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Depressive symptoms, anxiety and social stress are associated with diminished cardiovascular reactivity in a psychological treatment-naive population

Xiao Liu [a,b,c,1], Weichun Lin [d,1], Jingjing Huang [a], Zhengyu Cao [a,b,c], Maoxiong Wu [a,b,c], Zhiteng Chen [a,b,c], Wengen Zhu [e], Ziqi Tan [f], Peng Yu [f], Jianyong Ma [g], Yangxin Chen [a,b,c], Yuling Zhang [a,b,c,*], Jingfeng Wang [a,b,c,*]

[a] Department of Cardiology, Sun Yat-Sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China
[b] Guangdong Province Key Laboratory of Arrhythmia and Electrophysiology, Guangzhou, China
[c] Guangdong Provincial Key Laboratory of Malignant Tumor Epigenetics and Gene Regulation, Guangdong-Hong Kong Joint Laboratory for RNA Medicine, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China
[d] Department of Gastroenterology, the Third Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China
[e] Department of Cardiology, the First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China
[f] Department of Endocrine, the Second Affiliated Hospital of Nanchang University, Jiangxi, China
[g] Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, United States

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ABSTRACT

Background: There is now an increasing appreciation of how psychological health can contribute to cardiovascular disease, called the mind-heart connection. A blunted cardiovascular reactivity to depression and anxiety may be responsible for the potential mechanism, however, with inconsistent results. Anti-psychological drugs have an effect on the cardiovascular system and, thus, may disturb their relationship. However, in treatment-naive individuals with psychological symptoms, no research has specifically evaluated the relationship between psychological state and cardiovascular reactivity.

Methods: We included 883 treatment-naive individuals who came from a longitudinal cohort study of Midlife in the United States. Symptoms of depression, anxiety, and stress were assessed by the Center for Epidemiologic Studies Depression Scale (CES-D), Spielberger Trait Anxiety Inventory (STAI), the Liebowitz Social Anxiety scale (LSAS) and the Perceived Stress Scale (PSS), respectively. Cardiovascular reactivity was measured using standardized, laboratory-based stressful tasks.

Results: Treatment-naive individuals with depressive symptoms (CES-D $\geq$ 16), anxiety symptoms (STAI $\geq$ 54), and higher stress levels (PSS $\geq$ 27) had lower cardiovascular reactivity as assessed by systolic blood pressure (SBP) reactivity, diastolic blood pressure (DBP) reactivity and heart rate (HR) reactivity ($P < 0.05$). Pearson analyses showed that psychological symptoms were correlated with lower SBP reactivity, DBP reactivity, and heart rate reactivity ($P < 0.05$). Multivariate linear regression showed that depression and anxiety were negatively related to lower cardiovascular reactivity (SBP, DBP and HR reactivity) after full adjustments ($P < 0.05$). Stress was associated with reduced SBP and DBP reactivity but with a nonsignificant association with HR reactivity ($P = 0.056$).

Conclusion: Depression, anxiety, and stress symptoms are associated with blunted cardiovascular reactivity in treatment-naive adult Americans. These findings suggest that blunted cardiovascular reactivity is an underlying mechanism linking psychological health and cardiovascular diseases.

* Corresponding authors at: Department of Cardiology, Sun Yat-Sen Memorial Hospital of Sun Yat-sen University, Guangzhou, China.
E-mail addresses: zhyul@mail.sysu.edu.cn (Y. Zhang), wjingf@mail.sysu.edu.cn (J. Wang).
[1] Co-first author.

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1. Introduction

The prevalence of psychological disorders is increasing worldwide and has become a global health concern (Berto et al., 2000; Trautmann et al., 2016). Evidence from epidemiological reports and meta-analyses suggests that depressive symptoms, anxiety, and stress are independent of conventional clinical risk factors for the incidence and development of cardiovascular diseases (Barefoot and Schroll, 1996; Carney et al., 1995; Allgulander, 2016; Anda et al., 1993), known as the "mind-heart connection". Although the underlying mechanisms of their association are still not thoroughly understood, at present, several underlying hypotheses have been proposed, such as the dysregulation of the autonomic nervous system, especially in response to stress, hyperactivity of the hypothalamic-pituitary-adrenal axis, and chronic proinflammatory states (Allgulander, 2016; Fiedorowicz, 2014). With regard to the dysregulation of the autonomic nervous system, there is a widely accepted hypothesis called the reactivity hypothesis, which states that repeated stress-related increases in cardiovascular function are assumed to accelerate a wear and tear on the artery walls, leading to endothelial dysfunction and linking depression to increased sympathetic activity, followed by a higher heart rate (HR) and decreased heart rate variability, ultimately contributing to cardiovascular diseases (Chida and Steptoe, 2010; Harris and Matthews, 2004; Schwartz et al., 2003; Kleiger et al., 1987; Krittayaphong et al., 1997).

Several studies have explored the relationship between psychological disorders and cardiovascular reactivity, especially depression. However, the results of these studies were inconsistent. A trial based on a small number of healthy women (N = 30) showed enhanced cardiovascular activity of depressive symptoms (Light et al., 1998). Several studies have also shown a positive association between depression and cardiovascular reactivity (Kleiger et al., 1987; Light et al., 1998; Matthews et al., 2005). However, their positive association was not found by some studies. In contrast, a potential negative correlation between mood disorders and cardiovascular reactivity was also reported (Carroll et al., 2007; Salomon et al., 2009; Guest et al., 2021).

