



Differential associations of depression and anxiety with stress-related biomarkers

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ABSTRACT

Background: A large body of research links depression and anxiety with markers of chronic stress, including cortisol dysregulation and systemic inflammation. However, it is unclear whether these associations reflect disorder-specific features or shared general distress, as diagnostic criteria and overlapping measures often conflate symptoms of both conditions.

Method: Using data from the MIDUS 2 and MIDUS Refresher studies (N = 1190; 806), we examined diurnal cortisol slope (DCS), C-reactive protein (CRP), interleukins (IL-6 and IL-10), tumor necrosis factor- α (TNF- α), and low-frequency heart rate variability (LF-HRV) in relation to Mood and Anxiety Symptom Questionnaire (MASQ) symptom dimensions: general distress (common to depression and anxiety), anhedonia (specific to depression), and anxious arousal (specific to anxiety).

Results: Across two large, population-based samples, anxious arousal predicted flatter DCS, higher CRP and IL-6, and lower LF-HRV, whereas anhedonia showed weaker and less consistent associations. Exploratory analyses using the Center for Epidemiologic Studies Depression Scale (CES-D), a widely used depression measure that also captures general distress and anxiety, replicated findings linking depression to biomarker dysregulation. However, the MASQ findings suggest that such associations may largely reflect anxiety-related arousal symptoms. Exploratory 10-year longitudinal analyses revealed bidirectional associations between anxious arousal and both flatter DCS and lower LF-HRV.

Conclusions: Findings suggest that there is overlooked nuance in research linking depression with cortisol, inflammation, and HRV. Depression measures might be confounded with anxiety symptoms, and the anxious arousal symptom cluster might be particularly strongly related to specific markers of chronic stress.

1. Introduction

Depression and anxiety are linked to chronic physical health conditions (Clarke and Currie, 2009). One likely mechanism underlying this association is stress-related physiological dysregulation. In particular, chronic hypothalamic-pituitary-adrenal (HPA)-axis hyperactivity and related systemic inflammation have been proposed as key mechanisms linking mood and anxiety disorders to physical health problems (Knezevic et al., 2023).

One widely used biomarker of HPA-axis activity is diurnal cortisol slope (DCS). Dysregulation of this rhythm often manifests as a flattened slope, reflecting a blunted decline across the waking day (Saxbe, 2008). Dysregulation can be heterogeneous, including both hypercortisolism and hypocortisolism, which may obscure associations when studies rely

on other cortisol measures, such as cortisol awakening response (CAR) or total daily output (Clow et al., 2010; Veen et al., 2011). Depressive subtypes have been found to correlate with different basal levels of cortisol, with atypical and recurrent depression linked to lower cortisol output, whereas melancholic and psychotic depression are linked to higher output (Booij et al., 2013; Juruena et al., 2018; Stetler and Miller, 2011). Empirical findings link flatter DCS to chronic stress and depression broadly defined—typically operationalized by self-report scales or clinical diagnosis (Adam et al., 2017). The sole meta-analysis examining the relationship between anxiety and DCS (Adam et al., 2017) reported a nonsignificant trend toward *steeper* slopes (possibly reflecting inclusion of both trait and state anxiety), while more recent findings align with theoretical expectations of flatter DCS in anxiety (Armer et al., 2018; Keefe et al., 2018; McCurdy et al., 2024). Given sparse, heterogeneous

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findings, the unique association between anxiety and DCS requires clarification.

Inflammatory biomarkers provide another indicator of stress-related dysregulation. A substantial literature links depression with elevated inflammatory markers, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) (Dowlati et al., 2010; Haapakoski et al., 2015; Osimo et al., 2020). As with cortisol, specific symptoms have been linked to inflammatory markers; for example, CRP and IL-6 have been specifically linked to anhedonic (Bekbbat et al., 2022) and atypical anergic symptoms (Zwiep et al., 2026). Some researchers have proposed that inflammatory dysregulation may characterize a distinct subtype of depression with inflammatory etiology (Kelly et al., 2021; Orsolini et al., 2022). Studies linking inflammatory markers to anxiety, however, are fewer and more equivocal (Costello et al., 2019; Glaus et al., 2018; Liukkonen et al., 2011). Some evidence suggests that these inconsistencies may reflect symptom heterogeneity, with stronger associations between inflammation and somatic symptoms than cognitive symptoms (Duivis et al., 2013). Evidence regarding interleukin-10 (IL-10) is also mixed, with some studies finding reduced IL-10 levels in generalized anxiety disorder and inverse associations with symptom severity (Hou et al., 2017; Sarmin et al., 2024). Overall, evidence supports an inflammation-depression link, while anxiety findings remain more limited.

Conceptual overlap between depression and anxiety complicates differentiation of their biomarker associations. Depression and anxiety are heterogeneous, highly comorbid, and bidirectionally related (Kelly et al., 2021; Watson, 2009), confounding interpretation of results based on clinical diagnoses and common depression measures, such as the Center for Epidemiologic Studies Depression Scale (CES-D), which include anxiety and general-distress items alongside depression-specific features. Thus, it is difficult to determine whether observed biomarker associations reflect depression, anxiety, or distress common to both. The tripartite model of depression and anxiety, and the Mood and Anxiety Symptom Questionnaire (MASQ) used to measure its dimensions, addresses this issue by distinguishing a common factor of general distress (GD, characterized by global negative affect), and disorder-specific dimensions of anhedonic depression (AD, reflecting lack of pleasure and interest) and anxious arousal (AA, representing somatic hyperarousal) (Clark and Watson, 1991).

Few studies have examined associations between MASQ symptom dimensions and stress biomarkers. Veen et al. (2011) found no associations between MASQ dimensions and diurnal decline, possibly due to a slope calculation that did not account for individual differences in sleep timing. By contrast, Doane et al. (2013) found GD and AA to be associated with flatter DCS when examined individually, but not when modeled simultaneously, possibly because including clinical diagnoses as simultaneous predictors introduced high conceptual overlap. In analyses of the Midlife in the United States (MIDUS) dataset, Rector et al. (2019) reported correlations between flatter DCS and several MASQ dimensions, but these analyses did not account for shared variance or isolate unique effects.

Research on MASQ dimensions and inflammatory markers is sparse, and symptom-specific findings in related studies have been mixed. Milaneschi et al. (2021) found that depression-specific symptoms positively predicted CRP and IL-6, whereas anxiety-specific and nonspecific somatic symptoms only predicted CRP. In contrast, Liukkonen et al. (2011) found elevated CRP in self-reported anxiety and comorbid depression/anxiety, but not in depression alone. In the MIDUS dataset, Zou et al. (2020) found that depression (assessed via CES-D) predicted higher CRP, whereas anxiety was unrelated to inflammatory markers. However, Zou et al. did not account for shared variance between disorders. These mixed findings underscore the need to disentangle common and unique associations of inflammatory markers with depression and anxiety, which may be obscured by measurement issues.

