] Lamers F, Bot M, Jansen R, et al. Serum proteomic profiles of depressive subtypes. Transl Psychiatry 2016;6:e851. https://doi.org/10.1038/tp.2016.115.
[50] Liu Y, Yieh L, Yang T, et al. Metabolomic biosignature differentiates melancholic depressive patients from healthy controls. BMC Genom 2016;17:669. https://doi.org/10.1186/s12864-016-2953-2.
[51] Poore HE, Watts AL, Friedman HP, Waldman ID. A broad internalizing dimension accounts for the genetic associations between personality and individual internalizing disorders. J Psychopathol Clin Sci 2022;131:857. https://doi.org/10.1037/abn0000782.
[52] Wang H, Wang M, Wang X, Feng T, Liu X, Xiao W. Complex associations between anxiety, depression, and resilience in a college student sample: a network analysis. Front Psychiatry 2025;16:1502252. https://doi.org/10.3389/fpsyt.2025.1502252 [PMID: 40438336; PMCID: PMC12117827].
[53] Wijnen J, Gordon NL, van 't Hullenaar G, Pont ML, Geijselaers MWH, Van Oosterwijck J, et al. An interdisciplinary multimodal integrative healthcare program for depressive and anxiety disorders. Front Psychiatry 2023;14:1113356. https://doi.org/10.3389/fpsyt.2023.1113356 [PMID: 37426091; PMCID: PMC10326275].
[54] Wu HS, Gao F, Given C. Living as a survivor: sleep disturbance, fatigue, depressive mood, and cognitive dysfunction after breast cancer treatment. Cancer Nurs 2023. https://doi.org/10.1097/NCC.0000000000001200.

[55] Laborde-Lahoz P, El-Gabalawy R, Kinley J, Kirwin PD, Sareen J, Pietrzak RH. Subsyndromal depression among older adults in the USA: prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. Int J Geriatr Psychiatry 2015;30(7):677–85.
[56] Kundakovic M, Rocks D. Sex hormone fluctuation and increased female risk for depression and anxiety disorders: from clinical evidence to molecular mechanisms. Front Neuroendocr 2022;66:101010. https://doi.org/10.1016/j.yfrne.2022.101010.
[57] Castagna PJ, Roye S, Calamia M, Owens-French J, Davis 3rd TE, Greening SG. Parsing the neural correlates of anxious apprehension and anxious arousal in the grey matter of healthy youth. Brain Imaging Behav 2018;12(4):1084–98.
[58] Florido A, Curtis VR, Pégard NC, Rodriguez-Romaguera J. Disentangling the neural circuits of arousal and anxiety-like behavior. Curr Top Behav Neurosci 2024. https://doi.org/10.1007/7854_2024_539.
[59] Seo D, Ahluwalia A, Potenza MN, Sinha R. Gender differences in neural correlates of stress-induced anxiety. J Neurosci Res 2017;95(1-2):115–25.
[60] Drioli-Phillips P, Oxlad M, LeCouteur A, Feo R, Scholz B. Men's talk about anxiety online: constructing an authentically anxious identity allows help-seeking. Psych Men Masc 2020;22(1):77–87.
[61] Fisher K, Seidler Z, King K, Oliffe J, Rice S. Men's anxiety: a systematic review. J Affect Disord 2021;295:688–702.
[62] Paulus DJ, Manning K, Hogan JBD, Zvolensky MJ. The role of anxiety sensitivity in the relation between anxious arousal and cannabis and alcohol use problems among low-income inner city racial/ethnic minorities. J Anxiety Disord 2017;48:87–94.
[63] Anker JJ, Kushner MG. Co-occurring alcohol use disorder and anxiety: bridging psychiatric, psychological, and neurobiological perspectives. Alcohol Res 2019;40(1):arcr.v40.1.03. https://doi.org/10.35946/arcr.v40.1.03.
[64] Mudie J. Substance use disorder and autonomic recovery. J Alcohol 2023. ⟨https://www.heraldopenaccess.us/journals/journal-of-alcoholism-drug-abuse-substance-dependence⟩ [Drug Ab, Sub Depend].
[65] Cummings CM, Caporino NE, Kendall PC. Comorbidity of anxiety and depression in children and adolescents: 20 years after. Psychol Bull 2014;140(3):816–45.
[66] Dong L, Freedman VA, Mendes de Leon CF. The association of comorbid depression and anxiety symptoms with disability onset in older adults. Psychosom Med 2020;82(2):158–64.