In addition, some antipsychotics (e.g., tricyclic antidepressants) have well-known cardiovascular side effects (Licht et al., 2015; Serodio et al., 2014). A growing number of studies have also shown an established link between antipsychotics and cardiovascular risk. These results indicate that antipsychotics have a significant effect on cardiovascular reactivity (Licht et al., 2009). Frequently, it is not possible to reliably distinguish between the cardiovascular reactivity effects of antipsychotics and the effects of psychological disorders themselves, which disrupts the relationship between psychological status and cardiovascular reactivity. However, limited studies about the association between psychological disorders or symptoms and cardiovascular reactivity have focused on previously untreated individuals.

Herein, by using a large general population-based cohort, we aim to comprehensively assess the association between psychological status (including depression, anxiety, stress) and cardiovascular reactivity in treatment-naive individuals.

2. Methods

2.1. Study population

The Midlife in the United States (MIDUS) cohort, a national, longitudinal study including a sample of adults aged 34–84 years, was first performed in 1995–1996 to investigate the role of psychological, behavioral, and social factors on age-related differences in physical and mental health. The MIDUS II biomarkers' Projects is an additional biological assessment of the MIDUS study containing 1255 participants, including 666 drawn from the random digit dialing respondents, 388 from the twins' study and an additional 201 from a supplementary survey of new participants of African Americans from Milwaukee, Wisconsin. Demographic and psychosocial data were obtained using telephone interviews and self-administered questionnaires. More details of the study protocol are outlined elsewhere (Dienberg Love et al., 2010).

Our sample for analysis is based on participants who undertook the brief form of the reactivity protocol. We excluded patients with insufficient data (n = 234) to calculate cardiovascular reactivity (i.e., systolic blood pressure [SBP], diastolic blood pressure [DBP], or HR data for at least one baseline epoch and one stressor epoch [i.e., participants with responses to the Stroop, Morgan and Turner Hewitt (MATH) or Paced Auditory Serial Addition Test [PASAT] were included]). Then, we further excluded those (n = 13) who had incomplete data for psychological scores (i.e., Center for Epidemiological Studies-Depression [CES-D] score, Perceived Stress Scale [PSS], Liebowitz Social Anxiety [LSAS], Spielberger State Trait Anxiety Inventory [STAI] scores). Then, patients with physician-diagnosed psychological disorders and a history of psychotherapeutic therapy or anxiolytic or hypnotic medication (n = 125) were excluded. The final sample for analysis in our present study was 883.

The study received approval from the Institutional Review Board for each participating MIDUS center, and written informed consent was obtained from all participants.

2.2. Cardiovascular reactivity

Cardiovascular reactivity was measured in the MIDUS 2 Biomarker Project using cardiovascular responses to two stressor tasks: a mental arithmetic task (PASAT or MATH) and a Stroop color-word matching task. This protocol has been outlined in detail elsewhere (Carol and Ryff, 2017) and is shown in Fig. 1.

Briefly, participants sat quietly for 11 min at rest during the baseline period and then undertook the first cognitive stress task lasting 6 min. After a 6-min recovery period, they undertook the second cognitive stress task, which also lasted 6 min. The psychological stressors included the Stroop color/word interference task, a mental arithmetic task that was presented in random order. For the Stroop task, a word, either of a congruent or incongruent color (e.g., the word "red" written in red letters versus the word "green" written in black letters), was presented on a computer screen. Participants responded to the answer that corresponded to the color of the letters rather than the color name by using a keypad. For the MATH mental arithmetic task, participants were required to complete several subtraction and addition problems, which were presented on the screen, followed by the word "equals" and an answer to the problem. A key, corresponding to yes or no, was pressed by participants to indicate whether the answer was correct. During all tasks, participants wore a Finometer blood pressure cuff placed on the middle finger of the nondominant hand and a heart rate monitor. Blood pressure and pulse rate were recorded automatically two times during the baseline condition and two times during the stressor conditions. Heart rate was monitored continuously from the beginning to the end of each process. In our study, baseline heart rate and baseline blood pressure were calculated as the average of two baseline periods. For both heart rate and blood pressure, cardiovascular reactivity was calculated as the difference between the scores of the baseline level and subsequent stressor task. If one baseline score was missing, the available baseline score was used for both. The reactivity scores for each stressor task were averaged to create a mean reactivity score for heart rate, systolic blood pressure and diastolic blood pressure.

2.3. Exposure variable of this study

2.3.1. Center for Epidemiologic Studies Depression Scale

The presence of depressive symptoms was evaluated using the CES-D. This 20-item questionnaire assesses symptoms of depression over the past two weeks using a 4-point Likert scale. The CES-D has demonstrated excellent internal consistency, with a Cronbach's alpha of 0.894 in the MIDUS II biomarkers project (Dienberg Love et al., 2010). The