Taken together, the literature suggests cortisol and inflammatory dysregulation are associated with both depression and anxiety, although

evidence for anxiety is weaker. Findings regarding disorder specificity are limited and inconsistent, and prior studies are constrained by reliance on measures and diagnostic categories confounded by overlapping symptoms and comorbidity. The MASQ, designed to parse general distress from disorder-specific symptom dimensions, can help identify which biomarker associations reflect shared GD or are unique to AD or AA. However, few studies in this area have used the MASQ, and those that have did not test for unique effects.

In the current study, we examined associations between MASQ dimensions and stress biomarkers (DCS, CRP, IL-6, IL-10, and TNF- α) in the MIDUS dataset. Based on the larger literature linking depression with these biomarkers, we hypothesized that: (1) DCS would be more strongly associated with AD and GD than with AA; (2) CRP and IL-6 would be associated with AD and GD, but not AA; and (3) IL-10 would be negatively associated with AA.

We conducted three exploratory analyses to contextualize primary findings. First, we examined whether findings extended to another autonomic stress biomarker: low-frequency heart rate variability (LF-HRV), which has been linked to depression (Koch et al., 2019) and anxiety (Chalmers et al., 2014). Unlike HF-HRV, which reflects parasympathetic activity more narrowly, LF-HRV reflects combined PNS/SNS input and impaired baroreflex sensitivity (Laborde et al., 2017; Thomas et al., 2019)—capturing a broader range of autonomic dysregulation—and is a stronger predictor of mortality risk and poor health outcomes (McCrory et al., 2023). Second, to contrast our tripartite approach with common undifferentiated depression analyses, we regressed outcome variables on the CES-D (Radloff, 1977), a widely used measure that blends general distress, anxiety, and depression-specific symptoms (Fechner-Bates et al., 1994). Third, we conducted longitudinal analyses examining prospective associations between MASQ dimensions and stress biomarkers over approximately 10 years. Research in this area has more commonly conceptualized stress-related physiological dysregulation as contributing to psychopathology (Beurel et al., 2020). However, reciprocal pathways are also plausible, as psychological distress may itself promote chronic hyperarousal and alter health-related behaviors linked to obesity and chronic disease risk (Mac Giollabhui et al., 2021). Moreover, longitudinal evidence regarding associations between specific depression/anxiety symptom dimensions and stress biomarkers remains limited, particularly for DCS (Adam et al., 2017).

2. Methods

2.1. Participants

We used publicly available data from the MIDUS study, a national longitudinal study of health and well-being (<https://midus.colectica.org>). MIDUS 1 (1995–1997) recruited 7108 noninstitutionalized, English-speaking adults from the contiguous United States aged 25–74 via random-digit dialing, siblings, 5 metropolitan oversamples, and a national twin subsample (Brim et al., 1999). MIDUS 2 (M2; 2004–2009) reinterviewed 4963 participants from the original MIDUS cohort and added a 592-person sample of Black participants from Milwaukee (Ryff et al., 2007). Later waves analyzed included follow-up MIDUS 3 (M3; 2013–2019) and MIDUS Refresher (MR; 2011–2016), which recruited a new cohort of 3577 adults.

We analyzed data from the Daily Diary and Biomarkers subprojects (Supplementary Fig. S1). Daily Diary and Biomarkers recruited subsamples of MIDUS respondents who had completed the phone interview and self-administered questionnaire in the main survey. In M2 Daily Diary, 2022 participants completed daily phone interviews and self-collected salivary cortisol four times daily (Almeida et al., 2009). In M2 Biomarkers, 1255 participants completed biomarker, psychological, and health assessments during overnight clinic stays at UCLA, Georgetown University, or the University of Wisconsin (Dienberg Love et al., 2010). Comparable protocols were followed in the M3 and MR

projects. MIDUS procedures were approved by institutional review boards at participating universities, and participants provided informed consent prior to participation.

2.2. Measures

Participants completed the 62-item MASQ during the Biomarker subproject (Ryff et al., 2007). They rated how well items described their past-week experiences on a 1–5 (not-at-all–extremely) scale. MASQ subscales reflect tripartite model components: General Distress (GD), Anhedonic Depression (AD), and Anxious Arousal (AA). GD items consisted of both anxious and depressive symptoms. MIDUS split AD into Loss of Interest and reverse-scored High Positive Affect, which we recombined into standard scaling. Score ranges were 23–115 (GD), 22–110 (AD), and 17–85 (AA). Prior studies show high internal consistency in MASQ subscales (GD $\alpha = .95$, AD $\alpha = .95$, AA $\alpha = .88$; Keogh and Reidy, 2000). Consistent with theory, GD anxious and depressive symptom subscales are strongly correlated ($r = .69$), while AD and AA are weakly correlated ($r = .32$; Watson, 2009). Cronbach's α in MIDUS ranged from .81–.93 (M2), .74–.95 (M3), and .78–.93 (MR).

Biomarker participants also completed the 20-item CES-D (Ryff et al., 2007), self-rating depressive affect, positive affect (reverse scored), somatic complaints, and interpersonal functioning on a 0–3 (rarely-or-none-of-the-time–most-or-all-of-the-time) scale. MIDUS rescored items 1–4, yielding possible scores of 20–80. Internal consistency was high ($\alpha = .89$ in M2 and M3, .88 in MR).

Inflammatory biomarkers were collected by fasting blood draw. IL-6, IL-10, and TNF- α were assayed via immunoelectrochemiluminescence (V-plex Custom Human Cytokine Kit; MSD). Intra-assay CVs were 4.73% (IL-6), 5.78% (IL-10), and 3.19% (TNF- α), while inter-assay CVs were 5–15%, 11–14%, and 7% respectively. CRP was initially measured in plasma via immunonephelometric assay (BNII nephelometer; Dade Behring). Samples with CRP values below assay range were later re-assayed via high-sensitivity immunoelectrochemiluminescence assay (Meso Scale Diagnostics #K151STG). Later MIDUS waves exclusively assessed CRP with high sensitivity MSD-based serum assays, and CRP values were harmonized across assay methods within the public-use data. CRP inter-assay CVs were 2.1–5.7% for plasma assays and 4.72–5.16% for serum assays; intra-assay CVs were 2.3–4.4% and 2.2–4.1%, respectively (Ryff et al., 2025).

