

Age and sex-related variability in the presentation of generalized anxiety and depression symptoms

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Abstract

Background: Generalized anxiety and depression are extremely prevalent and debilitating. There is evidence for age and sex variability in symptoms of depression, but despite comorbidity it is unclear whether this extends to anxiety symptomatology. Studies using questionnaire sum scores typically fail to address this phenotypic complexity.

Method: We conducted exploratory and confirmatory factor analyses on Generalized Anxiety Disorder (GAD-7) and Patient Health Questionnaire (PHQ-9) items to identify latent factors of anxiety and depression in participants from the Genetic Links to Anxiety and Depression Study ($N = 35,637$; 16–93 years). We assessed age- and sex-related variability in latent factors and individual symptoms using multiple logistic regression.

Results: Four factors of mood, worry, motor, and somatic symptoms were identified (comparative fit index [CFI] = 0.99, Tucker–Lewis Index [TLI] = 0.99, root mean square error of approximation [RMSEA] = 0.07, standardized root mean square residuals [SRMR] = 0.04). Symptoms of irritability (odds ratio [OR] = 0.81) were most strongly associated with younger age, and sleep change (OR = 1.14) with older age. Males were more likely to report mood and motor symptoms ($p < .001$) and females to report somatic symptoms ($p < .001$).

Conclusion: Significant age and sex variability suggest that classic diagnostic criteria reflect the presentation most commonly seen in younger males. This study provides avenues for diagnostic adaptation and factor-specific interventions.

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KEYWORDS

factor analysis, factor scores, GAD-7, genetic links to anxiety and depression study, heterogeneity, PHQ-9

1 | INTRODUCTION

Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are the most common psychiatric disorders worldwide (Kessler et al., 2005; Lim et al., 2018). Around 11% of the world's population experience clinically relevant symptoms within their lifetime (Lim et al., 2018) and they co-occur simultaneously or sequentially in 50%–80% of cases (Brown et al., 2001; Jacobson & Newman, 2017; Kroenke et al., 2007; Moffitt et al., 2007). MDD and GAD are heterogeneous conditions, meaning affected individuals can present with unique symptom combinations (Fried & Nesse, 2015a, 2015b). In research, questionnaire-derived sum scores are commonly used to identify cases or measure disorder severity (Fried & Nesse, 2015b; Jokela et al., 2019; Ohannessian et al., 2017). Sum scores are a symptom count, which assumes all symptoms equally and consistently contribute to a disorder (Fried & Nesse, 2015b). They also lack information on which symptoms are present for an individual and how those symptoms interact (Jokela et al., 2019). For instance, four underlying factors of generalized anxiety and depressive symptoms were identified in the UK Biobank: anxiety symptoms, psychomotor-cognitive impairment, neurovegetative states, and mood symptoms (Jermy et al., 2020). Exploring patterns of symptom co-occurrence instead of using sum scores may identify diagnostic subtypes of MDD, GAD, or their comorbid presentation, helping to refine diagnoses (Eeden et al., 2019).

The presentation of MDD symptoms varies across ages (Schaakxs et al., 2017). Older people have been shown to more often report somatic symptoms (Hegeman et al., 2012; Miloyan & Pachana, 2016; Schaakxs et al., 2017; Zhao et al., 2018). However, the age-dependent presentation of symptoms is difficult to detect using questionnaire-derived sum scores. While depression sum scores remain consistent across adulthood, older people are more likely to report fatigue, psychomotor agitation, and sleep problems,

whereas younger people are more likely to report irritability, concentration problems, and anxiety (Schaakxs et al., 2017). Similarly, endorsement of depression symptoms can vary by sex. Women are more likely to endorse somatic symptoms of fatigue, muscle tension, sleep problems, and appetite problems, whereas men are more likely to endorse suicidal ideation (Fried et al., 2014; Vesga-López et al., 2008). It is unclear whether symptom level age and sex variability extends to GAD symptomology. Given the use of brief measures of generalized anxiety and depression symptoms as the criteria for entry into the UK NHS Improving Access to Psychological Therapies (IAPT) service, it is important to understand how symptom presentations assessed by these measures might vary with age and sex.

1.1 | Aims

In the present study, we aim to (a) identify latent factors composed of MDD and GAD symptoms in participants from the Genetic Links to Anxiety and Depression (GLAD) Study and (b) assess how individual MDD and GAD symptoms and our identified factors were associated with age and sex.