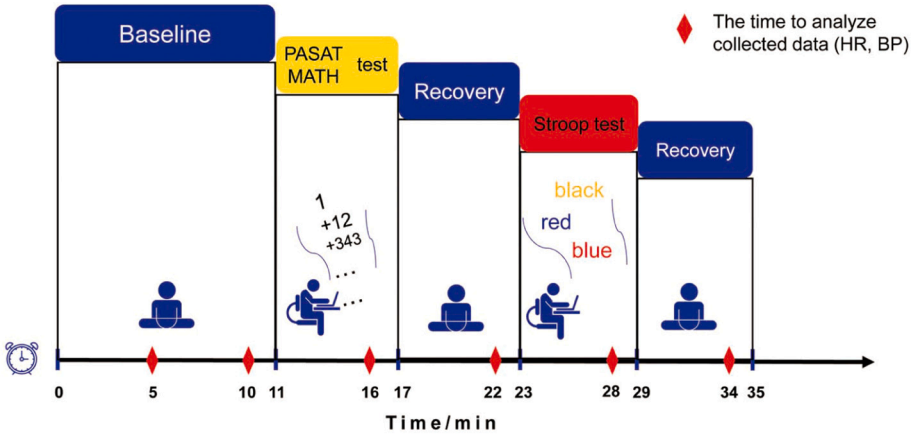

Fig. 1. Schematic illustration showing the trial protocol in the Midlife in the United States (MIDUS) study.
The general protocol order was as follows: participants sat quietly for 11 min resting at baseline and then undertook the first cognitive stress task, the mental arithmetic task (PASAT or MATH), lasting 6 min. After a 6-min recovery period, they undertook the second cognitive stress task (Stroop task), which also lasted 6 min. Finally, there was a 6-min recovery time. At each stage of the procedure, heart rate and blood pressure derived from electrocardiograph and finometer installed in the appropriate position on the participants were collected and analyzed every 5 min, twice during the 11-min baseline session and once for each subsequent six-minute session.
Abbreviations: BP, blood pressure; HR, heart rate; MATH, Morgan and Turner Hewitt; PASAT, Paced Auditory Serial Addition Test.

CES-D can be divided into four distinct factors: somatic symptoms, negative affect, positive affect, and interpersonal symptoms. Of these factors, three subscales – negative affect, somatic features, and interpersonal disturbances – are used to identify profiles of depressive symptoms. A higher score on each subscale indicates a higher degree of depressive symptoms. The cutoff for CES-D has been established as follows: a score of <16 indicates no presence of depressive symptoms (Liu et al., 2022), while a score of 16 or higher indicates the presence of such symptoms.

2.3.2. Spielberger Trait Anxiety Inventory

The STAI is a tool used to measure state and trait anxiety. The inventory consists of two forms: Form A (state questionnaire) and Form B (trait questionnaire). Each form includes a state scale, a trait scale, and a balanced scale. The state and trait scales are determined by asking respondents to rate themselves on 20 items that describe the presence or absence of anxiety (e.g., "I feel worried" vs. "I feel calm"). The items that reflect anxiety are referred to as negative items, while the items that reflect the opposite of anxiety are referred to as positive items. The balanced scale combines the reversed scores of positive items and the scores of negative items to arrive at an overall anxiety score. The Cronbach's alpha of the STAI in the MIDUS II biomarkers project was 0.908 (Dienberg Love et al., 2010). The cutoff value for the STAI has been established as follows: a score below 54 indicates the absence of anxiety symptoms, while a score of 54 or higher indicates the presence of such symptoms (Liu et al., 2022).

2.3.3. Liebowitz Social Anxiety scale

The LSAS used in the MIDUS cohort was adapted from the LSAS scale, which is a 24-item semistructured interview used to measure fear and avoidance in a variety of social and performance situations. The LSAS is widely considered the most popular and widely used measurement of social anxiety. In our study, a self-report version of the LSAS was used, consisting of 9 items that represent different social situations (e.g., talking to people in authority, going to a party, working while being observed). Participants were asked to rate their level of anxiety in each situation, with higher scores indicating a higher degree of social anxiety symptoms. The composite score for each item was calculated by averaging the responses. The Cronbach's alpha of the LSAS in the MIDUS II biomarkers project was 0.852 (Dienberg Love et al., 2010). The severity of anxiety in each situation was classified as follows: 1 "none", 2 "mild", 3 "moderate", and 4 "severe", as previously reported (Liu et al., 2022).

2.3.4. Perceived Stress Scale

The PSS is a 10-item questionnaire used to assess the level of stress experienced by participants. Each item asks about the frequency of a particular stress-inducing event (e.g., "In the past month, how often have you been upset because of something that happened unexpectedly?") and uses a 5-point scale, with higher scores indicating a higher degree of perceived stress. The scale was scored in a manner such that higher scores reflect greater perceived stress [$\alpha = 0.84$]. The Cronbach's alpha of the PSS in the MIDUS II biomarkers project was 0.864 (Dienberg Love et al., 2010). The levels of stress were categorized as follows: low (0–13), moderate (14–26), and high (27–40), as previously reported (Liu et al., 2022).

2.4. Control variables

Control variables were selected based on well-established relationships between cardiovascular reactivity and health. Race was coded as "Hispanic" or not. Education and marriage status were used as representatives of socioeconomic status. Education was coded as "high school or less" and "bachelor's degree or higher". Marriage status was coded as "unmarried" and "married" based on the current situation.

The remaining control variables included body mass index (BMI), calculated by dividing weight by height squared. Smoking status/drink status was coded as smoker/drinker or nonsmoker/nondrinker (former smokers/drinkers were categorized as nonsmokers/nondrinkers). Considering the known association between cardiovascular reactivity and several chronic conditions, a number of coexisting chronic conditions/diseases were included. The MIDUS 2 project collected a list of 20 medical conditions/illnesses, including heart disease, high blood pressure, circulation problems, blood clots, heart murmur, transient ischemic attack (TIA) or stroke, anemia or other blood disease, cholesterol problems, diabetes, asthma, emphysema/ chronic obstructive pulmonary disease (COPD), tuberculosis, positive TB skin test, thyroid disease, peptic ulcer disease, cancer, colon polyp, arthritis, glaucoma, and cirrhosis/liver disease.