Salivary cortisol was self-collected four times daily on Daily Diary days 2–5 (T1 waking, T2 30 min post-waking, T3 pre-lunch, T4 bedtime). Participants logged collection times, mailed logs with samples, and reported times by phone. About 25% of participants also used “smart boxes” with chips recording opening and closing times. Instructions prohibited caffeine, food, and brushing teeth before collection. Samples were analyzed via luminescence immunoassay (Almeida et al., 2009). Because Daily Diary and Biomarkers subprojects were completed separately within MIDUS, there was a temporal lag between MASQ assessments and cortisol collection. In M2, the absolute median lag was 10 months (IQR = 7–16 months; absolute range = 2–56 months). In MR, absolute median lag was 14 months (IQR = 8–19 months; absolute range = 3–36 months). 38% of M2 participants and 24% of MR participants completed Daily Diary prior to Biomarkers.

HRV data were collected during the Biomarker psychophysiology protocol. Electrocardiogram recordings captured two 300-second (5-minute) resting baseline epochs. Interbeat (RR) intervals were corrected for artifacts, and LF-HRV was computed and log-transformed (Ryff et al., 2007).

2.3. Analytic strategy

The analytic plan was preregistered prior to conducting analyses (<https://doi.org/10.17605/OSF.IO/PNDR7>).

Individuals with CRP > 10 $\mu\text{g/mL}$ were excluded from inflammatory analyses to avoid confounding by acute infection (Glaus et al., 2018).

For cortisol, we required ≥ 2 days of valid data, excluding days with extreme waking times (<4AM or >11AM), duration (>20 h or <12 h), or bedtime values > 10 nmol/L above CAR (Dmitrieva et al., 2013). Cortisol values > 3 SD above the mean were treated as missing because extreme salivary cortisol values may indicate invalid samples or contamination rather than biologically plausible basal cortisol levels (Veen et al., 2011). Inflammatory values were winsorized to 3 SD to reduce the influence of extreme but biologically plausible values (Hartanto et al., 2021; Karlamangla et al., 2022). Both cortisol and inflammatory values were log transformed to reduce positive skew.

To investigate differential associations of MASQ dimensions with biomarkers, we regressed DCS and inflammatory markers on GD, AD, and AA, controlling for age, sex, and smoking status as reported by MIDUS. Outcomes were first regressed on individual subscales (simple effects) and then simultaneously (unique effects). DCS was computed as the mean daily T1–T4 slope across collection days, as T1–T4 is the most common operationalization and least sensitive to ultradian pulsatility and daily acute stress variation (Adam et al., 2017; Clow et al., 2010).

We evaluated robustness of preregistered analyses by testing consistency of effects across independent samples and model types, rather than formally correcting for multiple comparisons (cf. Perneger, 1998; Streiner and Norman, 2011). Individual results that did not replicate across samples or model types were interpreted cautiously; conversely, consistent directionality across samples and models was treated as potentially meaningful even when individual results fell just below conventional significance thresholds. Exploratory and post-hoc analyses were treated as primarily hypothesis-generating regardless of significance.

As a post-hoc robustness check of primary findings, we reran simple- and unique-effects regression models with additional covariates: BMI, number of chronic health conditions, and any NSAID use. BMI was included to facilitate cross-study comparisons, given its widespread use as a covariate (Howren et al., 2009; Luppino et al., 2010; Majd et al., 2020), although BMI is an imprecise proxy for relevant metabolic constructs, and its causal role in these associations is ambiguous (Nuttall, 2015; Tomiyama et al., 2016). The following chronic health conditions were included in the count if reported as diagnosed by a physician: heart disease, high blood pressure, circulation problems, blood clots, transient ischemic attack/stroke, anemia/blood disease, cholesterol problems, diabetes, asthma, emphysema/COPD, thyroid disease, cancer, arthritis, and cirrhosis/liver disease. For DCS analyses, any steroid use was also included as a covariate. Steroid use was not included in other analyses, as this variable was constructed from Daily Diary data and thus not available for most participants and not collected at the same time as other biomarkers.

To assess sensitivity of DCS findings to the temporal offset between MASQ assessment and cortisol collection (the only biomarker collected at a separate time point), we reran M2 DCS analyses in a subsample restricted to participants whose assessments fell within six months of each other ($N = 140$). Sensitivity analyses were not extended to MR due to insufficient power ($N = 34$).

For longitudinal analyses, M2 served as baseline (T1) and M3 as follow-up (T2, ~ 10 years later). We tested whether T1 MASQ scores predicted T1–T2 biomarker change and vice versa.

3. Results

3.1. Descriptive statistics

Descriptive statistics are provided in Table 1 for M2 and MR samples (10-year follow-up data for the M2 cohort show similar descriptive statistics). Sample sizes vary across individual regressions due to variable-specific missing data within individuals.

Table 1

Descriptive statistics for study variables and demographics.

	Cortisol Analyses			Inflammatory Analyses	
	M2 (N = 862)	MR (N = 296)		M2 (N = 1190)	MR (N = 806)
Age	55.5 (± 11.5)	47.8 (± 11.8)	Age	54.6 (± 11.7)	50.9 (± 13.5)
MASQ-GD	35 (± 10.3)	35.9 (± 9.9)	MASQ-GD	35.2 (± 10.6)	35.3 (± 10.3)
MASQ-AD	36.6 (± 12.9)	37.9 (± 12.5)	MASQ-AD	37.4 (± 12.8)	37.7 (± 12.9)
MASQ-AA	22.0 (± 5.3)	21.8 (± 4.9)	MASQ-AA	22.0 (± 5.5)	21.6 (± 5.0)
DCS	-0.80 (± 0.36)	-0.60 (± 0.24)	log CRP	0.13 (± 0.47)	0.08 (± 0.47)
			log IL-6	-0.08 (± 0.27)	-0.12 (± 0.26)
			log IL-10	-0.62 (± 0.24)	-0.62 (± 0.21)
			log TNF- α	0.32 (± 0.14)	0.30 (± 0.13)
Female	485 (56.3%)	156 (52.7%)	Female	663 (55.7%)	411 (51.0%)
Race			Race		
White	722 (83.8%)	249 (84.1%)	White	943 (79.2%)	573 (71.1%)
Black	108 (12.5%)	17 (5.7%)	Black	202 (17.0%)	150 (18.5%)
NA/AN	8 (0.9%)	5 (1.7%)	NA/AN	13 (1.1%)	16 (2.0%)
Asian	2 (0.2%)	4 (1.4%)	Asian	4 (0.3%)	12 (1.5%)
NH/PI	0 (0.0%)	0 (0.0%)	NH/PI	0 (0.0%)	2 (0.2%)
Other	20 (2.3%)	18 (6.1%)	Other	25 (2.1%)	50 (6.2%)
Hispanic	30 (3.5%)	10 (3.4%)	Hispanic	38 (3.2%)	28 (3.5%)
Current Smoker	100 (11.6%)	19 (6.4%)	Current Smoker	177 (14.9%)	82 (10.2%)

Note: Values are $M (\pm SD)$ for continuous variables and $n (\%)$ for categorical variables. DCS was computed from log-transformed cortisol values.