2 | METHODS

2.1 | Study design

The GLAD Study is an ongoing study of anxiety and depression (Davies et al., 2019). Participants are recruited via an online platform from the general population and National Health Service organizations. Individuals above 16 years of age, living in the United Kingdom who have experienced depression or any anxiety disorder including

GAD, social anxiety disorder, panic disorder, agoraphobia, social phobia, and specific phobia are eligible. Participants complete the online questionnaire and donate a saliva sample. All participants provided full consent to take part and to the long-term storage of their data. Ethical approval was obtained from the London-Fulham Research Ethics Committee (REC reference: 18/LO/1218).

2.2 | Participants

Our analyses included 35,637 individuals who completed the online questionnaire before May 19, 2020 and had no missing data on age, sex, Generalized Anxiety Disorder (GAD-7), or Patient Health Questionnaire (PHQ-9). Participants reported their biological sex, ethnicity, highest education level, and mental health diagnoses. Age divided by 10 was used in analyses to aid odds ratio (OR) interpretation. Participants' age ranged from 16 to 93 years, with a mean of 38.1 years ($SD = 14.4$). The majority of the sample was female (79.6%), White (94.3%), and highly educated (Table 1). Overall, 88.2% of participants self-reported an MDD diagnosis and 76.6% a GAD diagnosis.

2.3 | Measures

2.3.1 | Depression and generalized anxiety symptoms

We measured current MDD symptoms with the PHQ-9 (nine items; Kroenke et al., 2001, 2010) and current GAD symptoms with the GAD-7 (seven items; Spitzer et al., 2006). These are commonly used self-report scales based on the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria (American Psychiatric Association, 2013). For both scales, individuals rated the frequency of symptoms experienced over the past 2 weeks. Items were rated on a four-point Likert-type scale with scores ranging from 0 (not at all) to 3 (nearly every day). All item scores were summed to create a severity sum score, with values ranging from 0 to 27 for the PHQ-9 and 0 to 21 for the GAD-7. Both scales were psychometrically valid with high test-retest reliability (GAD: $r = .83$; PHQ: $r = .84$), and internal consistency (GAD: $\alpha = .89$; PHQ: $\alpha = .83$; Löwe et al., 2008; Spitzer et al., 2006; Thorp et al., 2019).

2.4 | Statistical analyses

2.4.1 | Exploratory and confirmatory factor analyses

Polychoric correlation matrices were computed for all ordinal items (Hogado-Tello et al., 2008). To check for singularity/multicollinearity of items, the matrix was examined for values <0.30 and >0.90 . The matrix determinant, Bartlett's Test of Sphericity (Bartlett, 1950), Ordinal alpha (Gadermann et al., 2012), and the Kaiser-Meyer-Olkin

(KMO) statistic (Kaiser, 1974) were computed to assess whether the data were fit for exploratory factor analysis (EFA). Parallel analysis (Horn, 1965), Very Simple Structure (VSS; Revelle & Rocklin, 1979), and Velicer's Minimum Average Partial (MAP) criterion (Velicer, 1976) estimated the preliminary number of factors. See Supporting Information Material A and B.

EFA was performed in 70% of the sample using the weighted least squares method in the "psych" R package (Revelle, 2017), which is preferred for ordinal data (Forero et al., 2009; Lee et al., 2012). Factors were allowed to correlate using oblimin rotation. The following fit criteria indicated good fit: root mean square error of approximation (RMSEA) ≤ 0.05 , Tucker-Lewis Index (TLI) ≥ 0.95 , standardized root mean square residuals (SRMR) ≤ 0.05 , and a smaller Bayesian Information Criterion (BIC) relative to other models (Hu & Bentler, 1999). Items were retained in a factor for factor loadings of >0.3 and greater than loadings on all other factors. Where multiple models showed adequate fit, the model with factors that encompass the greatest number of items was chosen. To validate the EFA-derived model, confirmatory factor analysis (CFA) was conducted in the remaining 30% of the sample using the "lavaan" R package (Rosseel, 2012). Standardized fit statistics were interpreted (Hu & Bentler, 1999; Schreiber et al., 2006) and the comparative fit index (CFI) ≥ 0.95 was considered good fit. The CFA was computed in the full sample to provide overview fit statistics.

Two sensitivity analyses were conducted. First, items with a low loading (-0.3) on all factors were sequentially removed. If item removal did not substantially improve model fit, the item was retained. Second, the final model was computed for males and females separately to assess sex differences in factor structure.