2.5. Statistical analyses

The Kolmogorov–Smirnov test and Q-Q plots were used to analyze the normality of the data. Continuous variables are expressed as the mean ± standard deviation (M ± SD, normally distributed) and median (interquartile range [IQR], nonnormally distributed). Categorical variables were expressed as numbers (percentages). Pearson correlation analysis was conducted to calculate the correlation between cardiovascular reactivity and psychological scores. The association between cardiovascular reactivity and psychological scores was evaluated by multivariate linear regression analysis. Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 is adjusted for Model 2 plus age, sex, race, highest level of education, current marriage status, body mass index, smoking status, drinking status and the number of chronic conditions. The difference in cardiovascular reactivity scores between

participants with different levels of psychological scores was evaluated by group comparisons using Student's *t*-test or the Mann–Whitney *U* test. Furthermore, we performed extensive multivariate analyses with multiple imputation based on 5 replications and a chained equation approach method to maximize statistical power and minimize the bias of missing data. All analyses were performed using SPSS statistics version 26.0 (IBM Corp., Armonk, New York) or the R tool (version 4.0.1, R Foundation for Statistical Computing, Vienna, Austria). Graphic abstract was created with Biorender.com (Agreement number: WV251V7C3D). $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the study participants

Of the 1255 participants, we excluded those who did not complete the brief form of the reactivity protocol (n = 234) and those who had missing data for psychological scores (n = 13). Then, patients with physician-diagnosed psychological disorders and a history of psychotherapeutic therapy or anxiolytic or hypnotic medication (n = 125) were excluded. The final sample for analysis in our present study was 883. A sensitivity analysis revealed that there were no significant differences in ethnicity, BMI, education, current smoker, diastolic blood pressure, triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol, and creatinine between those included in the analyses compared with those with final included and excluded participants; There was a significant difference in sex, age, married status, current drinkers, presence of somatic conditions/illnesses, systolic blood pressure, and blood hemoglobin across the above groups (Supplement Table S1).

The demographic and socioeconomic characteristics of the individuals are shown in Table 1. Overall, the mean age was 53.2 years old, with a mean BMI of 29.8 kg/m^2; 480 individuals (54.4 %) were males, 33 individuals (3.7 %) were Hispanics, 545 individuals (61.8 %) were married, 351 individuals (39.8 %) had bachelor's degrees or higher, 124 individuals (14.0 %) were current smokers, and 601 individuals (68.1 %) were current drinkers. Additionally, 804 individuals (91.1 %) reported at least one or more somatic conditions/illnesses, and the average number of somatic conditions/illnesses was 3.6. Regarding psychiatric conditions, the average CES-D score in the present cohort was 7.7, and 105 individuals (11.9 %) had depressive symptoms (CES-D $\geq$ 16). The STAI score in our individuals was 33.6, and 20 (2.3 %) individuals had anxiety symptoms (STAI $\geq$ 54). The average score of the LSAS was 1.8, and 30 individuals (3.4 %) had scores higher than 3, suggesting mild levels of social anxiety on average and subclinical social anxiety symptoms. The average PSS score in the present study was 21.8, and 194 individuals (22.0 %) had high perceived stress symptoms (PSS $\geq$ 27). The median SBP reactivity, DBP reactivity and HR reactivity of individuals in our study were 12.3, 6.1 and 3.2, respectively.

3.2. Cardiovascular reactivity

This protocol of stressor tasks for measuring cardiovascular reactivity is shown in Fig. 1. As shown in Supplement Table S2, repeated measures (baseline, mean cardiovascular reactivity across stressor tasks) of analysis of variance confirmed that the stressor tasks increased cardiovascular responses for SBP, DBP and HR (all $P < 0.05$).

3.3. Correlation analysis between psychological scores and cardiovascular reactivity

The psychological scores for all variables of interest (CES-D, STAI, LSAS, PSS) were negatively correlated with cardiovascular reactivity, including SBP reactivity, DBP reactivity and HR reactivity (all $P < 0.05$), except LSAS and HR reactivity ($P = 0.123$) The effect sizes and other statistics of these correlations are presented in Table 2.

Table 1
Characteristics of final sample for analysis of depressive symptoms, anxiety and social stress and cardiovascular reactivity in a psychological treatment-naive general population.