Abbreviations: M2 = MIDUS 2; MR = MIDUS Refresher; MASQ = Mood and Anxiety Symptom Questionnaire; GD = General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α ; NA/AN = Native American/Alaska Native; NH/PI = Native Hawaiian/Pacific Islander.

3.2. Primary analyses

We conducted simple and unique-effects regressions, controlling for age, sex, and smoking status (see Table 2).

3.2.1. Diurnal cortisol slope analyses

We hypothesized that DCS would be more strongly associated with GD and AD than AA, but we found the opposite: AA was the strongest predictor of flatter DCS in M2 and the only significant predictor in MR.

In simple-effects models, DCS was significantly positively associated with all MASQ subscales in M2, such that DCS was flatter in individuals with higher MASQ subscale scores; however, this relationship was strongest with AA. In the MR sample, AA was the only significant predictor of DCS, with higher AA scores again predicting flatter slopes.

In the M2 unique-effects model, all MASQ subscales were

significantly associated with DCS, and AA was the strongest predictor of flatter DCS. The direction of GD's association reversed, such that higher GD predicted steeper DCS when controlling for AD and AA. The only association that replicated in the MR sample was AA.

3.2.2. Inflammatory marker analyses

We hypothesized that CRP and IL-6 would be positively associated with GD and AD, but not AA. However, our results showed that AA also predicted higher CRP and IL-6. In M2, proinflammatory markers displayed the same pattern as with DCS, where AA was in fact the strongest predictor of higher CRP and IL-6.

In M2 simple-effects models, CRP was significantly positively associated with AA only. IL-6 was positively associated with GD and AA. TNF- α was positively associated with AA only. In MR, simple-effects models showed positive associations between each MASQ subscale

Table 2Simple and Unique Effects Models: Standardized β Coefficients.

	M2 predictors					MR predictors			
	MASQ-GD	MASQ-AD	MASQ-AA	N		MASQ-GD	MASQ-AD	MASQ-AA	N
Simple effects									
DCS	0.074*	0.109**	0.155***	862	0.090	0.061	0.150**	295	
CRP	0.011	0.056	0.070*	1176	0.088*	0.141***	0.141***	801	
IL-6	0.061*	0.054	0.123***	1182	0.117**	0.195***	0.193***	794	
IL-10	0.075*	0.031	0.067*	1182	−0.004	0.069	0.045	792	
TNF-α	0.041	0.053	0.085**	1182	0.036	0.066	0.055	796	
LF-HRV	−0.063*	−0.028	−0.085**	1142	−0.016	−0.063	−0.079*	665	
Unique effects									
DCS	−0.116*	0.108*	0.187***	862	−0.001	0.012	0.146*	295	
CRP	−0.120**	0.084*	0.118**	1176	−0.082	0.139**	0.141**	801	
IL-6	−0.061	0.034	0.151***	1182	−0.123*	0.197***	0.196***	794	
IL-10	0.070	−0.021	0.029	1182	−0.117*	0.110*	0.075	792	
TNF-α	−0.060	0.049	0.107**	1182	−0.037	0.069	0.053	796	
LF-HRV	−0.015	0.009	−0.078*	1142	0.101*	−0.082	−0.111*	665	

Note: Inflammatory biomarkers and LF-HRV were log transformed prior to analysis. DCS was computed from log-transformed cortisol values. Covariates included age, sex, and smoking status.

Abbreviations: M2 = MIDUS 2; MR = MIDUS Refresher; MASQ = Mood and Anxiety Symptom Questionnaire; GD = General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α ; LF-HRV = Low Frequency Heart Rate Variability.

* $p < .05$, ** $p < .01$, *** $p < .001$.

and CRP as well as IL-6, while TNF- α was not significantly associated with any MASQ subscales.

In the M2 unique-effects model, all subscales were significantly associated with CRP, with AA having the largest effect size, such that those higher in AA had higher CRP. Only AA predicted IL-6 and TNF- α , with higher AA predicting higher levels of both markers. In MR, higher AD and AA both predicted higher CRP and IL-6. No MASQ subscales uniquely predicted TNF- α .

We hypothesized that anti-inflammatory IL-10 would be negatively associated with AA, but this was not supported. In M2 simple-effects models, IL-10 was positively associated with GD and AA. In the M2 unique-effects model, IL-10 was not associated with any MASQ subscale. In MR, IL-10 was not associated with any MASQ subscales in simple-effects models but was positively associated with AD in the MR unique-effects model.

Across both samples, the direction of GD associations reversed in all significant unique-effects results, such that GD predicted lower CRP in M2 and lower IL-6 and IL-10 in MR when controlling for AD and AA—paralleling the sign reversal observed with DCS above.

3.3. Robustness checks

3.3.1. Additional covariate models

Robustness-check findings for HRV are reported alongside the original HRV results in 3.4.3. All other robustness-check outcomes are reported here and in Table 3.

In M2, adding BMI, chronic condition count, and NSAID use (and steroid use for DCS analyses) attenuated many primary findings. In simple-effects models, GD no longer predicted DCS or IL-6; AA continued to predict DCS but no longer significantly predicted CRP or IL-10, and its association with IL-6 dropped to trend level. In unique-effects models, the only associations remaining significant were DCS with AD and AA, although AA continued to predict IL-6 and TNF- α at the trend level.

In MR, primary findings were more robust to the additional covariates. In simple-effects models, AA remained a significant predictor of CRP and IL-6, and GD and AD associations with those markers largely held. In unique-effects models, AD and AA remained significant predictors of IL-6, and AA uniquely predicted CRP. AA–DCS associations

were attenuated to nonsignificance in simple- and unique-effects models; however, effect directions were unchanged.

Overall, AA associations with IL-6 were the most consistently robust across samples and model types. AA–DCS findings were robust in M2 and directionally consistent in MR.

3.3.2. Temporal lag sensitivity analyses

To test the sensitivity of DCS findings—the only biomarker collected at a different time point from MASQ assessments—we reran M2 DCS analyses in a subsample restricted to participants who completed cortisol collection and MASQ assessments within six months of each other ($N = 140$). In simple-effects models, AD remained a significant predictor of DCS ($\beta = 0.192, p < .05$), and AA predicted DCS at trend level ($\beta = 0.163, p < .1$). In unique-effects models, all MASQ subscales remained significant predictors of DCS (GD: $\beta = -0.311, p < .05$; AD: $\beta = 0.252, p < .05$; AA: $\beta = 0.306, p < .05$). We note that the ≤ 6 -month subsample was insufficiently powered in MR for parallel analyses ($N = 34$).