2.4.2 | Age and sex-related variability generalized anxiety and depression

We conducted three sets of regression analyses with age and sex. First, we fitted linear regressions associating age/10 with PHQ-9 and GAD-7 sum scores while controlling for sex. Each item was transformed into a binary variable to indicate the presence or absence of the symptom; 0 was coded as no symptom, and 1–3 were coded as symptom present. Second, we fitted logistic regressions associating dichotomized symptoms with age per 10 years and sex. Sum scores were also controlled for, to assess only the occurrence of the individual symptom and account for cumulative symptom disorder severity (Schaakxs et al., 2017). For age, an OR > 1 indicated an association with being 10 years older and OR < 1 indicated an association with being 10 years younger. For sex, OR > 1 indicated an association with being female while an OR < 1 indicated an association with being male. Third, we regressed the CFA-derived factor scores on age and sex controlling for disorder severity, to identify symptom groups that may vary across age and between the sexes.

To investigate nonlinear relationships between age and generalized anxiety/depression symptoms, logistic regression models were computed using categorical age. Age was categorized into year groups of 16–23, 24–31, 32–39, 48–55, 56–63, and >64 to avoid a

TABLE 1 Demographic characteristics of the Genetics Links to Anxiety and Depression (GLAD) sample (N = 35,637)

	Male (N = 7265)		Female (N = 28372)		Total (N = 35637)	
	N	%	N	%	N	%
Age						
Mean (SD)	43 (14.58)		37 (14.16)		38 (14.41)	
Min	16		16		16	
Max	93		93		93	
Age-group						
16–25 years	1031	2.89	7210	20.23	8241	23.12
26–35 years	1582	4.44	7749	21.74	9331	26.18
36–45 years	1515	4.25	5162	14.48	6677	18.73
46–55 years	1633	4.58	4734	13.28	6367	17.86
56–65 years	1044	2.93	2637	7.40	3681	10.33
66–75 years	403	1.13	800	2.24	1203	3.37
76–85 years	52	0.15	74	0.21	126	0.36
86–95 years	5	0.01	6	0.02	11	0.03
Ethnicity						
White	6856	19.24	26781	75.15	33637	94.39
Mixed	138	0.39	743	2.08	881	2.47
Asian or Asian British	114	0.32	359	1.01	473	1.33
Black or Black British	32	0.09	143	0.40	175	0.49
Arab	8	0.02	25	0.07	33	0.09
Other	91	0.26	254	0.71	345	0.97
Highest education level						
GCSE/CSE	919	2.58	3385	9.50	4304	12.08
NVQ	690	1.94	2293	6.43	2983	8.37
A-levels	1463	4.11	6520	18.30	7983	22.41
University	3876	10.88	15114	42.41	18990	53.29
Self-reported diagnosis						
MDD ^a	6374	17.89	25037	70.26	31411	88.15
MDD only ^b	800	2.24	2915	8.18	3715	10.42
GAD ^a	5158	14.47	22143	62.13	27301	76.60
GAD only ^b	211	0.59	1030	2.89	1241	3.48
Anxiety disorder ^a	2121	5.95	8658	24.29	10779	30.24
Anxiety disorder only ^b	2027	5.69	8187	22.97	10214	28.66

Abbreviations: CSE, certificate of secondary education; GAD, generalized anxiety disorder; GCSE, general certificate of secondary education; MDD, major depressive disorder; NVQ, national vocational qualification.

^aIndividuals who reported the diagnosis regardless of comorbidities.

^bIndividuals who only reported that diagnosis with no comorbidities.

reduction in power. The middle group of 40–47 years was used as the reference group. Two post hoc sensitivity analyses were conducted. First, individuals who participated during the COVID-19 pandemic were excluded at three intervals: January 31, 2020 (first UK case; $N = 2456$), March 1, 2020 (higher awareness; $N = 1222$), and March 23, 2020 (first UK lockdown; $N = 342$). Second, regression analyses were replicated accounting for highest education level as a proxy for socioeconomic status in the model.

The false discovery rate (FDR) multiple testing correction was applied to all symptom and factor level analyses separately (Benjamini & Hochberg, 1995; see Supporting Information Material C). All analyses were conducted using R version 4.0.2. All R code can be found in <https://github.com/knthompson26/Age-sex-GAD7-PHQ9-GLAD>.