	Mean ± SD (%) (N = 883)
Demographic factors	
Age, years	53.2 ± 11.3
Sex, male, n (%)	480 (54.4)
Ethnicity (Spanish %)	
No	706 (80.0)
Yes	33 (3.7)
BMI	29.8 ± 6.4
Socioeconomic factors	
Education, % with bachelor's degree or higher	351 (39.8)
Marital status, % married	545 (61.8)
Health lifestyle	
Current smoking regularly, %	124 (14.0)
Current drinking, %	601 (68.1)
Medical	
Presence of somatic conditions/illnesses, %	804 (91.1)
No. of somatic conditions/illnesses	3.6 ± 2.7
Heart disease, n (%)	76(8.6)
High blood pressure, n (%)	294(33.3)
TIA or stroke, n (%)	25(2.8)
Diabetes, n (%)	102(11.6)
Emphysema/COPD, n (%)	22(2.5)
Cancers	107(12.1)
History of physician-diagnosed depression, %	71(8.0)
Laboratory measurement	
Systolic blood pressure, mmHg	130.6 ± 16.8
Diastolic blood pressure, mmHg	75.8 ± 10.1
Blood hemoglobin A1c %	5.81(5.6–6.2)
Triglycerides, mg/dL	192.6 ± 73.0
Total cholesterol, mg/dL	106.5(78.0–157.0)
LDL-C, mg/dL	53.0 (43.0–65.8)
HDL-C, mg/dL	102.0 (81.0–129.0)
Creatinine, mg/dL	0.8(0.7–1.0)
Psychosocial scores	
Depression	
CESD total score	7.7 ± 7.1
No depressive symptoms (<16), n (%)	778(88.1)
With depressive symptoms (≥16), n (%)	105(11.9)
Anxiety	
STAI score	33.6 ± 8.8
No anxiety symptoms (<54), n (%)	863(97.7)
With anxiety symptoms (≥54), n (%)	20(2.3)
LSAS	1.8 ± 0.5
Mild anxiety (<3), n (%)	853 (96.6)
Moderate to severe anxiety (3–4), n (%)	30(3.4)
Stress	
PSS score	21.8 ± 6.0
Low stress (0–13), n (%)	58 (6.5)
Moderate stress (14–26), n (%)	631(71.5)
Severe stress (≥27), n (%)	194(22.0)
Cardiovascular reactivity (median IQR))	
SBP reactivity	12.3(6.4, 18.5)
DBP reactivity	6.1(3.6, 9.0)
HR reactivity	3.2(1.5, 5.5)

Notes: Median (IQR) for nonnormally distributed data, Mean ± SD for normally distributed data, and n (%) for categoric variables.
Abbreviations: BMI, body mass index; CESD, Center for Epidemiologic Studies Depression Scale; STAI, Spielberger Trait Anxiety Inventory; LSAS: Liebowitz social anxiety; PSS, Perceived Stress Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; SD, standard deviation; LDL-C: low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack.

3.4. Comparison of cardiovascular reactivity between those with and without psychological symptoms

Furthermore, we used a cutoff value of 16 for the CES-D score to distinguish participants with depressive symptoms, a cutoff value of 54 for the STAI and a cutoff value of 3 for the LSAS to distinguish

Table 2
Correlations between depression, anxiety, stress, and cardiovascular reactivity in treatment naïve general population.

	CESD	STAI	SAS	PSS	SBP reactivity	DBP reactivity	HR reactivity
CES-D	1.00	0.759**	0.384**	0.726**	−0.213 **	−0.233**	−0.125 **
STAI	/	1.00	0.484**	0.772**	−0.194**	−0.198 **	−0.081*
LSAS	/	/	1.00	0.418**	−0.088**	−0.081*	−0.052
PSS	/	/	/	1.000	−0.215**	−0.201**	−0.0874*
SBP reactivity	/	/	/	/	1.000	0.748**	0.271**
DBP reactivity	/	/	/	/	/	1.000	0.371**
HR reactivity	/	/	/	/	/	/	1.000

Values are expressed as the Pearson correlation coefficient.
Abbreviations: CESD, Center for Epidemiologic Studies Depression Scale; STAI, Spielberger Trait Anxiety Inventory; LSAS: Liebowitz social anxiety; PSS, Perceived Stress Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.
* $P < 0.05$.
** $P < 0.01$.

participants with anxiety symptoms, and a cutoff value of 27 for the PSS to distinguish participants under clinically significant levels of stress. Then, we performed a comparison of cardiovascular reactivity between those with and without psychological symptoms. As shown in Fig. 2, participants with depressive symptoms (CES-D ≥ 16) had significantly lower levels of SBP reactivity, DBP reactivity and HR reactivity (all $P < 0.05$). Participants under clinically significant levels of stress (PSS ≥ 27) showed consistent results. However, participants with anxiety symptoms (SATI≥54) showed only lower SBP reactivity and DBP reactivity but no significant difference in HR reactivity ($P = 0.195$).