3.4. Exploratory analyses

3.4.1. Curvilinear analyses

We ran mean-centered quadratic regressions to test for curvilinearity in the associations between MASQ subscales and outcome variables (see Table 4). We found modest but significant U-shaped relationships between AD and IL-6 and IL-10 across simple and unique-effects models, such that higher levels of both IL-6 and IL-10 were observed at both low and high values of AD. These findings replicated in the MR sample.

3.4.2. Alternate depression measure

We regressed biomarker variables on CES-D total score to test whether a traditional measure of depression (which captures a blend of depression, general distress, and anxiety) is associated with biomarkers (see Table 5). In M2, higher CES-D total scores predicted flatter DCS, higher IL-6, and higher IL-10. In MR, higher CES-D predicted flatter DCS, higher CRP, and higher IL-6. Thus, in this sample, CES-D “depression” was related to cortisol and inflammatory markers.

Table 3
Simple and Unique Effects Models with Additional Covariates: Standardized β Coefficients.

	M2 predictors					MR predictors			
	MASQ-GD	MASQ-AD	MASQ-AA	N		MASQ-GD	MASQ-AD	MASQ-AA	N
Simple effects									
DCS	0.041	0.079*	0.099**	743	0.041	0.008	0.063	293	
CRP	−0.024	0.006	0.002	1170	0.056†	0.052†	0.089**	798	
IL-6	0.015	−0.003	0.051†	1176	0.086**	0.110***	0.137***	791	
IL-10	0.063*	0.016	0.045	1176	−0.009	0.056	0.034	789	
TNF-α	0.013	0.022	0.044	1176	0.027	0.028	0.027	793	
LF-HRV	−0.038	−0.001	−0.051†	1138	0.011	−0.008	−0.019	662	
Unique effects									
DCS	−0.089	0.091*	0.125**	742	0.025	−0.021	0.055	293	
CRP	−0.066	0.033	0.034	1170	−0.015	0.033	0.087*	798	
IL-6	−0.020	−0.013	0.068†	1176	−0.054	0.098**	0.138***	791	
IL-10	0.078†	−0.031	0.005	1176	−0.105†	0.096*	0.067	789	
TNF-α	−0.044	0.027	0.064†	1176	0.005	0.019	0.017	793	
LF-HRV	−0.027	0.028	−0.042	1138	0.049	−0.023	−0.042	662	

Note: Inflammatory biomarkers and LF-HRV were log transformed prior to analysis. DCS was computed from log-transformed cortisol values. Additional covariates: BMI, number of chronic health conditions, any NSAID use, and any steroid use (DCS analyses only), included alongside covariates from main analyses: age, sex, and smoking status.

Abbreviations: M2 = MIDUS 2; MR = MIDUS Refresher; MASQ = Mood and Anxiety Symptom Questionnaire; GD = General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α ; LF-HRV = Low Frequency Heart Rate Variability.

* $p < .05$, ** $p < .01$, *** $p < .001$, † $p < .10$.

Table 4
Curvilinear Simple and Unique Effects Models: Standardized β Coefficients.

M2 predictors									
	MASQ-GD	MASQ-GD ²	–	MASQ-AD	MASQ-AD ²	–	MASQ-AA	MASQ-AA ²	N
Simple effects									
DCS	0.00	0.11*		0.11**	0.01		0.12*	0.04	862
CRP	0.03	–0.03		0.07*	–0.03		0.10*	–0.05	1176
IL-6	0.07	–0.01		0.03	0.06*		0.14***	–0.02	1181
IL-10	0.04	0.06		–0.01	0.09**		0.04	0.03	1181
TNF-α	0.05	–0.01		0.05	0.00		0.05	0.05	1181
Unique effects									
DCS	–0.17**	0.10		0.12**	–0.03		0.17**	0.01	862
CRP	–0.09	–0.04		0.08*	–0.01		0.13**	–0.01	1176
IL-6	–0.04	–0.08		0.01	0.08*		0.15**	0.02	1181
IL-10	0.04	0.01		–0.03	0.07*		0.02	0.01	1181
TNF-α	–0.02	–0.09		0.05	0.02		0.05	0.10*	1181
MR predictors									
Simple effects									
DCS	0.09	0.00		0.04	0.07		0.20*	–0.07	295
CRP	0.06	0.03		0.14***	–0.01		0.14**	0.00	801
IL-6	0.08	0.06		0.17***	0.09*		0.18***	0.01	794
IL-10	–0.01	0.00		0.05	0.07*		0.04	0.01	792
TNF-α	0.01	0.03		0.05	0.06		0.05	0.01	796
Unique effects									
DCS	–0.01	–0.01		0.00	0.07		0.20*	–0.09	295
CRP	–0.11	0.05		0.14**	–0.02		0.15*	–0.02	801
IL-6	–0.16*	0.02		0.19***	0.08*		0.20***	–0.01	794
IL-10	–0.12	–0.04		0.10*	0.10*		0.07	0.00	792
TNF-α	–0.06	0.01		0.06	0.06		0.05	–0.01	796

Note: Squared terms (e.g., MASQ-GD²) represent quadratic effects. Inflammatory biomarkers were log transformed prior to analysis. DCS was computed from log-transformed cortisol values. Covariates included age, sex, and smoking status.

Abbreviations: M2 = MIDUS 2; MR = MIDUS Refresher; MASQ = Mood and Anxiety Symptom Questionnaire; GD = General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α .

* $p < .05$, ** $p < .01$, *** $p < .001$.

Table 5
CES-D Models: Standardized β Coefficients.

	M2 CES-D	N	MR CES-D	N
DCS	0.175***	862	0.136*	295
CRP	0.050	1173	0.142***	801
IL-6	0.112***	1179	0.196***	794
IL-10	0.084**	1179	0.033	792
TNF- α	0.055	1179	0.051	796
LF-HRV	–0.075**	1139	–0.064	664

Note: Inflammatory biomarkers and LF-HRV were log transformed prior to analysis. DCS was computed from log-transformed cortisol values. Covariates included age, sex, and smoking status.

Abbreviations: M2 = MIDUS 2; MR = MIDUS Refresher; CES-D = Center for Epidemiologic Studies Depression Scale; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α ; LF-HRV = Low Frequency Heart Rate Variability.

* $p < .05$, ** $p < .01$, *** $p < .001$.

3.4.3. Heart rate variability

We investigated whether the pattern of AA as the strongest biomarker predictor might generalize to another index of stress-related autonomic dysregulation by regressing log LF-HRV on MASQ subscales (see Table 2). Indeed, AA was the strongest predictor of lower LF-HRV in all M2 and MR models. AD did not significantly predict LF-HRV in either sample. We regressed LF-HRV on the CES-D model as well, and higher CES-D predicted lower LF-HRV in M2, while marginally predicting lower LF-HRV in MR. This again demonstrated that “depression” can predict biomarker outcomes when using a measure that includes symptoms overlapping with anxiety.