[67] Byansi W, Galvin M, Chiwaye L, Luvuno Z, Kim AW, Sundararajan R, et al. Adverse childhood experiences, traumatic events, and mental health among adults at two outpatient psychiatric facilities in Johannesburg, South Africa: a cross-sectional analysis. BMC Psychiatry 2023;23(1):581. https://doi.org/10.1186/s12888-023-05085-0.
[68] Wang SK, Feng M, Fang Y, Lv L, Sun GL, Yang SL, et al. Psychological trauma, posttraumatic stress disorder and trauma-related depression: a mini-review. World J Psychiatry 2023;13(6):331–9.
[69] Ploski JE, Vaidya VA. The neurocircuitry of posttraumatic stress disorder and major depression: insights into overlapping and distinct circuit dysfunction–a tribute to Ron Duman. Biol Psychiatry 2021;90(2):109–17.
[70] Smoller JW. The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. Neuropsychopharmacology 2016;41(1):297–319.
[71] Tafet GE, Nemeroff CB. The links between stress and depression: psychoneuroendocrinological, genetic, and environmental interactions. J Neuropsychiatry Clin Neurosci 2016;28(2):77–88.
[72] Negeri ZF, Levis B, y Sun, He C, Krishnan A, Wu Y, et al. Accuracy of the patient health questionnaire-9 for screening to detect major depression: updated systematic review and individual participant data meta-analysis. BMJ 2021;375. https://doi.org/10.1136/bmj.n2183.
[73] Gjerdingen D, Crow S, McGovern P, Miner M, Center B. Postpartum depression screening at well-child visits: validity of a 2-question screen and the PHQ-9. Ann Fam Med 2009;7(1):63–70.
[74] Kocalevent RD, Hinz A, Brähler E. Standardization of the depression screener patient health questionnaire (PHQ-9) in the general population. Gen Hosp Psychiatry 2013;35(5):551–5.
[75] Patel JS, Oh Y, Rand KL, Wu W, Cyders MA, Kroenke K, et al. Measurement invariance of the patient health questionnaire-9 (PHQ-9) depression screener in U.S. adults across sex, race/ethnicity, and education level: NHANES 2005–2016. Depress Anxiety 2019;36(9):813–23.
[76] Tibubos A, Otten D, Zöller D, et al. Bidimensional structure and measurement equivalence of the patient health questionnaire-9: sex-sensitive assessment of depressive symptoms in three representative German cohort studies. BMC Psychiatry 2021;21:238. https://doi.org/10.1186/s12888-021-03234-x.
[77] Bauer EA, Wilson KA, Phan KL, Shankman SA, MacNamara A. A neurobiological profile underlying comorbidity load and prospective increases in dysphoria in a focal fear sample. Biol Psychiatry 2023;93(4):352–61.
[78] Chen C. Recent advances in the study of the comorbidity of depressive and anxiety disorders. Adv Clin Exp Med 2022;31(4):355–8.
[79] Kunugi H, Hori H, Ogawa S. Biochemical markers subtyping major depressive disorder. Psychiatry Clin Neurosci 2015;69(10):597–608.
[80] Cartwright C, Gibson K, Read J, Cowan O, Dehar T. Long-term antidepressant use: patient perspectives of benefits and adverse effects. Patient Prefer Adherence 2016;10:1401–7. https://doi.org/10.2147/PPA.S110632.
[81] de Vries YA, Roest AM, Burgerhof JGM, de Jonge P. Initial severity and antidepressant efficacy for anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder: an individual patient data meta-analysis. Depress Anxiety 2018;35(6):515–22.
[82] Carvalho Silva R, Pisanu C, Maffioletti E, Menesello V, Bortolomasi M, PROMPT consortium, et al. Biological markers of sex-based differences in major depressive disorder and in antidepressant response. Eur Neuropsychopharmacol 2023;76:89–107.
[83] Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. Am J Psychiatry 2000;157(9):1445–52.
[84] Moderie C, Nuñez N, Fielding A, Comai S, Gobbi G. Sex differences in responses to antidepressant augmentations in treatment-resistant depression. Int J Neuropsychopharm 2022;25(6):479–88.
[85] US Preventive Services Task Force. Screening for depression and suicide risk in adults: US preventive services task force recommendation statement. JAMA 2023;329(23):2057–67.
[86] Collendani D, Barbaranelli C, Anselmi P. Fast, smart and adaptive: using machine learning to optimize mental health assessment and monitor change over time. Sci Rep 2025;15(1):6492. https://doi.org/10.1038/s41598-025-91086-w.