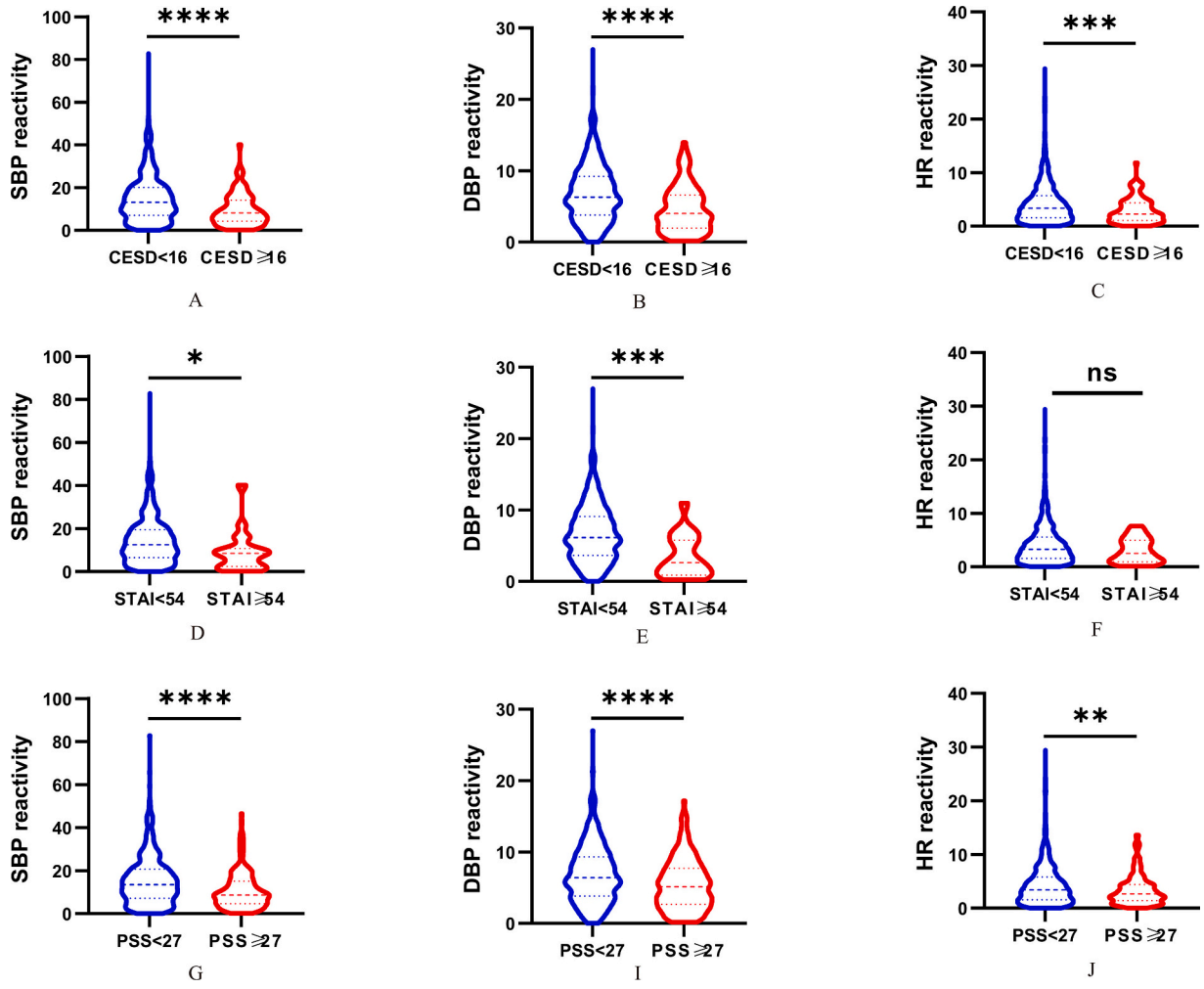

Fig. 2. Violin plot illustrating the distribution of SBP reactivity, DBP reactivity and HR reactivity by psychological status in the treatment-naive general population. A–C: Depressive symptoms; D–F: anxiety symptoms; G–I: degree of stress. Psychological status was assessed by psychological scores. Depressive symptoms were assessed by using the Center for Epidemiologic Studies Depression Scale (CES-D), and CES-D ≥ 16 was defined as depressive symptoms. Anxiety symptoms were assessed by the Spielberger Trait Anxiety Inventory (STAI), and STAI ≥ 54 was regarded as anxiety symptoms. The degree of stress was assessed by the Perceived Stress Scale (PSS) and PSS ≥ 27 is considered a high perceived stress level. Comparison between groups with Student's *t*-test; *$P < 0.05$; **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$, ns: $P > 0.05$. The thick dashed line in the violin plot indicates the median of the psychological scores, and the thin dashed line indicates the interquartile range between the 25th and 75th percentiles.
Abbreviations: BP, blood pressure; HR, heart rate; ns, statistically not significant.

3.5. Associations between psychological scores and cardiovascular reactivity

To further elucidate the association between psychological scores and cardiovascular reactivity, we performed univariate and multivariate linear regression analyses. As shown in Table 3, all psychological scores, including CES-D, STAI, LSAS, PSS, were negatively associated with SBP reactivity, DBP reactivity and HR reactivity. Adjustment for age and sex (Model 2) and additionally adjusting for race, highest level of education, current marriage status, body mass index, smoking status, drinking status and number of chronic conditions (Model 3) did not eliminate the negative association between psychological scores and cardiovascular reactivity except PSS and HR reactivity ($P = 0.056$).

3.6. Subgroup analysis of and sensitivity analysis

The sex-stratified analyses showed that no significant difference for sex in the association between psychological scores and cardiovascular reactivity (SBP reactivity and HR reactivity). However, a stronger association was found between CES-D, STAI, PSS and DBP reactivity in males compared to females ($P < 0.05$) (Supplement Table S3).

In sensitivity analyses, the results yielded significant similarity with those of the participants with multiple imputation, except LSAS. (Supplement Table S4).

4. Discussion

4.1. Main findings

In this comprehensive assessment of cardiovascular reactivity with psychological status in a population without psychotherapeutic medication, we assessed the association between psychological status, including depression, anxiety, stress, and cardiovascular reactivity. We found that compared with people without psychological symptoms, people with depression, anxiety, and stress symptoms had significantly lower levels of SBP reactivity, DBP reactivity and HR reactivity. Furthermore, we found that all psychological scores, including CES-D, STAI, LSAS, and PSS, were negatively correlated with SBP reactivity, DBP reactivity and HR reactivity. The inverse association between psychological scores and lower cardiovascular reactivity persisted after adjustments for age, sex, race, education, marital status, body mass index, smoking, drinking and chronic diseases, although there was no significant difference between stress symptoms and HR reactivity ($P = 0.056$).