3 | RESULTS

3.1 | EFA

The item “Worrying too much about different things” was excluded from EFA due to a polychoric correlation of 0.92 with the item “Difficulty controlling worrying.” For information on item endorsement and correlation structure, see Supporting Information Material D. EFA in 70% of the sample ($N = 24,946$) showed a four-factor solution best fit the data (Table 2). The RMSEA was slightly above the recommended threshold (Hu & Bentler, 1999). All other fit statistics indicated good model fit. All factors included two to five items, factor correlations ranged from 0.42 to 0.72 and the four-factor model explained 70% of the variance in the data. We labeled the four factors according to the loaded items: *mood*, *worry*, *somatic*, and *motor symptoms* (Figure 1). Factors did not neatly split into GAD and MDD symptoms, for example, *motor symptoms* contained one symptom from both the PHQ-9 and GAD-7. Five and six-factor models showed slightly better fit; however, these solutions were unsuitable as they included factors with zero items given the loading cut-off of 0.3. See Table S1 for EFA results with all items.

Number of factors	df	RMSEA (≤ 0.06)	RMSEA 90% CI	TLI (≥ 0.95)	BIC	SRMR (≤ 0.08)	Cumulative variance	Minimum item loading
1	90	0.175	[0.174, 0.176]	0.736	67,991	0.09	0.56	15
2	76	0.126	[0.125, 0.127]	0.863	29,469	0.05	0.63	6
3	63	0.104	[0.102, 0.105]	0.907	16,359	0.04	0.67	0
4	51	0.076	[0.075, 0.078]	0.950	6907	0.02	0.70	2
5	40	0.055	[0.053, 0.057]	0.974	2665	0.02	0.72	0
6	30	0.040	[0.038, 0.042]	0.986	931	0.01	0.74	0

Note: The cut off for each statistic to signify “good” fit is listed in each header (Hu & Bentler, 1999). The model with the lowest BIC is preferred. Cumulative variance is given as an indicator of the variance explained between items by the number of factors in each model. The best fitting and chosen model is indicated in bold.

Abbreviations: BIC, Bayesian information criterion; df, degrees of freedom; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residuals; TLI, Tucker–Lewis fit index.

3.1.1 | EFA sensitivity analyses

Concentration problems and subsequently irritability (items with the lowest loadings) were dropped from the EFA in an attempt to improve model fit. This solution then showed only a very slight improvement, thus the full model was retained (Table S2). This model was then fitted separately in males and females to check for sex differences in factor loadings. In males, the concentration problems item loaded onto the somatic symptoms factor rather than the mood factor as seen in the full and female only model (Figure S5).

3.2 | CFA

The CFA model is predefined to that identified by EFA, which provides a more stringent test of model fit compared with EFA (Thompson, 2004). The CFA in the remaining 30% of the sample ($N = 10,691$) confirmed that the four-factor model fit the data well. The RMSEA (0.068, 95% confidence interval [CI]: 0.067, 0.091) was still slightly above the threshold for good fit (Hu & Bentler, 1999), although lower than that for the EFA. The TLI (0.993), CFI (0.994), and SRMR (0.046) all indicated good fit (Hu & Bentler, 1999). The CFA was then rerun in the full sample to provide an overall model (CFI = 0.99, TLI = 0.99, RMSEA = 0.07, SRMR = 0.04). Factor scores for each individual were computed from this final model and used in the latent factor regression analyses.

3.3 | Age and sex-related variation in generalized anxiety and depression

3.3.1 | Sum scores

Women reported higher depression and generalized anxiety sum scores compared with men. When controlling for sex, age was

TABLE 2 Model fit statistics for exploratory factor analysis of one to six factors in the Genetic Links to Anxiety and Depression (GLAD) sample ($N = 35,637$; 15 items)