To assess robustness of primary LF-HRV findings, we reran regressions with additional covariates (BMI, chronic conditions count, and NSAID use), which are reported in Table 3. In these models, no associations remained significant, and AA predicted lower LF-HRV in M2 simple effects at the trend level.

3.4.4. Longitudinal analyses

Longitudinal analyses also highlighted AA as the MASQ dimension most associated with biomarkers (see Table 6).

We tested whether T1 biomarkers predicted T2 MASQ subscale scores while controlling for T1 MASQ subscale scores. In simple-effects models, flatter T1 DCS, higher CRP, and lower LF-HRV predicted increased AA 10 years later. In unique-effects models, lower LF-HRV predicted increased AA. T1 biomarkers did not predict change in AD.

We also tested the reverse direction—whether T1 MASQ subscale scores predicted T2 biomarkers while controlling for T1 biomarkers. In simple-effects models, higher T1 AD predicted a steeper T2 DCS, and both T1 GD and AA predicted decreased T2 LF-HRV. In the unique-effects model, higher T1 AA predicted flatter T2 DCS.

4. Discussion

A substantial body of research links depression to cortisol dysregulation and inflammation, but fewer studies have linked anxiety to these processes (Adam et al., 2017; Milaneschi et al., 2021). High comorbidity and nonspecificity in common symptom measures complicate efforts to disentangle specific associations with depression and anxiety symptoms. Depression measures and diagnoses often capture comorbid anxiety, and overlapping symptoms result in general distress saturating common assessments, which undermines diagnostic specificity (Kalin, 2020; Zbozinek et al., 2012). The MASQ addresses this problem by isolating disorder-specific factors and assigning items to subscales that load onto factors of general distress, depression-specific anhedonia, and anxiety-specific anxious arousal (Clark and Watson, 1991). By regressing stress-related biomarkers (DCS, CRP, inflammatory cytokines, LF-HRV) on MASQ subscales across two independent samples, we can disentangle shared and unique associations with depression and anxiety symptoms (Rector et al., 2019; Wardenaar et al., 2011).

We predicted that anhedonic depression and general distress symptoms would be the strongest predictors of DCS, CRP, and IL-6 due to the

Table 6
Longitudinal Simple and Unique Effects Models: Standardized β Coefficients.

M2 biomarkers predicting change in MASQ subscales (T1–T2)					M2 MASQ subscales predicting change in biomarkers (T1–T2)				
Simple effects									
Outcomes (M3)					Predictors (M2)				
	MASQ-GD	MASQ-AD	MASQ-AA	N		MASQ-GD	MASQ-AD	MASQ-AA	N
M2 DCS	0.02	0.02	0.11*	450	M3 DCS	−0.07	−0.11*	0.09	310
M2 CRP	0.05	0.05	0.09*	584	M3 CRP	0.03	0.04	0.03	585
M2 IL-6	0.03	0.01	0.02	586	M3 IL-6	0.05	0.04	0.01	587
M2 IL-10	−0.02	−0.02	−0.01	586	M3 IL-10	0.02	0.03	0.04	587
M2 TNF- α	0.00	0.04	0.02	586	M3 TNF- α	0.05	0.05	0.05	587
M2 LF-HRV	−0.07	−0.05	−0.10*	573	M3 LF-HRV	−0.09*	−0.01	−0.09*	432
Unique effects									
	MASQ-GD	MASQ-AD	MASQ-AA	N		MASQ-GD	MASQ-AD	MASQ-AA	N
M2 DCS	−0.03	0.01	0.06	450	M3 DCS	−0.10	−0.09	0.15*	310
M2 CRP	−0.01	0.02	0.05	584	M3 CRP	−0.01	0.05	0.02	585
M2 IL-6	0.01	0.01	−0.01	586	M3 IL-6	0.08	0.01	−0.05	587
M2 IL-10	−0.01	0.00	0.00	586	M3 IL-10	−0.04	0.03	0.05	587
M2 TNF- α	−0.02	0.04	0.00	586	M3 TNF- α	−0.01	0.05	0.04	587
M2 LF-HRV	−0.01	−0.02	−0.07*	573	M3 LF-HRV	−0.10	0.07	−0.05	432

Note: Inflammatory biomarkers and LF-HRV were log transformed prior to analysis. DCS was computed from log-transformed cortisol values. Covariates included age, sex, and smoking status.
Abbreviations: M2 = MIDUS 2; M3 = MIDUS 3; MASQ = Mood and Anxiety Symptom Questionnaire; GD = General Distress; AD = Anhedonic Depression; AA = Anxious Arousal; DCS = Diurnal Cortisol Slope; CRP = C-Reactive Protein; IL-6 = Interleukin-6; IL-10 = Interleukin-10; TNF- α = Tumor Necrosis Factor- α ; LF-HRV = Low Frequency Heart Rate Variability.
* $p < .05$, ** $p < .01$, *** $p < .001$.

preponderance of depression findings in the literature (Adam et al., 2017; Milaneschi et al., 2021; Saxbe, 2008; Zou et al., 2020), and the comparatively limited and inconsistent evidence for anxiety (Armer et al., 2018; Doane et al., 2013; Duivis et al., 2013; Glaus et al., 2018; Keefe et al., 2018; Liukkonen et al., 2011; McCurdy et al., 2024). However, our results suggested the opposite; across many biomarkers, anxious arousal was the most salient predictor. For DCS, AA was consistently associated with flatter slopes across all models in both samples, whereas the associations with GD and AD were weaker, less consistent, and did not replicate in MR. AA–DCS associations persisted in M2 post-hoc robustness analyses with additional covariates, while effects attenuated to nonsignificance in MR but remained consistent in direction. These findings suggest that anxiety-specific anxious arousal symptoms may be especially related to HPA-axis dysregulation.

Results regarding inflammatory markers were more heterogeneous than those for cortisol or HRV. Across samples, AA was most consistently associated with higher CRP and IL-6, whereas associations with TNF- α and IL-10 were weaker and less consistent. AD was not a consistent linear predictor of any inflammatory markers in M2, but predicted CRP and IL-6 comparably to AA in MR; curvilinear models showed replicated associations between AD and IL-6 and IL-10 across samples. TNF- α associations were especially inconsistent, with significant associations with AA in M2 failing to replicate in MR—a pattern that parallels less consistent TNF- α findings in the broader depression literature (Haapakoski et al., 2015). Post-hoc robustness analyses with additional covariates showed substantial attenuation of effect sizes; inspection of model results suggested BMI was a particularly influential covariate, consistent with its well-established associations with both inflammatory markers and affective symptoms. The most robust associations were with IL-6, where AA trended significant ($p < .1$) across models in M2, and where both AD and AA remained significant predictors across MR models. AA also remained a significant predictor of higher CRP in MR models but not M2. Given inconsistent prior findings regarding anxiety associations with inflammatory markers (Costello et al., 2019; Milaneschi et al., 2021), the replicated associations between AA and higher CRP and IL-6 across two national samples are noteworthy. More broadly, our findings suggest that commonly reported depression-inflammation associations may obscure important nuances when measures fail to discriminate anxious arousal symptoms from general distress and other

depression-specific symptoms.