Although a few studies have attempted to assess the association between psychological disorders or symptoms and cardiovascular reactivity, the results were inconsistent. Some early studies have discovered that depressive symptoms are linked to elevated cardiovascular reactivity (Light et al., 1998; Matthews et al., 2005). Importantly, further inspection revealed that most of these small-scale previous studies yielded statistically null results by a systematic review (Kibler and Ma, 2004). The pooled effect size of depression and systolic, diastolic, and heart rate responses from 11 studies was not statistically significant, which provides limited support for the hypothesis that psychological disorders are associated with elevated cardiovascular reactivity (Kibler and Ma, 2004). Additionally, most previous researchers did not exclude participants who underwent psychotherapeutic treatment. Previous exposure to psychotherapeutic medication may impact cardiovascular responsiveness (Licht et al., 2015; Serodio et al., 2014; Licht et al., 2009). Herein, after excluding individuals taking antidepressants or other medications for psychiatric conditions, we only focused on treatment-naive individuals with psychological symptoms. We first showed that depression, anxiety, and stress were negatively associated with cardiovascular reactivity, independent of age, sex, race, education, current marriage status, body mass index, smoking status, drinking and chronic diseases.

Notably, sex plays an important role in mood disorders and cardiovascular disease. Statistically, women are nearly 8 % more likely than men to experience a major depressive episode in their lifetime (25 % vs. 17 %) (Kessler et al., 2010). Previous studies have also shown that female ovarian hormone fluctuations affect a woman's sensitivity to stress, brain structure and function, and inflammatory activity and response. These effects are highly context-dependent (Slavich and Sacher, 2019). In experiments that included only thirty healthy women, Light et al. found that the depressive symptoms group had a higher cardiovascular response after receiving a stress stimulus (Light et al., 1998). Another study also found that patients with high depression scores were more likely to be women, and it also showed that patients with higher depression scores have a higher average heart rate during daily life (Krittayaphong et al., 1997). However, Carroll et al. also found that women were more likely to have higher depression scores, but they found that depression scores were negatively associated with systolic

Table 3
Linear regression analysis of association between psychological scores and cardiovascular reactivity in treatment naïve general population.

	Systolic blood pressure reactivity			Diastolic blood pressure reactivity			Heart rate reactivity		
	R^2	*B*	*P* value	R^2	*B*	*P* value	R^2	*B*	*P* value
CESD									
Model 1	0.045	−0.319	<0.0001	0.054	−0.127	<0.0001	0.156	−0.062	<0.0001
Model 2	0.117	−0.236	<0.0001	0.093	−0.105	<0.0001	0.028	−0.073	<0.0001
Model 3	0.098	−0.181	0.003	0.074	−0.074	0.0002	0.037	−0.061	0.005
STAI									
Model 1	0.38	−0.236	<0.0001	0.039	−0.088	<0.00001	0.007	−0.332	0.016
Model 2	0.11	−0.168	<0.0001	0.082	−0.071	<0.00001	0.011	−0.449	0.045
Model 3	0.096	−0.129	0.008	0.069	−0.045	0.011	0.028	−0.039	0.022
LSAS									
Model 1	0.008	−1.743	0.009	0.007	−0.581	0.016	0.003	−0.341	0.123
Model 2	0.094	−0.795	0.217	0.060	−0.374	0.118	0.011	−0.449	0.045
Model 3	0.093	−1.484	0.044	0.067	−0.628	0.002	0.029	−0.525	0.041
PSS									
Model 1	0.046	−0.384	<0.0001	0.040	−0.130	<0.0001	0.007	−0.050	0.012
Model 2	0.115	−0.274	<0.0001	0.080	−0.100	<0.0001	0.018	−0.064	0.002
Model 3	0.103	−0.241	0.001	0.071	−0.072	0.004	0.031	−0.047	0.056

Notes: Model 1 is unadjusted. Model 2 is adjusted for age and sex. Model 3 is additionally adjusted for age, sex, race, highest level of education, current marriage status, body mass index, current smoking status, current drinking status and number of chronic conditions. Regression coefficients (B), R^2 and *p* values displays for the linear regression model.

Abbreviations: CESD, Center for Epidemiologic Studies Depression Scale; STAI, Spielberger Trait Anxiety Inventory; PSS, Perceived Stress Scale; LSAS, Liebowitz Social Anxiety scale.

blood pressure and heart rate reactions (Carroll et al., 2007). This suggests a potential sex difference in psychological status and cardiovascular reactivity. In the present study, the proportion of males in the population we included was 54.4 %, which demonstrated a good generality of sex. Meanwhile, we also adjusted our results for sex. However, a sex-specific subgroup analysis was not conducted in the present study, and the potential sex differences in psychological status and cardiovascular reactivity in treatment-naive individuals need to be explored by further studies.

Studies have demonstrated a firm link between stress exposure and an increased risk of cardiovascular disease (Eddy et al., 2017). Notably, relatively limited studies have assessed stress and cardiovascular activity. An early study (N = 100) showed that undergraduates with high perceived levels of stress have a lower pulse rate reactivity without any adjustment (Ginty and Conklin, 2011). We also observed a statistically significant negative association between high stress levels assessed by PSS scores and reduced SBP and DBP reactivity; however, the association was not statistically significant with HR reactivity after adjusting for more confounders in Model 3. Further prospective studies are needed to confirm our results.

Regarding heart rate changes, previous studies have found a negative correlation trend between depression and heart rate in Caucasians and the opposite in Blacks (Haeri et al., 1996). In this study, the majority were not Spanish (77.6 %), and the relatively homogenous population may limit the generalization to other races. In addition, obesity also has a certain impact on heart rate because the sympathetic nervous system of obese people may have a poor response to stimuli (Tentolouris et al., 2003; Quilliot et al., 2008; Brydon et al., 2008), promoting the negative associations between psychological disorders and cardiovascular reactivity.