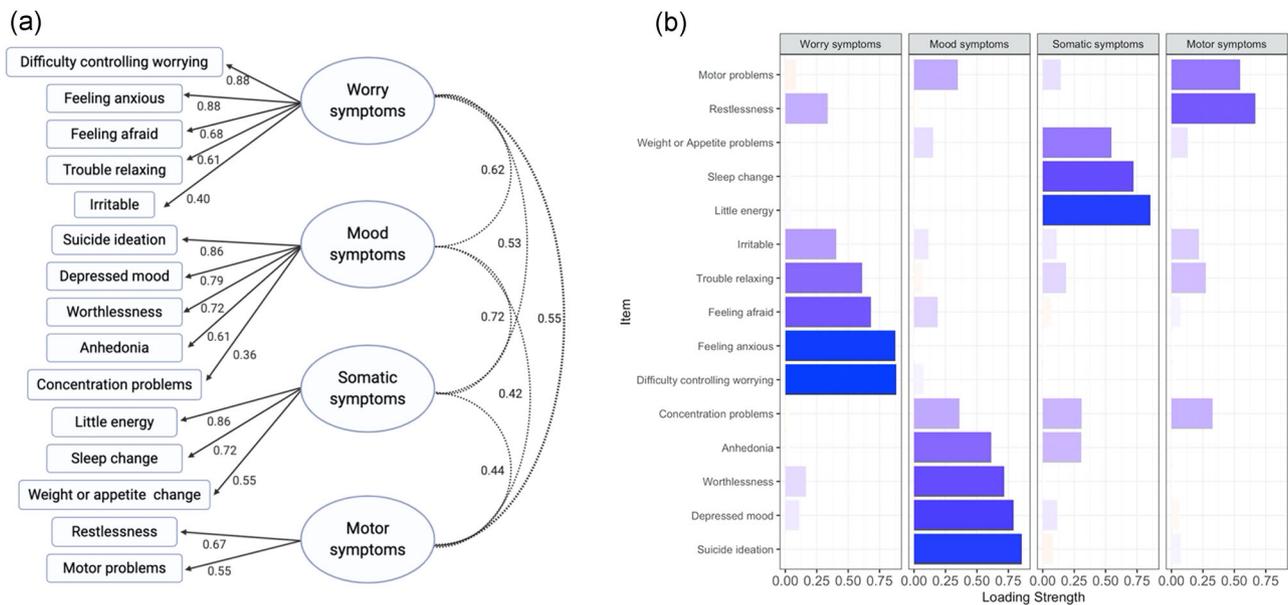


FIGURE 1 Exploratory factor analysis of GAD-7 and PHQ-9 items in the Genetic Links to Anxiety and Depression (GLAD) Study ($N = 35637$; 15 items). (a) The path diagram, item factor loadings, and between-factor correlations for the four factors of worry symptoms, mood symptoms, somatic symptoms, and motor symptoms are shown. (b) The loading strength for every item on each of the identified factors are shown. Dark blue indicates a positive factor loading, white indicates no factor loading, and red indicates a negative factor loading. GAD-7, Generalized Anxiety Disorder; PHQ-9, Patient Health Questionnaire

significantly associated with a 0.95 lower PHQ-9 ($p < .001$) and a 0.98 lower GAD-7 sum score ($p < .001$).

3.3.2 | Individual symptoms

Eight symptoms were associated with younger age and four with older age, when controlling for sex, generalized anxiety severity and depression severity (Figure 2a). Irritability and suicide ideation were most strongly associated with younger age, followed by restlessness, weight/appetite problems, motor problems, little energy, feeling anxious, and concentration problems. Sleep change was most strongly associated with older age, followed by difficulty controlling worrying, worrying too much and trouble relaxing. See Table S3 for full OR and CI values.

More symptoms were associated with being male than female (Figure 2a). Weight/appetite problems, little energy, sleep change, difficulty controlling worrying, and worrying too much were more likely endorsed by females, while suicide ideation, anhedonia, depressed mood, restlessness, worthlessness, concentration problems, and motor problems were more likely endorsed by males. See Table S3 for full OR and CI values.

These associations were replicated using categorical age groups. Categorical age measurement also identified symptom occurrence that cannot be captured by continuous age. Individuals who were 16–23 or over 64 years were less likely to report concentration problems, little energy, trouble relaxing, weight or appetite problems and worthlessness (Figure S6). This suggests a nonlinear relationship, where individuals of middle age are more likely to report these symptoms.

3.3.3 | Latent factors

Table 3 displays age and sex associations with each symptom categorized by the four corresponding factors. When controlling for sex, generalized anxiety severity and depression severity, younger age per 10 years was significantly associated with 0.008 lower motor symptoms ($p < .001$), and with 0.003 lower somatic symptoms ($p < .001$; Figure 2b). When controlling for age, generalized anxiety severity and depression severity, males were more likely to report mood ($\beta = -.04$, $p < .001$), and motor symptoms ($\beta = -.02$, $p < .001$), while females were more likely to report somatic symptoms ($\beta = .06$, $p < .001$; Figure 2b).

As expected, the derived factor scores were highly correlated with GAD-7 and PHQ-9 sum scores (Figure S7). In post hoc sensitivity analyses, regressions were computed without controlling for GAD-7 and PHQ-9 severity sum scores. We observed similar associations for sex, but younger age was associated with all factors (Figure S8). This is likely due to the over-representation of younger individuals in the GLAD sample; thus, the original model was retained.