Contrary to our hypothesis, AA did not reliably predict lower IL-10. If anything, the observed trend was weakly positive—consistent across samples and models, although only the M2 simple-effect model reached significance. Associations with GD and AD were similarly weak and inconsistent across samples. Our hypothesis was based on evidence from two small case-control studies finding lower IL-10 in patients with GAD compared to healthy controls and inverse associations between IL-10 and symptom severity (Hou et al., 2017; Sarmin et al., 2024). Differences in the present study’s design may explain our discrepant findings: the two prior studies relied on clinical diagnoses, employed case-control comparisons rather than continuous regressions, and tested associations in small clinical samples rather than in a broad population sample. The depression literature shows a similar pattern, with more consistent associations with CRP and IL-6 than with IL-10 or TNF- α (Dowlati et al., 2010; Osimo et al., 2020).

Across biomarkers and samples, the direction of GD associations consistently reversed in unique-effects models, suggesting that GD’s simple-effects associations reflect GD-AA covariance rather than an independent contribution of general distress. This is consistent with statistical suppression: when AA and AD are controlled, GD no longer reflects its covariance with AA, thus producing observed coefficient sign reversals. This pattern lends credence to our dimensional framework; biomarker associations commonly attributed to broad depression may be driven by specific symptom dimensions, with AA appearing to be the dominant contributor in many analyses.

We also found curvilinearity in inflammatory analyses. Both low and especially high AD consistently predicted elevated IL-6 and IL-10, while moderate AD predicted lower levels. This pattern, which replicated across samples, could reflect weakened immune response or behavioral withdrawal in moderate or early-stage depression, versus heightened immune dysregulation driven by impaired negative feedback in more severe/recurrent depression (Liu et al., 2019). This nonlinear pattern is consistent with growing evidence that the inflammation-depression link may be stronger within subtypes and may be obscured in analyses that do not account for within-disorder heterogeneity (Bekhhbat et al., 2022; Zwiep et al., 2026).

Our exploratory investigation of LF-HRV revealed a similarly striking pattern to that found in DCS and to a lesser extent inflammatory

markers. AA was again the strongest predictor of diminished LF-HRV, consistently across models and samples, whereas AD was not associated with LF-HRV. These effects attenuated to nonsignificance, but retained direction, in robustness-check models including a count of diagnosed chronic conditions. This raises the possibility that the AA construct may capture symptoms of chronic health conditions relevant to LF-HRV. Our results stand in contrast to meta-analyses finding no anxiety diagnosis to be associated with LF-HRV (Chalmers et al., 2014) and those finding lower LF-HRV in major depression relative to healthy controls (Koch et al., 2019). This discrepancy may reflect our use of dimensional predictors in a population sample rather than diagnostic comparisons of clinical samples and healthy controls, as well as the greater symptom specificity of the MASQ relative to diagnostic cut-offs that are likely confounded by overlapping symptoms and general distress.

Expanding on our same-wave results, longitudinal analyses showed a bidirectional relationship between AA and stress biomarkers. Although these results were less consistent and showed weaker associations, these associations are noteworthy given the ~10-year interval between predictors and outcomes and our procedure of controlling for T1 outcomes. Our results are somewhat consistent with prior literature showing that cortisol and inflammation can prospectively predict depression (Adam et al., 2017; Kelly et al., 2021; Mac Giollabhui et al., 2021; Valkanova et al., 2013) and anxiety (Glaus et al., 2018; Mac Giollabhui et al., 2025), and that psychopathology may contribute to later cortisol dysregulation (Doane et al., 2013) and higher inflammation (Copeland et al., 2012; Duivis et al., 2011).

Our results suggest that the well-established association between depression and stress biomarkers may obscure an important nuance: this link may be driven more by anxious arousal than by depressive symptoms. This potential misattribution reflects a common problem that depression measures and diagnostic criteria are confounded by anxiety and nonspecific distress. To illustrate, we conducted exploratory analyses using the widely used CES-D depression measure as the predictor. This approach provides a useful comparison, because it shows that if we had followed the common practice of using broad depression scales, we would have concluded that depression predicts DCS, inflammation, and HRV, consistent with much of the existing literature (e.g., Adam et al., 2017; Koch et al., 2019; Valkanova et al., 2013). Only after disaggregating symptoms into unique and common clusters does anxious arousal emerge as the strongest predictor of these biomarkers.

Perhaps it is not surprising that anxious arousal, which assesses symptoms of autonomic arousal (e.g., heart racing), would be particularly associated with biomarkers relating to autonomic dysregulation, such as cortisol and inflammation. Chronic SNS hyperactivity produces physiological strain (i.e., allostatic load) on the HPA axis by promoting glucocorticoid receptor resistance, which can impair adaptive cortisol regulation reflected in DCS blunting (McEwen, 2007). This glucocorticoid resistance may also weaken the anti-inflammatory effects of cortisol, contributing to sustained elevations in proinflammatory cytokines and chronic systemic inflammation (Knezevic et al., 2023). These processes may amplify symptoms directly related to autonomic activation, such as those assessed by anxious arousal, while also creating a reciprocal pathway through which anxious arousal symptoms could contribute to HPA-axis dysregulation and chronic systemic inflammation. This framework might also help clarify why comorbid depression and anxiety—or depressive presentations marked by anxious arousal—are consistently associated with poorer health outcomes and greater treatment resistance than depression alone (Fava et al., 2008).

Taken together, these findings contribute to a growing literature suggesting that the biological substrates of affective disorders, including neuroendocrine and inflammatory dysregulation, may align more closely with dimensional constructs than with categorical diagnostic boundaries (Morris et al., 2022). These findings also highlight anxious arousal as a potentially important target to mitigate the physiological burden linked to affective disorders.

Associations between stress biomarkers and anxious arousal—and to a lesser extent anhedonia—replicated across samples, and patterns emerged across biomarkers; however, effect sizes appeared modest. Additional robustness models controlling for BMI, chronic health conditions, and anti-inflammatory medication use showed further effect size attenuation, although key biomarker patterns remained. Nevertheless, such effect sizes are typical in population-level psychobiological research, where biomarker variance is associated with numerous interacting behavioral, medical, environmental, and genetic factors, and do not appear trivial when compared to relevant benchmarks (Funder and Ozer, 2019; Gignac and Szodorai, 2016). Moreover, heterogeneity in the expression and etiology of depression and anxiety may attenuate aggregate population-level effects that may be stronger within specific symptom clusters, biologically distinguishable disorder subtypes, nonlinear models, or other clinically meaningful subgroups (Kelly et al., 2021).