Depression, anxiety, and stress are diseases with a high prevalence and often coexist. Previous animal studies have shown that mice under chronic stress experience increased anxiety and depressive-like behavior (Meduri et al., 2013). In a population under chronic stress, a cross-sectional study also reported that 64 % of patients had anxiety and 33 % had depressive-like symptoms (Wiegner et al., 2015). Our results also found that these three are negatively correlated with cardiovascular reactivity, but due to the limitations of the experiment, we did not have an in-depth understanding of how these three interact with each other and the complex relationship with cardiovascular reactivity.

Comparison with previous studies.

Our results reinforced some previous experiments that examined the association between psychological status and cardiovascular reactivity in diverse populations, although limited reports have adjusted for antidepressants or other antipsychotics. For example, cross-sectional studies based on the general population showed negative associations for SBP and HR and depression symptoms but not DBP (Carroll et al., 2007). Another general population-based study also found a negative association between depression symptoms and cardiovascular reactivity (Phillips, 2011). Consistent results were observed in patients with coronary artery disease. However, chronic diseases, such as cardiovascular diseases, are important confounders; additionally, it is worth noting that high levels of depressive and related symptomatology are common among people with established chronic diseases (Lane et al., 2002). A report that enrolled those free of cardiovascular disease showed that patients with major diagnosed depressive disorder have attenuated cardiovascular reactivity and impaired recovery compared with healthy participants. Our present study also adjusted for chronic diseases and showed consistent results. Overall, the above studies in diverse populations further support the reactivity hypothesis (Chida and Steptoe, 2010; Harris and Matthews, 2004; Schwartz et al., 2003) for mind-heart connections that contribute to physical health and disease.

Furthermore, we also found that compared with people without psychological symptoms, people with higher psychological status scores (proportional to mood disorder levels) had significantly lower cardiovascular reactivity. By excluding individuals treated with antipsychological drugs, we focused only on relatively homogeneous individuals with a large sample size, further supporting the possibility of a negative association between psychological status and cardiovascular reactivity (Salomon et al., 2009; York et al., 2007).

4.2. Underlying mechanism

The relationship between psychological disorders and cardiovascular reactivity remains controversial. There are several mechanisms that may explain the negative association between psychological disorders and cardiovascular reactivity.

First, studies of neuroendocrine function have revealed that individuals with depression exhibit heightened activation of the sympathetic nervous system (Carney et al., 2005). Prolonged exposure to β-adrenergic receptor agonists at high levels can lead to a decline in postsynaptic receptor sensitivity and density (Colucci et al., 1981). Thus, this situation will affect the function of the heart. In fact, there is a growing body of evidence that suggests that people with significant levels of depression may have reduced sensitivity (Charney et al., 1982; Mills et al., 2004) and density (Wood et al., 1986; Jeanningros et al., 1991). Second, as our study (Liu et al., 2021) and other studies (Miller, 2020; Osimo et al., 2019) have shown, psychological dysfunction is associated with inflammation. Inflammation plays a critical role in the incidence and development of cardiovascular diseases and strongly links psychological health with heart diseases (Piña et al., 2018). Various studies have shown that patients with depression have elevated proinflammatory cytokines, such as C-reactive protein (Osimo et al., 2019), interleukin-6 (Liu et al., 2021), and tumor necrosis factor-α (Das et al., 2021), which may lead to cardiomyocyte and endothelial dysfunction (Piña et al., 2018; Chrysohoou et al., 2018). Additionally, the reduced reactivity associated with depression may align with the nonresponse pattern of allostatic load, according to the allostatic load theory (McEwen, 1998). This may indicate an overstimulation of the hypothalamic-pituitary-adrenocortical axis or other compensatory responses and could serve as an indicator of cardiovascular diseases risk through compensatory mechanisms. However, it is crucial to note that this hypothesis requires further testing. Finally, behavioral factors, such as nutritional or physical activity patterns, may also be responsible. Patients with depression are unlikely to engage in regular exercise or consume a balanced diet (Varghese et al., 2020).

4.3. Study strength and limitations

To the best of our knowledge, this is the first study to explore the relationship between psychological status and cardiovascular reactivity in treatment-naive individuals with psychological symptoms. Our results support the mind-heart-body connection-association between psychological health and cardiovascular disease. In addition, we cover depression, anxiety, and stress, with a relatively large cohort, two of which-anxiety and stress-have been poorly studied in relation to cardiovascular reactivity, thus providing greater insight into the study of psychological disorders and cardiovascular disease. However, several limitations should be acknowledged. First, this was a cross-sectional study, indicating that causality is impossible to determine. Second, although some confounding factors were adjusted, unmeasured and insufficiently measured variables would cause the possibility of residual confounding factors. For example, individuals who experience childhood adversity have a blunted physiological response (Bourassa et al., 2021). Third, there are multiple scoring systems for measuring mood status, and due to data restriction, we did not verify our results with different scoring systems.

5. Conclusions

The study found a negative association between psychological symptoms and cardiovascular reactivity in treatment-naive adult

Americans. These findings suggest that blunted cardiovascular reactivity is an underlying mechanism linking psychological health and cardiovascular diseases.

CRediT authorship contribution statement

J. F-W and Y. L-Z was responsible for the entire project and revised the draft. X-L, W. C-L and J. J-H, performed the data extraction and statistical analysis, interpreted the data, and drafted the first version of the manuscript. X-L contributed to the conception and design of the work and revised the manuscript. All authors participated in the interpretation of the results and prepared the final version of the manuscript.

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Conflict of interest

No conflict of interest was declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.02.150.

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