3.4 | Post hoc sensitivity analyses

Neither excluding participants who had answered either the GAD-7 or the PHQ-9 during the pandemic nor including educational attainment as a covariate led to a substantial change of any of our results as effect sizes across models were highly similar and confidence intervals overlapped (for details, see Tables S4–S12).

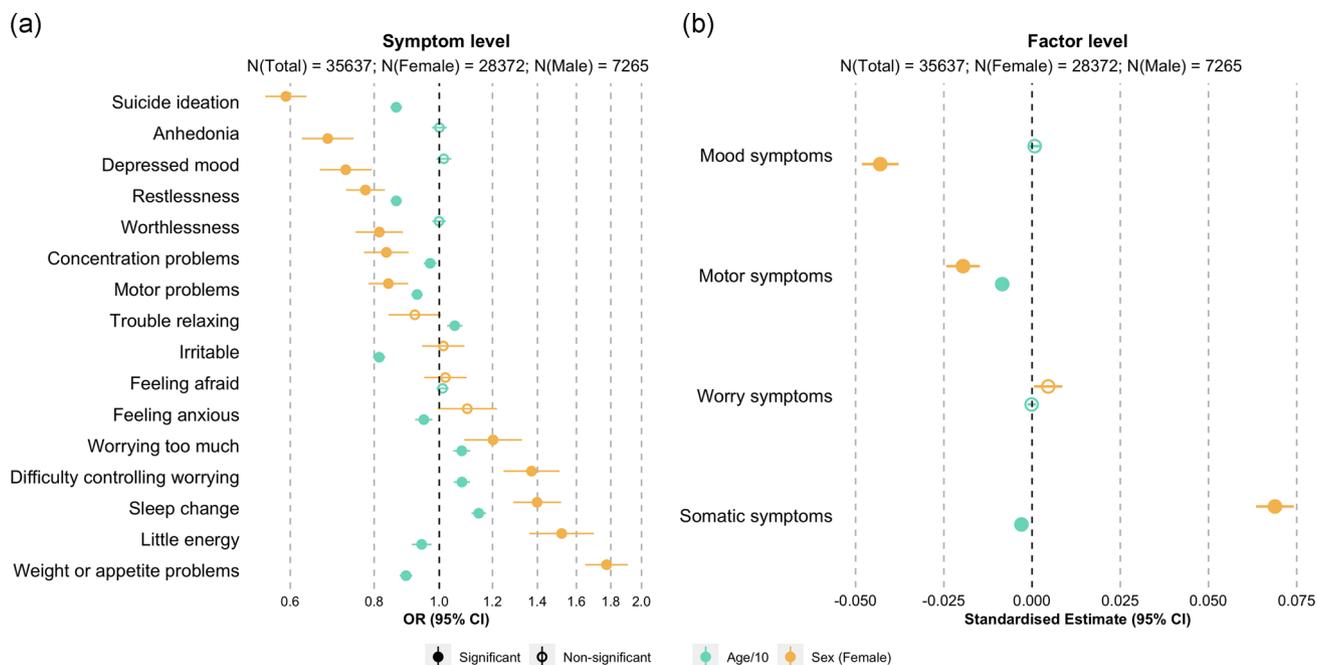


FIGURE 2 Age- and sex-related variation in generalized anxiety and depression in the Genetic Links to Anxiety and Depression (GLAD study; $N = 35,637$). (a) Odds ratios (OR) and 95% confidence intervals (CI) for the association between all GAD-7 and PHQ-9 items and age (per 10 years) in blue and sex in yellow are shown. (b) Standardized estimates and 95% confidence intervals for the association between four factors of GAD-7 and PHQ-9 symptoms and age (in blue) and sex (in yellow) are shown. For age, points on the right of each panel indicate an association with older age per 10 years and points to the left indicate an association with younger age per 10 years. For sex, points to the right of each panel indicate an association with being female, to the left indicate an association with being male. Filled circle points indicate significant associations while accounting for multiple testing using FDR correction. Transparent circle points indicate nonsignificant associations while accounting for multiple testing using FDR correction. GAD-7, Generalized Anxiety Disorder; FDR, false discovery rate; PHQ-9, Patient Health Questionnaire

4 | DISCUSSION

Generalized anxiety and depressive symptoms in 35,637 GLAD participants were represented by a four-factor model of mood, worry, somatic, and motor symptoms that varied by age and sex. The mood factor was associated with being male, with corresponding symptoms of suicide ideation and concentration problems more likely reported by younger men. The motor factor and corresponding symptoms were also more likely reported by younger men. The worry factor showed no association with age or sex. However, its corresponding symptoms of feeling anxious and irritable were more often reported by younger participants, trouble relaxing by older participants, and difficulty controlling worrying by older women. The somatic factor was associated with being young and female, consistent with its symptoms of little energy and weight/appetite problems. However, sleep change was more likely to be reported by older women. Overall, individual symptoms provide more information on age variation in symptom occurrence, whereas sex variation is apparent across both individual symptoms and factors.