We note several limitations of our study. First, although the large MIDUS samples support generalizability to the U.S. population, Asian and Hispanic Americans are underrepresented. White Americans are overrepresented, and Black participants are mostly from the Milwaukee oversample, which may limit generalizability. Second, because the MASQ assesses *current* depression and anxiety, the effects of past psychopathology may be missed, leaving some shared variance with stress-related biomarkers unaccounted for. Third, for the same-wave analysis between DCS and the MASQ, there is a temporal gap (10-month median) between participant completion of the Daily Diary and Biomarkers subprojects in the MIDUS studies, with some participants completing DCS data prior to the MASQ and others vice versa. Such a length of time is sufficient for meaningful change in both psychological state and cortisol rhythm. However, sensitivity analyses restricted to participants whose assessments fell within six months revealed directionally consistent and if anything stronger associations, suggesting this temporal gap did not substantively distort findings. Moreover, the significant ~10-year longitudinal associations between AA and DCS suggest that these relationships may be durable over longer time periods, though effect sizes may differ in a truly simultaneous assessment. Fourth, cortisol, inflammatory markers, and HRV are only a subset of relevant stress-related biomarkers. While selected for their relevance to stress-related pathways linking affective disorders to chronic health conditions, they do not capture the full psychiatric metabolomic landscape in which inflammatory and neuroendocrine dysregulation is embedded (Cavaleri et al., 2026). We recommend that future studies examine differential associations between depression and anxiety with a broader range of biomarkers, including aggregated allostatic load indices and metabolomic profiles, to better elucidate both stress pathways and opportunities for diagnostic and treatment precision. Fifth, associations between affective symptom dimensions and inflammatory markers were substantially attenuated when adjusting for BMI, warranting further investigation of BMI's role in these associations. BMI is an imprecise proxy for relevant metabolic constructs; therefore, attenuation of associations when controlling for BMI should be interpreted cautiously. Future studies should formally test whether BMI may function as a confounder, mediator, or collider in these relations. Sixth, the AA subscale of the MASQ may capture somatic symptoms (e.g., heart racing) that can arise from medical conditions other than anxiety, which could independently drive both elevated AA scores and biomarker dysregulation. However, to the extent that AA symptoms—regardless of their source—consistently predict inflammation, cortisol dysregulation, and lower HRV, their association with stress biomarkers underscores their relevance to physiological burden. Future studies should examine whether these associations differ across specific medical conditions and anxiety disorder diagnoses, to better differentiate anxiety-specific effects of autonomic arousal. Finally, dimensional MASQ subscales do not map precisely onto clinical diagnoses of depression and anxiety. Thus, MASQ findings from a population sample may not generalize to clinical settings (Boschen and Oei, 2007). However, the MASQ may offer an

advantage over clinical diagnoses, which are likely confounded by comorbidity and symptom overlap, obscuring the unique contributions of distinct symptom dimensions. This advantage is evident in our findings, which identify autonomic arousal symptoms as one key link between psychopathology and stress-related physiological dysregulation.

5. Conclusion

We assessed how shared and disorder-specific symptom dimensions of depression and anxiety are differentially associated with chronic stress biomarkers. Across two large population-based samples, anxious arousal emerged as the most consistent predictor of flatter DCS, elevated inflammatory markers CRP and IL-6, and reduced LF-HRV, although effect sizes were modest and attenuated when controlling for BMI and other chronic health conditions. These results suggest that psychopathology symptoms related to autonomic arousal represent an important pathway linking affective disorders to physiological dysregulation. Our findings challenge us to look at the common finding of a depression-biomarker link with nuance, as some associations attributed to depression may reflect anxiety-spectrum symptoms embedded within broad depression measures and diagnostic categories, consistent with growing evidence that the biology of affective disorders better maps onto dimensional rather than categorical constructs.

CRedit authorship contribution statement

Yiqing Alice Fan: Writing – review & editing, Formal analysis, Data curation. **Evelyn Behar:** Writing – review & editing, Supervision. **Peter B. Fitzgerald:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Kathleen C. Gunthert:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of adherence to CPNEC's guideline for reporting analyses of big data repositories open to the public

- Prior publications using MIDUS by the authors.** The following manuscripts by the authors included analyses of MIDUS data: Fan, Y. A., Behar, E., Cohen, A. I., Law, C., & Gunthert, K. C. (under review). The relationship between daily stress and hot flashes in women of menopausal age. Fitzgerald, P. B., Fan, Y. A., Peterson, C., DelAngelo, M. H., & Gunthert, K. C. (under review). Longitudinal effects of anger expression on social support.
- Novelty of the current study.** The present study is distinct from prior work using MIDUS. It applied the tripartite model of depression and anxiety to examine differential cross-sectional and longitudinal associations of MASQ symptom dimension subscales with stress-related biomarkers, accounting for shared variance. Biomarkers analyzed included diurnal cortisol slope, inflammatory markers (CRP, IL-6, IL-10, TNF- α), and low-frequency heart rate variability. To our knowledge, no prior MIDUS studies have simultaneously examined these biomarker domains using MASQ subscales to test for differential and bidirectional longitudinal associations.
- Relationship to prior MIDUS studies.** Several prior studies using MIDUS data have examined associations between depression and anxiety variables and stress-related biomarkers. Rector et al. (2019) examined associations between cortisol indices and psychosocial factors but did not model unique effects of MASQ symptom dimensions. Zou et al. (2020) examined associations between depression (assessed via CES-D), anxiety (assessed via HADS-A), and inflammatory markers. However, their analyses did not apply a dimensional framework that separates general distress from disorder-specific symptom dimensions, nor did they model shared versus unique effects. Both of these studies are cited in the manuscript and are conceptually distinct from the present work, which applies the tripartite model to examine differential and bidirectional

longitudinal associations between symptom dimensions and multiple biomarkers across two MIDUS samples.

- Multiple testing considerations.** Our analytic approach was guided by theory and prior literature rather than exploratory variable selection. We focused on the consistency and replication of patterns across biomarkers, samples (MIDUS and MIDUS Refresher), and analytic approaches, rather than on individual statistically significant findings. This approach reduces the likelihood that findings reflect spurious associations arising from multiple testing.
- Use of AI-assisted technologies.** During manuscript preparation, the authors used ChatGPT (OpenAI) to assist with shortening and restructuring the introduction to align with journal requirements. All content changes were reviewed and curated by the authors, who take full responsibility for manuscript content.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with shortening and restructuring portions of the introduction to align with journal formatting requirements. The authors reviewed and revised all suggestions and retain full responsibility for the accuracy, interpretation, and content of the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psychneuen.2026.107958](https://doi.org/10.1016/j.psychneuen.2026.107958).

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