Similar to previous work on generalized anxiety and depressive symptomatology (Ballard et al., 2018; Beard & Björgvinsson, 2014; Clark & Watson, 1991; Kertz et al., 2013), our four-factor model demonstrates that these are not two distinct underlying constructs. Importantly, we replicated the generalized anxiety and depression

factor structure identified in the UK Biobank (Jermy et al., 2020) in a separate, large, and clinically relevant cohort. Thus, our findings demonstrate the need to address the appropriateness of current diagnostic classifications. One difference between our findings and those from the UK Biobank was that they found concentration problems loaded onto the motor factor; we found this for men only. This could suggest two things: First, there are sex differences in the occurrence of concentration problems and the GLAD Study factor representation reflects a more female picture of generalized anxiety and depression. Second, a cognitive factor of depression and/or generalized anxiety symptomatology may exist that is not captured by the questions comprising both the PHQ-9 and the GAD-7 (LeMoult & Gotlib, 2019).

Our study replicates research that shows variation in depression symptoms across age and sex, that is not captured by sum scores (Fried et al., 2014; Schaakxs et al., 2017), and extends this by providing evidence for similar trends in generalized anxiety symptomatology. Men were more likely to report all motor and mood symptoms. This includes the two main DSM-5 MDD symptoms of depressed mood and anhedonia, which suggests that classic diagnostic criteria reflect presentation most commonly seen in younger men. One contributor could be that men are more likely to have lower perceived social support than women, which has been associated with higher risk of anhedonia, depressed mood, worthlessness, and suicidal ideation (Jokela et al., 2019). In our study, women were

TABLE 3 Age and sex-related variability in the four factors of Generalized Anxiety Disorder 7-item (GAD-7) and Patient Health Questionnaire-9 (PHQ-9) symptoms in the Genetic Links to Anxiety and Depression (GLAD) Study ($N = 35,637$)

Factor	Age variability	Sex variability	Symptom	Age variability	Sex variability
Mood symptoms	-	M	Suicide ideation	↓	M
			Depressed mood	-	M
			Worthlessness	-	M
			Anhedonia	-	M
Worry symptoms	-	-	Difficulty controlling worrying	↑	F
			Feeling anxious	↓	-
			Feeling afraid	-	-
			Trouble relaxing	↑	-
			Irritable	↓	-
Somatic symptoms	↓	F	Little energy	↓	F
			Sleep Change	↑	F
			Weight or appetite problems	↓	F
Motor symptoms	↓	M	Restlessness	↓	M
			Motor problems	↓	M

Abbreviations: ↑, associated with greater age; ↓, associated with younger age; - no association; F, associated with being female; M, associated with being male.

more likely to report somatic symptoms, consistent with previous findings (Fried et al., 2014). We found that the association between sex and reporting somatic symptoms varied with age, contrary to previous research which found older people were more likely to experience somatic depression symptoms (Hegeman et al., 2012; Schaakxs et al., 2017). Our findings show that older women were more likely to report sleep change and younger women were more likely to report little energy and weight/appetite problems. Sleep problems in older adults could be partly secondary to age-related physical processes (Foley et al., 2004; Smagula et al., 2016), as the circadian system, sleep homeostatic mechanisms, and sleep-related hormone secretion change with advancing age (Li et al., 2018). In our study, age and sex had no association with the worry factor. However, individual symptoms loading on the worry factor differed by age and sex: younger people reported feeling anxious and irritable, whereas older women worried too much and had difficulty controlling their worrying. This replicates findings that older individuals worry about health-related problems (Basevitz et al., 2008; Gonçalves & Byrne, 2013) and worry-related anxiety symptoms could be enhanced by the occurrence of somatic sleep problems in older age (Gould et al., 2016; Lenze et al., 2005). Our findings may have substantial implications for the IAPT service in the United Kingdom that provides psychological treatment for depression and anxiety

(Griffiths & Griffiths, 2015). IAPT uses GAD-7 and PHQ-9 sum scores to assess severity and ascertain which patients gain treatment. Understanding varying age and sex presentations in GAD-7 and PHQ-9 could benefit decision-making around who gains access to treatment.

Some study limitations merit acknowledgment. First, the majority of individuals were White, female, and highly educated. This slightly limits our interpretation of the finding that symptoms vary by sex. However, our sample size was large and our findings are based on more than 7000 male participants providing sufficient power to detect sex differences. Nevertheless, replication is needed in more ancestrally diverse samples (Bailey et al., 2019). Second, our analyses were cross-sectional and mood symptoms tend to decline over time whereas low levels of somatic symptoms persist (Eeden et al., 2019). Symptom profiles may vary with age and across the course of the disorder, requiring longitudinal data to better understand this. Third, participants reported severe levels of anxiety and depression (Davies et al., 2019). This could suggest men taking part have more severe symptoms due to the under-detection and under-reporting of milder forms of depression and anxiety by males (Albert, 2015). Fourth, the PHQ-9 and GAD-7 assess a limited range of symptoms; disorder heterogeneity would be better captured by more detailed scales. However, long questionnaires can lead to participant fatigue and, hence, missing data in large samples, requiring a considered balance

between detailed phenotyping and participating burden. Moreover, the PHQ-9 and GAD-7 do not assess the direction of symptom occurrence. For example, somatic symptoms such as appetite or sleep change, do not differentiate between less or greater appetite, or more or less sleep. Thus, older individuals could experience problems sleeping during the night, whereas younger individuals could sleep too much (Schaakxs et al., 2017). Finally, we do not address the multidimensionality in symptom presentations of other anxiety disorders, such as panic disorder and agoraphobia. Although the GAD-7 is considered an adequate screener for all anxiety disorders in the APTservice (Beard & Björgvinsson, 2014; Clark, 2011), more research is needed to explore age and sex variation in social anxiety disorder, panic disorder, agoraphobia, social phobia, and specific phobia with more specific questionnaires.

Our study highlights key next steps for generalized anxiety and depression research. Rather than using sum scores, future studies should account for symptom and factor level presentation of generalized anxiety and depression to gain an accurate reflection of symptom profiles and individual disability. Furthermore, adopting factors within the diagnostic framework may better represent individual burden and subsequently provide possible treatment avenues. Factor-level based scores rather than sum scores have been shown to increase precision in treatment response trajectories (Ballard et al., 2018). Investigating individual symptom presentation could also provide avenues for symptom-specific risk factors (Jokela et al., 2019), beneficial treatment types (Boschloo et al., 2019), and individual response to treatment (McElroy et al., 2019). For example, mood and somatic symptoms showed larger improvement from antidepressant medication compared with cognitive behavioral therapy (Boschloo et al., 2019). Our findings have important implications for young people, particularly young men. Not only are young men at higher risk of depressed mood and suicide ideation (Mackenzie et al., 2019) than women, but concentration problems and restlessness that they experience can negatively impact educational attainment and early career goals (Davies et al., 2018). However, our findings were independent of the education level of our participants. Our findings also provide avenues to better understand anxiety and depression in later life. Many standardized tools including the GAD-7 were designed for measurement in younger individuals (Bryant et al., 2008). Future research that incorporates age-appropriate symptoms would be particularly informative for tracking the longitudinal course of disorders and clinical use in older populations (Lenze et al., 2005).

5 | CONCLUSION

Our study provides new insights into underlying factors of generalized anxiety and depression symptoms. We identified four factors of mood, worry, somatic, and motor symptoms. Individual symptom and factor endorsement varied significantly dependent on the age and sex of the individual. The current study supports the utilization of individual symptoms or groups of symptoms over the commonly used sum score approach. The results provide possible avenues for

diagnostic improvement and treatment intervention by accounting for age- and sex-related variation in symptoms of generalized anxiety and depression.

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CONFLICT OF INTERESTS

Prof Breen has received honoraria, research or conference grants and consulting fees from Illumina, Otsuka, and COMPASS Pathfinder Ltd. Prof Hotopf is principal investigator of the RADAR-CNS consortium, an IMI public private partnership, and as such receives research funding from Janssen, UCB, Biogen, Lundbeck and MSD. Prof McIntosh has received research support from Eli Lilly, Janssen, and the Sackler Foundation, and has also received speaker fees from Illumina and Janssen. Prof Walters has received grant funding from Takeda for work unrelated to the GLAD Study. The other authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available to approved researchers, subject to registration and application process conducted by the GLAD Study. All R code for the current analyses is open access and can be found at <https://github.com/knthompson26/Age-sex-GAD7-PHQ9-GLAD>.

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